

**The importance of cognitive deficits for
forensic mental health patients with
schizophrenia or schizoaffective
disorder: violence, medication, and
remediation.**

Ken William O'Reilly

D.Psych.Sc., M.Sc., B.Sc.

(02162822)

Department of Psychiatry

School of Medicine

Trinity College Dublin

Dublin, Ireland

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Declaration

I declare that this thesis has not been submitted as an exercise for a degree at this or any other university.

Contribution and ownership of work

The patient work that formed the basis of this thesis was conducted by members of the Forensic Mental Health Research Group at the Republic of Ireland's National Forensic Mental Health Service, academically attached to the Department of Psychiatry, Trinity College Dublin. All contributors are acknowledged at the end of each chapter of the thesis, the findings of which have been published in peer reviewed journals. All research studies were initiated and led by the author of this thesis.

My specific and independent contributions to the PhD thesis consisted of:

- 1) Study design – conceiving and designing all studies and selecting the assessment battery
- 2) Conceiving and developing the therapy content – or principles of cognitive remediation training (CRT), as outlined in the study protocol, chapter 4, and for empirical study 3, chapter 5
- 3) Ethics application – for empirical studies 1, 2, and 3
- 4) Trial registration for the randomised controlled trial (RCT)
- 5) Recruiting participants and obtaining informed consent
- 6) Supervising the delivery of the therapy – oversight of the CRT therapists
- 7) Developing a database and coding all data in addition to conducting all initial statistical analysis
- 8) Producing the initial draft and later the final draft of all academic articles following input from others

I agree to deposit this thesis in the University's open access institutional repository or allow the library to do so on my behalf, subject to Irish Copyright Legislation and Trinity College Library conditions of use and acknowledgment.

Signed: _____

Acknowledgments

My experience with Ireland's National Forensic Mental Service (NFMHS) began during an elective placement at The Central Mental Hospital as part of my training in clinical psychology. Throughout my training the scientific method and the associated values of creative conjecture, rational scepticism, and fallibilism, had been emphasised as the only appropriate way to seek the 'truth'. With reference to a variety of frameworks and models born of the scientific process, I had been encouraged to grasp 'reality' in all its complexities, with the purpose of improving outcomes for patients, clients, and their families. However, it was only during my sixth and final placement at the Central Mental Hospital (CMH), that I witnessed these values actualised. Here was a service fearlessly committed to both academic and clinical excellence, and one which made the unfashionable decision of refusing to see a distinction between the two. After completing the placement, I resigned myself to working within another area of healthcare as it was not possible to directly apply to the National Forensic Mental Health Service for employment.

A year later my mother Breeda informed me that a split position had been advertised at the NFMHS and the Department of Psychiatry, Trinity College Dublin. The position also involved rebuilding the psychology service as head of discipline. Sometime after I had been on placement at the CMH all the psychologists had left the service. At last a chance to combine a clinical and research career as well as an opportunity to mould the direction of psychology within a forensic setting. I prepared diligently with the help of my then girlfriend Lenka. The interview involved candidates making a brief presentation titled 'Forensic Mental Health the Next Frontier'. My initial memory of the interview was that it went badly. I was grilled by nine people, three of which were full professors, and their non-verbals were not good. One interviewer claimed that I did not realise the significance or importance of the post to which I was applying. Following the interview, I met my mother in the lobby of a nearby hotel. She consoled me, and during this post mortem I realised my answers had not been

altogether bad, although perhaps a little rough around the edges. Three weeks later I received a phone call telling me I had got the job.

I would therefore first and foremost like to acknowledge my mother Breeda for her continued support and encouragement, for pushing me to achieve more, and for believing in me no matter what setbacks I faced. And to parody Frank Sinatra, 'Yes' there have been a few. I would also like to acknowledge Lenka, who is now my wife, for tolerating my obsession with psychology, other interests and perseverations, and for her unwavering stoical support throughout the duration of this and other projects. Whilst I gave a Ridley Scott 'alien birth' to this PhD, she produced two beautiful children, Emma and Alex. Staying on the theme of family, I would also like to acknowledge my father John, who for the past five years would periodically and quietly enquire as to when the project would be complete. Dad as I write these acknowledgments, you will be reassured to know the end is in sight. My grandmother aged ninety-five also deserves a special mention. She's the only person I know where its complementary and not derogatory to say she doesn't look a day past eighty!

A person is fortunate to meet one mentor during the entirety of their lifetime. During this PhD I have met two, Professor Harry Kennedy, Executive Clinical Director of the Central Mental Hospital, and the Department of Psychiatry, Trinity College Dublin, and Professor Gary Donohoe, who at time of commencement of this project was an Associate Professor of Clinical Psychology with the Department of Psychiatry, Trinity College Dublin. I have endeavoured to learn as much as I could from you both. This has not always been easy as I have had my own personality and eccentricities to contend with. I am grateful to Professor Kennedy, who is something of a polymath, playing bass for a punk band, in addition to having artistic talent. I remember how generously he gave his time, his can-do attitude, his competitiv spirit, his open mindedness, his political acumen, and I am thankful for the intellectual rigor and verve that he brought to the project. I am also grateful to Professor Gary Donohoe for his time, and for his professional advice. Throughout this project no matter how busy he himself has been and although located in Galway he has always been available for advice and

consultation. Professor Donohoe has opened my eyes to the importance of thinking big, the skill and persistence involved in grant writing, of networking, and international collaboration. Since I have known Professor Donohoe his career has skyrocketed and he was made a full professor of psychology at the National University of Ireland, Galway. Thus, he has provided lots of inspiration. Because I already had a doctorate in clinical psychology prior to commencing this project in some ways the thesis was a sort of professional risk, one which involved a lot of work, but also uncertainty regarding personal payoff or career progression. However, given what I have learnt from Professors Kennedy and Donohoe, and the impact of the project on patient care at the NFMHS, I can say with confidence that it has been worth it, the risk has paid off, and the journey has been worthwhile.

I am also grateful to Professor Michael Gill who is my named supervisor and who has always been supportive of my role within the Department of Psychiatry. In addition, I would like to thank Professor Aiden Corvin, Head of the Department of Psychiatry, who also has been very supportive and contributed to the project.

I would also like to thank my friends and colleagues at the Central Mental Hospital and elsewhere, particularly Dr. Ciaran Coyle, clinical psychologist, Dr Paul O'Connell, consultant forensic psychiatrist, and Dr Danny O'Sullivan, clinical psychologist, all of which played an invaluable part getting the studies off the ground, in addition to making important contributions every step of the way. At the time of the commencement of this project there way only two clinical psychologists, namely Ciaran and I, employed at the Central Mental Hospital. I am pleased to say that the psychology service has grown considerably since this time and now boasts six full time psychologists, with hopefully more to follow.

Moreover, I would like to thank all the clinical psychologists in training, assistant psychologists, research assistants, and master's students, who have contributed to this project, many of whom gave their time voluntarily. I am pleased that since their involvement with the project most have commenced or completed training in clinical psychology or are now like Dr Muireann O'Donnell valued colleagues working within the NFMHS. I would also like to thank those from other

disciplines like psychiatric registrars, occupational therapists and psychiatric nurses who contributed to and facilitated the project.

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Finally, thank you everyone for making this journey light hearted and fun. I hope you too have enjoyed this road less travelled.

Preface

“It was in vain to sit still and wish for what was not to be had; and this extremity roused my application. We had several spare yards, and two or three large spars of wood, and a spare topmast or two in the ship; I resolved to fall to work with these, and I flung as many of them overboard as I could manage for their weight, tying every one with a rope, that they might not drive away. When this was done I went down the ship's side, and pulling them to me, I tied four of them together at both ends as well as I could, in the form of a raft, and laying two or three short pieces of plank upon them crossways, I found I could walk upon it very well, but that it was not able to bear any great weight, the pieces being too light. So I went to work, and with a carpenter's saw I cut a spare topmast into three lengths, and added them to my raft, with a great deal of labor and pains. But the hope of furnishing myself with necessaries encouraged me to go beyond what I should have been able to have done upon another occasion”

Daniel Defoe (1719) *Robinson Crusoe*. Chapter 4. London: Penguin

“Everyone can and should be a scientist. Because being a scientist just means wanting to understand the world and using the only method of doing so that works, namely, to be puzzled, to be mistaken, to guess how one might be mistaken and how the grand authorities who can't imagine that they could be mistaken often are. And not to be satisfied with bad explanations. One's own or anyone else's. That is explanations that could have been otherwise, and you would be none the wiser. That's the critical attitude. It's the only access to reality that we have. Use it. It's fun!”

David Deutsch: Royal Society Fellow, Quantum Physicist, Oxford

Professor. Science Festival Dubai 2014:

<https://www.youtube.com/watch?v=DSk5RsUD9j4>

Summary

Forensic Mental Health Services (FMHS) provide care and treatment to a minority of people with mental illness like schizophrenia or schizoaffective disorder, who come into contact with law enforcement agencies (Kennedy et al., 2006; McFadden 1999). Within the Republic of Ireland and other jurisdictions, most forensic mental health patients have a diagnosis of schizophrenia or schizoaffective disorder (Jansman-Hart et al., 2011). Cognitive impairment is increasingly recognised as a key feature of these disorders (Kahn and Keefe, 2013). To date, the importance of cognitive impairments for patients hospitalised within FMHS has scarcely been examined. This thesis seeks to address this gap in knowledge in two ways. First, by clearly describing the problem, namely investigating the prevalence and importance of cognitive impairments for forensic patients with schizophrenia and schizoaffective disorder. Second, by exploring what can be done to improve patients' cognitive impairments.

The first chapter provides an introduction and describes FMHS and the importance of cognitive impairment for understanding functional outcomes for patients with schizophrenia and schizoaffective disorder. This chapter draws primarily from research concerning the relevance of cognitive impairment for functional outcomes amongst non-forensic patients (Kahn and Keefe, 2013). The association between mental disorders like schizophrenia and schizoaffective disorder and acts of serious violence like homicide is introduced, as are studies examining a link between cognitive impairment and acts of violence. In addition, pharmacological and psychological approaches for improving cognition are described. The chapter concludes by providing an outline of the three empirical studies which form the heart of the thesis.

The second chapter describes the first empirical study, which examines the relationship between cognitive impairment and unplanned reactive inpatient violence. Multivariate analysis demonstrated that cognitive impairment could account for a large proportion of the variance of inpatient violence. For this national cohort the mean composite score on a neuropsychological battery

specific to the cognitive impairments experienced by patients with schizophrenia and schizoaffective disorder was more than three standard deviations (SD) lower than the nonclinical population mean.

The third chapter describes an empirical study examining the relationship between the potentially harmful effects of pharmacotherapy (specifically anticholinergic burden), cognitive impairment, and the ability to benefit from multimodal treatment programs. The results of this study indicate that the cognitive impairment experienced by forensic mental health patients is associated with anticholinergic burden, and that anticholinergic burden was associated with treatment progression only via cognitive impairment.

The fourth chapter describes a protocol for a registered intention to treat (ITT) randomised controlled trial (RCT) of cognitive remediation training (CRT) for most of a national cohort of patients with schizophrenia or schizoaffective disorder. The chapter provides a review of meta-analyses of randomised controlled trials of (CRT) involving non-forensic patients.

The fifth chapter is an empirical study describing the completed RCT. Our RCT is one of only a handful of RCTs which have been conducted within FMHS. The key findings were that the group receiving CRT showed significant improvements on the primary measure of cognition, and secondary measures of cognition including visual and working memory, compared to a waiting list control group receiving treatment as usual (TAU). Cognitive improvements were maintained during the eight-month follow up period. Eighty-five percent of patients said they benefited from participating in CRT when provided with a confidential exit interview.

The sixth and final chapter reviews the thesis in its entirety. Each study is linked with existing theories and knowledge explaining how they progress the field. The strengths and limitations of the thesis are also reviewed. The chapter concludes by taking a prophetic glance to the future outlining the many ways, which a focus on cognition could lead to changes in care and treatment for patients with schizophrenia and schizoaffective disorder.

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List of Abbreviations

FMHS	Forensic Mental Health Services
95% CI	95 percent confidence interval
ACB	Anticholinergic Cognitive Burden Scale
ANOVA	Analysis of variance
AUC	Area under the curve
CAINS	Clinical Assessment Interview of Negative Symptoms
CMH	Central Mental Hospital
CONSORT	Consolidated Standards of Reporting Trials
CPZeq:	Chlorpromazine equivalents
CRT	Cognitive remediation training/ therapy
D-3	DUNDRUM-3 Programme Completion Scale
DSM-5	American Psychiatric Association Diagnostic and Statistical Manual 5 th Edition
DSM-IV-TR	Diagnostic and statistical manual of mental disorders fourth edition text revision
DUNDRUM	Dangerousness, understanding, recovery and urgency manual
FDA	US Food and Drugs Administration
HCR-20	Historical Clinical Risk Management - 20 Version 2
ICD-10	International Classification of Diseases, 10 th Edition
IQ	Intelligence Quotient
MANOVA	Multivariate analysis of variance
MCCB	MATRICES Consensus Cognitive Battery
MSCEIT	Mayer-Salovey-Caruso Emotional Intelligence Test
NART	National adult reading test
NFMHS	National forensic mental health service
NMDA	N-methyl-D-aspartate receptor
OR	Odds ratio
PANSS	Positive and negative syndrome scale
ROC	Receiver operating characteristic
SCID	Structured Clinical Interview of DSM-IV

SD	Standard deviation
SOFAS	The social and occupational functioning assessment scale
SPSS	Statistical package for the social sciences, version 22
TAU	Treatment as usual
TOPF-UK	Test of premorbid functioning, UK Edition
WAIS	Wechsler adult intelligence scale
WHO	World Health Organisation

1. Chapter 1: Introduction and background

1.1 Forensic Mental Health Services

Forensic Mental Health Services (FMHS) can be defined as those services that provide care and treatment for a minority of patients with mental illnesses such as schizophrenia who come into contact with law enforcement agencies as a consequence of their mental disorder, or who cannot be safely managed within another service and require specialised secure care (Kennedy, 2002; McFadyen, 1999). The offences carried out by forensic patients are heterogeneous in nature and range from public order offences to acts of very serious violence including multiple homicide. Consequently, FMHS have a dual role in providing patients with care and treatment, whilst simultaneously protecting the public from further harm through involuntary detention and risk management (Kennedy, 2002; O'Reilly et al., 2015). Notwithstanding some international variation (Jansman-Hart et al., 2011), this dual role is frequently codified into law as is the case with the Republic of Ireland's Criminal Law (Insanity) Act, 2006 Section 11(2).

Internationally, many psychiatric patients are now managed within specialised Forensic Mental Health Services (FMHS), which interact with the criminal justice system (Fakoury and Priebe, 2000; de Tribolet-Hardy and Habermeyer, 2016). One explanation for the international demand for forensic services is the deinstitutionalisation of psychiatric care (O'Neill et al., 2002; Priebe et al., 2008; Jansman-Hart et al., 2011; Chow and Priebe, 2013; O'Reilly et al., 2019). This shift to less restrictive community-based mental health care has occurred in many countries including the United Kingdom, Germany, Austria, Italy, the Netherlands, Denmark, Spain, Switzerland, Canada, New Zealand, Australia and the United States (Jansman-Hart et al., 2011). Whilst the move to community-based care was welcomed in principle its implementation has been criticised. The primary criticism is that where community-based care models have been implemented, they have frequently been insufficiently resourced to provide an appropriate range of levels of care for patients with serious mental disorders (Jansman-Hart et al., 2011; Sharma et al., 2015). Crucially the architects of the

deinstitutionalisation movement did not attempt to determine the amount of beds required to prevent or reduce adverse outcomes like suicide or homicide; a defining feature of a well-functioning mental health care system (O'Reilly et al., 2019). It has been argued that an unintended consequence of deinstitutionalisation, in addition to stricter laws regarding involuntary detention, is that many patients' first therapeutically meaningful contact with mental health services occurs via the criminal justice system (Gray et al., 2000; O'Neill et al., 2002; Crocker et al., 2011). Like for example, being assessed by a forensic psychiatrist during a prison clinic. According to this perspective whereas previously violent assaults or problematic behaviour, like destruction of property, or fire setting, arising out of mental illness led to an involuntary admission to a psychiatric hospital they now lead to criminal charges (Hodgins, 2001; Crocker et al., 2011; Jansman-Hart et al., 2011). The criminal justice system therefore has become a pathway for accessing mental health care and treatment for some patients incapacitated by their mental illness, who fail to appreciate and understand their circumstances or recognise a need for treatment (Gray et al., 2000).

In keeping with the movement to community-based care models and stricter laws regarding involuntary detention the demand for forensic beds continues to increase internationally (de Tribolet-Hardy and Habermeyer, 2016). Within England and Wales, the number of forensic inpatients rose by 45% from 1996 to 2006 (Jansman-Hart et al., 2011). It has been estimated that across western Europe there are approximately five forensic beds per hundred thousand inhabitants (Priebe et al., 2008).

Forensic patients are typically hospitalised for longer periods compared to general psychiatric patients (Fazel et al., 2016). The mean length of stay within FMHS within a European context is approximately five years (Davoren et al., 2015; Fazel et al 2016; Vollm et al., 2017). However, it would not be unusual for forensic patients to be detained for periods greater than five years (Buchanan et al., 2011). It is likely that the dual role played by FMHS regarding protecting society on the one hand and the needs of the patient on the other is a contributing factor to lengthy admissions (Shah et al., 2011; Davoren et al., 2015).

Notwithstanding international variations in legal and administrative frameworks governing admission and discharge, in most countries involuntary detention is reviewed periodically by independent legal authorities (Jansman-Hart et al., 2011). For example, within the Republic of Ireland the need for continued involuntary hospitalisation is independently assessed by mental health review boards or mental health tribunals, in accordance with criminal or civil mental health law (Criminal Law Insanity Act, 2006 & 2010; Mental Health Act, 2001). Length of stay is in part a function of patient ability to participate, engage, and benefit from psychosocial treatment programmes targeting violence risk and mental health needs, as scrutinised by mental health review boards or tribunals (Richter et al., 2018).

Internationally, most patients hospitalised within FMHS suffer from schizophrenia or schizoaffective disorder with estimates ranging from 50-60% (Jansman-Hart et al., 2011; de Tribolet-Hardy and Habermeyer, 2016). For the Republic of Ireland, however, the vast majority of forensic mental health patients (approximately 90%) have a diagnosis of schizophrenia or schizoaffective disorder (O'Reilly et al., 2015). Within the Republic of Ireland only a small minority of patients would have other diagnoses such as a bipolar affective disorder, major depressive disorder, intellectual disability, or autism (O'Reilly et al., 2015).

1.2 Schizophrenia and schizoaffective disorder

Schizophrenia and schizoaffective disorders are currently classified as psychotic disorders within psychiatry's two major nosological systems, DSM-5 and ICD-10 (American Psychiatric Association, 2013; WHO, 1993). Both disorders are characterised by behavioural, cognitive, and emotional dysfunction (American Psychiatric Association, 2013; WHO, 1993). For a patient to be diagnosed with schizophrenia they must present with symptoms such as delusions, hallucinations, or disorganised speech, for a one-month period, which in addition to other symptoms are associated with a marked decline in social and occupational

functioning (DSM-5; American Psychiatric Association, 2013). The diagnosis of schizoaffective disorder can be distinguished from schizophrenia by the presence of a major mood episode (depressive or manic) concurrent with psychotic symptoms, and a decline in social and occupational functioning may not necessarily be present (DSM-5; American Psychiatric Association, 2013). There has been a longstanding debate within academic psychiatry about whether schizoaffective disorder is a valid diagnostic category (Malhi et al., 2008). Clear distinctions between schizophrenia and schizoaffective disorder have not been found using neuropsychological or neurocognitive tests, neuroimaging, molecular neurobiology, or genetic epidemiology studies (Malhi et al., 2008). There is some evidence however that those patients with schizoaffective disorder have a better prognosis, but this can probably be explained by the diagnosis itself not requiring a patient to experience social and occupational dysfunction. Despite these findings, both the American Psychiatric Association and the World Health Organisation (WHO, 1993) continue to support the distinction between the two disorders.

The prognosis for the majority of patients with schizophrenia is poor and meta-analytic studies indicate that only one in seven patients with schizophrenia achieve functional and symptomatic remission sustained over time (Jääskeläinen et al., 2013; American Psychiatric Association, 2013). One explanation for the rate of recovery is the degree of cognitive impairment associated with these disorders (Kahn and Keefe, 2013). However, to date the importance and prevalence of cognitive impairment for forensic patients with schizophrenia and schizoaffective disorder has scarcely been examined (O'Reilly et al., 2015). Moreover, the significance of these cognitive impairments for patients with schizophrenia even within general psychiatric settings has been marginalised (Kahn and Keefe, 2013).

1.3 Cognitive problems amongst patients with schizophrenia and schizoaffective disorder

Although not a core diagnostic feature of DSM-5 (American Psychiatric Association, 2013) or ICD-10 (WHO, 1993), cognitive impairment has a long history of being associated with schizophrenia and schizoaffective disorder (Kraepelin, 1893; Bleuler, 1950; Kahn and Keefe, 2013; Green, 2006). Up to 85% of patients with schizophrenia experience some form of cognitive impairment, where impairment is defined as scoring two standard deviations (SD) below the nonclinical population mean on a cognitive test (Kontaxaki et al. 2014). The cognitive tests on which patients perform poorly include not only neuropsychological or neurocognitive tests of attention, memory, and executive functioning, but also tests of social cognition such as perception of affect, emotional awareness, theory of mind, context sensitive processing, and emotional reasoning (Ochsner, 2008). Both neurocognitive and social cognitive impairments represent a major source of disability for patients with schizophrenia and schizoaffective disorder, accounting for more of the variance of functional outcome than psychotic symptoms (Kahn and Keefe, 2013). Patients with severe cognitive impairments have difficulties functioning day to day, finding meaningful employment, and living independently (Kahn and Keefe, 2013). Importantly, the cognitive impairments associated with schizophrenia and schizoaffective disorder are present prior to the onset of psychosis and found in medication naïve patients (Kahn and Keefe, 2013).

The cognitive impairment experienced by patients with schizophrenia or schizoaffective disorder is hypothesised to arise in part because of neurodevelopmental processes like synaptic pruning, which lead to a lag in development, or presents as a decline in cognitive ability (Keshavan et al., 1994). Consistent with this hypothesis, certain forms of crystallised cognitive ability, like verbal intelligence, do not appear to be seriously affected by the illness and remain relatively unimpaired (Keefe, 1995; Kahn and Keefe, 2013; Joyce, 2013; Aylward et al., 1984). Presumably because information associated with verbal intelligence was acquired prior to the lag in development or decline in cognitive

ability. However, preserved verbal intelligence may mask less apparent but debilitating cognitive impairments like attention, memory, and executive functioning (Keefe, 1995; Aylward et al. 1984).

Standardised batteries have now been developed to assess the specific cognitive impairments associated with schizophrenia, of which the MATRICS Consensus Cognitive Battery (MCCB) is one example (Nuechterlein et al., 2008). The MCCB assesses the following seven cognitive domains: processing speed, attention and vigilance, verbal memory, visual memory, working memory, reasoning and problem solving and social cognition (Nuechterlein et al., 2008). The magnitude of cognitive impairment is particularly pronounced when measured using composite scores derived from instruments like the MCCB, which aggregate deficits across cognitive domains affected by the illness (Joyce, 2013). This general impairment, which is observed on the composite score of test batteries may underpin performance across cognitive domains and is likely to be the major source of functional impairment (Joyce, 2013; Dickinson et al., 2011).

1.4 Violence and schizophrenia

There is robust evidence consisting of multiple meta-analyses and systematic reviews indicating an association between schizophrenia and violence and homicide in particular (Fazel et al. 2009). The rate of homicide amongst patients with schizophrenia is ten times the rate of homicide within the general population (Fazel et al., 2009). Also, violence towards caregivers is more common than has previously been believed. Within one study examining the prevalence of violence against caregivers by patients with schizophrenia, of 277 caregivers 76% reported they had experienced a violent assault from their relative (Kageyama et al., 2018). The relationship between major mental illnesses and violence may historically have been downplayed in part for fear of increasing stigma (Tory, 2011). Paradoxically the most effective way of decreasing stigma may be ensuring that those patients who are at greatest risk of acting violently receive appropriate care and in some cases involuntary psychiatric treatment (Tory, 2011).

Violent acts carried out by patients with schizophrenia are complex and cannot always be explained by psychotic symptoms. Some individuals with schizophrenia or schizoaffective disorder are violent at a young age prior to the onset of psychosis, others become chronically violent after the first psychotic episode even when receiving medication, and there are those who commit a single act of violence during their lifetime (Fazel et al., 2009; Nielssen et al., 2010; Tengström et al., 2001; Hodgins, 2008). Violent acts amongst this population appear to be driven in part by some of the same risk factors as violence in general (Fazel et al., 2009; Larg et al., 2009; Witt et al., 2013; Webster et al., 1997). Risk prediction schemes such as the Historical-Clinical- Risk-20 (HCR-20; Webster et al., 1997) take advantage of this and assess violence proneness or propensity by including several equally weighted items (Dawes, 1979), many of which are not specific to schizophrenia or mental disorder but are associated with suboptimal functioning (Witt et al., 2013). Many of these functional difficulties are likely to be underpinned by the cognitive decline or lag in cognitive development experienced by patients with schizophrenia or schizoaffective disorder (Soyka, 2011; Kahn and Keefe, 2013).

Violence has been robustly associated with cognitive deficits in meta-analyses, systematic reviews, and large prospective studies, concerning brain injury, delinquency, intellectual disability, and prisoners (Fazel et al., 2011; Farrington and Welsh, 2007; Holland et al., 2002; Silver and Nedelec, 2018). In contrast, evidence concerning an association amongst patients with schizophrenia or schizoaffective disorder is contradictory and harder to interpret (Witt et al., 2013). For patients with schizophrenia, some studies have found a positive relationship between impaired cognition and violence whereas others have not (Weiss et al., 2012). The causal nature of this relationship is therefore unclear. One challenge when interpreting this literature is that the studies typically assume that violence is a homogenous entity. This may be a mistake. It is likely that the cognitive problems experienced by patients with schizophrenia and schizoaffective disorder are particularly relevant for unplanned reactive violence, but may be less relevant for instrumental violence, which is executively complex (Heuston et al., 2003) and may be delusionally driven (Barratt and Felthous, 2003).

For some patients impaired cognitive ability may be a distal risk factor for violence, with psychotic symptoms like delusions being the proximal mediating factor (O'Reilly et al., 2015). Those patients whose delusions appear to be functionally linked or relevant to their violent act may not have the most pronounced cognitive impairments, but none the less experience more general and specific cognitive impairments compared to nonclinical controls (Bentall et al., 2009). The cognitive impairments that patients do experience may be relevant to the violent act but obscured within a sample of non-delusional patients also experiencing cognitive problems. For example, some patients may be impaired in their general ability to reason, whilst experiencing specific psychotic symptoms (Moynihan et al 2018) at the time of the violent act. Distal risk factors like general cognitive impairment may therefore be obscured by proximal risk factors like anger or delusions within uncontrolled samples of patients with schizophrenia and schizoaffective disorder. The distinction between unplanned reactive violence and premeditated instrumental violence, in addition to the distinction between proximal and distal risk factors, may account for discrepancies amongst studies examining the relationship between cognition and violence. Identifying the kind of violence carried out by patients with schizophrenia and whether cognition is a distal or proximal risk factor may help elucidate whether there is a causal relationship between cognition and specific forms of violence. Should this be so, it is possible that interventions for improving the cognitive impairments experienced by patients with schizophrenia or schizoaffective disorder may reduce risk of reactive violence or have an indirect effect on psychotic violence.

1.5 Pharmacological approaches for improving cognition

Currently, pharmacological attempts to remediate the cognitive impairment experienced by patients with schizophrenia or schizoaffective disorder have been unsuccessful (Harvey and Bowie, 2012). However, there is emerging evidence that medications targeting cholinergic receptors may have some benefit. In a recent meta-analysis, Choi et al. 2013 found that for patients with schizophrenia, cholinergic medications led to marginal improvement in verbal memory and

moderate improvements in spatial memory (Choi et al., 2013). The cholinergic system is a series of pathways from the basal forebrain radiating throughout the cerebral cortex and involved in regulating attention and memory (Chudasama et al., 2004; Sarter et al., 2005). For older adults it has been demonstrated that cholinergic antagonists impair memory whereas agonists enhance memory (Drachman and Leavitt, 1974). Also, for patients with Alzheimers disease cholinesterase inhibitor therapies have become an important treatment where they have been shown to induce significant symptomatic improvement (Summers et al., 1986; Hampel et al., 2018). Separate to medications targeting the cholinergic system there have been efforts to enhance glutamate transmission because of evidence suggesting a hypofunction of glutamatergic signalling via NMDA receptors (Kantrowitz et al., 2012; Falkenberg et al., 2014). Glutamate is the most widely distributed excitatory neurotransmitter in the brain and also acts as an intermediate in cerebral energy metabolism (Rothman et al., 2003). However, in contrast to cholinergic medications the recent meta-analysis conducted by Choi et al., (2013), did not support the use of glutamate agonists for improving cognition, although some benefit was observed for negative symptoms.

The reason why these medications are not more successful is unclear. Excessive synaptic pruning may limit the potential for improving cognition via neurotransmitters (Keshavan et al., 1994). The use and dose of concurrent medications may also be important (Harvey and Bowie, 2012). Concurrent medications may have a harmful effect on patients' cognitive ability via the same mechanism as the cognitive enhancing agents, namely the cholinergic system (Nebes et al., 2005; Campbell et al., 2009). Many of the medications administered to patients with schizophrenia or schizoaffective disorder possess anticholinergic properties (Chew et al., 2006; Buchanan, 2005). Pharmacological treatments when aggregated may therefore create a considerable anticholinergic burden. Anticholinergic burden might impair ability to benefit from psychosocial treatments. No study has yet examined whether the effect of anticholinergic burden on 'real world' functioning is mediated via impaired cognitive ability. Anticholinergic burden may lead to increased cognitive impairment, which in turn might affect treatment progression. Several studies have been conducted that

suggested that discontinuing anticholinergic medications had a positive effect on cognition amongst patients with schizophrenia (Baker et al., 1983; Mori et al 2002; Drimer et al., 2004; Ogino et al., 2011; Desmaris et al., 2014). One pathway for reducing cognitive impairments experienced by patients with schizophrenia or schizoaffective disorder and for improving ‘real world’ functioning may be by minimising medications which have an anticholinergic burden.

1.6 Psychological approaches for improving cognition

Cognitive remediation training (CRT) is a psychological approach that has shown potential to improve cognitive impairments for patients with schizophrenia or schizoaffective disorder within non-forensic settings (Wykes et al., 2011; Cella et al., 2015). CRT is a behaviourally based training approach designed to help patients improve their cognitive abilities and ‘real world’ functioning. A variety of therapies exist under the CRT umbrella but most aim to either strengthen patients’ basic cognitive capacities through a process of drill and practice, or to teach patients more effective ways to deploy cognitive resources using meta-cognitive strategies. CRT is also a nonthreatening activity, which patients’ report to enjoy, and focuses on experiences of success and mastery (Rose and Wykes, 2008). A recent meta-analysis by Wykes involving non-forensic or general mental health patients demonstrated that CRT is an effective intervention for improving cognitive and functional outcomes for patients with schizophrenia or schizoaffective disorder (Wykes et al., 2011). Within the Wykes meta-analysis, the average patient who received CRT improved performance on cognitive tasks by an effect size of .5 (Cohens d) and .42 on patient functioning. However, the evidence base for CRT within a forensic mental health setting is limited.

To date only two randomised trials have been conducted within a forensic mental health setting. One was a small pilot study investigated the feasibility of improving social cognition amongst forensic mental health patients (n = 21 Social CRT vs n = 15 TAU; Taylor et al., 2015). The second study mixed forensic mental health patients with general mental health patients. Mixing patient groups

may undermine the confidence with which the findings can be generalised to forensic mental health patients (Ahmed et al., 2015). Of note within this study the forensic mental health patients were significantly more cognitively impaired on working memory and verbal learning than the general mental health patients. In addition to the limited evidence for CRT within a forensic setting there are also questions about the generalisability or transportability of psychological interventions like CRT from a non-forensic setting to a forensic setting. In contrast to most community patients, forensic patients are involuntarily detained and consequently may not readily occupy the role of ‘customer’. Many forensic patients may also have poor insight into their need for treatment and may be ambivalent or have negative attitudes towards participating or adhering to interventions, both of which are sometimes captured by violence risk measures (Webster et al., 1997). Therefore, there is a requirement that studies specific to the forensic mental health setting including RCTs be conducted to determine the transportability and effectiveness of non-forensic treatment programmes, in addition to developing forensic specific interventions (Tunis et al., 2003; Marchand et al, 2011).

1.7. Thesis Aims, Hypotheses and Overview

This thesis aims to understand the importance of cognitive impairments for forensic mental health patients with schizophrenia or schizoaffective disorder. To date the importance of cognitive impairments for patients hospitalised within forensic mental health services has scarcely been examined. I seek to address this knowledge gap in two ways. First, by clearly describing the problem, namely investigating the mean level of cognitive impairment experienced by patients with schizophrenia or schizoaffective disorder amongst a national cohort of forensic mental health patients, as well as clarifying the significance of these deficits for explaining social and occupational functioning in general, and violent behaviour in particular. Second, by exploring what can be done to improve cognitive functioning. Specifically, whether anticholinergic burden arising from polypharmacy is associated with cognitive impairments and ability to benefit from

psychosocial treatment programmes, and whether CRT may be useful for improving cognitive functioning.

Study 1 (Chapter 2): Prospective cohort study of the relationship between neuro-cognition, social cognition and violence in forensic patients with schizophrenia and schizoaffective disorder

This study involved recruiting patients from a national forensic cohort at the Republic of Ireland's Central Mental Hospital, which is part of National Forensic Mental Health Service; assessing cognitive impairments, and separately and independently assessing psychotic symptoms, patient 'real world' functioning, violence risk and actual violent assaults over a twelve-month period. The aim of the study was to determine the mean level of cognitive impairment within the national cohort and to determine the relationship between cognitive impairment and acts of violence prospectively over a twelve-month period.

It was hypothesised that a) neurocognitive and social cognitive deficits are determinants of reactive in-patient violence and b) that the relationship between neurocognitive deficits and violence would be mediated by risk factors such as deficits in social reasoning, increased symptoms, impaired social functioning and increased violence proneness.

This study resulted in the following peer reviewed publication:

O'Reilly, K., Donohoe, G., Coyle, C., O'Sullivan, D., Rowe, A., Losty, M., McDonagh, T., McGuinness, L., Ennis, Y., Watts, E., Brennan, L., Owens, E., Davoren, M., Mullaney, R., Abidin, Z., Kennedy, G. H. (2015). Prospective cohort study of the relationship between neuro-cognition, social cognition and violence in forensic patients with schizophrenia and schizoaffective disorder. *BMC Psychiatry*. 15:155.

Study 2 (Chapter 3): Anticholinergic burden in schizophrenia and ability to benefit from psychosocial treatment programmes: a 3-year prospective cohort study.

This study also involved recruiting patients from a national forensic cohort at the Republic of Ireland's Central Mental Hospital, which is part of the National Forensic Mental Health Service; assessing cognitive impairment, and anticholinergic burden, participation, engagement, and benefit from psychosocial treatment programmes over a three-year period. The aim of the study was to determine if anticholinergic burden would be associated with cognitive impairments, which in turn would affect treatment progression, namely patient's ability to participate, engage and benefit from psychosocial treatment programmes. If this is so, one possible future intervention to improve cognitive impairments within this patient group would be to reduce anti-cholinergic burden by discontinuing unnecessary medications.

It was hypothesised that a) the relationship between anticholinergic burden and ability to benefit from psychosocial treatment programmes would be mediated by cognitive ability, when controlling for age, gender, baseline performance on psychosocial treatment programmes, total antipsychotic dose, and symptoms, and b) that the 'mediation relationship' between medication, cognition, and programme completion would be specific to anticholinergic burden and not total antipsychotic dose; and that the mediation would be specific to cognition, and not to symptoms or functioning when cognition is controlled for.

This study resulted in the following peer reviewed publication:

O'Reilly, K., O'Connell, P., Donohoe, G., Coyle, C., O'Sullivan, D., Azvee, Z., Maddock, C., Sharma, K., Sadi, H., McMahon, M., Kennedy, H.G. (2016). Anticholinergic burden in schizophrenia and ability to benefit from psychosocial treatment programmes: a 3-year prospective cohort study. *Psychological Medicine*. 46(15):3199–211.

Study 3 (Chapter 4): Study Protocol: A randomised controlled trial of cognitive remediation for a national cohort of forensic mental health patients with schizophrenia or schizoaffective disorder.

This study protocol involved registering the randomised controlled trial with ClinicalTrials.gov and developing the principles underpinning the CRT intervention, developing the study methodology, and recruiting participants from the National Forensic Mental Health Services Central Mental Hospital.

This study resulted in the following peer reviewed publication:

O'Reilly, K., Donohoe, G., O'Sullivan, D., Coyle, C., Mullaney, R., O'Connell, P., Maddock, K., Nulty, A., O'Flynn, P., O'Connell, C., Kennedy, G. H. (2016). Study protocol: a randomised controlled trial of cognitive remediation for a national cohort of forensic mental health patients with schizophrenia or schizoaffective disorder. *BMC Psychiatry*. 16:5.

Study 4 (Chapter 5): A randomized controlled trial of cognitive remediation for a national cohort of forensic patients with schizophrenia or schizoaffective disorder.

This study involved delivering and evaluating the effectiveness of a cognitive remediation programme, involving forty-two individual sessions and fourteen group sessions for patients, fifty-six sessions in total, using an intention to treat (ITT) randomised controlled trial methodology with a national cohort of forensic patients with schizophrenia or schizoaffective disorder. The aim of the study was to discover if CRT would be an effective and valued intervention for forensic mental health patients.

It was hypothesised a) that patients allocated to cognitive remediation training (CRT) would improve on the primary outcome measure, cognition at the end of treatment, and at eight months follow up, b) That patients allocated to CRT would improve on specific neurocognitive and social cognitive domains at end of

treatment and eight months follow up, c) that patients allocated to CRT would experience improvements in negative and disorganised symptoms, d) That patients allocated to CRT would experience improvements in real world functioning, moves to lower level of security, and that patients' functional improvements or moves to lower levels of security would be mediated by cognitive gains, e) that patients would experience CRT as a satisfactory and efficacious intervention.

This study resulted in the following peer reviewed publication:

O'Reilly, K., Donohoe, G., O'Sullivan, D., Coyle, C., Corvin, A., O'Flynn, P., O'Donnell, M., Galligan, T., O'Connell, P., Kennedy, H.G. (2018). A randomized controlled trial of cognitive remediation for a national cohort of forensic patients with schizophrenia or schizoaffective disorder. *BMC Psychiatry*. 19:27.

2. Chapter 2: Study/Empirical paper 1: Prospective cohort study of the relationship between neuro-cognition, social cognition and violence in forensic patients with schizophrenia and schizoaffective disorder

This chapter describes the first empirical paper. This study was published in BMC psychiatry in 2015. –

O'Reilly, K., Donohoe, G., Coyle, C., O'Sullivan, D., Rowe, A., Losty, M., McDonagh, T., McGuinness, L., Ennis, Y., Watts, E., Brennan, L., Owens, E., Davoren, M., Mullaney, R., Abidin, Z., Kennedy, H.G. (2015). Prospective cohort study of the relationship between neuro-cognition, social cognition and violence in forensic patients with schizophrenia and schizoaffective disorder. *BMC Psychiatry*, 15:155.

Research Question:

- To determine the mean level of cognitive impairment within the national cohort and to determine the relationship between cognitive impairment and acts of violence prospectively over a twelve-month period.

2.1 Abstract

Background

There is a broad literature suggesting that cognitive difficulties are associated with violence across a variety of groups. Although neurocognitive and social cognitive deficits are core features of schizophrenia, evidence of a relationship between cognitive impairments and violence within this group has been mixed.

Methods

We prospectively examined whether neurocognition and social cognition predicted inpatient violence amongst patients with schizophrenia and schizoaffective disorder (n = 89; 10 violent) over a 12-month period. Neurocognition and social cognition were assessed using the MATRICS Consensus Cognitive Battery (MCCB).

Results

Using multivariate analysis neurocognition and social cognition variables could account for 34% of the variance in violent incidents after controlling for age and gender. Scores on a social cognitive reasoning task (MSCEIT) were significantly lower for the violent compared to nonviolent group and produced the largest effect size. Mediation analysis showed that the relationship between neurocognition and violence was completely mediated by each of the following variables independently: social cognition (MSCEIT), symptoms (PANSS Total Score), social functioning (SOFAS) and violence proneness (HCR-20 Total Score). There was no evidence of a serial pathway between neurocognition and multiple mediators and violence, and only social cognition and violence proneness operated in parallel as significant mediators accounting for 46% of variance of violent incidents. There was also no evidence that neurocognition mediated the relationship between any of these variables and violence.

Conclusions

Of all the predictors examined, neurocognition was the only variable whose effects on violence consistently showed evidence of mediation. Neurocognition

operates as a distal risk factor mediated through more proximal factors. Social cognition in contrast has a direct effect on violence independent of neurocognition, violence proneness and symptom severity. The neurocognitive impairment experienced by patients with schizophrenia spectrum disorders may create the foundation for the emergence of a range of risk factors for violence, including deficits in social reasoning, symptoms, social functioning, and HCR-20 risk items, which in turn are causally related to violence.

2.2 Introduction

Most patients diagnosed with schizophrenia are never violent. However, there is a small but significant association between schizophrenia and violence and with homicide in particular (Fazel et al., 2009; Nielssen and Large, 2010; Naudts and Hodgins, 2006) . The relationship between violence and schizophrenia is thought to arise primarily from active symptoms such as delusions and co-morbid problems particularly substance misuse (Fazel et al., 2009; Nielssen and Large, 2010; Naudts and Hodgins, 2005; Richard-Devantoy et al., 2013) . But there is a link between schizophrenia and vulnerability to substance misuse and an increased risk of violence remains even when substance misuse is taken into account (Richard-Devantoy et al., ,2013; Pickard and Fazel, 2013). Also, violent acts carried out by people with schizophrenia are complex and cannot always be explained by psychotic symptoms alone. Some people with schizophrenia can become violent at a young age prior to the onset of psychosis, whereas others become chronically violent after the first psychotic episode even when receiving medication, and there are those who commit only a single act of violence during their lifetime (Fazel et al., 2009; Naudts and Hodgins, 2005; Tengström et al., 2001). Furthermore, the violent acts carried out by people with schizophrenia appear to be driven by some of the same risk factors as violence in general (Tengström et al., 2001; Erb et al., 2001; Large et al., 2009; Georgiev et al., 2013). Violence risk prediction schemes such as the Historical-Clinical-Risk-20 (HCR-20) (Webster et al., 1997; Risk Management Authority of Scotland, 2008) take advantage of this and assess violence proneness by including a large number

of equally weighted items (Dawes, 1979) that are not specific to schizophrenia or mental disorder but are associated with suboptimal functioning. For example, substance misuse, homelessness, employment problems, relationship problems, lack of social support, history of victimisation and criminal history, are all risk factors for violence (Abidin et al., 2013; Singh et al., 2011; Witt et al., 2013). Many of these difficulties are likely to be underpinned by the cognitive decline experienced by patients with schizophrenia (Soyka, 2011; Kahn and Keefe, 2013; Keshavan, 1994; McGlashan, 2006; Brent et al., 2014). Neurocognitive impairments may therefore represent a common or distal risk factor whose influence on violence is mediated by a range of more proximal risk factors.

Impaired neurocognition and social cognition in schizophrenia

Although not a core diagnostic feature in DSM-5 (American Psychiatric Association, 2013) or ICD-10 (WHO, 1993), cognitive impairment has always been associated with schizophrenia (Kahn and Keefe, 2013; Kraepelin, 1893; Bleuler, 1950). Contemporary research has quantified this association using a range of neuropsychological tests. On these measures patients with schizophrenia perform worse than healthy controls by as much as 2 standard deviations (Kahn and Keefe, 2013). The cognitive impairments are also thought to occur prior to the onset of psychosis (Kahn and Keefe, 2013), and crucially they also occur in medication naïve patients (Kahn and Keefe, 2013). Standardised batteries have been developed to assess the cognitive problems experienced by patients with schizophrenia, of which the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) is one example (Nuechterlein et al., 2008). The cognitive tasks on which patients perform poorly include not only neuropsychological or neurocognitive tests of memory, attention, and executive functioning, but also tests of social cognition such as perception of affect, emotional awareness, theory of mind, context sensitive processing, and emotional reasoning (Ochsner, 2008). Like neurocognitive deficits, many of these social cognitive problems are thought to be

stable across phases of illness and linked to suboptimal functioning (Kahn and Keefe, 2013; Green et al., 2012). For example, three tests - emotional reasoning (using the Mayer-Salovey-Caruso Emotional Intelligence Test MSCEIT), theory of mind and social relationship perception all predicted real world functioning at twelve months for patients experiencing first episode psychosis (Horan et al., 2012). Social cognitive problems appear to account for additional variance of 'real world' social functioning even when controlling for neurocognition (Fett et al., 2011). Recent evidence also suggests that deficits in social cognition may mediate the relationship between neurocognitive impairments and positive symptoms, which have traditionally been seen as two separate domains (Green et al., 2012; Lam et al., 2014). Because of the importance of the construct of social cognition for real world functioning and because of its strong psychometric properties, the managing emotion branch of the MSCEIT was included as a separate domain within the MCCB (Nuechterlein et al., 2008). Finally, both neurocognitive and social cognitive problems represent a major source of disability for patients with schizophrenia, accounting for more of the variance in functional outcome than symptoms (Kahn and Keefe, 2013; Fett et al, 2010; Lamb et al., 2014). Patients with severe cognitive impairments have difficulties functioning day to day, finding meaningful employment and living independently (Kahn and Keefe, 2013).

Impaired neurocognition and violence in schizophrenia

An association between neurocognition and violence has been documented in meta-analyses and reviews concerning brain injury, delinquency, and intellectual disability even when controlling for genetic and socioeconomic factors (Fazel et al, 2011; Farrington and Welch, 2007; Holland et al., 2002). In contrast findings from the schizophrenia and violence literature are contradictory and harder to interpret. One recent meta-analysis failed to support a relationship between psychosis, neurocognition and violence (Witt et al., 2013). The analysis examined a variety of cognitive factors including lower total scores on the full-scale

Wechsler Adult Intelligence Scale (WAIS), lower scores on the verbal subscale of the WAIS, lower scores on the performance subscale of the WAIS, lower total scores on the National Adult Reading Test (NART), and poorer executive functioning (higher perseverative errors on the Wisconsin Card Sorting Test). However, Witt et al 2013 advised caution in ruling out a relationship between cognition and violence because of the large amount of case studies suggesting a link and because other systematic reviews have identified that theory of mind, insight and attitudinal cognition may be risk factors for violence (Singh et al., 2011). In addition, two other recent literature reviews exploring the relationship between cognition and violence produced equivocal findings (Naudts and Hodgins, 2006; Weiss, 2012). None of the studies reviewed assessed the range of neurocognitive deficits associated with schizophrenia as outlined in the MATRICS consensus battery.

Impaired social cognition and violence in schizophrenia

In comparison with neurocognitive deficits, problems with social cognition are likely to be particularly relevant to violence risk (Singh et al., 2011). But because social cognition is also a multidimensional construct a variety of measures have been developed to measure these processes (Gallagher and Varga, 2015). Social cognitive processes are also thought to occur in an informational processing stream with perception of affect and emotional awareness occurring before more abstract processes such as emotional reasoning (Ochsner, 2008). Many of the constructs which fall under the social cognitive umbrella have their own historical roots and have grown out of a variety of literatures. For example, it is possible to make distinctions between the constructs of theory of mind, mentalisation and empathy (Lysaker et al., 2010; Lysaker et al., 2013; Lysaker et al., 2014). Theory of mind, the ability to attribute mental states to oneself and to others and the realisation that others have mental states different from one's own is primarily associated with the field of autism research. Mentalisation, the ability to understand mental states when one's attachment system is activated has its roots

within the psychodynamic, borderline personality disorder and attachment literature. Empathy undoubtedly involves theory of mind but also includes the ability to experience a compassionate emotional response in relation to another's suffering and is primarily associated with developmental and social psychology. Theory of mind, mentalisation and empathy have all been related to violence in schizophrenia (Abu-Akel and Abushua'leh, 2004). However, because research on social cognition and schizophrenia is in its infancy there have been difficulties developing psychometrically sound and agreed upon instruments for measuring different components of social cognition (Nuechterlein et al., 2008). In particular it has been challenging to measure empathy in schizophrenia in part due to the limitations of self-report questionnaires (Bragado-Jimenez and Taylor, 2012). It was for this reason the managing emotions branch of the MSCEIT was the only social cognitive measure to be selected for use within the consensus battery of cognitive deficits in schizophrenia (Nuechterlein et al., 2008).

Instrumental and reactive violence in schizophrenia

Few of the studies exploring the relationship between cognition and violence in schizophrenia have included measures of social reasoning or made a distinction between instrumental and reactive violence. Instrumental violence is predatory, goal directed and complex requiring forethought and sequential planning, whereas reactive violence is impulsive, defensive and executively simple (Heuston and Stanford, 2003; Woodward and Porter, 2002; Cornell et al., 1996; Barratt and Felthous, 1993). Cognitive scientists have argued that reason, judgement, and decision making are not adequately measured by intelligence tests and are distinct domains of ability (Toplak et al., 2011). Impaired ability to foresee potential outcomes and to weigh up the pros and cons of social consequences is likely to contribute to reactive and less sophisticated forms of instrumental violence. Also, it is noteworthy that mankind's ability to reason has been credited as the primary factor responsible for the historical decline of violence (Pinker, 2011). The faculty of reason as defined by our knowledge of the world and our ability to use this

knowledge in the pursuit of goals has allowed mankind to perceive conflict as a problem to be solved, to develop cultural institutions to deter violence, and to think through the social consequences of our actions (Pinker, 2011). Social reasoning from this perspective is in part social knowledge, innate social cognitive ability, and acquired skill. The distinction between instrumental and reactive violence may also help account for some of the discrepancies observed in the literature regarding the relationship between cognition and violence. For instance, Naudts and Hodgins, 2006, found that people with schizophrenia who have a long history of aggressive behaviour have better executive functioning than those who become violent after illness onset. But the study failed to make a distinction between instrumental and reactive violence, and it may be that those with long histories of aggressive behaviour were primarily committing instrumental acts thus requiring higher levels of executive functioning.

Paradigms for measuring violence in schizophrenia

There is much to recommend the study of inpatient violence for the purpose of disentangling the relationship between neurocognition and violence. The accurate measurement of violence in the community is beset by several methodological challenges such as reliance on self-report, or information being documented in police files concerning arrest or conviction. All of these may be incomplete. Violence in the community however is likely to be a more realistic test of risk assessment and prediction. In contrast, measures of staff-observed inpatient violence are likely to be more objective and complete, though the number of actual incidents of violence is likely to be reduced by intensive nursing care and de-escalation. Both inpatient and outpatient violence occur in instrumental and reactive varieties. Also, meta-analytic reviews have found that the strength and direction of violence risk factors are the same for inpatient and outpatient violence (Fazel, 2009; Singh et al., 2011; Witt et al., 2013). To date only a few inpatient prospective studies have been carried out to explore the relationship between neurocognitive deficits and violence (Foster et al., 1993; Krakowski and Czobor,

1993; Nazmie et al., 2013). All of these studies have found a positive relationship in samples of patients with schizophrenia. None of these studies examined neurocognitive deficits as a distal risk factor for violence or ‘root cause’ whose effect is mediated through more proximal risk factors such as social cognitive deficits, psychiatric symptoms, day to day social functioning and violence risk. Similarly, no study has focused on emotional and social reasoning whilst controlling for other risk factors.

Aims

We hypothesised that for forensic patients with schizophrenia or schizoaffective disorder that a) neurocognitive and social cognitive deficits would be determinants of violence and b) that the relationship between neurocognitive deficits and violence would be mediated by risk factors such as deficits in social reasoning, increased symptoms, impaired social functioning and increased violence proneness.

2.3 Method

Study Design

This is a naturalistic 12-month prospective observational cohort study of cognitive ability (neurocognition and social cognition) as a determinant of violence amongst patients with schizophrenia and schizoaffective disorder in a forensic hospital. Data were gathered from 2012-2013. All assessments for each individual were completed on average over a one-month time period. Patients were followed up from the point of assessment for 12 months or until discharge to observe if they had been involved in a violent incident. The assessment consisted of the MATRICS Consensus Cognitive Battery (MCCB) an assessment of neurocognition and social cognition (Nuechterlein et al., 2008), The Social and Occupational Functioning Assessment Scale (SOFAS) (Rybarczyk, 2011), an assessment of ‘real world’ social functioning and the Positive and Negative

Symptom Scale (PANSS) (Kay et al., 1987) an assessment of symptom severity. The Historical Clinical and Risk 20 (HCR-20) was used as an assessment of violence proneness or 'risk' (Webster et al., 1997). Each of these domains was assessed by researchers who were blind to the results of the other assessments. Several patients who consented and participated in the cognitive assessment refused to take part in an assessment of symptoms.

Participants and Setting

The study was approved by the National Forensic Mental Health Service Research and Audit Ethics and Effectiveness committee. All participants gave written informed consent.

The National Forensic Mental Health Service for Ireland provides specialised care for adults who have a mental disorder and are at risk of harming themselves or others. All patients are detained under forensic mental health legislation or special parts of the Mental Health Act, or are conditionally discharged to supervised community places under forensic mental health legislation. At the time of the study the National Forensic Mental Health Service (NFMHS) for Ireland had 94 secure inpatient beds at high, medium and low levels of therapeutic security (Kennedy, 2002) located on a single campus, the Central Mental Hospital (CMH), and 13 supervised community beds for those discharged subject to conditions (Pillay et al., 2008). The CMH is the only secure forensic psychiatric hospital for the Republic of Ireland, a population of 4.6 million.

In total 123 patients were deemed eligible to participate during the recruitment phase. Of these, 8 patients declined to take part, 9 were discharged before they could complete the assessment, 1 patient was judged to be feigning during the assessment, and 1 patient did not complete the cognitive assessment.

All participants were diagnosed independently of other assessments by a consultant forensic psychiatrist using the Structured Clinical Interview for DSM-IV-TR (First et al., 2002). Participants were selected if they met DSM-IV-TR

criteria for schizophrenia or schizoaffective disorder. A total of 89 participants (76 with schizophrenia, 13 with schizoaffective disorder) met the inclusion criteria and consented to participate in the study. A further 15 with other diagnoses were excluded. Of the 89 participants, 8 were being supervised in the community for part of the follow-up period and 81 were hospital in-patients throughout.

Five (5.6%) of the 89 were female. The average age of the 89 patients who participated in the study was 40 years. The mean length of stay was 7.5 years (SD 9.5), median 4.7 years, and mode 5.2 years.

Cognitive Assessment

Patients were assessed using the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus assessment battery of cognitive deficits in schizophrenia (Nuechterlein et al., 2008), and also the Test of Premorbid Functioning TOPF-UK (Weschler et al, 2011). These assessments were carried out at the same time by masters' level Assistant Psychologists.

The MATRICS battery covers seven cognitive domains: Processing speed; Attention/ vigilance; Working memory; Verbal learning; Visual learning; Reasoning and problem solving; Social Cognition assessed using social reasoning tasks for managing emotions taken from the Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT) (Mayer et al., 2002; Mayer et al., 2003), the Managing Emotions subtest of the MSCEIT is a social reasoning test. The test comprises of vignettes of various situations, specified goals, and options for coping with the emotions and social situations depicted in these vignettes. Participants are required to indicate the effectiveness of each solution ranging from one (very ineffective) to five (very effective). We will refer to the sub-test of the MSCEIT used within the MCCB throughout this paper as a measure of social cognition, while acknowledging that there are other measures and other constructs. In validation studies, and in antipsychotic trials of stable patients, the MATRICS demonstrated excellent reliability, minimal practice effects and

significant correlations with measures of functional capacity with test-retest reliability of 0.9 for the overall composite score in the original validation study (Nuechterlein et al., 2008). This value has been consistently found in multisite clinical trials. For example, the reliability was 0.88 in the 29-site study mentioned above (Keefe et al., 2011).

There is evidence that the six neurocognitive sub-scales of the MATRICS can be expressed as three factors (Burton et al., 2013), but only by excluding the MSCEIT social cognition sub-scale, with an associated loss of sensitivity to social function (Burton et al., 2013). Fett et al., 2011 have found in a meta-analysis that social cognition is more closely related to social outcomes than is neurocognition. There is also a growing awareness that non-social and social cognition are separable dimensions. Therefore, the MCCB scoring system now provides an option for a neurocognitive composite that does not include the social cognition sub-scale (Green et al., 2014). We believe it shows greater fidelity to the design of the MATRICS to first analyse all sub-scales including the social cognition scale separately, and to give the results also for the MATRICS composite score. We have therefore presented results for all seven subscales, and we have combined the six neurocognitive sub-scales into a single neurocognitive composite scale. To analyse neurocognition separately from social cognition a composite neurocognition score was calculated from the mean t-score for the first six items of the MATRICS battery (excluding social cognition) not correcting for age, gender, and education. This method of calculating a composite measure of neurocognition without being contaminated by the social cognitive domain has been widely used within the literature (Mancuso et al., 2011).

Scores for estimated pre-morbid intelligence (TOPF-UK) were not adjusted for education as an estimate of premorbid ability because the symptoms associated with mental disorder can affect educational attainment. A small number of patients (12 of 89) could not complete the TOPF-UK because of literacy problems. The mean estimated premorbid IQ was 96.

Functional Performance

The SOFAS (Rybarczyk, 2011) was completed by a member of the multidisciplinary team responsible for the care of the patient, who was blind to the other assessments including the cognitive assessment. Functioning assessments were obtained for 86 of the 89 participants.

Symptom Assessment

A PANSS (Kay et al., 1987) assessment was completed on 77 of the 89 patients. The PANSS assessments were completed independently of the cognitive assessments by a psychiatric registrar and an assistant psychologist trained in its use. The PANSS is designed to be scored for positive, negative and general symptoms, and a total symptom score. Because symptoms may overlap with personality traits relevant to violence such as impulse control, affect regulation, narcissism, and paranoid cognitive personality style (Nestor, 2002), the total symptom score may be as good or better a predictor of violence than the positive symptom score alone.

Assessment of violence risk and need for therapeutic security

The HCR-20 (Webster et al., 1997), a measure of risk of violence was assessed by forensic psychiatry higher trainees (equivalent to US fellow) who were blind to the other assessments. (MD and ZA). The HCR-20 is amongst the most extensively validated risk assessment schemes for use within forensic mental health settings (Risk Management Authority of Scotland, 2008). The historical scale contains ten 'static' items: previous violence, young age at first violent incident, relationship instability, employment problems, substance misuse problems, history of major mental illness, psychopathy, childhood maladjustment, personality disorder, and prior supervision failure. The psychopathy item was omitted because it is not routinely assessed. The clinical scale contains five 'current' items sensitive to change including lack of insight, negative attitudes,

active symptoms of major mental illness, impulsivity and unresponsiveness to treatment. The risk scale contains five ‘future’ items: plans lack feasibility, exposure to destabilisers, lack of personal support, noncompliance with remediation attempts and stress. All items are given equal weight (Dawes, 1979). We have previously described the extent to which the HCR-20 and its individual items when measured at baseline do or do not predict subsequent violence in this population (Abidin et al., 2013). In the present study the HCR-20 is taken as the means of controlling for violence proneness at baseline.

The DUNDRUM-1 triage security instrument (Kennedy et al., 2010) is a static assessment of the need for therapeutic security. It is used as a means of comparing the patients in this forensic hospital with those in forensic hospitals elsewhere. The DUNDRUM-1 triage security instrument includes eleven items rating the seriousness of violence, need for specialist treatments and other indicators of need for high, medium or low levels of therapeutic security. A mean item score of between 3 and 4 indicates a need for high security, between 2 and 3 for medium security, 2 for low security, 1 for open hospital or community settings (Flynn et al. 2011). Item 1 rates the severity of the most serious violent act, ranging from 0 for none to 4 for fatal or potentially fatal violence.

Assessment of Violence

A psychiatric trainee (EW) who was blind to the scores on other assessments reviewed the incident report forms, patient’s clinical notes and legal forms recording incidents of restraint or seclusion, as well as a separate log of incidents kept in the nursing operational management office. This process identified all violent incidents from multiple cross-referenced sources, following the assessments up to the date of discharge or twelve months follow-up. The 8 patients in supervised community residences for part of the follow-up period were monitored in the same way. An individual was classified as violent if they were the clear instigator or co-aggressor, and if the incident involved harm to staff or other patients. The first violent incident was taken as a means of defining

violence as a binary outcome. This outcome measure lends itself to both the receiver operating characteristic (ROC) area under the curve analysis (AUC) and to binary logistic regression and so this has become the recommended way of studying factors predicting violence and other discrete outcomes (Risk Management Authority of Scotland (2008); Whittington et al., 2013). Very few patients were violent more than once in the follow-up period so that frequency of violence can be studied only in very large samples.

Violence was further classified into reactive and instrumental violence using Woodward and Porter's coding scheme (Woodworth and Porter, 2002)

Medication

A chlorpromazine equivalent (CPZeq) was calculated for each participant as a measure of his/her relative daily dose of antipsychotic medications (Woods, 2003; Haddad, 2010; Taylor et al., 2012).

Data Analysis

All data were analysed using SPSS-22 (IBM Corp. Released 2013).

Demographics and differences between violent and nonviolent groups are presented in Table 2.1.

To correct for multiple hypothesis testing for the seven cognitive domains comprising the MATRICS battery group differences across all subtests and the neurocognitive and MATRICS composites were analysed using multivariate analysis of variance, with age and gender entered as co-variates. Group differences across cognitive domains and composite scores were analysed using one-way ANOVAs. Bonferroni correction was applied as a conservative check on multiple hypothesis testing. Similarly, for the PANSS and HCR-20 all subscales including the total scales were analysed using multivariate analysis of variance, with age and gender as co-variates.

The ability of baseline measures to discriminate those who during the follow-up period committed violent incidents was analysed using the receiver operating characteristic (ROC) area under the curve (AUC). An association was deemed significant if the lower limit of the 95% confidence interval of the AUC was greater than 0.5, the line of random information.

Correlations were calculated using Spearman's non-parametric method as violence is a binary variable.

SPSS PROCESS macro model 4 (Hayes, 2013) was used to analyse mediation relationships between antecedent factors such as neurocognition, social cognition, and the dichotomous outcome violence (Figure 2.1). Age and gender were entered as co-variants in all mediation analysis. SPSS PROCESS macro is a computational tool for path analysis-based moderation and mediation analysis. Various measures of effect size for indirect effects are generated in mediation models. Effect sizes were calculated as regression coefficients in the first instance and later as odds ratios to facilitate interpretation. Bootstrapping was used to estimate indirect effects, and 95% bias-corrected confidence intervals were used for the indirect effects using 1,000 bootstrap samples. A confidence interval for an odds ratio that does not contain a score of one indicates statistically significant mediation.

Mediation effects were in each case examined for all combinations to determine the direction of the causal effect. If a relationship between an antecedent factor, a mediating factor and violence does not hold true when the order of antecedent and mediating factors is switched this has been taken as support for preferring one pathway (an ordering of factors) over another.

We also tested more complex mediation models involving two or more mediators employed SPSS PROCESS macro models 4 (parallel) (figure 2.2) and model 6 (figure 2.3) (serial) (Hayes, 2013). These models were regarded as exploratory.

2.4 Results

The mean follow-up period (n=89) was 1.22 years (SD 0.44). There were 107.4 person-years at risk. During the follow-up period, 10 of the 89 patients with schizophrenia-schizoaffective disorders committed violent acts (base rate 9.7/100 person-years at risk). Note that only the first violent incident for each person was counted. All violent incidents were coded (Woodworth and Porter, 2002) as reactive violence, with two rated as also having a minor instrumental element. On the DUNDRUM-1 item 1 measure of seriousness of violence (scored 0 to 4 where '4' is fatal or life threatening) eight violent incidents were rated '2' and the remaining two were rated '1'.

A relationship between gender and violence did not reach statistical significance, as 2/10 who were violent were female, compared to 3/79 who were not violent, Fisher's exact test= 4.39, p=0.095.

All of the participants had a history of past violence as recorded by the HCR-20 and DUNDRUM-1 triage security instrument. On item 1 of the DUNDRUM-1 triage security instrument, 62 patients scored '4', indicating a history of homicide or life-threatening violence to others and 20 scored '3' indicating other serious violence. On the HCR-20 item 1. 86 scored '2' indicating a history of serious or repetitive violence to others.

The mean score on the DUNDRUM-1 eleven item scale was 29.5 (SD 5.0) and for the DUNDRUM-1 nine item scale omitting self-harm items, the mean score was 27.1 (SD 3.9), a mean score per item of 3.0 (SD 0.4). The mean for the Total HCR-20 In was 20.8 (SD 5.7), median 21.0, mode 17.

The mean t-score of the MATRICS composite score for all patients was 17.9 (SD 13.2, range -11.0 to 51.0). The published population norm is a t-score of 50 (SD 10). This group of forensic hospital patients with schizophrenia is therefore more than three standard deviations below the population norm. Table 2.1 shows that for the group who were not violent during follow-up the MATRICS composite represented as a mean t-score was 20.9 (SD 14.0). The violent group was even more impaired (12.8, SD 9.1).

Differences in cognitive ability between violent and nonviolent groups

One-way MANOVA showed that violent patients had significantly worse neurocognitive and social cognitive abilities than non-violent patients (Pillai's Trace $V = 0.339$, $F(8, 78) = 5.008$, $p < 0.001$, Partial Eta squared = 0.339) after controlling for age and gender.

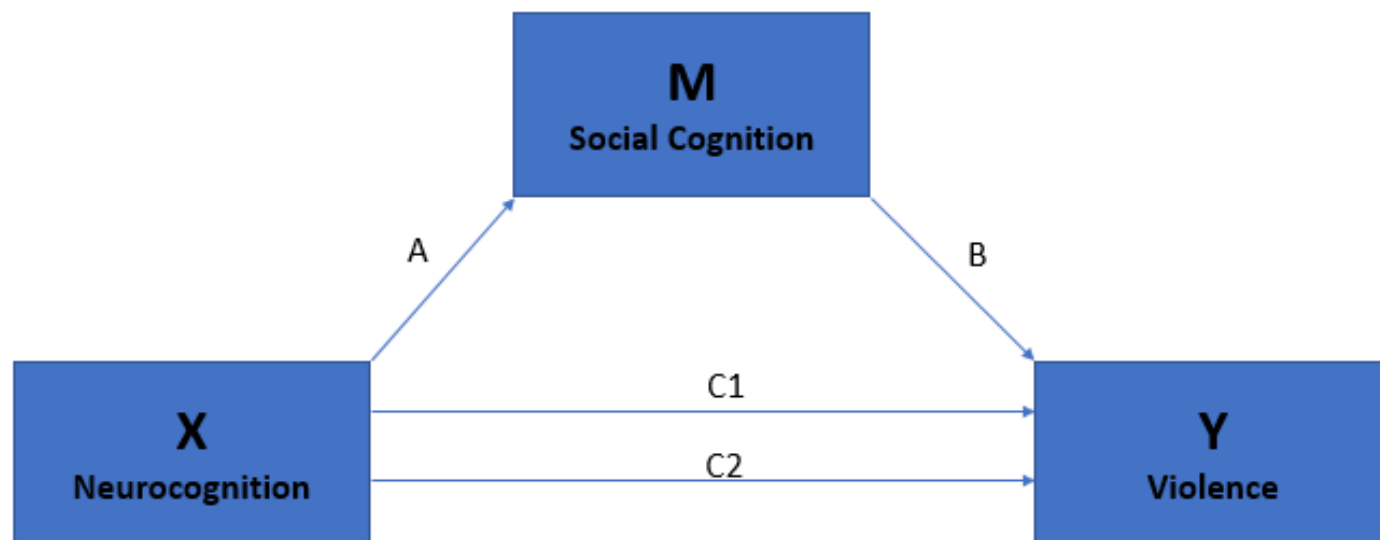
Violent patients performed significantly worse than non-violent patients on the MATRICS domains of processing speed, verbal learning, social cognition and the MATRICS total composite (Table 2.2). Following Bonferroni correction for multiple testing the violent and non-violent groups differed only on the verbal learning domain and the social cognitive domain. The magnitudes of the differences between violent and nonviolent groups are also presented as effect sizes (Cohen's d) in Tables 2.1 and 2.2.

For PANSS scores, one-way MANOVA showed that violent patients had significantly higher levels of psychopathology (Pillai's Trace $V = 0.172$, $F(4, 70) = 3.639$, $p < 0.009$, Partial Eta squared = 0.172) (Table 2.1).

One-way MANOVA showed that HCR-20 total scores for risk of violence were higher for violent patients (Pillai's Trace $V = 0.149$, $F(3, 83) = 4.839$, $p < .004$, Partial Eta squared = 0.149). (Table 1)

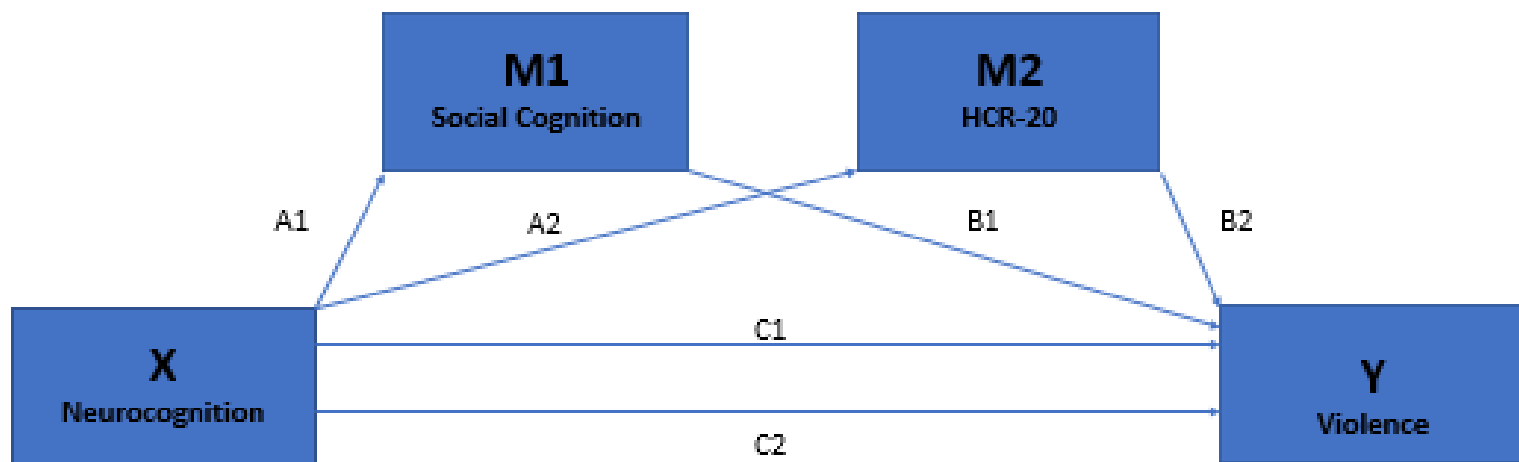
Table 2.1. Mean SD comparisons between violent and non-violent groups after controlling for age and gender as co-variants. Effect sizes and AUC for receiver operating characteristics (ROC)													
	ANOVA							Effect Size			Receiver operating characteristic		
	Non-violent n=79		Violent n=10		F-statistic (df 1,87)	P value	Partial Eta squared	D	95% CI		AUC	95% CI	
	Mean	S.D.	mean	S.D.					lower	upper		lower	upper
Age	40.9	12.7	36.1	9.4	1.342	0.250	-	0.38	-0.27	1.04	0.62	0.45	0.80
Length of stay (years)	8.0	9.7	3.0	5.0	2.243	0.13	-	0.50	-0.16	1.16	0.73	0.54	0.91
Chlorpromazine eqvs	538	366	772	397	3.6	0.063	-	0.64	-0.03	1.30	0.67	0.46	0.88
Pre-morbid IQ (TOPF-UK)	96.0	12.6	96.8	8.1	0.023	0.879	-	0.06	-0.72	0.84	0.49	0.31	0.67
PANSS Total	62.5	20.0	90.1	19.4	12.2	0.001	.157	1.38	0.58	2.19	0.84	0.71	0.97
PANSS Positive	13.7	7.0	21.6	8.7	9.32	0.003	.113	1.21	0.41	2.01	0.79	0.65	0.93
PANSS Negative	18.9	7.9	25.0	6.5	6.175	0.111	.078	0.98	0.19	1.78	0.71	0.55	0.87
PANSS General	29.02	10.3	43.6	10.4	14.202	.000	.163	1.49	0.68	2.31	0.86	0.73	0.99
HCR-20 Total score	20.8	5.7	28.2	8.0	14.04	0.000	.142	1.26	0.57	1.94	0.78	0.59	0.96
HCR-20 Historical	12.9	2.7	15.2	4.5	5.178	.025	.057	0.763	0.09	1.43	0.75	0.55	0.95
HCR-20 Current	4.50	2.63	7.2	2.78	12.59	.001	.129	1.91	0.51	1.87	0.76	0.59	0.94
HCR-20 Risk	3.39	2.12	5.8	2.29	10.06	.002	.106	1.064	0.39	1.74	0.77	0.62	0.71
SOFAS	59.2	17.2	35.6	18.9	14.9	0.001	-	1.29	0.61	1.98	0.83	0.66	0.99
DUNDRUM-1 (11 item)	29.54	5.01	27.4	7.1	.994	0.322	.012	0.334	-0.33	0.99	0.44	0.21	0.66
DUNDRUM-1 (9 item)	27.8	3.93	23.9	6.93	3.275	0.074	.037	0.607	-0.06	1.27	0.38	0.16	0.60

**Figure 2.1. Mediation model 4:
Single mediator**



A = Effect of X on Y mediated via M
B = Direct effect of M on Y adjusted for X
C1= Direct effect of X on Y unmediated by M
C2= Direct effect of X on Y after mediation via M

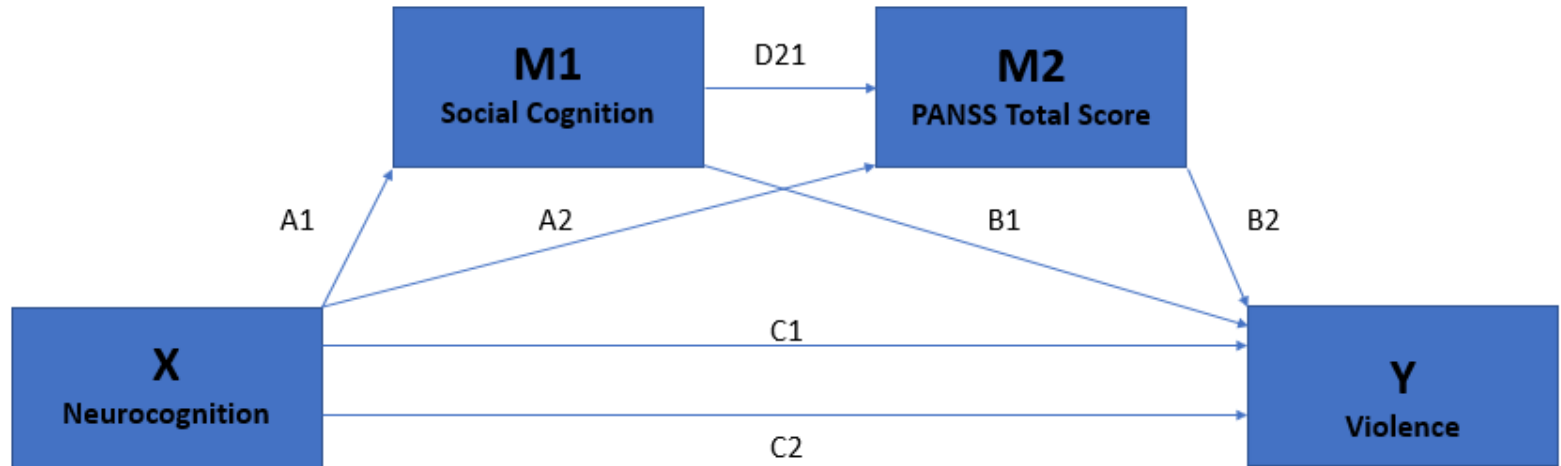
**Figure 2.2. Mediation model 4:
Two or more mediators: Parallel
Model**



A1 = Effect of X on Y mediated via M1
A2 = Effect of X on Y mediated via M2

C1 = Direct effect of X on Y unmediated
C2 = Direct effect of X on Y after parallel
mediation via M1 and M2

Figure 2.3. Mediation model 6: Two or more mediators: Serial model.



A1 = Effect of X on Y mediated via M1
A2 = Effect of X on Y mediated via M2

C1 = Direct effect of X on Y unmediated
C2 = Direct effect of X on Y after parallel mediation via M1 and M2
D21=Effect of X on Y mediated serially through M1 and M2

Table 2.2 Mean (SD) comparisons for t-scores on MATRICS domains and composites, comparing violent and non-violent groups after controlling for age and gender as co-variants, effect sizes and AUC for receiver operator characteristics (ROC)

MATRICS Domains and Composites	ANOVA							Effect Size d			Receiver Operating Characteristic		
	Non-violent n=79		Violent n=10		F-statistic	P value	Partial Eta squared	d	95% CI		AUC	95% CI	
	Mean	S.D	Mean	S.D	(df 1,87)				lower	upper		lower	upper
Processing Speed	24.82	15.5	18.50	10.2	5.242	0.025	0.058	0.76	0.10	1.43	0.65	0.51	0.79
Attention	28.4	11.1	23.8	10.4	2.43	0.122	0.028	0.52	-0.13	1.18	0.62	0.43	0.81
Working Memory	31.3	12.7	32.8	8.4	0.053	0.818	0.001	0.24	-0.41	0.90	0.45	0.30	0.60
Verbal Learning	33.9	7.6	28.4	4.5	7.56	0.007*	0.082	0.92	0.25	1.59	0.72	0.58	0.86
Visual Learning	32.7	12.6	26.5	11.9	2.57	0.11	0.029	0.53	-0.12	1.20	0.64	0.46	0.82
Reasoning	35.9	7.4	35	5.4	0.808	0.371	0.009	0.30	-0.35	0.96	0.51	0.33	0.68
Social Cognition	35.7	11.0	24.4	6.3	11.57	0.001*	0.12	1.14	0.46	1.82	0.81	0.71	0.90
Neuro-cognitive composite	31.1	9.3	27.5	6.7	3.05	0.084	0.035	0.58	-0.07	1.24	0.61	0.45	0.76
MATRICS Total Composite	20.9	14.0	12.8	9.1	5.720	0.019	0.063	0.80	0.13	1.47	0.67	0.53	0.81

*Is significant following Bonferroni Correction.

Predicting Violence

Three of the seven neurocognitive domains of the MATRICS - processing speed, verbal learning, and social cognition had AUCs significantly greater than random. The MATRICS composite was also significantly better than random (Table 2.2). The social cognitive domain of the MATRICS had the highest AUC. Although the MATRICS composite was predictive of violence the Neurocognitive composite without the addition of the Social Cognitive Domain was not.

The total HCR-20 score, PANSS positive, PANSS negative, PANSS general and PANSS total scores all had ROC AUC scores that were significantly better than random.

Correlations between cognition, real world functioning, violence risk and violence

Table 2.3 depicts non-parametric Spearman correlations between cognition (both neurocognition and social cognition), social functioning using the SOFAS, proneness to violence (risk of violence) using the HCR-20 total score, history of homicide or lethal violence (DUNDRUM-1 item 1) and actual violence during the follow-up period. These can be summarised as showing that social cognition and neurocognition correlated positively with each other and with social function (SOFAS). They correlated negatively with symptom severity (PANSS Total), violence proneness (HCR-20 Total score), and subsequent actual violent acts. It is notable that neurocognition did not correlate directly with PANSS positive symptoms, though it did correlate negatively with PANSS negative symptoms and PANSS general symptoms. Social cognition (MSCEIT/MATRICES) tended to have the strongest correlations with all symptom measures and with subsequent violence, while neurocognition had stronger correlations with the HCR-20 and SOFAS scores. An incidental finding was that less impaired social cognition was associated

with a history of lethal or life-threatening violence (a score of '4' on DUNDRUM-1 item 1).

Mediation between Neurocognition, Social Cognition and Violence

The relationship between neurocognition and violence was completely mediated by the social cognitive domain of the MATRICS, after co-varying for age and gender (Table 2.4).

Figure 2.1 shows the mediation model in schematic form. Table 2.4 shows these effects expressed as odds ratios.

Table 2.3. Spearman correlations. Each column is divided into three rows. These are the Spearman correlation coefficient, p value, and number of participants for each row.

		1	2	3	4	5	6	7	8	9	10	11
1	Social Cognition	-										
2	Neuro-cognition Composite	0.397 .001 89	-									
3	MATRICES Composite (includes neuro-cognition and social cognition)	0.541 .001 89	0.984 .001 89	-								
4	PANSS Total	-0.461 .001 77	-0.338 .003 77	-0.405 .001 77	-							
5	PANSS Positive	-0.361 .007 77	-0.149 .195 77	-0.217 .058 77	0.773 .000 77	-						
6	PANSS Negative	-0.398 .001 77	-0.359 .001 77	-0.406 .001 77	0.729 .001 77	0.323 .004 77	-					
7	PANSS General	-0.473 .001 77	-0.298 .009 77	-0.371 .001 77	0.917 .001 77	0.735 .001 77	0.571 .001 77	-				
8	HCR-20 Total	-0.252 .017 89	-0.314 .003 89	-0.343 .001 89	-0.666 .001 77	0.567 .001 77	0.543 .001 77	0.614 .001 77	-			
9	SOFAS	0.411 .001 86	0.521 .001 86	0.556 .001 86	-0.617 .001 77	-0.438 .001 77	-0.499 .001 77	-0.542 .001 77	-0.616 .001 86	-		
10	History of Homicide or lethal violence D1 item 1	0.254 .016 89	-0.021 .848 89	0.028 .759 89	-0.210 .067 77	-0.145 .207 77	-0.197 .087 77	-0.092 .425 77	-0.215 .043 89	0.082 .453 86	-	
11	Violence	-0.340 .001 89	-0.122 .255 89	-0.194 .069 89	0.343 .002 77	0.293 .010 77	0.214 .062 77	0.362 .001 77	0.308 .003 89	-0.351 .001 86	-0.288 .006 89	-

Table 2.4: In all cases the outcome (Y) is ‘violent act’. X is the hypothesised determinant factor and M is the hypothesised mediating factor.

M	C1: Direct effect X on Y before mediation			C2: Direct effect X on Y After mediation			A: Mediated effect X on Y via M			B: Direct effect M on Y		
	OR	95% CI		OR	95% CI		OR	95% CI		OR	95% CI	
		lower	Upper		lower	Upper		Lower	upper		Lower	upper
X=Neurocognitive composite	0.929	0.850	1.016									
social cognition				0.989	0.893	1.095	0.932	<u>0.849</u>	<u>0.976</u>	0.869	<u>0.779</u>	<u>0.970</u>
PANSS				0.955	0.836	1.092	0.947	<u>0.821</u>	<u>0.994</u>	1.069	<u>1.016</u>	<u>1.125</u>
SOFAS				1.008	0.904	1.124	0.916	<u>0.788</u>	<u>0.997</u>	0.931	<u>0.882</u>	<u>0.982</u>
HCR-20 Total				0.972	0.881	1.072	0.950	<u>0.831</u>	<u>0.997</u>	1.214	<u>1.058</u>	<u>1.393</u>
X=social cognition	0.864	<u>0.781</u>	<u>0.957</u>									
Neurocognition				0.869	<u>0.779</u>	<u>0.970</u>	0.997	0.934	1.031	0.989	0.893	1.095
PANSS				0.886	<u>0.774</u>	<u>0.986</u>	0.958	0.791	1.034	1.054	0.997	1.114
SOFAS				0.906	0.811	1.012	0.964	0.817	1.052	0.953	0.901	1.007
HCR-20 Total				0.890	<u>0.803</u>	<u>0.987</u>	0.973	0.870	1.065	1.187	<u>1.025</u>	<u>1.374</u>
X=symptoms (PANSS total score)	1.067	<u>1.017</u>	<u>1.120</u>									
Neurocognition				1.069	<u>1.015</u>	<u>1.126</u>	1.006	0.985	1.126	0.955	0.836	1.092
Social cognition				1.054	0.997	1.114	1.029	0.995	1.107	0.886	0.774	1.014
SOFAS				1.042	0.986	1.102	1.037	0.909	1.136	0.935	0.867	1.009
HCR-20 Total				1.032	0.969	1.099	1.043	0.915	1.165	1.170	0.953	1.436
X=social function (SOFAS)	0.931	<u>0.887</u>	<u>0.978</u>									
Neurocognition				0.930	<u>0.881</u>	<u>0.982</u>	1.002	0.958	1.046	1.008	0.904	1.124
Social cognition				0.953	0.901	1.007	0.973	0.913	1.005	0.906	0.811	1.012
PANSS				0.935	0.867	1.009	0.972	0.866	1.092	1.042	0.986	2.633
HCR-20 Total				0.971	0.920	1.024	0.942	0.753	1.008	1.320	<u>1.095</u>	<u>1.614</u>
X=violence proneness (HCR-20 Total score)	1.228	<u>1.075</u>	<u>1.403</u>									
Neurocognition				1.214	<u>1.058</u>	<u>1.393</u>	1.012	0.956	1.085	0.972	0.881	1.072
Social cognition				1.187	<u>1.027</u>	<u>1.371</u>	1.055	<u>1.000</u>	<u>1.166</u>	0.890	<u>0.797</u>	<u>0.987</u>
PANSS				1.170	0.953	1.436	1.102	0.817	2.175	1.032	0.984	1.107
SOFAS				1.320	<u>1.088</u>	<u>1.601</u>	1.058	0.759	1.392	0.971	0.917	1.022

Neurocognition appears to have no influence on violence independent of its effect on social cognition (Table 2.4). There was no evidence that neurocognition mediated the relationship between social cognition and violence. In total the effect of neurocognition, social cognition, and age and gender could account for 35% (Nagelkerke R^2) of the variance in incidence of violence.

PANSS Total Score as a Mediator between Neuro-cognition and Violence

The PANSS total score completely mediated the relationship between neurocognition and violence. The indirect effect of neurocognition on violence as mediated by the PANSS total score was $OR = 0.94$. There was no evidence that neurocognition mediated the relationship between psychiatric symptoms (PANSS total) and violence (Table 2.4). In total the effect of neurocognition, symptoms, and age and gender could account for 48% (Nagelkerke R^2) of the variance in the incidence of violence.

Social Functioning as a Mediator between Neurocognition and Violence

Social functioning (SOFAS) completely mediated the relationship between neurocognition and violence after controlling for age and gender. The indirect effect of neurocognition on violence as mediated by the SOFAS score was $OR = 0.91$. There was no evidence that neurocognition mediated the relationship between social functioning and violence. In total the effect of neurocognition, social functioning, and age and gender could account for 34% (Nagelkerke R^2) of the variance of violent incidents.

HCR-20 Violence Risk as a Mediator between Neuro-cognition and Violence

Violence proneness (risk of violence) as measured by the HCR-20 total score completely mediated the relationship between neurocognition and violence. The indirect effect of neurocognition on violence as mediated by the HCR-20 total was $OR = 0.95$. There was no evidence that neurocognition mediated the relationship between violence risk and violence. In total the effect of neurocognition, HCR-20, and age and gender could account for 35% (Nagelkerke R^2) of the variance of violent incidences.

Neurocognition as the foundation for the emergence of violence risk factors

In addition to the consistent evidence of mediation between neurocognition and violence (Table 2.4), there was evidence that the relationship between social cognition and violence was mediated in part by social functioning (SOFAS), and the relationship between social functioning (SOFAS) and violence was mediated in part by violence proneness (HCR-20 violence risk). To test the hypothesis that neurocognitive impairments represent the foundation for the emergence of a range of risk factors for violence such as social cognitive deficits, increased symptoms, impaired functioning and HCR-20 violence risk we constructed a serial mediation model (figure 3, model 6 of the PROCESS macro; Hayes, 2013). When all four mediating factors were entered into a serial mediation model between neurocognition and violence, there was no evidence of serial mediation from neurocognition, to social cognition, to psychiatric symptoms, to social functioning, to HCR-20 violence proneness. Nor was there evidence of serial mediation between any three of the four mediating variables. Also, there no evidence of serial mediation between any two of the four mediating variables.

When all four mediating variables are entered into a parallel mediation model (figure 2.2, model 4 of the PROCESS macro; Hayes, 2013) there is no evidence of an indirect mediated effect between neurocognition and violence. When every combination of three out of the four mediating variables is entered into the parallel mediation model (Model 4) there was again no evidence for an indirect mediated effect between neurocognition and violence. When each possible pair of the four mediating variables was entered in the parallel model (model 4) there was evidence that the total indirect effect between neurocognition and violence was significant, completely mediated by social cognition and HCR-20 violence risk as two parallel pathways from neurocognition to violence (total indirect effect expressed as odds ratio 0.896, 95% CI 0.730 – 0.971). Altogether this model could account for 46% of the variance of violent incidents. There were no other robust effects mediated by any other pair of mediating factors.

Social cognition and symptoms as a mediator between neurocognition and violence

Although psychiatric symptoms did not mediate the relationship between social cognition and violence (Table 2.4), because of the link between delusions and violence (Fazel et al., 2009; Singh et al., 20011; Witt et al., 2013) and the association between social cognition and symptoms (Table 2.3), we wanted to investigate whether there would be evidence of serial mediation between neurocognition and violence when social cognition and symptoms were added to the model (Process Macros Model 6). We omitted the measure of violence proneness or risk (HCR-20) because of likely overlap in content between some items in the HCR-20 and the measure of symptom severity (PANSS). As set out above, there was no evidence that social cognition and symptoms mediated the relationship between neurocognition and violence, either serially or in parallel.

2.5 Discussion

Main findings

In this prospective cohort study of forensic hospital patients with schizophrenia and schizoaffective disorder we found a robust association between cognitive (neurocognitive and social cognitive) deficits and violence. Using multivariate analysis, the cognitive domains measured by the MCCB could account for 34% of the variance in violent incidents after controlling for age and gender during a 12 month follow up. Both nonviolent and violent patients had significant impairments in neurocognition and social cognition. The mean MCCB composite was three standard deviations below a nonclinical mean. Also, even though these forensic patients were admitted because of a prior history of violence, most were not violent during the period of study. Of all the MCCB domains, performance on the social reasoning test (MSCEIT) produced the largest effect size.

When the influence of neurocognition on violence was explored using mediation analysis, neurocognition emerged as a distal risk factor whose effect on violence occurred through more proximal risk factors. The relationship between neurocognition and violence was completely mediated by social cognition (MSCEIT), violence proneness (HCR-20 Total Score), psychiatric symptoms (PANSS total), and social functioning (SOFAS). There was also evidence of parallel mediation from neurocognition through social cognition and through violence proneness (violence risk, HCR-20 Total Score) to violence. This may cast some light on why risk factors within the HCR-20 such as employment problems and prior supervision failure that ought to operate mainly in the community, none-the-less remain predictive in hospital. These risk items may be markers of general dysfunction underpinned by cognitive impairment. In contrast to neurocognition, social cognition as measured by a social reasoning task (MSCEIT) had a direct effect on violence even when controlling for violence proneness (HCR-20 Total Score), psychiatric symptoms (PANSS), and neurocognition. The direct effect of social

cognition on violence was however attenuated to insignificance by mediation through a measure of general social function (SOFAS).

Differences between violent and nonviolent group during 12 month follow up

The greatest difference between violent and nonviolent groups was on the MATRICS social cognition domain, a social and emotional reasoning task assessing patients' ability to manage emotions. Significant differences were also observed for the neurocognitive measures of verbal learning and processing speed. There was no significant difference between chlorpromazine equivalents of antipsychotic medication between violent and nonviolent groups. In this prospective study of violent outcomes, social cognition measured at baseline produced ROC AUCs comparable with the HCR-20, one of the most widely used violence risk assessment and management schemes. Impaired emotional and social reasoning ability as measured by the MSCEIT appeared to be a determinant of reactive, impulsive violent behaviour.

Mediation Analysis

These findings were further explored using mediation analysis. There was no evidence that neurocognition had an effect on violence independent of social cognition. The composite measure of neurocognition was only related to violence in so far as it affected social and emotional reasoning. Using this model, neurocognitive difficulties amongst people with schizophrenia spectrum disorders in a forensic hospital did not have a direct effect on violence but neurocognitive problems leading to difficulties with social and emotional reasoning did.

For patients with schizophrenia and schizoaffective disorder the relationship between neurocognition and violence was also completely mediated by

symptoms (PANSS total score), by social functioning (SOFAS) and by violence proneness (HCR 20 Total Score). Although neurocognitive impairments are thought to occur before the onset of psychosis and to underpin functional impairment to be sure of the causal direction we tested all possible combinations of factors. There was no evidence that neurocognition mediated the relationship between any of the described variables and violence. Of all of the variables examined, neurocognition was the only independent variable whose effects on violence consistently showed evidence of mediation. Neurocognition therefore appears to be a distal risk factor for violence whose influence only becomes manifest through more proximal risk factors such as social cognition, symptoms, functioning and the risk factors contained within the HCR-20.

There was a significant indirect effect of neurocognition on violence that was mediated by social cognition and violence proneness (HCR-20 Total Score) in parallel. This was the only higher order mediation found, though this may reflect the size of the sample. The effect of social cognition on violence was independent of violence proneness and symptoms.

Strengths

This study contained a number of methodological strengths. First to our knowledge this is the only prospective cohort study of patients with schizophrenia and schizoaffective disorder that has examined the relationship between cognition (neurocognition and social cognition) and violence using the MATRICS Consensus Cognitive Battery (MCCB). The MCCB demonstrated its value within a forensic setting. There was evidence of concurrent validity including large and moderate correlations with independently rated measures of social functioning, psychiatric symptoms and violence proneness (violence risk).

Second, for the most part violence is not a homogenous entity. This difficulty was overcome by using an established coding scheme for classifying instrumental and reactive violence. All violent acts in this study were reactive. Violent acts often contain instrumental and reactive elements and those prone to premeditated or instrumental violence also often act violently on impulse or reactively. However, it is less common for those who are mainly prone to reactive violence to be instrumentally violent (Cornell et al., 1996). The association between cognitive impairment (neurocognition and social cognition) and violence observed in this prospective study is strictly speaking an association with reactive acts of violence. However, Table 2 shows a retrospective association between the seriousness of the violence leading to admission to the forensic hospital and the MSCEIT measure of social cognition in the MCCB that is positive, the more socially competent, the more serious was the past violence (Pearson $r = 0.246$, $p=0.020$, $n=89$). These acts were usually delusionally driven and were not always reactive. There is some evidence for differing developmental origins of schizophrenia that may be associated with different patterns of violence (Naudts and Hodgins, 2006; Hodgins, 2008; Hodgins et al, 2014). Clarifying this relationship will require further study.

Third, this study is one of a small number of prospective cohort studies of patients with schizophrenia and schizoaffective disorder evaluating cognitive (neurocognitive and social cognitive) determinants of violence against persons (Foster et al., 1993; Krakowski and Czobor, 2012; Nazmie, 2013) and therefore satisfies the temporal and association criteria for causal inference.

Limitations

The patients in this study were predominantly male. It is therefore possible that different processes mediate violence in female patients. The study also took place within a secure forensic setting which may limit the generalisability of the findings for non-forensic community settings, or prisons. However, within

any setting whether community or forensic, patients with schizophrenia who are at risk of violent behaviour are best identified using a reliable and valid risk assessment instrument. This study assessed violence proneness in forensic patients using the range of violence risk factors captured by the HCR-20 which has been validated in many settings (Webster et al.,1997).

It has also been suggested that inpatient and outpatient violence are not comparable and that the structured routine, close observation and proximity to others within inpatient settings may be a determinant of violence. However, recent research suggests that the risk factors predictive of outpatient violence are also predictive for inpatient violence. A history of substance abuse for example is a robust risk factor for violence amongst psychiatric patients in outpatient settings but is also a risk factor for violent behaviour within inpatient settings, even where substance abuse prior to violent behaviour can be ruled out (Abidin et al., 2013). Similarly, within forensic settings (hospital and community residences) medication adherence is carefully monitored and controlled but this risk factor remains predictive (Abidin et al., 2013).

Although it was not possible to assess psychiatric symptoms concurrently with violent acts in this study, there were significant baseline differences between violent and nonviolent groups on the PANSS total score. Because the neurocognitive decline observed amongst patients with schizophrenia is thought to occur before the onset of psychosis (Soyka, 2011; Kahn and Keefe, 2013) as does the impairment in social cognition (Green et al., 2012) it would be reasonable to infer that cognition (neurocognition and social cognition) influences symptoms rather than the other way around. However, because the PANSS data was assessed at baseline only, it is not possible to be more definitive concerning whether psychiatric symptoms immediately preceded violent incidents. Although mediation effects between neurocognition, social cognition, symptoms, social functioning, violence proneness (risk) and violence worked only one-way, causal statements about the relationship between neurocognition, psychiatric symptoms and violent behaviour therefore must be qualified.

We did not find evidence for serial or higher order parallel mediation pathways involving psychiatric symptoms, but this may be due to the size of the cohort. Further studies with larger numbers would be helpful.

Implications

These results are in keeping with the wider literature suggesting that cognitive difficulties (neurocognitive and social cognitive difficulties) are a risk factor for violence in many diagnostic groups (Fazel et al., , 2011; Farrington and Welch, 2007; Holland et al., , 2002; Krakowski and Czobor, 2012). The nature of social cognition is itself a matter for continuing research and debate, although it is already recognised that deficits in social cognition occur in a range of mental disorders including autism and schizophrenia (Gallagher and Varga, 2015). Recent genetic research has demonstrated an overlap amongst the many single nucleotide polymorphisms for schizophrenia, bi-polar affective disorder, attention deficit hyperactivity disorder and autism (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013). An overlap symptom profile or phenotype has been described for patients with schizophrenia and patients with autism spectrum disorder, consisting of selected symptoms from the PANSS negative and general symptom scales (Kästner et al., 2015). A recent empirical review has shown that the relationship between neurocognition and functioning in schizophrenia is significantly mediated by social cognition so that neurocognition influences social cognition which in turn influences functioning (Lam et al., 2014; Schmidt et al., 2011). More specifically the finding that social cognitive difficulties as measured by the MATRICS/MSCEIT were directly related to violence is also in keeping with social cognitive theories of violence and with evolving social reasoning being credited for the historical decline of violence (Pinker, 2011).

The indirect influence of neurocognition on violence may also help explain some of the discrepancies observed within the literature, where some studies

have found a relationship between cognition and violence whereas others have not. Also, although much work has been done identifying risk factors for violence in people with schizophrenia and schizoaffective disorder the relationships amongst risk factors have been scarcely studied. One cross-sectional study has reported that in patients with schizophrenia, mentalisation, defined as the ability to attribute mental states to others, mediates the relation between psychopathy and type of aggression. This mediation is facilitated by a specific mentalising profile characterised by the presence of intact cognitive and deficient emotional mentalising capacities associated with deliberate aggression (Bo S et al., 2014). Deficits in mentalisation have also been associated with self-reported aggression in cross-sectional studies (Bo S et al., 2013). The current study sheds light on the relationship between a range of variables and subsequent actual violence.

Research on related constructs such as mentalisation and metacognition may help guide future research on treatment. Mediation analysis may help elucidate the relationship between a range of variables which could be targeted by psychological intervention. Deficits in mentalisation for example may mediate attachment styles and the expression of personality traits or personality clusters (Bo S et al., 2013). Also, although measures of metacognition have not been found to distinguish between forensic and non-forensic patients with schizophrenia (Mitchell, et al., 2012), metacognition may mediate symptom severity and social dysfunction (Bo S et al., 2015). Evidence of the relationship between delusions and violence in schizophrenia that is mediated through anger and confirmed by temporal proximity may represent an experimental confirmation of this concept (Coid et al., 2013; Ullrich et al., 2013). The relationship between delusions, anger and violence (Kennedy et al., 1992; Kennedy, 1992) has at times been referred to as ‘affect-logic’ (Kennedy, 1992; Ciompi, 1989; Ciompi, 1991).

Recently several psychotherapeutic approaches have been developed to improve various neurocognitive and social cognitive domains in schizophrenia including cognitive remediation therapy (Wykes et al., 2011; Wykes and

Spaulding, 2011; Subramaniam et al., , 2012), metacognitive approaches (Moritz et al., , 2014; Dimaggio and Lysaker, 2015) and mentalisation- based treatment (Brent et al., 2014; Naughton et al., , 2012), all of which may prove useful for reducing violence risk for patients with schizophrenia.

Improvements in social and emotional reasoning on an ability test such as the MSCEIT may be a useful intermediary marker regarding the effectiveness of these programmes. This study formed part of the preliminary work for a study of cognitive remediation therapy in schizophrenia and schizoaffective disorder. We believe there is now a need for a range of studies of means to improve neurocognition and social cognition in patients with schizophrenia in order to improve social function and reduce risk factors for violence and other adverse outcomes.

The findings of this study may also have implications for understanding mental capacity amongst patients with schizophrenia. The current legal model that distinguishes between dynamic impairments of mental capacity supposedly due to psychiatric symptoms and fixed impairments of mental capacity due to intellectual disability may prove to be a false dichotomy. The legal model assumes that when symptoms of schizophrenia spectrum disorders resolve, general and function specific mental incapacities will also resolve. This may also prove to be a false assumption. However, there is some tentative evidence that the metacognitive therapy of Moritz et al., 2014, may enhance functional mental capacities relevant to competence and legal status (Naughton et al., 2012).

Conclusions

Research in schizophrenia should concentrate on functional outcomes. Violence is itself evidence of impaired social function, as well as a cause of stigma. In this study, impairments of neurocognition and social cognition experienced by forensic patients with schizophrenia and schizoaffective disorder accounted for a large portion of the variance of subsequent violent

behaviour. However, the link is nuanced and indirect. Deficits in social reasoning may be more important than other neurocognitive abilities. Neurocognition appears to be linked to violence insofar as it affects higher level social reasoning processes, psychiatric symptoms, social functioning, and violence proneness as measured by the HCR-20 violence risk scores. The neurocognitive difficulties experienced by forensic patients with schizophrenia and schizoaffective disorder may therefore create the foundation for a range of risk factors and impairments of function, which in turn are causally related to violence.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

KO'R originated the conception and design of the study and the analysis and interpretation of the data, with substantial involvement also of GD and HGK. CC, DO'S, AR, ML, TMcD, LMcG, YE, EW, LB, EO, RM, MD and ZA all contributed substantially to the acquisition of data and all met the guidelines for authorship. All authors have read and approved the final manuscript.

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3. Chapter 3: Empirical paper 2: Anticholinergic burden in schizophrenia and ability to benefit from psychosocial treatment programmes: a 3-year prospective cohort study

This chapter describes the second empirical paper. This study was published in Psychological Medicine in 2016.-

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Research Question:

- The aim of this study was to determine if anticholinergic burden would be associated with cognitive impairments, which in turn would affect patient's ability to participate, engage and benefit from psychosocial treatment programmes.

3.1 Abstract

Background: Many medications administered to patients with schizophrenia possess anticholinergic properties. When aggregated, pharmacological treatments may result in a considerable anticholinergic burden. The extent to which anticholinergic burden has a deleterious effect on cognition and impairs ability to participate in and benefit from psychosocial treatments is unknown.

Method: Seventy patients were followed for approximately three years. The MATRICS Consensus Cognitive Battery (MCCB) was administered at baseline. Anticholinergic burden was measured with the anticholinergic cognitive burden scale (ACB). Ability to benefit from psychosocial programmes was measured using the DUNDRUM-3 Programme Completion Scale (D-3) at baseline and follow up. Psychiatric symptoms were measured using the PANSS. Total antipsychotic dose was measured using chlorpromazine equivalents. Functioning was measured using the Social and Occupational Functioning Assessment Scale (SOFAS).

Results: Mediation analysis found that the influence of anticholinergic burden on ability to participate and benefit from psychosocial programmes was completely mediated by the MCCB. For every 1 unit increase on the ACB Scale, change scores for the Dundrum-3 decreased by -0.27 points. This relationship appears specific to anticholinergic burden and not total antipsychotic dose. Also, mediation appears to be specific to cognition and not psychopathology. Baseline functioning also acted a mediator but only when MCCB was not controlled for.

Conclusions: Anticholinergic burden has a significant impact on patient ability to participate in and benefit from psychosocial treatment programmes. Physicians need to be mindful of the cumulative effect that medications can have on patient cognition, functional capacity and ability to benefit from psychosocial treatments.

3.2 Introduction

The neurocognitive theory of schizophrenia has demonstrated explanatory reach (Deutsch, 2011, Kahn and Keefe, 2013). Cognitive impairment accounts for a range of outcomes including ability to live independently, employment, quality of life and reactive violence in addition to response to antipsychotic medication (Kim et al., 2008; Change et al., 2013; Kahn and Keefe 2013; O'Reilly et al., 2015). Although pharmacotherapy is the primary treatment for the symptoms of schizophrenia (Leucht et al., 2012) such as delusions and hallucinations, it is less effective for negative symptoms like lack of motivation, nor is it effective for cognitive impairment (Harvey and Bowie, 2012; Nielsen et al., 2015). Only 1 in 7 patients achieve recovery when defined as clinical and social adaptation sustained over time (Jääskeläinen et al., 2013). Psychosocial treatments are generally used to address the functional disability that characterises schizophrenia (Grant et al., 2012). Unfortunately, cognitive problems may also interfere with the effectiveness of these interventions (Green et al., 2000; Kurtz, 2011; O'Reilly et al., 2016).

To facilitate the development of cognitive enhancing agents the US National Institute of Mental Health devised a neuropsychological battery for treatment studies, the MATRICS consensus cognitive battery (MCCB; Nuechterlein et al., 2008). The US Food and Drug Administration (FDA) require that cognitive enhancing agents be supported by both evidence of change in cognitive performance and improvements in 'real world' functioning (Buchanan et al., 2005). Currently pharmacological attempts to enhance cognition amongst patients with schizophrenia have been unsuccessful (Harvey and Bowie, 2012). The reason for this is unclear. Excessive synaptic pruning may limit the potential for improving cognition via neurotransmitters (Keshavan et al., 1994; Harvey and Bowie, 2012; Sekar et al., 2016). But the use and dose of concurrent medications may also be important (Harvey and Bowie, 2012). One mechanism through which a deleterious effect of concurrent medications might occur is via the cholinergic system (Nebes et al., 2005; Campbell et al., 2009). The cholinergic system is a series of pathways from the basal forebrain

radiating throughout the cerebral cortex and involved in regulating attention and memory (Chudasama et al., 2004; Sarter et al., 2005).

Most antipsychotic medications administered to patients with schizophrenia possess anticholinergic properties (Chew et al., 2008). The side effect profile of antipsychotic medication is also sometimes treated with anticholinergic agents. In recognition of this the FDA-NIMH-MATRICES Guidelines for Clinical Trial Design of Cognitive-Enhancing Drugs require that first-generation antipsychotics can be utilised in clinical trials but only with no additional anticholinergic agents (Buchanan et al., 2011). Over 50% of people with schizophrenia also have other psychiatric or general medical conditions which require treatment (Green et al., 2003; Jones et al., 2004). Many medications for treating these complaints have anticholinergic properties. Pharmacological treatments when aggregated may create a considerable anticholinergic burden that impairs cognition, functional capacity and ability to benefit from psychosocial treatments amongst a group of patients who are already cognitively impaired (Vinogradov et al., 2009; O'Reilly et al., 2015).

To our knowledge only one study has investigated whether anticholinergic burden moderates the effectiveness of behavioural treatments (Vinogradov et al., 2009). Serum anticholinergic activity uniquely accounted for 20% of the variance in change of global cognition following a programme of cognitive remediation therapy, independent of age, IQ or symptom severity. A limitation of this study was that it consisted of patients who were treatment responsive and who volunteered to participate in 50 hours of intensive therapy. Moreover, the study was limited to cognitive outcome and did not examine anticholinergic burden effects on functional status. Because cognitive impairment in schizophrenia is an important treatment priority and because cognitive deficits are known to affect patients' ability to benefit from psychosocial programmes it is important to understand whether anticholinergic burden affects patients' ability to benefit from treatments.

- 1.) We hypothesised that the relationship between anticholinergic burden and ability to benefit from psychosocial treatment programmes would be mediated by cognitive ability, when controlling for age, gender, baseline performance on psychosocial treatment programmes, total antipsychotic dose, and symptoms.
- 2.) We hypothesised that the mediation relationship between medication, cognition, and programme completion would be specific to anticholinergic burden and not total antipsychotic dose; and that the mediation would be specific to cognition, and not to symptoms or functioning when cognition is controlled for.

3.3 Methods

This was a naturalistic 3-year prospective observational cohort study of anticholinergic burden, cognitive ability and patient benefit from psychosocial treatment programmes. Data were gathered from 2012 to 2015. Baseline data was gathered in 2012. Follow up data was gathered until the end of 2015. All of the assessments were completed by assessors who were blind to the results of the other assessments

Participants and setting

The National Forensic Mental Health Service for Ireland provides specialised care for adults who have a mental disorder and are at risk of harming themselves or others. At the time of the study the National Forensic Mental Health Service (NFMHS) had 94 secure inpatient beds located on a single campus, the Central Mental Hospital (CMH), and 13 supervised community beds for those discharged subject to conditions. The CMH is the only secure forensic psychiatric hospital for the Republic of Ireland.

Inclusion criteria were having a diagnosis of schizophrenia or schizoaffective disorder and being judged to be able to provide informed consent. A total of 123 patients were invited to participate during 2012. Of these 8 patients declined to take part. 15 patients did not have a diagnosis of schizophrenia or schizoaffective disorder as assessed by a consultant psychiatrist using the Structured Clinical Interview for DSM-IV (SCID; First et al., 2002). Of the 100 remaining, 19 patients were discharged and one patient died before they could complete the programme completion assessment at follow up, one patient was judged to be feigning during the assessment, and one patient did not complete the cognitive assessment, while eight patients did not complete the Positive and Negative Syndrome Scale assessment (PANSS; Kay et al., 1987). Of the 70 patients that remained in the study 59 patients has a SCID diagnosis of schizophrenia and 11 a diagnosis of schizoaffective disorder. 66 patients were male (94%) and 4 were female (5.7%). The mean age of patients in the study was 39 years (SD 11.1).

The mean length of stay at baseline for the 70 patients was 7.69 years (SD 8.07), median 5.79. Of the 70 patients included in the study 62 remained in the study until 2015 (88%) Seven patients were discharged during the 3 year follow up and one patient died. As assessments were carried out every six months, the last assessment was taken. Demographic details and the sample characteristics are presented in Table 3.1.

Cognitive assessment

Patients were assessed using the Measurement and Treatment to Improve Cognition in Schizophrenia (MATRICS) Consensus assessment battery of cognitive deficits in schizophrenia (MCCB), and also the Test of Premorbid Functioning TOPF-UK. The mean MCCB composite score was 21.32, (SD 14).

Scores for estimated pre-morbid intelligence (TOPF-UK; Wechsler 2011) were not adjusted for education as an estimate of premorbid ability because the symptoms associated with mental disorder can affect educational attainment. A small number of patients (n=7) could not complete the TOPF-UK because of literacy problems. The mean estimated premorbid IQ was 96.8 (SD 12.0).

Functional performance

The SOFAS was completed by a member of the multidisciplinary team responsible for the care of the patient, who was blind to the other assessments including the cognitive assessment (Rybarczyk, 2011). The mean score on the SOFAS was 57 (SD 20).

Programme Completion

The Dundrum-3 Programme Completion Scale (D-3) is a structured clinical judgment instrument taken from the DUNDRUM toolkit, which assesses whether patients have participated in, engaged and benefited from psychosocial programmes (Kennedy et al. 2010). An independent review found that the scale met requirements for routine outcome measures examining functioning, recovery, risk and placement pathways within forensic mental health populations (Shinkfield & Ogloff, 2014). The Dundrum-3 Programme Completion Scale has also been shown to distinguish significantly between groups of patients at different levels of therapeutic security within a forensic setting (Davoren et al, 2012); and it has been shown to predict moves between levels of therapeutic security and to predict conditional discharge from a secure hospital (Davoren et al, 2013).

The Dundrum-3 Programme Completion Scale (D-3) has seven items measuring outcomes for programmes concerning physical health, mental health, drugs and alcohol, problem behaviours, self-care and activities of daily

living, education occupation and creativity, and family and social networks. These items are intended to cover the domains of health defined by the WHO (1986), which holds that health is *"a resource for everyday life, not the objective of living. Health is a positive concept emphasizing social and personal resources, as well as physical capacities."* Each item is rated on a 5-point scale with lower scores representing a higher level of participation, sustained engagement and change. Engagement is demonstrated through more than simply having attended all sessions of a programme. This battery of assessments encompasses the range of interventions typically offered for patients with schizophrenia in a modern forensic hospital over a time scale of years rather than months. Annual audits during the period of this study showed that patients achieved a target of 25 hours a week of timetabled therapeutic activity and represents 'treatment as usual'.

The mean D-3 Score at baseline was 16.5, (SD 6.63) which is the total score for all seven items. The mean D-3 at follow up was 15.0, (SD 7.36) Change scores were calculated by subtracting the D-3 score at follow up from the D-3 at baseline to estimate the strength of the anticholinergic effect. The mean change score over the follow up period was 1.52 SD (5.22).

Symptom assessment

A PANSS assessment was completed on all 70 patients who remained in the study (Kay et al., 1987). The PANSS assessments were completed by a psychiatric registrar and an assistant psychologist trained in its use, who were blind to the cognitive assessments. The mean PANSS Total score at baseline was 64 (SD 22).

Medication

A recent review indicated that evidence is not sufficiently robust for any one of a number of methods for calculating dose equivalence for different antipsychotic medications to be considered as a gold standard, and justification should be offered for the method chosen in a particular study (Patel et al., 2013). A chlorpromazine equivalent (CPZeq) was calculated for each participant as a measure of his/her relative daily dose of antipsychotic medications (Woods et al 2003; Haddad et al 2010; Taylor et al 2012). CPZeq was selected for calculating antipsychotic dose as it is a widely used and coherent method, appeared to have face validity for the purposes of the study, and produces similar results to other approaches such as the British National Formula (BNF) and Defined Daily Dose (Sweileh et al., 2014). The mean chlorpromazine score at baseline was 529.15mg/day, (SD 339.45).

Anticholinergic Burden

Anticholinergic burden was assessed using the Anticholinergic Cognitive Burden scale (ACB; Boustani et al. 2008). The ACB scale was developed by a multidisciplinary expert panel based on a systematic review of medications with known anticholinergic activity likely to have an effect on cognition. The ACB scale contains 88 listed medications. Each listed medication can be rated on a four-point scale (0-3). 0 = no anticholinergic activity, 1 = mild anticholinergic activity, 2 = moderate anticholinergic activity, and 3 = severe anticholinergic activity. The total anticholinergic burden is then calculated by aggregating the score for each listed medication. The ACB scale has been validated in a range of studies (Salahudeen et al., 2015).

The ACB was scored from prescription charts by a consultant psychiatrist (PO'C) the week prior to the baseline cognitive assessment. The mean ACB score at baseline was 4.40 (SD 2.80), mode 3; 75% of the sample had an ACB

Table 3.1 Demographics and sample characteristics

	<i>n</i> = 70 Mean (range)	Median	SD
Age (years)	39.5	37.5	11.1
Gender	66 male, 4 female		
Length of stay at baseline (years)	7.73	5.79	8.07
Length of follow up period (years)	2.94	3.24	0.84
Follow up Dundrum-3	15.01	13	7.36
Change Score Dundrum-3	1.52	1	5.22
Estimate of Premorbid Intelligence TOPF-UK (standard score)	96.8	98	11.9
MCCB Composite (t score)	21.3	21.5	14.25
SOFAS	56.64	59	19.72
PANSS Total Score	64.12	60	21.67
CPZeq (mg/day)	529.15	471	339.45
ACB score	4.40 (14)	3	2.80

D-3, DUNDRUM-3 Programme Completion Scale; TOPF, Test of Premorbid Functioning; MCCB, Matrics consensus cognitive battery; SOFAS, Social and Occupational Functioning Assessment Scale; PANSS, Positive and Negative Symptom Scale; CPZeq, chlorpromazine equivalent; ACB, Anticholinergic Cognitive Burden scale.

Table 3.2: Medications contributing to the anti-cholinergic cognitive burden scale (ACB) score. Numbers (No.) are the numbers of patients receiving each medication. Note also that no patients were prescribed benzodiazepines.

Score of 1	No	Score of 2	No	Score of 3	No
Atenolol	10	Carbamazepine	1	Chlorpromazine	3
Captopril	1			Clomipramine	2
Ranitidine	1			Clozapine	46
Codeine	1			Olanzapine	34
Frusamide	1			Oxybutynin	3
Haloperidol	7			Paroxetine	1
Methodone	2			Procyclidine	21
Prednisolone	2			Promethazine	1
Quinidine	1			Quetiapine	3
Risperidone	9			Scopalomine	19
				Tolterodine	2

score less than 6. Table 3.2 shows that many of the medications contributing to ACB score were non-psychiatric. No benzodiazepines were prescribed.

Statistical analysis

Distributions of all measures were screened for outliers and evaluated for normality. One case was assessed as being an outlier on the ACB scale using an outlier labelling method and visual inspection of plots. This case was winsorised to the value of the next highest case not considered an outlier. Four cases were determined to be outliers for the change score on the D-3. These cases were also winsorised to the next highest or lowest case not considered to be an outlier. Following the removal of outliers both the ACB score and the Change Scores on the D-3 were normally distributed. The variables age, baseline 2012 D-3 and CPZeq were not normally distributed and were transformed using log10 and Srt transformation. The PANSS Total Score and the MCCB total score met criteria for a normal distribution and did not require any transformations.

A paired sample t-test was used to calculate whether there was a significant difference between patient's performance on the D-3 at baseline and three years follow up. Morris and DeShon's (2002) within group effect size formula was used to calculate the magnitude of the effect size over a 3-year period.

SPSS PROCESS macro model 4 (Hayes, 2013) was used to analyse mediation relationships between anticholinergic burden measured by the ACB scale and change over a 3-year period in scores on the D-3. Unstandardised effect sizes were generated for the mediation models using 10,000 bootstrap samples and 95 % bias-corrected confidence intervals were calculated. Age and gender were entered as covariants for all coefficients (Fig 3.1).

Six specific mediation analyses were carried out to test the specificity of the relationship between anti cholinergic burden, cognition, and patient ability to participate in and benefit from treatment programmes (change in D-3 score).

First, we examined whether cognitive ability as measured by the MCCB Total Score would mediate the relationship between anticholinergic burden and change on the D-3, when controlling for age, gender, baseline performance on the D-3, psychiatric symptoms as measured by the PANSS total score, and antipsychotic dose. Second, we examined whether MCCB also mediated an effect of dose (CPZ eq) on change in D-3 as an alternative to a specific effect of ACB. Third, we examined whether psychiatric symptoms as measured by the PANSS total score would mediate the relationship between anticholinergic burden and the change scores for the D-3, controlling for age, gender, cognition as measured by the MCCB total score, antipsychotic dose and baseline performance on the D-3. Fourth, we examined whether baseline functioning as measured by the SOFAS would mediate the relationship between anticholinergic burden and change scores on the D-3, when controlling for age, gender, baseline performance on the Dundrum Programme Completion Scale, cognition as measured by the MCCB total score, antipsychotic dose, and psychiatric symptoms. Fifth, we examined whether cognition (MCCB total score) would act as mediator when additionally controlling for baseline functioning (SOFAS), and whether baseline functioning (SOFAS) would act as a mediator for when cognition (MCCB) was not controlled.

Ethical standards

This study was approved by the research ethics and effectiveness committee of the National Forensic Mental Health Service and complied with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All participants gave written informed consent.

3.4 Results

Magnitude of change over a 3-year period within a forensic mental health service

The mean follow-up period ($n = 70$) was 2.94 years SD .840. The mean change on Dundrum-3 was -1.528 units SD 5.22. This was a significant change (paired $t = 2.448$, $df = 69$, $p < .017$; 95% confidence interval (CI), 2.77 to 0.28). The Pearson correlation between baseline Programme Completion and Programme Completion at 3-year follow up was $r = 0.726$ (Table 3.3). The magnitude of effect of three years of treatment in a forensic mental health service using the Dundrum 3 Programme Completion Scale was 0.295 (Cohen's d).

Anticholinergic burden and change in programme completion scores over three years

The MCCB total score completely mediated the relationship between anticholinergic burden (ACB) and the change in D-3 scores, when controlling for age, gender, baseline programme completion, total antipsychotic dose (CPZeq), and total psychopathology (PANSS). The unstandardised indirect effect of anticholinergic burden as measured by the ACB scale through cognition as measured using the MCCB total score was -.27, (95% CI -.58 to -.0545) (Table 3) which can be read that for every 1-point increase on the ACB scale changes on the Dundrum Programme Completion (D-3) scale decrease by -.27 points.

Cognition as a mediator between chlorpromazine equivalents and change in programme completion score

To test the hypothesis that anticholinergic burden and not total antipsychotic dose had a specific effect on cognition which in turn influenced the functional outcome of programme completion we constructed a mediation model where

CPZeq was the independent variable and controlled for anticholinergic burden, age, gender, psychopathology, and baseline programme completion. There was no evidence of a direct effect or an indirect effect via cognition for CPZeq on programme completion, when controlling for ACB and other variables.

Total psychopathology as a mediator between anticholinergic burden and change scores for 3 years and programme completion

To test the hypothesis that the effects of anticholinergic burden were specific to cognition and not psychopathology in general we constructed a model where PANSS total score was the proposed mediator controlling for age, gender, baseline programme completion, CPZeq, and the MCCB Total score. There was no evidence of an indirect effect of PANSS total score on change in D-3 scores when controlling for other variables.

Social and occupational function (SOFAS) as a mediator between anticholinergic burden and change in programme completion scores over 3 years

To test the hypothesis that the effect of anticholinergic burden was specific to cognition we constructed a mediation model where the effect of anticholinergic burden on change in D-3 score was mediated by social and occupational functioning (SOFAS) controlling for age, gender, baseline programme completion, MCCB total Score, CPZeq, and PANSS Total score. Social and Occupational functioning as measured by the SOFAS significantly mediated the relationship between ACB and change in programme completion but only when the MCCB total was removed from the model.

Cognition as a mediator between anticholinergic burden and change in programme completion scores when controlling for social and occupational functioning.

When controlling for social and occupational functioning at baseline the MCCB Total score no longer mediated ACB and change in D-3 scores (Table 3.4).

Supplementary post hoc analysis

A post hoc analysis exploring the mediation relationship between ACB, cognition (MCCB Total Score) and disability or functioning (SOFAS) was also conducted, controlling for age, gender, psychopathology (PANSS Total) and medication (CPZeq). This analysis again used Process and 10,000 bootstrapped samples. In total the model accounted for 59% of the variance of functioning (SOFAS). The direct effect of ACB on functioning (SOFAS) was not significant (-.7657, 95% CI -2.4759 to .9445). However, the mediated effect via cognition (MCCB), was significant (-1.4651, 95% CI -2.5479 to -.6905). For every 1-point increase in anticholinergic burden as measured using the ACB scale functioning declined by 1.4651 points (SOFAS).

This effect was specific to cognition (MCCB) being the mediator and psychopathology (PANSS Total) did not mediate the relationship between ACB and functioning when cognition was controlled for (-.4508, 95% CI -1.558 to .4978). Furthermore, the effect was specific to anticholinergic burden and not total antipsychotic dose. In other words, CPZeq did not affect functioning (SOFAS) via cognition, when ACB was controlled for (.0028, 95% CI -.0026 to .0089).

Figure 3.1: C1, Direct effect of X on Y, before mediation via M; C2, direct effect of X on Y after mediation via M; A, indirect effect of X on Y mediated via M; B, direct effect of M on Y, adjusted for X.

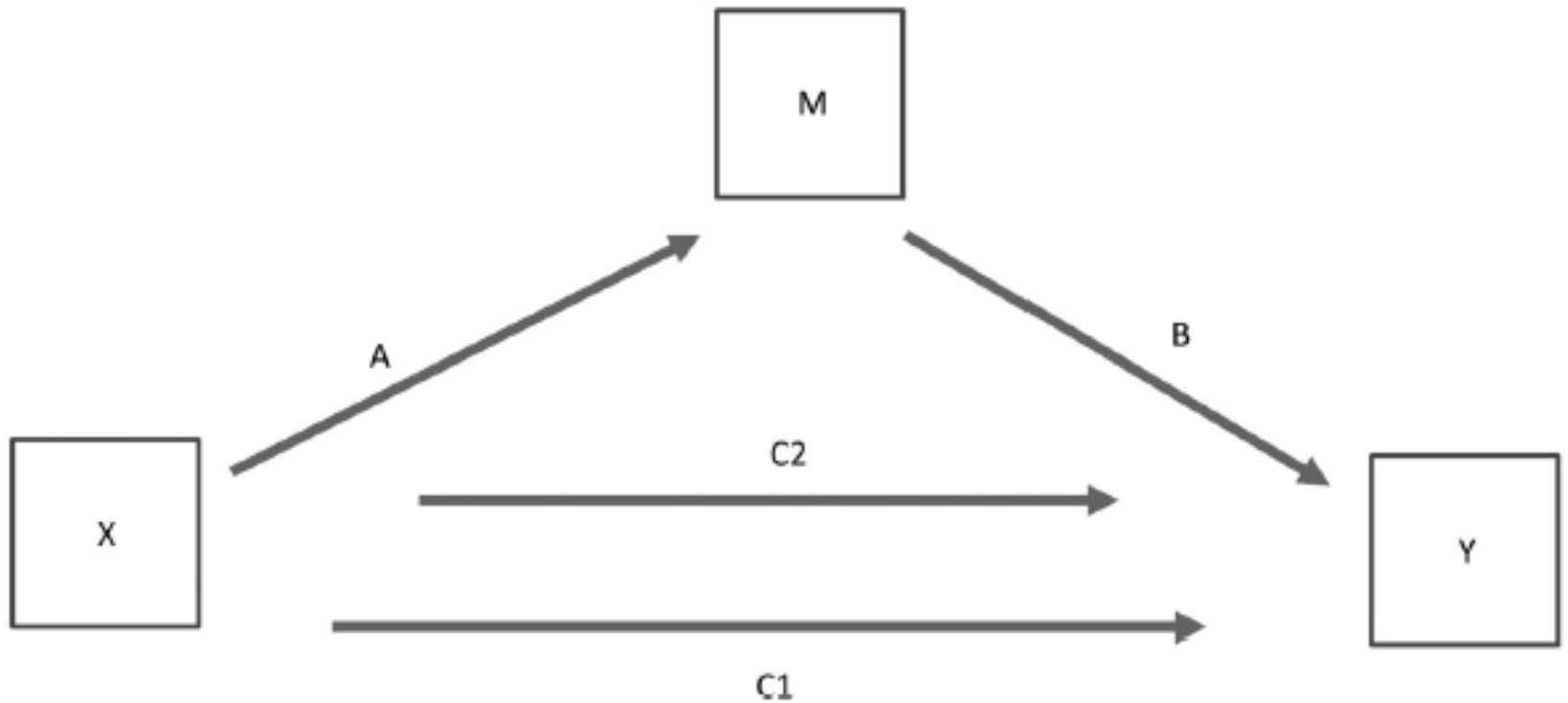


Table 3.3: Pearson correlations, n=70 and significance (p) values

	ACB	MCCB Total	Change Scores PC	Baseline PC	3 Years PC	PANSS Total	CPZEq	Baseline SOFAS
ACB	-							
MCCB Total	-.547 .000	-						
Change Scores D-3	-.167 .168	.290 .015	-					
Baseline D-3	.340 .004	-.429 .000	.176 .145	-				
3 Years Follow up D-3	.414 .000	-.578 .000	-.516 .000	.735 .000	-			
PANSS Total	.384 .001	-.403 .001	-.228 .058	.617 .000	.700 .000	-		
CPZEq	.402 .001	-.250 .037	-.049 .686	.348 .003	.294 .013	.419 .000	-	
Baseline SOFAS	-.523 .000	.603 .000	.235 .050	-.719 .000	-.790 .000	-.631 .000	-.342 .004	-

ACB=Anticholinergic Cognitive Burden scale, MCCB=Matrices consensus cognitive battery, Change Scores PC = DUNDRUM-3 Programme completion Change Scores, Baseline PC= DUNDRUM-3 programme completion score at baseline, 3 years PC = DUNDRUM-3 programme completion score at follow-up, PANSS= Positive and negative symptom scale, CPZEq= Chlorpromazine Equivalent, SOFAS= Social and Occupational Functioning Assessment Scale

Table 3.4: Regression and mediation coefficients. In all cases, the outcome (Y) is ‘Change in DUNDRUM-3 Programme Completion Scores’. X is the hypothesised determinant factor and M is the hypothesised mediating factor. **Total Sample n=70**

N = 70	Change in Programme Completion		C1: Direct Effect of X on Y before Mediation			C2: Direct Effect of X on Y after Mediation			A: indirect Effect of X on Y mediated via M			B: Direct Effect of M on Y adjusted for X		
	R2	P	Unstandardised effect size	95% CI		Unstandardised effect size	95% CI		Unstandardised effect size	95% CI		Unstandardised effect size	95% CI	
Mediator				Lower	Upper		Lower	Upper		Lower	Upper		Lower	Upper
Model 1														
X = ACB	.33	.000	-.3653	-.8555	.1250									
M = MCCB						-.0908	-.6214	.4397	-.2744	-.5897	-.0545	.1104	.0148	.2060
Model 2														
X = CPZeqv	.33	.000	1.2032	-3.8297	6.2362									
M = MCCB						.7165	-4.1716	5.6046	.4867	-.6244	2.4977	.1104	.0148	.2060
Model 3														
X = ACB	.33	.000	-.2236	-.7837	.3364									
M = PANSS						-.0908	-.6214	.4397	-.1328	-.4043	.0624	-.0989	-.1612	-.0365
Model 4														
X = ACB	.41	.000	-.0908	-.6214	.4397									
M = SOFAS						.0529	-.4555	.5612	-.1437	-.4033	.0244	.1242	.0416	.2067
Model 5														
X = ACB	.41	.000	-.0761	-.5538	.4017									
Y = MCCB						.0529	-.4555	.5612	-.1289	-.3904	.0308	.0666	-.0280	.1611
Model 6														
X=ACB	.34	.000	-.3653	-.8555	.1250									
M = SOFAS						-.0761	-.5538	.4017	-.2892	-.6079	-.0674	.1421	.0630	.2212

CI, Confidence interval; ACB, Anticholinergic Cognitive Burden scale; MCCB, Matrics consensus cognitive battery; CPZEq, chlorpromazine equivalent; PANSS, Positive and Negative Symptom Scale; SOFAS, Social and Occupational Functioning Assessment Scale. In all cases, the outcome (Y) is ‘Change in DUNDRUM-3 Programme Completion Scale scores’. X is the hypothesized determinant factor and M is the hypothesized mediating factor. Total sample n = 70/ Models 1, 2, 3 include age, gender, DUNDRUM-3 Programme Completion Scale (D-3) baseline scores; PANSS Total, MCCB Total, and CPZeq. Models 4 and 5 also include SOFAS in addition to age, gender, D-3 Baseline, PANSS Total, MCCB Total and CPZeq. Model 6 does not included or control for MCCB and contains ACB, SOFAS, age, gender, PANSS Total, and CPZeq. In each case the dependent variable (Y) is change scores on the D-3.

3.5 Discussion

This is the first study to demonstrate that anticholinergic burden has a negative impact on the outcomes of psychosocial treatment programmes for patients with schizophrenia or schizoaffective disorder. This adverse effect on psychosocial treatments appears to be mediated specifically through impaired cognitive capacity. The patients within this prospective cohort were cognitively impaired at baseline and had a mean MCCB t-score composite of 21.3, which is almost 3SD below the nonclinical mean. A score of this size approximates the cognitive abilities of individuals with a moderate intellectual disability. The cognitive ability of patients within this sample is especially striking given that their estimated premorbid IQ was found to be in the average range. Anticholinergic burden in part appeared to be a determinant of cognitive ability and psychosocial treatment outcomes. Within this study for every 1-unit increase on the Anticholinergic Cognitive Burden (ACB) Scale, patients change scores on a scale measuring participation and benefit from psychosocial treatment programmes decreased by -0.27 points. This decrease needs to be taken in context that the mean change score on the Dundrum-3 Programme Completion (D-3) scale was 1.52 over the 3-year period (Cohen's $d = 0.29$). The range of D-3 score was however very wide (Table 1). Anticholinergic burden impairs cognition, which in turn impairs the ability to benefit from treatment programmes, even when controlling for a range of confounding variables including age, gender, antipsychotic dose and symptom severity.

These findings appear to be specific to anticholinergic burden and cognition. The effect of total antipsychotic dose on change in programme completion was not mediated by cognition. Since no benzodiazepines were prescribed, these could not have contributed to slowed processing speed. Moreover, total psychopathology (PANSS) did not mediate the effect of anticholinergic burden on change in programme completion scores. Clinicians' ratings of patients psychosocial and occupational functioning (SOFAS) also did not mediate the relationship between anticholinergic burden and change in programme

completion when cognition was controlled for. But SOFAS did mediate the relationship between anticholinergic burden and programme completion when cognitive ability was removed from the model, presumably because functioning is in part dependent on cognitive capacity.

Our post-hoc analysis also demonstrates that anticholinergic burden may potentially impact on patient disability as measured by the SOFAS. This effect again is specific to cognition as demonstrated by mediation analysis. Mediation analysis also shows that the effect of ACB on SOFAS is specific to anticholinergic burden and not total antipsychotic dose (CPZeq). This may have implications for rehabilitation in schizophrenia.

The findings of this study may go some way to explaining why Wunderink et al. (2013) found that dose reduction of antipsychotic medication was linked with superior functional but not symptomatic remission in comparison to maintenance treatment at seven year follow up. Reductions in anticholinergic burden may have been the mechanism responsible for this improved psychosocial functioning. It has been suggested that treatments like CBT may not be as helpful for patients with schizophrenia as for some other problems (Jauhar et al. 2014). But psychological interventions have a robust evidence base for a range of disorders (Carr, 2009). One reason for reduced efficacy in schizophrenia may be that cognitive impairments affect patients' ability to attend to, process, store, and use the information offered during psychological interventions (Green et al., 2000; Kurtz, 2011). This study illuminates a possible iatrogenic effect that pharmacotherapy can have on cognition and functioning, which in turn affects the outcome of psychosocial treatment. Cognitive ability and anticholinergic burden should therefore routinely be considered as moderators in clinical trials of psychological therapy for patients with schizophrenia.

We do not propose that anticholinergic burden is the sole cause of cognitive impairments amongst patients with schizophrenia or even the major cause, because these difficulties have been observed in medication naïve patients

(Kahn and Keefe, 2013). However, our findings do suggest that anticholinergic burden may have adverse effects for patients with schizophrenia. There are studies suggesting that there is a widespread decrease in muscarinic receptors in the brains of people with schizophrenia (Scarr et al., 2013) including post mortem studies (Mancama et al., 2003; Zavitsanou et al., 2004; Newell et al., 2007; Gibbons et al., 2013) and a brain imaging study (Raedler et al., 2003). Similar to older patients, or those with dementia, people with schizophrenia are likely to have a vulnerable brain with a paucity of cholinergic neurons (Tune, 2001; Campbell et al., 2009; van Haren et al., 2011; Harvey and Bowie et al. 2012; Kahn et al 2015; Grey et al., 2015; Kubota et al., 2015). Physicians are therefore required to conduct careful risk benefit decisions and collaborate with patients regarding the medications they prescribe. The ACB scale may be a useful clinical tool for helping physicians and patients make these decisions. Because verbal intelligence in people with schizophrenia is largely intact (Michel et al 2013), it may be particularly challenging for physicians to identify declines or impairments in other cognitive domains. Also, cognitive screening instruments may not be helpful as they do not take account of a patient's premorbid intellectual ability or be sensitive enough to change (Lezak, 2012). Therefore, comprehensive neuropsychological assessment using psychometrically robust and functionally relevant instruments may be important in the planning of care and treatment for people with schizophrenia.

This study has a number of methodological strengths as well as limitations. Strengths include a sample of most of a national cohort of forensic patients diagnosed with schizophrenia or schizoaffective disorder. This sample was followed up over a 3-year period. The use of the MCCB measure for assessing cognitive problems in schizophrenia and controlling for a range of confounders including psychopathology and antipsychotic dose are also strengths. Furthermore, all measurements were conducted independently of each other.

Limitations in this study include the specialist sample consisting entirely of forensic patients which may raise questions regarding the generalisability of the results to other samples of patients with schizophrenia. Patient participation

and benefit from psychosocial treatment programmes was measured using the D-3 which has been specifically developed and recommend for this patient group. This scale takes account of the wide range of psychosocial interventions provided for hospitalised patients over a 3-year period. Because no attempt is made here to distinguish between treatment responses to different treatment programmes, the overall effect measured is a measure of ‘treatment as usual’ with multi-disciplinary delivery of programmes. The sample in this study was cross-sectional rather than an incident series of new admissions. To achieve an incident sample of sufficient size, a very prolonged study over as much as a decade would have been required, or a multi-centre study.

The current study supports the validity of the ACB scale given its correlations with the MCCB, SOFAS, and D-3. However, it is important to point out a number of criticisms have been levelled at anticholinergic burden scales. There is no consensus for how to calculate anticholinergic burden. Although a bioassay of serum anticholinergic activity (SAA) has in the past been considered the gold standard it is only a marker of anticholinergic activity in serum, and not in the brain (Hori et al. 2014). Also, dosage is not considered within clinical scales such as the ACB and medications are unlikely to have a simple 0:1:2:3 ratio in relation to dose or in relation to each other. However, a number of studies have found that unit weighting as used in the ACB scale is quite robust for making predictions (Dawes 1979). Unit weighting performs particularly well where the criterion (in this case central anticholinergic effect) cannot be quantified and this is precisely the case regarding anticholinergic burden (Dawes, 1979). Unit weighting also performs well when there is not a straightforward relationship between the predictor variables and the criterion (Dawes, 1979), and there is considerable individual variation in absorption, distribution, rate of metabolism, formation, and excretion of pharmacologically active metabolites (Pollock 2000). A third criticism of anticholinergic scales is that there is variability in the quantification of anticholinergic burden across different instruments. However, unit weighting is also viable when it is difficult to develop a regression model because of a larger number of

predictors. There are more than 600 medications that have anticholinergic activity (Chew et al. 2008). Finally, because medications with anticholinergic properties do not have a straight forward relationship with cognitive decline the correlation between scales may be a better measure of construct validity than the Kappa coefficient (Lertxundi et al., 2013).

Although a number of confounding factors were controlled for there was no attempt to manipulate any variable and therefore the study only approximates a causal design. The value of this study is that it establishes a case for an intervention study using meaningful outcome measures concerning treatment engagement and response, and ‘real world’ functional outcomes. A number of studies have been conducted that suggested that discontinuing anticholinergic treatments has a positive effect on cognition amongst patients with schizophrenia (Baker et al., 1983; Mori et al., 2002; Drimer et al., 2004; Ogino et al., 2011; Desmaris et al., 2014). But no study has yet examined whether improvements in cognition following reduction in anticholinergic burden, have in turn affected ‘real world’ functioning.

Conclusion

Anticholinergic burden as measured by the ACB scale had a significant impact on patient ability to participate and benefit from psychosocial treatments within a forensic hospital as measured by change in the D-3 scale.

Anticholinergic burden appears to impair cognitive ability and ‘real world functioning’, which in turn affects patient ability to participate in and benefit from psychosocial programmes. Physicians need to be mindful of the cumulative effect that psychiatric and other medications can have on cognitive ability, functional capacity, and ability to participate and benefit from psychosocial treatments.

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Declaration of interest

The authors declare that they have no conflicts of interest.

4. Chapter 4: Study Protocol: A randomised controlled trial of cognitive remediation for a national cohort of forensic mental health patients with schizophrenia or schizoaffective disorder

This chapter describes the background to cognitive remediation training (CRT) and its potential relevance to the field of forensic mental health. The protocol was published in BMC Psychiatry in 2016.-

O'Reilly, K., Donohoe, G., O'Sullivan, D., Coyle, C., Mullaney, R., O'Connell, P., Maddock, C., Nulty, A., O'Flynn, P., O'Connell, C., Kennedy, H.G. (2016). Study protocol: a randomised controlled trial of cognitive remediation for a national cohort of forensic mental health patients with schizophrenia or schizoaffective disorder. *BMC Psychiatry*, 16:5.

4.1 Abstract

Background: Evidence is accumulating that cognitive remediation therapy (CRT) is an effective intervention for patients with schizophrenia or schizoaffective disorder. To date there has been no randomised controlled trial (RCT) cohort study of cognitive remediation within a forensic hospital. The goal of this study is to examine the effectiveness of cognitive remediation for forensic mental health patients with schizophrenia or schizoaffective disorder.

Methods: An estimated sixty patients will be enrolled in the study. Participants will be randomised to one of two conditions: CRT with Treatment as usual (TAU), or TAU. CRT will consist of 42 individual sessions and 14 group sessions. The primary outcome measure for this study is change in cognitive functioning using the MATRICS Consensus Cognitive Battery (MCCB). Secondary outcomes include change in social and occupational functioning, disorganised symptoms, negative symptoms, violence, participation in psychosocial treatment and recovery. In addition to these effectiveness measures, we will examine patient satisfaction

Discussion: Cognitive difficulties experienced by schizophrenia spectrum patients are associated with general functioning, ability to benefit from psychosocial interventions and quality of life. Research into the treatment of cognitive difficulties within a forensic setting is therefore an important priority. The results of the proposed study will help answer the question whether cognitive remediation improves functional outcomes in forensic patients with schizophrenia and schizoaffective disorder. should be routinely offered to forensic mental health patients. Forensic mental health patients are detained for the dual purpose of receiving treatment and for public protection. There can be conflict between these two roles perhaps causing forensic services to have an increased length of stay compared to general psychiatric admissions. Ultimately a focus on emphasising cognition and general functioning over symptoms may decrease tension between the core responsibilities of forensic mental health services.

Trial Registration: ClinicalTrials.gov Identifier: NCT02360813. Trial registered February 4th, 2015 and last updated May 1st 2015.

4.2 Introduction

Forensic Mental Health Services (FMHS) provide treatment for a minority of people with mental illnesses such as schizophrenia who come into contact with law enforcement agencies as a consequence of their mental disorder, or who cannot be safely managed within another service and require specialised therapeutically safe and secure care and treatment for a period of time (Kennedy, 2002; McFadyen, 1999). The offences carried out by mental health patients are heterogeneous and range from public order offences to homicide. It is possible to divert mentally ill patients charged with less serious offences to general psychiatric services especially when detention in prison would be detrimental to their health (McInerney et al., 2013). Forensic patients are often judged to have lacked mental capacity to form a criminal intent at the time of the offence. These patients are deemed to be not responsible or diminished in responsibility for what they have done due to deficits in comprehension, reasoning, and judgment (Packer, 2009). The ‘insanity defence’ available in some jurisdictions is a special example of a loss of capacity within the context of criminal charges such as homicide or serious assault. Patients facing criminal charges and who receive a verdict of not guilty by reason of insanity are admitted to a forensic hospital so that they can receive treatment and to ameliorate the risk of future violence (McFadyen, 1999). Frequently the dual role of providing treatment and public protection is codified in law as is the case for the Republic of Ireland’s Criminal Law (Insanity) Act (2006) section 11(2) (Criminal Law Insanity Act, 2010). In these circumstances independent tribunals tasked with reviewing patients’ detention are asked to consider the welfare and safety of the person and also the public interest (Criminal Law Insanity Act, 2010). Forensic mental health services therefore have the dual role of treating and caring for the patient and representing their interests, whilst simultaneously protecting the public from further harm through involuntary detention and risk management (Buchanan and Grounds, 2011; Andreasson et al., 2014).

Length of stay within Forensic Mental Health

Forensic mental health patients are typically hospitalised for longer periods than their non-forensic counterparts (Ricketts et al., 2001; Shah et al., 2011; Andreasson et al., 2014; Sharma et al., 2015; Fazel et al., 2016). International comparisons of length of stay are difficult to establish because they are hampered by differences in patient groups and criminal law (Andreasson et al., 2014). For the Republic of Ireland, the vast majority of forensic mental health patients have a diagnosis of schizophrenia or schizoaffective disorder with a small minority having bipolar or depressive disorder. A diagnosis of personality disorder would not ordinarily meet the criteria of mental disorder under Irish law and would thus not qualify to receive compulsory mental health care in either the civil or forensic services (Mental Health Act 2001 and Criminal Law (Insanity) Act 2006). Even when acknowledging differences in patient populations it would not be unusual for patients to be detained within a European context for periods greater than five years (Shah et al., 2011). It is likely that the dual role played by forensic mental health services regarding the needs of the patient on the one hand and society on the other is a contributing factor to lengthy admissions (Buchanan, 2011).

Limitations of pharmacotherapy for treating schizophrenia

The primary treatment strategy for patients with schizophrenia or schizoaffective disorder is pharmacotherapy using antipsychotic medication, a proven and efficacious intervention for the positive symptoms of schizophrenia i.e. delusions and hallucinations (Leucht et al. 2012). Following initial gains however, pharmacotherapy has limited efficacy for improving patient functioning. Antipsychotics are not effective for treating the neurocognitive deficits associated with schizophrenia such as problems with attention, memory and executive functioning; nor do they have efficacy for treating stable, trait-like social cognitive deficits such as emotional perception, theory of mind, context sensitive processing, or emotional reasoning (Keefe et al.,

2007). Antipsychotics have also limited efficacy for treating negative symptoms such as avolition, anhedonia, apathy, blunted affect, asociality, and alogia (Kane et al., 2010; Swartz et al., 2007). It is the neurocognitive impairment, social cognitive impairment, and negative symptoms experienced by patients with schizophrenia that are the strongest contributors to functional outcome (Green, 1996; Green, 2000; Green, 2004; Kirkpatrick and Fischer, 2006). Meta-analyses consistently demonstrate that both neurocognitive and social cognitive deficits in addition to negative symptoms account for more of the variance of suboptimal functioning than positive symptoms (Green, 1996; Velligan et al., 1997; Green et al., 2000; Norman et al., 2000; Green et al., 2004, Lysaker and Davis, 2004; Kurtz et al., 2005; Milev et al., 2005; Kirkpatrick and Fischer, 2006; Cohen et al., 2007; Kahn and Keefe, 2013). Specifically, neurocognitive and social cognitive difficulties affect the ability to live independently, to engage in meaningful work and to benefit from psychosocial treatment programs. Ultimately these impairments impact on patients' quality of life (Brekke et al., 2007; Kahn and Keefe, 2013). Also, negative symptoms are probably partially attributable to cognitive impairments (Ventura et al., 2009). Because of the centrality of neurocognitive problems for patient functioning and because neurocognitive and social cognitive deficits occur prior to the onset of psychotic symptoms it has been argued that schizophrenia should be reconceptualised as a cognitive rather than a psychotic disorder (Kahn and Keefe, 2013). Moreover, it has been suggested that the development of new therapies for improving functional outcomes for patients with schizophrenia has been impeded by emphasising the psychotic features of the disorder (Kahn and Keefe, 2013).

Limitations of psychological and occupational interventions within forensic mental health

To address patients' suboptimal functioning and violence risk factors, forensic mental health services use an eclectic mix of occupational therapy and

psychosocial treatment programmes. Many of these interventions have a limited evidence base within forensic mental health practice (Lindqvist and Skipworth, 2000; Blackburn, 2004; O'Connell et al., 2012; Williams et al., 2014). But some specific programmes such as 'reasoning and rehabilitation' have been formally assessed, using violent behaviour and attitudes as outcome measures (Cullen et al., 2012; Reese-Jones et al., 2012; Skeem et al., 2015). Also, concern has been expressed that patients with schizophrenia and other psychotic disorders may not be able to benefit from such programmes due to their negative symptoms and cognitive deficits (Green et al., 2000; Brekke et al., 2007). Recently we found that a nationally representative cohort of forensic mental health patients with schizophrenia and schizoaffective disorder scored more than three standard deviations below the population mean on the MATRICS Consensus Battery for cognitive deficits in schizophrenia (O'Reilly et al., 2015). Amongst patients with schizophrenia difficulties can occur at any point of the informational processing stream (Ochsner, 2008; Lezak, 2012). Therefore, forensic mental health patients with schizophrenia may not possess the necessary motivation and basic cognitive abilities to attend to the information being presented, store the information within their memory and utilise the information when presented with future problems and challenges. But because psychological interventions have a robust evidence base for a variety of mental disorders (Carr, 2009) it is probable that patients with schizophrenia could benefit from such interventions if their cognitive abilities could be partially remediated, or if their self-efficacy and intrinsic motivation were enhanced.

Cognitive Remediation Therapy

One approach that has shown potential to improve patients' cognitive and motivational difficulties in non-forensic settings is cognitive remediation therapy (Wykes et al., 2011; Wykes and Spaulding, 2011; Cella et al., 2015). Cognitive remediation therapy is a behaviourally based training approach

designed to help patients improve their cognitive abilities and 'real world' functioning. A variety of therapies exist under the cognitive remediation umbrella but most aim to either strengthen patients' basic cognitive capacities through a process of drill and practice, or to teach patients more effective ways to deploy cognitive resources using meta-cognitive strategies. Cognitive remediation is a nonthreatening activity which patients enjoy and focuses on success and mastery experiences and therefore has the potential to increase self-efficacy (Rose et al., 2008). A recent meta-analysis by Wykes has demonstrated that cognitive remediation is an effective intervention for patients with schizophrenia (Wykes et al., 2011). Within the Wykes meta-analysis, the average patient with schizophrenia or schizoaffective disorder who received cognitive remediation improved performance on cognitive tasks by an effect size of about .5 (Cohens d) and .42 on patient functioning. Also, cognitive remediation therapy has been shown to produce durable improvements in cognition and functioning (Wykes et al., 2011). And there is evidence that cognitive remediation can optimise patients' responses to psychosocial rehabilitation (Spaulding, 1999).

But the evidence base for cognitive remediation within a forensic mental health setting is limited. To date only two randomised trials have been conducted. One study investigated the feasibility of improving social cognition amongst forensic mental health patients (Taylor et al., 2015). The second study mixed forensic mental health patients with general mental health patients, which may undermine the confidence with which the findings can be generalised to forensic mental health patients as a whole (Ahmed et al., 2015). Of note within this study the forensic mental health patients were significantly more cognitively impaired on working memory and verbal learning than the general mental health patients. However, both studies produced positive outcomes on a range of measures including recognising emotion, neurocognition, aspects of patient functioning and patient satisfaction and therefore provide cause for optimism. Cognitive remediation therefore may be a promising intervention for forensic mental health patients. In theory cognitive remediation approaches

have the potential not only to improve patients' cognitive abilities and day to day functioning, but also contribute to patients' ability to benefit from additional psychosocial and violence risk reduction programmes, thereby enhancing recovery and perhaps reducing length of stay.

Functional capacity and public protection

The separation between patient care and treatment, and public protection may be a false dichotomy. Although the link between violence and schizophrenia is typically attributed to psychotic symptoms such as delusions and hallucinations, many violence risk factors within this population concern suboptimal functioning (Webster et al., 1997; Witt et al., 2013; Ullrich et al., 2014). Violence risk prediction or violence proneness schemes take advantage of this and place the same weight on items concerning suboptimal functioning as on items concerning psychotic symptoms or other risk factors (Webster et al., 1997; Ullrich et al., 2014). Homelessness, employment problems, relationship difficulties, substance misuse, stress etc. are all risk factors for violence (Webster et al., 1997). Many of the violence risk factors associated with suboptimal functioning are probably related to the cognitive difficulties experienced by patients with schizophrenia. It may also be that forensic patients are more functionally impaired than their non-forensic counterparts thus increasing their violence proneness and creating the circumstances for them to come into contact with law enforcement agencies (O'Reilly et al., 2015). Using a prospective cohort design, we have recently demonstrated that deficits in neurocognition and social cognition accounted for a large portion of the variance of reactive violence carried out by forensic hospital patients with schizophrenia (O'Reilly et al., 2015). We also found that neurocognitive deficits act as a distal risk factor whose effects on reactive violence were mediated by more proximal factors such as problems with social reasoning, impaired functioning, symptoms and violence proneness (O'Reilly et al., 2015).

Prioritising patient functioning over symptoms

Improving and where possible restoring patient functioning is central to psychiatric care. But services may be guilty of emphasising the medical treatment of symptoms over interventions designed to restore patient functioning. For instance, a recent investigation by the Schizophrenia Commission into the provision of care for people with psychosis in England found inpatient settings to be “anti-therapeutic” with medication being prioritised over psychological interventions (Schizophrenia Commission, 2012). Concerning community care and treatment, one retrospective longitudinal study examining 25,000 Swedish patients with schizophrenia found an increase in the rate of adverse outcomes from 1972 to 2009. Amongst this cohort there was an increase in premature death, violent crime, and suicide (Fazel et al., 2014). The increase in the number of adverse outcomes was notably associated with a decrease in the numbers of inpatient beds and an increase of patients living in the community (Schizophrenia Commission, 2012). This finding may be explained by pressure to discharge patients who do not possess the necessary functional capacity to cope in the community but have received antipsychotic medication. Clearly patients with low levels of functioning need high levels of support delivered in either an appropriately resourced community or hospital setting. But by placing greater emphasis on treating and managing the cognitive difficulties that underpin functional impairments, it may also be possible to reduce violence and other adverse outcomes. Although forensic mental health services have a dual responsibility to provide care, in addition to managing and decreasing violence risk, these are not necessarily conflicting roles. The prioritisation of cognition and function over symptoms may resolve the conflict between treatment and public protection. Any conflict that does occur between care and public protection is more likely to be a by-product of the limitations of particular treatment approaches and conceptual paradigms. Because a focus on the cognitive and functional deficits experienced by forensic mental health patients has the potential to bring the twin goals of patient care and public protection into

alignment, evaluating the effectiveness of cognitive remediation is an important research priority.

Current Study

To date there has been no randomised controlled cohort study evaluating cognitive remediation therapy within a forensic hospital. Therefore, an important objective is to conduct a trial of cognitive remediation therapy examining the feasibility, effectiveness, functional outcomes and patient satisfaction for a nationally representative cohort of forensic mental health patients. We do not know whether cognitive remediation is an effective rehabilitation approach within this setting for improving cognition, reducing negative symptoms and improving general functioning. Equally it is not clear whether cognitive remediation has the ability to synergistically combine with routine psychosocial and violence risk management programs and to enhance patients' ability to benefit from these interventions. Finally, it is not clear whether forensic mental health patients would find it useful to participate in an intensive programme of cognitive remediation.

Hypotheses

The current study will aim to: 1) to test the efficacy of cognitive remediation training for improving patient cognition, symptoms and functioning, where functioning includes measures of participation in psychosocial treatment programmes, recovery, and dynamic violence risk, 2) to establish patient satisfaction with cognitive remediation training within a forensic setting.

4.2 Method

The method was informed by the Clinical Trials Assessment Measure for psychological treatments, which is an instrument designed to assess the quality

of psychological trials (Wykes et al., 2008). The Clinical Trials Assessment Measure covers the domains of sample characteristics; allocation to treatment (including allocation concealment, blinding, and randomisation); comparison treatments; outcome assessment (including standardized outcomes and blinding of participants); treatment description (including protocol and fidelity assessment); and appropriate analysis (such as intention-to-treat analysis). The validity measures for adherence to the protocol will include rate of enrolment, rate of retention, tests of the success of blinding, and the number of patients who complete the primary outcome measures. This is a single centre randomised controlled trial.

Ethics, consent and permissions

The study was approved by the Research, Ethics and Audit Committee of the National Forensic Mental Health Service (NFMHS) and the School of Medicine Ethics Committee, Trinity College Dublin. All patients participating in the study will provide informed signed consent.

Setting

The NFMHS provides specialised care for adults who have a mental disorder and are at risk of harming themselves or others. At the time of the study the NFMHS had 94 secure inpatient beds located on a single campus (The Central Mental Hospital, CMH), and 13 community beds. The CMH is the only secure forensic psychiatric hospital for the Republic of Ireland, a population of 4.6 million.

Participants

Approximately sixty patients under the care of the Central Mental Hospital will be recruited to participate in this study. Inclusion criteria are having a

diagnosis of schizophrenia or schizoaffective disorder established using the Structured Clinical Interview for the Diagnostic and Statistical Manual IV (SCID) (First et al., 2002) and being proficient in English. Exclusion criteria are being acutely psychotic, being judged too dangerous to participate in treatment (positive symptoms combined with aggressive or self-harming behaviour in the last month) or being over 65 years of age. Inclusion criteria are broad and exclusion criteria are minimal because we are primarily interested in investigating whether CRT will be effective for a nationally representative cohort of forensic mental health patients.

Randomisation and treatment allocation

Upon enrolment in the study participants will be randomised to cognitive remediation and a waiting list control group receiving treatment as usual (TAU) by the clinical director of the Central Mental Hospital using 'select cases' 'random samples' (select cases random number generator) function in SPSS V21 (IBM Corporation, 2013). Fig. 4.1 is a CONSORT diagram outlining patient allocation. Patients randomised to receiving TAU will be offered the intervention upon completion of the study. The clinicians conducting the therapy sessions will be different from the research team carrying out the assessments. The sequence of randomisation will be concealed from the research team carrying out the baseline and outcome assessments i.e. blinded assessment. All participants will be trained not to reveal their study condition prior to each follow up assessment. Should the blind be broken this will be noted. Furthermore, all assessors will be asked to guess whether participants were receiving TAU or CRT for each of the follow up assessments to see if they perform at a chance level of accuracy. Patient participation in CRT will be shared with their treating psychiatrist. The socio-demographic characteristics of the cognitive remediation group and the waiting list control group will then be compared on a range of measures e.g. age, sex, dose of antipsychotic medication (expressed as chlorpromazine equivalents) (Woods,

2003; Haddad et al., 2010; Taylor et al., 2012), pre-morbid IQ (estimated from TOPF-uk) (Weschler, 2011), MATRICS global composite scores, MATRICS domain scores, Social Cognitive Scores (Nuechterlein et al., 2008; Stone et al., 1998; Baron-Cohen et al., 2001), real world functioning (SOFAS), psychiatric symptoms (PANSS), negative symptoms (CAINS) and violence proneness (HCR-20) (Rybarczyk, 2011; Kay et al., 1987; Kring et al., 2013; Webster et al., 1997)

Cognitive Remediation Therapy

Cognitive remediation therapy is a behaviourally based training programme designed to improve cognitive problems associated with schizophrenia and schizoaffective disorder (Wykes et al., 2011; Wykes and Spaulding, 2011; Cella et al., 2015). Patients allocated to cognitive remediation will receive three individual sessions a week and one group session for approximately 14 weeks, 56 sessions in total.

The focus of the individual sessions is to enhance patients' basic cognitive abilities through drill and practice and to introduce patients to a variety of meta-cognitive strategies to compensate for reduced performance according to need (Cella et al., 2015). Meta-cognitive strategies may be distinct for particular cognitive domains e.g. the strategies of problem identification, breaking problems into parts, brainstorming, sequencing, monitoring, and reflecting may be particularly useful for problem solving. Whereas strategies such as visualisation, chunking, association, rehearsal etc. may be helpful to compensate for memory difficulties. And strategies like self-verbalisation may be useful to enhance attentional abilities.

The focus of the group sessions is to help patients normalise and develop insight into their cognitive difficulties, to receive support and encouragement,

and to generalise gains (Medalia, 2009). A detailed manual has been developed to guide the delivery of the CRT support group.

Cognitive remediation operationalised by nine treatment principles.

Our cognitive remediation therapy is a principle driven intervention consisting of nine treatment principles (Table 4.1) and is in keeping with the recommendations of a task force on Principles of Therapeutic Change that Work, sponsored by the American Psychological Association and the North American Society for Psychotherapy Research (Gastonguay, 2006). In addition to the CRT literature the approach is also influenced by the success of multi-systemic therapy (MST), an empirically supported treatment for conduct disorder. Multi-systemic therapy is a flexible intervention operationalised by treatment principles rather than a prescriptive session format (Henggeler et al., 1998). Conduct disorder, like schizophrenia is a heterogeneous disorder and also has a history of being considered refractory to psychological interventions. In contrast to manualised protocols, principle driven interventions like MST aim to provide clinicians with flexible heuristics rather than a set of tightly defined procedures prescribed at specific times in therapy. The emphasis on broad treatment principles rather than a scripted session format is therefore to facilitate a patient centred approach, which is responsive to each patient's own unique strengths and vulnerabilities.

Our cognitive remediation programme also aims to align the goals of forensic mental health services with the goals of individual patients. For example, forensic mental health services may have a number of goals for their patients concerning physical health, mental health, substance misuse, harmful behaviour and occupational and recreational functioning (Davorn et al., 2012)

Figure 4.1. CONSORT Flow Diagram.

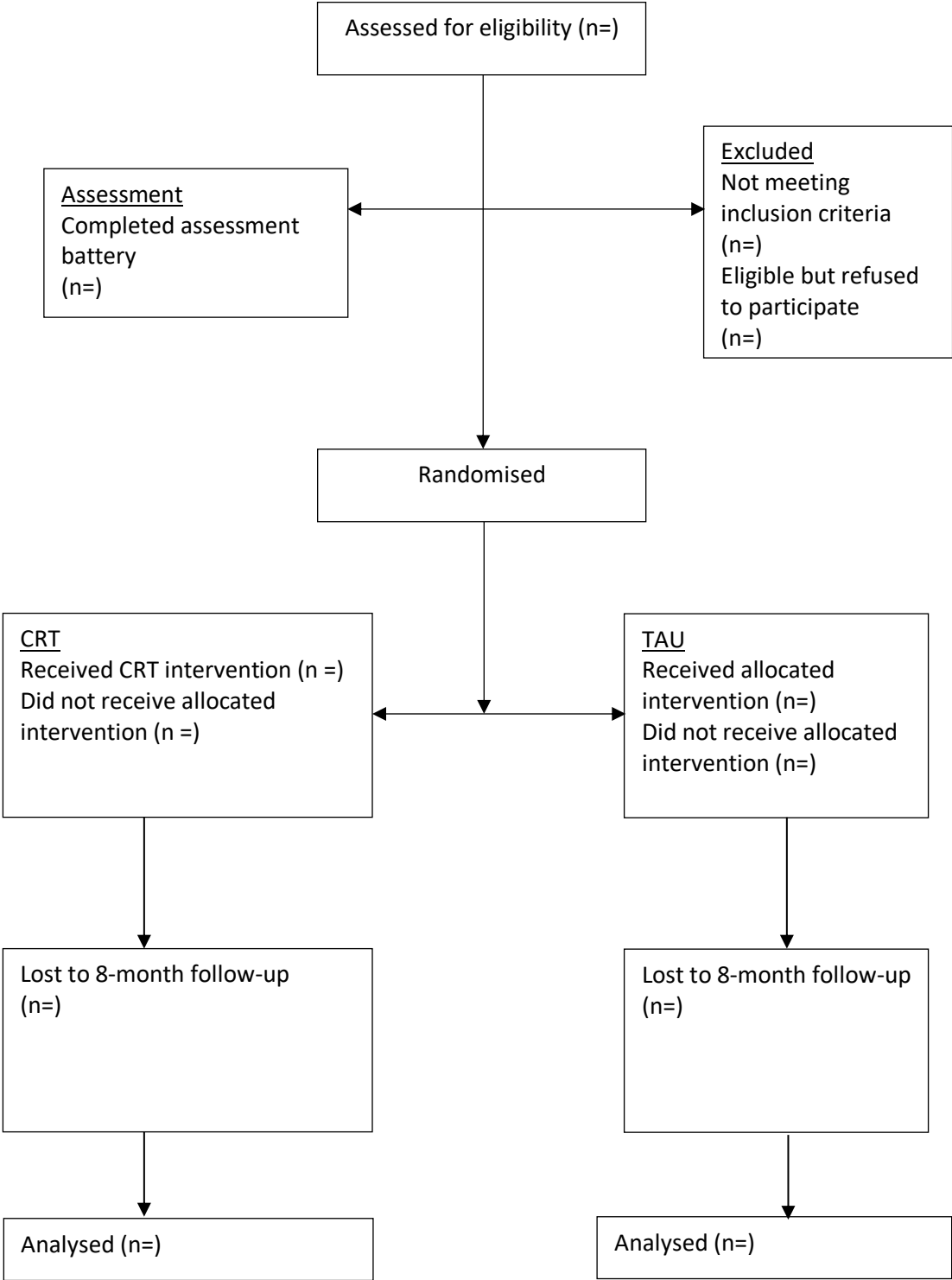


Table 4.1. Principles guiding cognitive remediation intervention

Principle 1, Relationship Building: A major focus of each session is to prioritise the development of a strong therapeutic relationship. The therapeutic relationship will be strengthened by providing a credible rationale for participation, explicitly linking the cognitive remediation to patients' goals, promoting success experiences, making participation enjoyable, providing positive reinforcement, and managing ruptures, which may occur during the course of the intervention.

Principle 2, Collaborative Goal Setting: So as to promote 'buy in' patients will be encouraged to develop a series of short term, medium term, and long-term goals. Patients neuropsychological and risk assessments e.g. HCR-20, DUNDRUM toolkit, will be shared with patients to create a platform to develop goals. An explicit connection will also be drawn between cognitive difficulties and patients' aspirations. Short term goals may include having the concentration required to watch a TV programme or to read a book. Medium term goals may include patients' ability to self-medicate or move to a less secure unit. Long term goals may include returning to work, and developing relationships outside the hospital.

Principle 3, Session Structure: Each session will begin with a mood check to establish rapport or identify problems followed by agenda setting, implementation of the agenda items, and summaries before moving to the next agenda item. The session will end by giving patients the opportunity to provide feedback.

Principle 4, Content of the sessions: The sequencing of interventions will be informed both by patients' goals and their unique strengths and vulnerabilities as documented by neuropsychological assessment. Cognitive domains at the start of the informational processing stream e.g. attention and vigilance, working memory etc will typically be prioritised over those occurring later e.g. comprehension and social problem solving. This is because difficulties associated with higher level cognitive processes may be a result of problems with more basic processes such as attention and memory. As patients demonstrate some improvement in core cognitive skills higher level domains will be targeted. Clinical judgement will be required to determine if patients achieve a basis level of mastery in certain cognitive domains or if a ceiling has been reached before progressing to more complex domains. CRT therapists should carefully assess whether patients are improving on core domains e.g. verbal memory etc., and if these improvements are being maintained over time.

Principle 5, Pacing: Therapists are encouraged to avoid trying to squeeze too much into each session or to work on too many problems simultaneously because it takes time to consolidate skills. In other words, patients need opportunities to repeat tasks again and again to improve performance, which is referred to as massed practice. Throughout the intervention each session should build on the next and be targeted at concrete goals. Patients should be provided with feedback on their progress towards goals. Newly acquired skills should not be abandoned once developed but refreshed during future sessions. Patients may also need breaks between tasks. This down time is a good opportunity to ask patients about their lives and to strengthen the therapeutic relationship.

Principle 6, Errorless Learning and Scaffolding: Task difficulty should be set so that patients obtain a high level of success on each task to avoid faulty learning and to enhance moral. Patients will be required to obtain a success rate of 80% before the cognitive demands of the task are increased. Where problems are encountered therapists should provide scaffolding and model successful completion of tasks.

Principle 7, Meta cognitive Strategies: A major focus of each session will be to explicitly teach patients meta-cognitive strategies which are somewhat independent of basic cognitive ability and can be flexibly applied across situations. Examples of meta-cognitive strategies include goal setting, visualisation, focusing on one thing at time, self-verbalisation, planning, breaking problems into parts, sequencing, chunking, advantage disadvantage analysis, perspective taking, monitoring performance, reflecting on performance etc. It is particularly important to explicitly model the effective use of meta cognitive strategies for patients. The effectiveness of strategies should be carefully assessed using a behavioural experiment framework. The use of strategies should be consolidated as evidenced by generalisation before additional meta-cognitive strategies are introduced. When mastery of basic strategies has been consolidated patients can be encouraged to simultaneously use multiple strategies.

Principle 8 Generalisation: Patients will be encouraged to utilise their cognitive skills outside of remediation sessions by participating in a support group. The focus of the support group will be helping patients to develop a shared understanding of the cognitive deficits associated with schizophrenia, to develop an awareness of how these deficits affect their lives, to identify situations where they can apply their cognitive skills, to obtain encouragement and support from other members of the group on how to implement these skills, to strengthen narratives where success has been achieved. In addition to the above positive group participation in and of itself may enhance cognitive processes as it requires patients to monitor their thoughts, reframe from interruptions, structure their contributions, and reflect on feedback.

Principle 9 Managing Ambivalence: Patients ambivalence towards participating should be met in a non-defensive empathic manner. Advantages and disadvantages of participating should be listed using pen and paper to ease the burden on working memory and to model effective problem solving. Patients should be gently reminded of their goals and their initial commitment to participate for the duration of the intervention. Ways of making the cognitive remediation more relevant or enjoyable should be actively explored.

These goals may vary in their level of explicitness, consist in a number of sub-goals, and vary in the extent to which they are communicated to patients. Also, in some cases the patients may not share the services goals but rather be a passive participant in the rehabilitative process. For instance, they may not agree that they have a substance misuse problem, have a mental illness or be at a high risk of violence. In these cases, the service, psychiatrist, key-worker, multidisciplinary team and other parties are the customers of the intervention and not the patient. In contrast the starting point of our cognitive remediation intervention is to help patients to clearly and explicitly articulate their goals. Explicit links are then drawn between cognitive difficulties and patient aspirations and cognitive remediation is then offered as a vehicle which can help actualise goals. Every attempt is made to facilitate the patient to take on the role of customer. We agree with Lindqvist and Skipworth who argue that it is the hopes of the patient which are decisive for recovery (Lindqvist and Skipworth, 2000a; Lindqvist and Skipworth, 2000b).

Like MST our nine treatment principles are general statements that can be easily remembered and applied, which identify relational conditions, therapist behaviours, and classes of interventions likely to lead to change. The treatment principles attempt to integrate the specific theories and techniques advocated by the CRT literature e.g. self-verbalisation or monitoring, errorless learning, scaffolding etc. combined with research into what makes psychological interventions effective in general e.g. emphasising the therapeutic relationship, offering a credible rationale for treatment, and routinely evaluating progress (Wampold, 2015).

Wykes defines self-monitoring, errorless learning and scaffolding as follows (Wykes et al., 2011). Self-monitoring is a technique for rehearsal of both the task instructions as well as task completion and can be accomplished by using verbalisation of the task instructions overtly or covertly. Errorless learning is a technique whereby the therapist minimises opportunities for the participant to make errors. For example, individuals only attempt tasks where they have an 80% success rate. Finally, scaffolding is a technique where the therapist

pressurises the learning system where by the therapist challenges the participants to complete more challenging tasks but with the assistance of the therapist or alternatively is encouraged to use compensatory strategies.

Our nine treatment principles are also in keeping with recent developments within the CRT literature, where it has been found that the therapeutic relationship, emotional state, and the motivation of participants, in addition to an emphasis on skills transfer, all play an important role in treatment success (Wykes and Spaulding, 2011; Huddy et al., 2012; Subramaniam et al., 2009; Savine and Braver, 2012; Medalia and Saperstein, 2011). For example, working alliance contributes to the success of CRT (Huddy et al., 2012); positive mood facilitates creative problems solving (Subramaniam et al., 2009); intrinsic motivation can be enhanced by providing a personalised context that links treatment with everyday life, and also by tailoring the intervention to the learning goals of each participant (Savine and Braver, 2012; Medalia and Saperstein, 2011); and functioning outcomes are best achieved by combining CRT with other rehabilitation programmes (Wykes et al., 2011).

It is also hoped that the nine treatment principles will form a bridge between abstract theoretical models and the concrete interventions carried out during sessions. Our approach combines models of cognitive remediation such as drill and practice aiming to strengthen cognitive performance as well as teaching meta-cognitive strategies aiming to compensate for cognitive function, whilst at the same time emphasising the process of therapy e.g. relationship building, goal setting, managing ambivalence etc.

In practical terms each session will involve practicing discrete cognitive functions identified by the MATRICS consensus cognitive battery (Nuechterlein et al., 2008) e.g. attention, working memory, verbal memory, visual memory, comprehension, problem solving and social cognition. A variety of pen and paper materials will be used to achieve this aim. A free open source version of the Dual N-back computer programme

(<http://brainworkshop.sourceforge.net>) will also be used to help patients develop and modulate their attentional resources in addition to their working memory (visual and spatial) and processing speed. Over the course of the intervention as patients make progress the cognitive remediation procedures will gradually increase in difficulty.

The cognitive remediation will be delivered by Masters' level Assistant Psychologists and the cognitive remediation support group will be delivered by multidisciplinary professionals including psychiatric registrars, occupational therapists and psychiatric nurses. All therapists contributing to the cognitive remediation programme will attend a three-day training course prior to delivering the intervention. All therapists will attend weekly supervision sessions where fidelity to the treatment principles will be actively monitored. Fidelity to the treatment will also be assessed by observing adherence to the nine treatment principles during randomly selected individual and group treatment sessions.

Treatment as usual

Participants in both conditions will receive treatment as usual from hospital clinicians. At a minimum, this will consist of antipsychotic pharmacotherapy and a therapeutically safe and secure environment appropriate to the individual patient's needs (Kennedy, 2007; Pillay et al., 2008) however most patients are expected to be involved in a range of therapies provided (Kennedy et al., 2010) by multidisciplinary team members, including psychiatrists, clinical psychologists, psychiatric nurses, occupational therapists and social workers (Kennedy et al., 2010).

Medication will be managed separately by the consultant psychiatrists responsible for the patients' care and may change over the duration of the study as required. Both antipsychotic dose and anticholinergic burden will be

measured at each assessment point as these may be important treatment moderators (Vinogradov et al., 2009).

The number of routine therapeutic hours each patient receives in the treatment as usual (control) and the cognitive remediation group will be recorded from patient's progress notes/ medical charts each week. A narrow definition of therapeutic activity will be applied to prevent over inclusion: a therapy will be defined as any activity that is occurring on a consistent or regular basis targeting specific goals and designed to address patients' forensic mental health needs. From this perspective regular occupational therapy, cognitive behavioural work, psycho-education, harmful behaviour programmes, substance misuse interventions, group programmes etc. would be defined as therapeutic activities, in contrast multidisciplinary team meetings, general interviews or assessments, physical exercise and general vocational or educational work will not be seen as therapies.

Assessment Battery

All assessors will complete a training programme prior to administering study related assessments. For assessments that require clinical judgment (e.g. symptom severity measures), assessors will observe a number of interviews carried out by an experienced consultant psychiatrist whilst simultaneously rating patients' performance. The inter-rater reliability of assessors will also be measured as part of the training programme for assessors. Primary and secondary outcome measures are presented in Table 4.2.

Primary outcome measure: change in global cognitive functioning

Cognitive functioning among study participants will be assessed at baseline, end of treatment (approximately 6 months) and 8 months follow up using the MATRICS Consensus Cognitive Battery (MCCB) global composite score (Nuechterlein et al. 2008). The MATRICS battery covers seven cognitive

domains: processing speed; attention/ vigilance; working memory; verbal learning; visual learning; reasoning and problem solving; social cognition assessed using social reasoning tasks for understanding and managing emotions taken from the Managing emotions subtest of the Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT) which is a social reasoning test. The test comprises of vignettes of various situations, and options for coping with the emotions depicted in these vignettes (Mayer et al., 2002; Mayer et al., 2003). Participants are required to indicate the effectiveness of each solution ranging from one (very ineffective) to five (very effective). In validation studies, and in antipsychotic trials of stable patients, the MATRICS demonstrated excellent reliability, minimal practice effects and significant correlations with measures of functional capacity. It is hypothesised that there will be a group by time interaction (CRT vs TAU) on the total score of the MATRICS battery at the end of treatment approximately 6 months and at 8 months follow up.

Table 4 2: Outcome Measures

Primary Outcome Measure	MATRICES Consensus Cognitive Battery Composite Score (MCCB)
Secondary Outcome Measure	MCCB Domain Scores Social Cognitive Assessments <ul style="list-style-type: none">• The Reading the Mind in the Eyes Test• The Faux Pas Recognition Test• The MSCEIT Social and Occupational Functioning Assessment Scale (SOFAS) Positive and Negative Syndrome Scale (PANSS) – negative and disorganised scales Clinical assessment interview for negative symptoms (CAINS) Historical Clinical Risk -20 (HCR-20) Dundrum Programme Completion Scale Dundrum Recovery Scale
Validity Checks	Rate of enrolment, rate of retention, rate of completion of primary outcome measures, success of blinding
Patient satisfaction survey	Service user developed interview.

Secondary Outcome Measures

Change in specific cognitive domains

The MATRICS battery will also be used to assess change in specific cognitive domains for study participants. The processing speed, attention/ vigilance, working memory, visual learning, verbal learning, reasoning/ problem solving and social cognitive domains of the MATRICS battery will all be used as secondary outcome measures. It is hypothesised that there will be a group (CRT vs TAU) by time interaction on the MATRICS domain scores at the end of treatment and eight month follow up (Nuechterlein et al., 2008)

Real World Functioning

Secondary outcome measures will include the Social and Occupational Functioning Assessment Scale (SOFAS; Rybarczyk et al., 2011). The SOFAS is a continuous scale (0–100) with verbal tethers so that higher scores represent superior functioning. It is similar to the Global Assessment of Functioning Scale however it does not include the severity of psychiatric symptoms. Again, it is hypothesised that there will be a group (CRT vs TAU) by time interaction at the end of treatment and eight months follow up.

Psychiatric Symptoms

Secondary outcome measures will also include the scores on the disorganised and negative symptoms scales from the five-factor Positive and Negative Syndrome Scale (PANSS) and the total score from the Clinical Assessment Interview for Negative Symptoms (CAINS) (Kay et al., 1987; Kring et al., 2013). The PANSS contains 30 items measuring psychopathology associated with schizophrenia, 7 items assess positive symptoms, seven items assessing negative symptoms and 16 items assess general psychopathology. A five-factor model of the PANSS will be used to evaluate outcomes because CRT is

thought to have a specific impact on negative and disorganised symptoms (Cella et al, 2014). The CAINS is a 13-item interview for measuring negative symptoms associated with schizophrenia. It contains 9 items for assessing problems

with motivation and pleasure and 4 items for assessing problems with emotional expression. Again, it is hypothesised that there will be a group (CRT vs TAU) by time interaction at the end of treatment and eight months follow up.

Violence Risk

Violence risk will be assessed with the Historical and Clinical Risk Management Scale 20 (HCR-20) a measure of violence risk, sometimes referred to as violence proneness (Webster et al., 1997). The HCR-20 is among the most widely used violence risk assessment schemes. The HCR-20 contains ten historical or static items, five current or clinical items and five future risk items. Both the clinical and risk items are thought to be dynamic in nature in that they can change over time and are amenable to therapeutic intervention. Because the historical items are static in nature only the dynamic items will be used as a secondary outcome measurement. Violence risk will only be measured at baseline and eight months follow up. Again, it is hypothesised that there will be a group (CRT vs TAU) by time interaction. The HCR-20 will be rated approximately every six months by the treating multidisciplinary team and researchers.

Programme Completion and Recovery

It is hoped that there will be differences between participants receiving CRT compared to TAU on their ability to benefit from additional psychosocial treatment programmes offered. Participant ability to benefit from additional psychosocial treatment will be assessed with the Dundrum-3 Programme

Completion scale rated by psychiatric registrars and by patients' multidisciplinary teams blind to the intervention (Kennedy et al., 2010). The Dundrum-3 is a structured clinical judgment instrument which assesses whether patients have participated in, engaged and benefited from psychosocial programmes and consists of seven items: physical health, mental health, drugs and alcohol, problem behaviours, self-care and activities of daily living, education occupation and creativity and family and social networks. Each item is rated on a five-point scale with lower scores representing a higher level of participation and engagement. Patient ability to recover within a forensic setting will be assessed with the Dundrum-4 Recovery Scales (Kennedy et al., 2010). The Dundrum 4 contains six items: stability, insight, therapeutic rapport, leave, dynamic risk and victim sensitivity. Similar to the DUNDRUM-3 Programme Completion Scale, each item of the DUNDRUM-3 is also rated on a five-point scale with lower scores representing greater progress towards recovery. The Dundrum-3 Programme Completion Scale has been shown to significantly distinguish between levels of security within a forensic setting and the Dundrum-4 Recovery Scale has been shown to distinguish those given unaccompanied leave outside of a secure forensic setting. Programme completion and recovery will only be measured at baseline and eight months follow up. Again, it is hypothesised that there will be a group (CRT vs TAU) by time interaction.

Patient satisfaction measure

An interview developed by service users will be used to explore patient satisfaction with cognitive remediation (Rose et al., 2008). The interview will inquire about the following areas: 1) task difficulty, 2) experience of sessions, 3) relationship with therapist and 4) impact of CRT on daily life. The interview will be administered by a social worker who will be independent of treatment and assessment teams, to the intervention and to other assessments. Patients

will be reassured that their responses will be anonymously recorded i.e. that their names will not be connected with the feedback they provide.

Feasibility measures

The feasibility outcomes include rate of enrolment, rate of retention, the success of blinding, and the number of patients who complete the primary outcome measures. psychiatric registrars and by patients' multidisciplinary teams blind to the intervention (Kennedy et al., 2010).

Proposed analysis

Data analysis will be carried out using an intention to treat methodology (Montori, 2001). Data from all enrolled participants will therefore be used in the analysis regardless of their level of participation in the study. Missing data will be estimated using multiple imputation (Ruben, 1987). The interaction between time i.e. baseline vs. 6 month and treatment condition (CRT vs TAU) on our primary outcome variable (MCCB composite cognition score) will be examined rather than between group differences, because tests of group difference average Time 1 (baseline) and Time 2 (6 month) assessments across the groups and consequently will be less sensitive to change. The interaction between time and treatment condition will be assessed using a repeated measure ANOVA with age and gender entered as covariates. This analysis will also be repeated at follow up using all three data points. An a priori estimate of statistical power was completed using G*Power 3.1 (Faul et al., 2010).

Assuming a correlation greater than or equal to .5 between baseline and 6-month MCCB composite and a medium effect size (i.e. $f = .25$), the power to detect a statistically significant interaction between time and treatment conditions (i.e. CRT vs TAU) is adequately powered i.e. greater than or equal to .80. Should we find a statistically significant time X treatment condition interaction, post-hoc probing of the interaction will be completed with

Bonferroni corrections applied where appropriate to maintain an alpha of 0.05. SPSS PROCESS Macro Model 4 will be used to explore mechanisms of action should we find a positive impact of CRT. For example, whether change in cognition leads to a change in functioning, or whether a change in negative symptoms leads to a change in functioning etc. Change score will be calculated by subtracting the scores at baseline from the scores following the intervention. Age and gender will be entered as covariates in all mediation analysis. Bootstrapping will be used to estimate indirect effects, and 95 % bias-corrected confidence intervals using 1,000 bootstrap samples will be applied. A confidence interval that does not contain zero indicates statistically significant mediation ($p < 0.05$).

4.4 Discussion

Forensic mental health services have a dual role in treating and caring for patients with mental disorders while also protecting the public from recidivist acts of violence. This study aims to address both of these goals by attempting to alleviate or ameliorate the likely common underlying deficits leading to functional impairment and violence.

Recently there has been a shift in emphasis within the field of schizophrenia research from focusing on positive symptoms such as delusions and hallucinations to patients' cognitive abilities and functional outcomes (Wunderink et al., 2013). Positive symptoms can be fairly successfully treated with medication however to date there is a lack of effective pharmacological treatments for cognitive difficulties and negative symptoms (Keefe et al., 2007; Leucht et al., 2012). It is these difficulties which are associated with patients' ability to function day to day (Keefe et al., 2007). Also, many risk factors for violence for mentally disordered patients concern suboptimal functioning.

CRT appears to be an effective intervention for community patients with schizophrenia for improving cognitive deficits (Wykes et al., 2011). There is also evidence that the cognitive improvements brought about by CRT lead to improvements in patient functioning. Because forensic mental health patients tend to be hospitalised for a longer duration than those in the community there is an unrealised opportunity to improve cognition and restore functioning within forensic services (Sharma et al. 2015). The results of the proposed study will help to answer the question whether cognitive remediation therapy is an effective intervention strategy for forensic mental health patients.

Specifically, it will test whether a nationally representative cohort of forensic mental health patients with schizophrenia or schizoaffective disorder benefit from cognitive remediation and whether patients are satisfied with the intervention.

A focus on cognition as a primary treatment target also has the potential to reduce violence risk in two ways. First it could help patients who are

cognitively impaired benefit from specialised psychosocial programmes targeting the risk of violence. Second it could improve general functional ability. By placing the emphasis on cognition and functional ability over symptoms any conflict between the two roles played by forensic mental health services could be reduced thus improving recovery and decreasing patients' length of stay.

Limitations

The protocol has some limitations. A weakness of the study is the lack of an active control group beyond treatment as usual (TAU). An additional weakness is that it will not be possible to keep medication constant for the duration of the study. The confined environment of a forensic hospital may also present fewer opportunities for practicing and applying cognitive skills. In a non-quantitative narrative review of over 100 psychological intervention studies it was estimated that extra-therapeutic factors such as the persons' social environment accounted for approximately 40 % of the variance of the outcome of interventions (Lambert and Barley, 2002). Forensic services almost by definition limit patients' freedom. And there can be conflict within forensic mental health services between safety and security on the one hand, and the provision of a therapeutic environment on the other. However, these disadvantages will be offset by the consistency of the daily milieu for the intervention and TAU groups, a consistency that cannot be achieved for groups living in the community.

Strengths

A major strength of the study is that CRT is being offered to a nationally representative cohort of forensic mental health patients with schizophrenia or schizoaffective disorder. The findings regarding efficacy and patient satisfaction will therefore inform whether CRT could or should be rolled out in

forensic mental health services across other jurisdictions. A second strength of the study is the large battery of outcome measures for assessing the efficacy of the intervention, evaluating domains of cognition, functioning, symptoms, programme completion, recovery and violence risk. Finally, the patients themselves will also play a role in assessing the usefulness of the intervention by participating in a confidential interview.

Trial Status

The trial is currently enrolling by invitation. Trial Registration: ClinicalTrials.gov Identifier: NCT02360813. First received: February 4, 2015.

Abbreviations

CRT: cognitive remediation therapy; HCR-20: Historical-Clinical-Risk Management-20; TOPF: test of premorbid functioning;

MATRICES: measurement and treatment research to improve cognition in schizophrenia; MCCB: MATRICES consensus cognitive battery; MSCEIT: Mayer-Salovey-Caruso emotional intelligence test; SOFAS: the social and occupational functioning assessment scale; PANSS: positive and negative syndrome scale; CAINS: clinical assessment interview for negative symptoms; MST: multi-systemic treatment; NFMHS: national forensic mental health service; CMH: Central Mental Hospital; CPZeq: chlorpromazine equivalents; SPSS-22: statistical package for the social sciences, version 22.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

KO'R originated the conception and design of the study and will perform the analysis and interpretation of the data, with substantial involvement also of GD and HGK. DO'S, CC, P O'C, RM, CM, P O'F, C'OC, all met the guidelines for authorship. All authors have read and approved the manuscript.

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5. Chapter 5: Empirical paper 3: A randomised controlled trial of cognitive remediation for a national cohort of forensic patients with schizophrenia or schizoaffective disorder.

This chapter describes and analyses the findings of the completed randomised controlled trial of cognitive remediation. The randomised controlled trial was published in BMC Psychiatry in 2019.-

O'Reilly, K., Donohoe, G., O'Sullivan, D., Coyle, C., Corvin, A., O'Flynn, P., O'Donnell, M., Galligan, T., O'Connell, P., Kennedy, H.G. (2018). A randomized controlled trial of cognitive remediation for a national cohort of forensic patients with schizophrenia or schizoaffective disorder. *BMC Psychiatry*. 19:27.

Research Question:

- The aim of this study was to determine if a cognitive remediation training (CRT) would be an effective and acceptable treatment for improving cognition and associated functional outcomes for a national forensic cohort of patients with schizophrenia or schizoaffective disorder.

5.1 Abstract

Background: Evidence is accumulating that Cognitive Remediation Training (CRT) is effective for ameliorating cognitive deficits experienced by patients with schizophrenia and accompanying functional impairment. There has been no randomized controlled trial of CRT using a nationally representative population of forensic patients, despite the significant cognitive deficits frequently present within this group.

Methods: 65 patients with schizophrenia or schizoaffective disorder were enrolled in a single blind randomized controlled trial of CRT versus treatment as usual (TAU); representing 94% of those eligible within a national forensic cohort. The primary outcome measure was the composite score of the MATRICS Consensus Cognitive Battery (MCCB). Secondary outcome measures included neurocognitive and social cognitive domains, symptoms, and 'real world' functioning. Patient satisfaction was examined using an exit interview. Participants were reassessed at eight months follow up. All data were analysed using an intention to treat design (ITT).

Results: For the primary outcome measure, the MCCB composite score, there were significant differences between those who participated in CRT and those receiving TAU at both end of treatment and eight months follow up (Cohen's $d=0.34$). Significant improvements were observed in visual and working memory. Mediation analysis found that those who cognitively benefited from CRT had corresponding improved functioning, and more net positive therapeutic moves i.e. moves to units with lower security within the hospital. Ninety-six percent believed their cognitive gains positively affected their daily lives.

Conclusions: CRT may be an acceptable and efficacious intervention for forensic patients with schizophrenia or schizoaffective disorder.

Trial Registration: ClinicalTrials.gov Identifier: NCT02360813. Trial registered Feb 4th, 2015, last updated May 1st 2015.

5.2 Introduction

Only one in seven patients with schizophrenia achieves functional and symptomatic remission sustained over time (Jääskeläinen et al., 2013). One explanation for the rate of recovery is the degree of cognitive impairment associated with the disorder (Kahn and Keefe, 2013). Approximately 85% of patients with schizophrenia experience cognitive impairment (Kontaxaki et al., 2014). The magnitude of cognitive impairment is particularly pronounced when measured using composite scores derived from instruments like the MATRICS Consensus Cognitive Battery (MCCB), which aggregate deficits across cognitive domains affected by the illness (Joyce, 2013; Kahn and Keefe, 2013). The development of the MCCB has also facilitated direct comparisons of groups of patients regarding the extent of their cognitive impairments (Nuechterlein and Green, 2006; O'Reilly et al. 2015). Within a sample of 2,616 stable patients participating in North American clinical trials the mean score on the MCCB was approximately 2.5 SD below the nonclinical mean (Georgiades et al., 2017). However, there may be groups of patients who are even more impaired. Forensic patients are detained under mental health legislation with histories of social dysfunction including violence and are often excluded from mainstream research on schizophrenia (O'Reilly et al., 2016). Amongst a national cohort of forensic patients, we found that the mean MCCB composite was more than 3 standard deviations (SD) below the nonclinical mean i.e. a level traditionally associated with moderate intellectual disability (O'Reilly et al., 2015). In line with systematic reviews of cognitive difficulties experienced by non-forensic patients, the cognitive impairments experienced by forensic patients are also associated with difficulties in 'real-life' functioning and impaired ability to benefit from psychosocial treatment programs (Green, 1996; O'Reilly et al., 2016; Richter et al. 2018). Addressing the cognitive impairments experienced by forensic patients is therefore an important objective (O'Reilly et al., 2016).

Cognitive remediation training (CRT) is a behaviorally based treatment for the cognitive deficits associated with schizophrenia. CRT purports to take

advantage of ‘neuroplasticity’ through a process of learning known as ‘drill and practice’, in addition to explicitly teaching meta-cognitive strategies (O’Reilly et al., 2016). For community patients, there is evidence that CRT is effective for ameliorating cognitive impairment and the associated functional difficulties. A meta-analysis of randomized controlled trials involving 2,104 participants found evidence of an effect size (Cohen’s *d*) of 0.44 on a composite measure of cognition and an effect size of 0.42 for ‘real world’ functioning (Wykes et al., 2011). There is also evidence that internet delivered cognitive training may be effective for some patients (Donohoe et al. 2018). In keeping with stage-based theories of illness, forensic patients may require different interventions due to the magnitude of their cognitive impairment and social dysfunction, and because of the forensic context in which treatment is offered (McGorry et al., 2014; O’Reilly et al., 2016). However, a modified form of CRT could be a particularly useful for this population. Specifically, within a forensic setting CRT may facilitate patients to assume the role of ‘customer’, in line with both research on the importance of goal consensus for the outcome of psychotherapy, and recovery theory (Wampold, 2015; O’Reilly et al., 2016). In contrast to many patients’ limited insight into their symptoms and violence risk (Davorn et al., 2015), patients with schizophrenia often have an awareness of their cognitive impairments and are willing to engage in treatment (Gilleen et al., 2011). Following successful completion of CRT forensic patients may be more likely to engage in programs targeting insight, substance misuse, and violence risk.

To date there has been limited investigation of the effectiveness of CRT for forensic patients (O’Reilly et al., 2016). Only two randomised controlled trails have been conducted (Taylor et al. 2016; Ahmed et al., 2015). One study (Taylor et al. 2016) investigated the feasibility of improving social cognition; the second study (Ahmed et al., 2015) mixed forensic patients with general mental health patients who were less cognitively impaired. Both trials reported cognitive gains. Neither of these studies adopted the use of a consensus measure of cognitive deficits such as the MCCB. Consequently, it is difficult

to estimate the overall degree of cognitive impairment experienced by the participants. It is therefore unknown whether existing studies generalise to forensic patients who may be more severely impaired (O'Reilly et al., 2016). This study seeks to address these gaps by testing the efficacy of CRT using a national representative cohort of forensic patients with schizophrenia or schizoaffective disorder. This study may be regarded as an effectiveness study and a robust evaluation of the transportability of CRT to a 'real-world' setting (Tunis et al., 2003; Marchand et al., 2011). Our model of CRT is outlined in detail within our study protocol and has been specifically developed for forensic patients (O'Reilly et al., 2016). We operationalized CRT using nine treatment principles (Table 5.1). We chose to adopt flexible principles rather than a tightly manualized format in keeping with the common factors model of psychological therapies (O'Reilly et al., 2016; Wampold, 2015; Gastonguay, 2006; McGuire, 2008; Henggeler et al. 1998) in order to be sensitive to working with forensic patients who have variable levels of ability and unique problems and needs.

Hypotheses

- That patients allocated to CRT would improve on the primary outcome measure, cognition at the end of treatment, and at eight months follow up.
- Patients allocated to CRT would improve on specific neurocognitive and social cognitive domains at end of treatment and eight months follow up.
- That patients allocated to CRT would experience improvements in negative and disorganised symptoms.
- That patients allocated to CRT would experience improvements in real world functioning, net moves to lower level of security, and that patients' functional improvements or moves to lower levels of security would be mediated by cognitive gains.
- That patients would experience CRT as a satisfactory and efficacious intervention.

Table 5.1: Principles guiding cognitive remediation intervention

Principle 1, Relationship Building: A major focus of each session is to prioritise the development of a strong therapeutic relationship. The therapeutic relationship will be strengthened by providing a credible rationale for participation, explicitly linking the cognitive remediation to patients' goals, promoting success experiences, making participation enjoyable, providing positive reinforcement, and managing ruptures, which may occur during the course of the intervention.

Principle 2, Collaborative Goal Setting: So as to promote 'buy in' patients will be encouraged to develop a series of short term, medium term, and long-term goals. Patients neuropsychological and risk assessments e.g. HCR-20, DUNDRUM toolkit, will be shared with patients to create a platform to develop goals. An explicit connection will also be drawn between cognitive difficulties and patients' aspirations. Short term goals may include having the concentration required to watch a TV programme or to read a book. Medium term goals may include patients' ability to self-medicate or move to a less secure unit. Long term goals may include returning to work and developing relationships outside the hospital.

Principle 3, Session Structure: Each session will begin with a mood check to establish rapport or identify problems followed by agenda setting, implementation of the agenda items, and summaries before moving to the next agenda item. The session will end by giving patients the opportunity to provide feedback.

Principle 4, Content of the sessions: The sequencing of interventions will be informed both by patients' goals and their unique strengths and vulnerabilities as documented by neuropsychological assessment. Cognitive domains at the start of the informational processing stream e.g. attention and vigilance, working memory etc will typically be prioritised over those occurring later e.g. comprehension and social problem solving. This is because difficulties associated with higher level cognitive processes may be a result of problems with more basic processes such as attention and memory. As patients demonstrate some improvement in core cognitive skills higher level domains will be targeted. Clinical judgement will be required to determine if patients achieve a basis level of mastery in certain cognitive domains or if a ceiling has been reached before progressing to more complex domains. CRT therapists should carefully assess whether patients are improving on core domains e.g. verbal memory etc., and if these improvements are being maintained over time.

Principle 5, Pacing: Therapists are encouraged to avoid trying to squeeze too much into each session or to work on too many problems simultaneously because it takes time to consolidate skills. In other words, patients need opportunities to repeat tasks again and again to improve performance, which is referred to as massed practice. Throughout the intervention each session should build on the next and be targeted at concrete goals. Patients should be provided with feedback on their progress towards goals. Newly acquired skills should not be abandoned once developed but refreshed during future sessions. Patients may also need breaks between tasks. This down time is a good opportunity to ask patients about their lives and to strengthen the therapeutic relationship.

Principle 6, Errorless Learning and Scaffolding: Task difficulty should be set so that patients obtain a high level of success on each task to avoid faulty learning and to enhance moral. Patients will be required to obtain a success rate of 80% before the cognitive demands of the task are increased. Where problems are encountered therapists should provide scaffolding and model successful completion of tasks.

Principle 7, Meta cognitive Strategies: A major focus of each session will be to explicitly teach patients meta-cognitive strategies which are somewhat independent of basic cognitive ability and can be flexibly applied across situations. Examples of meta-cognitive strategies include goal setting, visualisation, focusing on one thing at time, self-verbalisation, planning, breaking problems into parts, sequencing, chunking, advantage disadvantage analysis, perspective taking, monitoring performance, reflecting on performance etc. It is particularly important to explicitly model the effective use of meta cognitive strategies for patients. The effectiveness of strategies should be carefully assessed using a behavioural experiment framework. The use of particular strategies should be consolidated as evidenced by generalisation before additional meta-cognitive strategies are introduced. When mastery of basic strategies has been consolidated patients can be encouraged to simultaneously use multiple strategies.

Principle 8 Generalisation: Patients will be encouraged to utilise their cognitive skills outside of remediation sessions by participating in a support group. The focus of the support group will be helping patients to develop a shared understanding of the cognitive deficits associated with schizophrenia, to develop an awareness of how these deficits affect their lives, to identify situations where they can apply their cognitive skills, to obtain encouragement and support from other members of the group on how to implement these skills, to strengthen narratives where success has been achieved. In addition to the above positive group participation in and of itself may enhance cognitive processes as it requires patients to monitor their thoughts, reframe from interruptions, structure their contributions, and reflect on feedback.

Principle 9 Managing Ambivalence: Patients ambivalence towards participating should be met in a non-defensive empathic manner. Advantages and disadvantages of participating should be listed using pen and paper to ease the burden on working memory and to model effective problem solving. Patients should be gently reminded of their goals and their initial commitment to participate for the duration of the intervention. Ways of making the cognitive remediation more relevant or enjoyable should be actively explored.

5.3 Methods

Aim

This study aims to test the efficacy of cognitive remediation training (CRT) using a nationally representative cohort of forensic patients with schizophrenia or schizoaffective disorder.

Design

This study is a single blind randomized controlled trial of CRT versus treatment as usual (TAU) within a forensic setting.

Setting

The Republic of Ireland's National Forensic Mental Health Service (NFMHS) provides care and treatment for adults who have a mental disorder and are at risk of harming themselves or others. At the time of the study the NFMHS had 94 secure inpatient beds located on a single campus (The Central Mental Hospital, CMH). The CMH is the only medium and high secure forensic hospital for the Republic of Ireland, a population of 4.7 million (Flynn et al., 2011).

Participants

Criteria for inclusion in the trial were being a forensic inpatient with schizophrenia or schizoaffective disorder. The diagnosis of schizophrenia or schizoaffective disorder was established by a consultant psychiatrist using the Structured Clinical Interview for the Diagnostic and Statistical Manual IV (SCID-I) for axis I. Exclusion criteria were: being cared for on an acute unit, lacking capacity to consent, being too dangerous to participate in treatment (positive symptoms combined with aggressive or self-harming behavior in the

last month), or being over 65 years of age. Capacity to consent to participation was assessed by the treating consultant psychiatrist. Inclusion criteria were broad and exclusion criteria were minimal because we were primarily interested in investigating the effectiveness of CRT for a nationally representative cohort of forensic patients with schizophrenia or schizoaffective disorder. Sixty-nine patients met inclusion criteria, of whom 65 (95%) provided consent. The Test of Pre-morbid Functioning UK Edition (TOPF-UK) (Weschler, 2011) was used in combination with a developmental and educational history. None had a pre-morbid diagnosis of developmental intellectual disability and mean TOPF was within the normal range. All 65 patients who chose to participate had a history of violence and 46% had a history of homicide. Schizophrenia was the diagnosis for 50 (76%) and schizoaffective disorder for 15 (24%). DUNDRUM-1 mean item score was 2.9 (SD 0.46, range 2.2 to 3.8) in keeping with a medium secure level of need (Kennedy et al., 2010). The DUNDRUM-1 triage security instrument is a static assessment of the need for therapeutic security at the time of admission. Socio-demographic and baseline characteristics of all participants are presented in Table 5.2. Of note, this sample was particularly cognitively impaired with a mean MCCB t-score of 21, 3 SD lower than a nonclinical population mean. The mean Historical Clinical Risk Management version 2 score (Webster et al., 1997; HCR-20) score for the total sample was 26, SD 5.7.

Table 5.2:

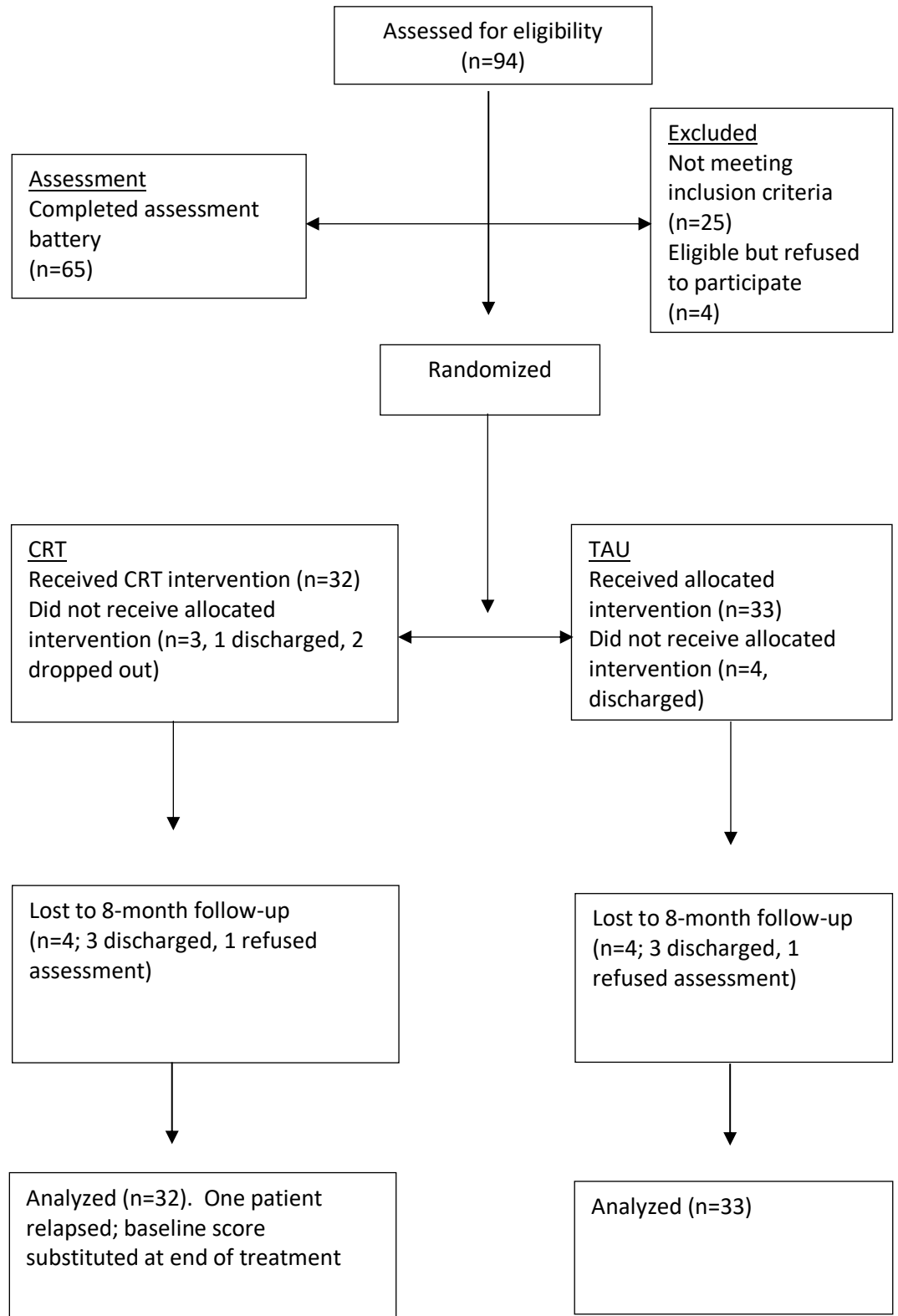
	TAU (N = 33)		CRT (N = 32)		T	Df	p
	Mean	SD	Mean	SD			
Male/ female	27/6		28/4				
Age	39.30	9.51	42.68	9.74	-1.41	63	0.16
NGRI/ other	18/15		19/13				
CPZeq	472.15	313.52	505.31	362.14	-0.39	63	0.69
ACB	4.09	2.59	3.40	2.49	1.08	63	0.28
MCCB Modified	31.97	9.53	33.19	8.33	-0.54	63	0.58
MCCB	20.30	14.80	22.18	13.61	-0.53	63	0.59
Speed of processing	25.45	14.31	25.65	13.47	-0.05	63	0.95
Working memory	32.09	12.70	32.68	13.96	-0.18	63	0.85
Verbal learning	34.69	7.93	35.71	7.89	-0.52	63	0.60
Visual learning	29.42	12.98	33.65	11.50	-1.38	63	0.17
Problem solving	33.21	8.64	36.43	8.90	-1.48	63	0.14
Social cognition (MSCEIT)	36.96	15.32	35.00	10.93	0.59	63	0.55
Eyes of the mind	20.56	7.62	20.96	5.10	-0.24	54.42	0.80
Faux Pas	38.84	17.25	46.34	11.65	-2.00	54.71	0.05
SOFAS	58.36	13.66	61.06	10.94	-0.87	63	0.38
PANSS Positive symptoms	9.90	5.03	9.65	4.51	0.21	63	0.83
PANSS Negative symptoms	17.09	6.55	15.37	5.54	1.13	63	0.25
PANSS Disorganization	10	4.37	9.68	4.11	0.29	63	0.76
PANSS Excitement	7.30	2.74	7.00	3.6	0.38	63	0.70
PANSS Emotional dysfunction	7.84	2.46	8.53	3.48	-0.91	63	0.36
DUNDRUM-1	2.84	0.52	3.02	0.40	-1.49	59.87	0.14
HCR-20	27.45	5.66	25.12	5.63	1.66	63	0.10
Male/ female Chi square 0.40, df = 1, p = 0.52, Age/ gender Chi square 0.15, df = 1, p = 0.69							

Randomization and treatment allocation

Following enrolment participants were randomized using SPSS V21 to CRT or a waiting list control group receiving treatment as usual (TAU). Figure 4.1 outlines patient allocation (CONSORT diagram). The research team was blinded to group allocation. The clinicians conducting the therapy sessions were different from the research team carrying out the assessments. All patients participating in the study were trained not to reveal their study condition prior to each assessment. Evaluators were tested for ability to ‘see through’ blinding at the end of the study and follow-up. For clinical reasons patient participation in CRT was shared with their treating psychiatrist.

After randomization, 29 (88%) of 33 patients in the control group met criteria for schizophrenia and 4 (12%) for schizoaffective disorder, while in the intervention group 21 (66%) met criteria for schizophrenia and 11 (34%) for schizoaffective disorder. However, the two groups did not differ significantly for any measure of neurocognitive or social cognitive ability, symptom severity or functional ability (TABLE 5.2). A further sensitivity analysis showed that two groups defined by diagnosis (schizophrenia and schizoaffective disorder) did not differ significantly in any of the variables shown in Table 5.2.

Figure 5.1. CONSORT Flow Diagram.



Cognitive remediation training

CRT is designed to improve cognitive problems associated with schizophrenia and schizoaffective disorder (Wykes et al., 2011). Our cognitive remediation training is a principle driven intervention consisting of nine treatment principles, which are flexibly applied during delivery of the intervention (O'Reilly et al., 2016; Table 5.1). Principle driven approaches are in keeping with the recommendations of a task force on Principles of Therapeutic Change that Work, sponsored by the American Psychological Association and the North American Society for Psychotherapy Research (Gastonguay, 2006) and are also in keeping with a review of effectiveness and common factors (Wampold, 2015). Psychotherapy principle driven approaches integrate research concerning empirically supported treatments (EST) with research concerning the moderating influence of the therapeutic relationship (Wampold, 2015; Gastonguay and Beutler, 2006; Henggeler, 1998). Patients allocated to CRT received three individual sessions a week and one group session for approximately 14 weeks, 56 sessions in total. Most therapists were masters level psychologists, two therapists were psychiatrists, and another was an occupational therapist. Our CRT program has been extensively described in the study protocol and consisted of a combination of pen and paper and computerized materials (O'Reilly et al., 2016). Fidelity to the CRT principles was routinely assessed by randomly observing CRT therapists and by weekly supervision.

Treatment as usual TAU

Participants in both conditions received TAU from hospital clinicians. At a minimum, this consisted of antipsychotic pharmacotherapy and a therapeutically safe and secure environment appropriate to the individual patient's needs (Richter et al. 2018; Flynn et al., 2011; Kennedy et al., 2010; Kennedy, 2002; Davoren, 2013). The system for delivering 'treatment as usual' has been described and shown to be effective in reducing a measure of

violence proneness, the HCR-20 (Richter et al., 2018). This draws on principles of multi-modal treatment (McGuire, 2008) and multi-systemic treatment (Henggeler et al., 1998). Most patients were expected to be involved in a range of therapies. These interventions are organized under seven pillars of care that may be regarded as treatment as usual within a forensic setting: physical health, mental health, drugs and alcohol, problem behaviors, independent living, education-occupation-creativity, and family relationships (Kennedy et al., 2010; Davoren et al., 2013). Medication was managed by psychiatrists responsible for the patients' care. Antipsychotic dose CPZeq and anticholinergic burden ACB were measured at each assessment point (O'Reilly et al., 2016).

Primary outcome measure: change in global cognitive functioning at end of treatment

Cognitive functioning among study participants was assessed at baseline and end of treatment using the MATRICS Consensus Cognitive Battery (MCCB) global composite score Battery (Nuechterlein, 2006). The MATRICS battery covers seven cognitive domains: processing speed; attention/ vigilance; working memory; verbal learning; visual learning; reasoning and problem solving; and social cognition. Like other cognitive remediation trials, we had trouble with the attentional-vigilance domain of the MCCB which is measured using a Continuous Performance Test (Fisher et al., 2009). The Continuous Performance Test is administered via computer and because of technical difficulties during the trial we excluded this task from our composite score. Consequently, the MCCB composite was created by averaging the scores over all other domains. In keeping with the recommendations in the MCCB manual we used age and gender corrected scores (Nuechterlein and Green, 2006).

Secondary outcome measures

Cognitive functioning was also assessed at eight months follow up using the MCCB composite.

Change in specific cognitive domains

The processing speed, working memory, visual learning, verbal learning, reasoning/ problem solving and social cognitive domains of the MCCB were used as secondary outcome measures.

Social cognitive measures

Changes in social cognition were assessed using the Managing Emotions subtests of the Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT) contained within the MCCB (MSCEIT; Mayer et al., 2003). This was supplemented with the Reading the Mind in the Eyes Test (Baron-Cohen et al., 2001) and the Faux Pas Recognition Test (Stone et al., 1998).

Psychiatric symptoms

A five-factor model of the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) consisting of positive, negative, disorganized, excitement and emotional dysfunction was used to evaluate outcomes because CRT is thought to have a specific impact on negative and disorganized symptoms (Cella et al., 2014).

Real world functioning

The Social and Occupational Functioning Assessment Scale (SOFAS) was used to assess real world functioning (Goldman et al., 1992) (DSM-IV-TR

2000, 4th ed). Higher scores representing superior functioning. The SOFAS was completed by a member of the treating MDT as they were judged best placed to rate the patients functioning.

Positive moves from more secure to less secure units or discharge to community services

Patients at the CMH are stratified according to level of therapeutic security (Kennedy, 2002; Pillay et al. 2008). Patients are moved from more secure wards to less secure wards and eventually to the community as they progress along the recovery pathway. The placements correspond to levels of risk, symptom severity, and the patient's overall level of functioning. A positive move represented transfer from a higher to a lower level of security. A negative move represented a transfer from a lower to higher level of security. The net number of positive moves that occurred during the trial was summed for each patient over the duration of the study i.e. at 8 months follow up. For the male patients five positive moves separate the acute unit from living in the community. For female patients who reside on a mixed ward with acute and stable patients one positive move separates them from the community.

Patient satisfaction measure

A service-user developed interview for evaluating patient experience of CRT was used to explore patient satisfaction with the intervention (Rose et al., 2008). The interview was administered at the end of treatment by a social worker who was independent of treatment and assessment teams and blind to the intervention and to other assessments. Patients were reassured that all responses were anonymously recorded i.e. that their names were not connected with the feedback they provided.

Statistical analysis

Data analysis was carried out using intention to treat methodology (ITT) (Montori and Guyatt, 2001). Data from all enrolled participants was used in the analysis regardless of participants' level of participation in the study using last observation carried forward. The ITT methodology was also utilized at the 8 months follow up to detect whether patients continued to benefit from participating in CRT. All data were analyzed using SPSS V 21. One patient who participated in CRT relapsed at the end of treatment. A decision was made to substitute this patient's data from baseline for the patient's end of treatment analysis in keeping with the ITT methodology.

ANOVA and chi-squared tests were used to examine baseline differences between CRT and TAU groups following randomization. At the end of treatment and at 8 months follow up ANCOVAs were carried out in which performance for the outcome of interest i.e. primary and secondary outcomes, was entered as the dependent variable, group (CRT or TAU) as independent variable, and baseline performance on the dependent variable was entered as covariate.

Three mediation analyses were also carried out in line with the study protocol. This was to clarify whether changes in cognition associated with CRT were linked to 'real world' functional outcomes including being moved to a unit with a lower level of security i.e. whether changes in cognition were associated with functional change. Mediation analyses were conducted using Hayes's SPSS PROCESS Macro Model 4 (Hayes, 2013). Bootstrapping (10,000 bootstrap samples) was used with 95% bias corrected confidence intervals were applied. In the first mediation analysis, (Table 5.4 model A) the dichotomous variable CRT vs TAU was the independent variable, real world functioning (SOFAS at end of treatment) was the dependent variable, and neurocognitive functioning (MCCB composite at end of treatment; primary outcome) was the mediating variable. For the second mediation analysis CRT vs TAU was the independent variable, MCCB at eight months follow up

(secondary outcome) was the mediator, and 'real world' functioning (SOFAS at eight months follow up), was the dependent variable (Table 5.4, model B). Baseline MCCB and baseline SOFAS were entered as covariates for both analyses. For the third mediation analysis (Table 5.4 model C) CRT vs TAU was the independent variable, net positive moves over the course of the study i.e. at 8 months follow up, was the dependent variable and neurocognitive functioning (MCCB composite at end of treatment; primary outcome) was the mediation variable to explore the impact that CRT vs TAU had on net positive moves over the course of the study. Because moves occurred throughout the study the MCCB at the end of treatment was entered at the mediator rather than the MCCB at 8 months follow up. Baseline MCCB and gender were entered as covariates for mediation analyses.

5.4 Results

At the end of treatment 29 patients remained in the CRT group (90%) and twenty-eight patients remained in the TAU group (85%). At 8 months follow up 25 patients remained in both groups (78% and 76%). Table 3.

Primary cognitive outcome measures at end of treatment, and outcome at 8 months follow up.

Differences in MCCB composite scores were compared between the CRT and TAU groups at both end of treatment (primary outcome) and 8-month follow up, using ANCOVAs co-varying for baseline MCCB composite performance. A significant difference in favor of CRT was observed on the MCCB composite at end of treatment (Cohen's $d=0.34$). This difference in favor of CRT for the MCCB composite remained significant at 8 months follow up (Cohen's $d=0.34$) (Table 5.3).

Secondary cognitive outcome measures at end of treatment and 8 months follow up.

Significant differences were found between CRT and TAU for the MCCB domains of working memory and visual memory at end of treatment; cognitive improvements were not solely attributable to change in the MCCB composite. At 8 months follow up the difference between CRT and TAU was at trend level for working memory, however, the significant difference for visual learning was maintained. There were no significant differences between the other neurocognitive domains at end of treatment or at 8 months follow up (Table 5.3).

Table 5.3: Outcome measures comparing three time points, baseline, end of treatment period and eight months follow-up after treatment.

Outcome measures	TAU (N=33)						CRT (N=32)						Post			Follow up (8 months)		
	Baseline		Post		Follow up		Baseline		Post		Follow up		F	p	d	F	p	d
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD						
MCCB modified	31.97	9.53	33.00	9.84	33.14	10.25	33.19	8.33	36.10	8.23	36.35	8.13	4.78	0.03	0.34	4.04	0.04	0.34
Speed of processing	25.45	14.31	26.72	14.11	28.93	17.01	25.65	13.47	28.93	14.17	31.21	14.67	1.49	0.22	0.15	1.41	0.29	0.14
Working memory	32.09	12.70	32	12.9	32.45	13.20	32.68	13.96	36.43	14.5	36.53	12.57	6.67	0.01	0.32	3.90	0.05	0.31
Verbal learning	34.69	7.93	34.33	8.38	35.24	7.98	35.71	7.89	36.53	8.78	38.25	8.22	0.82	0.36	0.25	2.24	0.13	0.37
Visual learning	29.42	12.98	31.63	14.15	30.18	12.26	33.65	11.50	41.25	11.37	37.78	11.91	8.82	0.00	0.79	4.61	0.03	0.62
Problem solving	33.21	8.64	35.03	9.06	34.93	9.15	36.43	8.90	35.75	8.82	36.71	7.98	0.93	0.33	0.08	0.01	0.86	0.20
Social cognition (MSCEIT)	36.96	15.32	38.30	12.81	37.09	14.79	35.00	10.93	37.71	10.77	37.56	10.85	0.06	0.80	0.04	0.95	0.33	0.03
Reading the mind in the eyes test	20.56	7.62	21.59	7.10	21.77	7.68	20.96	5.10	22.36	5.36	22.03	5.06	0.23	0.63	0.12	0.08	0.77	0.01
Faux pas recognition test	38.84	17.25	41.12	14.90	42.48	15.39	46.34	11.65	48.10	12.44	48.62	10.14	0.84	0.36	0.50	0.50	0.48	0.47
SOFAS	58.36	13.66	60.45	14.96	61.81	14.52	61.06	10.94	62.62	12.49	62.03	11.87	0.01	0.90	0.16	0.36	0.54	0.01
Net positive moves	-	-	-	-	.515	.939	-	-	-	-	0.59	0.75	-	-	-	0.10	0.74	0.09
PANSS positive	9.90	5.03	9.42	4.28	9.39	4.77	9.65	4.51	9.15	4.75	8.43	4.92	0.01	0.90	0.05	0.91	0.34	0.19
PANSS Negative	17.09	6.55	15.45	6.09	14.48	6.10	15.37	5.54	15.50	7.24	14.65	7.11	1.34	0.25	0.00	1.03	0.31	0.02
PANSS disorganisation	10.00	4.37	9.24	3.45	9.12	3.28	9.68	4.11	9.03	4.03	9.03	3.76	0.00	0.99	0.05	0.02	0.87	0.02
PANSS excitement	7.30	2.74	6.60	2.96	6.21	2.79	7.00	3.6	7.40	3.61	7.18	3.43	3.29	0.07	0.24	4.09	0.04	0.31
PANSS negative emotions	17.09	6.55	8.18	4.41	7.27	2.41	15.37	5.54	7.78	2.76	7.68	2.65	1.09	0.29	0.10	0.12	0.72	0.16

Social cognitive outcome measures at end of treatment and 8 months follow up.

There were no significant differences in the MCCB social cognition task at end of treatment or 8 months follow up. The general cognitive differences that were observed occurred in the absence of any changes in social cognition.

Symptom measures

There was no significant difference in any of the PANSS factors at end of treatment. At 8 months follow up a significant difference was found in favor of the TAU group for the PANSS excitement factor. There were no significant differences between the CRT and TAU groups for any other PANSS factors.

Functioning measures.

There were no significant overall differences in the SOFAS scores at end of treatment or 8 months follow up, before mediation analysis.

Positive moves from more secure to less secure units or discharge to community services

There was no overall significant difference before mediation analysis in the number of net positive moves for the CRT group compared to the TAU group at 8 months follow up (Table 5.3).

Mediation analyses

In model A, neurocognitive function (MCCB composite at end of treatment) mediated the relationship between CRT and ‘real-world’ functioning (SOFAS) at end of treatment (Table 5.4) when controlling for baseline MCCB and

baseline SOFAS. Improved cognition associated with CRT was associated with improved 'real world' functioning. For every one-unit increase in MCCB score associated with participating in CRT there was an increase of 1.60 points on the SOFAS. However, this association did not reach statistical significance at 8 months follow up (Model B) (Table 5.4).

Participating in CRT and the net number of positive therapeutic moves by end of the study i.e. the 8 months follow up period, was also mediated by neurocognitive function as measured by the MCCB at the end of treatment, when controlling for baseline MCCB and gender (Model C). Those patients who participated in CRT and who benefited cognitively made more positive moves to lower levels of security within the hospital. For every one-unit increase in cognition associated with CRT there was an increase of 0.15 for the number of positive moves through the hospital (Table 5.4).

Patient experience of CRT

Twenty-seven of twenty-eight patients who remained in CRT participated in an anonymous interview evaluating patients' experience of CRT (Rose et al., 2008). One refused to participate, and one was discharged. Nearly all reported subjective improvements in cognition (96%) with most feeling the change was maintained at follow up (85%). Twenty-eight percent believed the change would last, 24% said it would change over time, and 24% said that if they did not practice their skills improvements would deteriorate. Ninety-six percent believed the cognitive gains they experienced had positively affected their daily lives. Subjective improvements were noted in a) social interaction, for example decreased interruptions and improving conversational skills; b) engagement in activities, for example participating in other psychosocial treatments; c) working with clinicians, for example remembering the content of multidisciplinary meetings; d) community functioning. Ninety-six percent said that participating had led to positive feelings about themselves and a sense of

achievement or confidence. Patients reported that their experience of the relationship with the CRT therapists was important to them (89%). A minority noted aspects that they disliked. Seven mentioned disliking specific tasks (26%). A small number reported anxiety during tasks (7%), some disliked the repetitive nature of sessions (7%). One (4%) disliked the time commitment and tiredness they experienced after sessions. Most said that participating made them aware of their limitations and provided them with insight into their cognitive difficulties (89%). Finally, 26% reported a sense of loss when CRT ended.

Table 5 4: Hayes process mediation model 4: Regression and mediation coefficients

	Change in Y		C1: direct effect of X on Y before mediation		C2: direct effect of X on Y after mediation		A: indirect effect of X on Y mediated via M		B: direct effect of M on Y adjusted for X	
	R^2	p	Unstandardized effect size	95% CI	Unstandardized effect size	95% CI	Unstandardized effect size	95% CI	Unstandardized effect size	95% CI
Model A										
$n = 69$	0.49	.000	0.49	-4.69, 5.68	-1.10	-6.27, 4.05	1.60	0.12, 4.21	0.88	0.16, 1.60
X = Group M = MCCBT1										
Model B										
X = Group M = MCCBT2	0.45	.000	-1.81	-6.83, 3.20	-2.39	-7.55, 2.77	0.55	-0.23, 2.63	0.30	-0.32, 0.93
Model C										
X = Group M = MCCBT1	0.12	0.04	0.06	-0.36, 0.48	-0.08	-0.50, 0.33	0.15	0.02, 0.38	0.07	0.02, 0.13

5.5 Discussion

The primary aim of this study was to test the effectiveness of CRT within a ‘real world’ population of forensic mental health patients experiencing severe cognitive impairment. The mean score for the forensic patients who enrolled in this study was approximately three standard deviations lower than a nonclinical mean as assessed using the MCCB composite. We were also interested in the acceptability of CRT and patients’ experience of the intervention. Five main outcomes were observed. First, patients who participated in CRT obtained significant improvements in the primary outcome measure, a composite score of the MCCB both at end of treatment and at eight months follow up. Second, there were significant improvements in specific cognitive domains including working and visual memory, but not social cognition. Third, there were no significant differences in symptoms (PANSS) apart from a difference in favor of the control group in the PANSS excitement factor. Fourth, there were no significant differences between CRT and TAU on routine measures of ‘real world’ functioning ascertained by the multidisciplinary team (SOFAS) or net positive moves. However, mediation analysis revealed that those who benefited neurocognitively from CRT had related improvement in functioning at the end of treatment (SOFAS); and more net positive therapeutic moves at follow up; there were meaningful functional gains associated with CRT but these gains were predicated on having improved measures of cognitive function. Conversely, those who received CRT but did not have improved cognitive function failed to make ‘real world’ functional gains. Fifth, the patients who were randomly assigned to CRT appeared to value the intervention. Ninety-six percent reported that their subjective neurocognitive ability had improved because of participating in CRT. Importantly 96% percent reported that the cognitive gains they achieved had positively affected their daily lives.

This study contributes to a body of work suggesting that CRT is an effective intervention for patients with schizophrenia or schizoaffective disorder, improving both cognitive and functional outcomes (Wykes et al., 2011; Taylor

et al., 2016; Ahmed et al. 2015). Although over 40 studies have been conducted, this study overcomes a potential weakness associated with randomized controlled trials namely selection bias (Tunis et al., 2003; Marchand et al., 2011). Those who participate in trials may not always be representative of the general population of patients. We believe this study demonstrates ecological validity because of the magnitude of cognitive impairment within the group, and of the sixty-nine patients who met the inclusion criteria in this national service, 65 agreed to take part representing a 94% uptake of those eligible to participate. This study also casts light on the mechanism of action of CRT using mediation analysis. Cognitive improvements associated with CRT were also associated with 'real world' functional improvements such as being moving to a unit with a lower level of security. CRT may have the potential to reduce length of stay in secure settings and create savings for services (Reeder et al., 2014).

We controlled for baseline cognition and baseline SOFAS and showed non-the-less that improved cognition associated with CRT was associated with improved 'real world' function (SOFAS). We also showed that when controlling for baseline MCCB and for gender, positive moves was non-the-less associated with improved neurocognition associated with CRT. It may be taken from this that baseline MCCB, SOFAS and gender were not predictors of response to CRT. To clarify the predictors of positive response however would require formal dismantling studies (Borkovec et al., 1998; Bell et al., 2013).

To date there have only been a small number of RCTs evaluating the effectiveness of psychological interventions within forensic mental health settings (O'Reilly et al., 2016; Cullen et al., 2012), and there has been an even smaller number evaluating CRT (Taylor et al. 2016; Ahmed et al., 2015). This may arise from the misconception that interventions which are efficacious in community settings will be equally effective within forensic settings despite patients being legally detained and potentially more impaired (O'Reilly et al., 2015; O'Reilly et al., 2016). Forensic services typically have a legally defined dual role requiring care and treatment and in addition public protection

(O'Reilly et al., 2016). Both roles may not always be aligned and in these cases, it is society and not the patient who is the 'customer', which is likely to affect engagement (O'Reilly et al., 2016). This study demonstrates that CRT has the potential to improve cognitive functioning for forensic patients in addition to helping patients adopt the role of 'customer' (O'Reilly et al., 2016). The forensic patients' response to participating in CRT is particularly striking with the majority of patients regarding the intervention positively. Patients' positive attitudes towards CRT are likely to be a result of our nine treatment principles, which emphasise the therapeutic relationship, and common factors associated with psychological interventions (Wampold, 2015). CRT may therefore play a useful role by engaging patients to participate in challenging psychological interventions like working on refractory symptoms, violence risk, substance misuse difficulties and pro-social attitudes.

There are limitations and strengths associated with this study. The primary limitation was the numbers of forensic patients available nationally. A robust evaluation of the effectiveness of CRT within forensic services will require a multicentre study involving international collaboration. A strength of this study is that it paves the way for such initiatives. Additional limitations were that medication could not be kept constant during the study, and the absence of an active control group. Additional strengths include having an appropriate dose of therapy (Richter et al., 2018; Wykes et al., 2011), the wide range of secondary outcome measures, and the ITT design.

Conclusion

CRT is an effective intervention for patient groups with schizophrenia experiencing severe cognitive impairments. Those who received CRT demonstrated improved global cognitive performance at the end of treatment and follow up. The high uptake of patients willing to participate, and the positive feedback received suggests that patients' regarded CRT as an acceptable and valued intervention.

Abbreviations

MCCB: MATRICS Consensus Cognitive Battery; SD: Standard Deviation. CRT: Cognitive Remediation training; TAU: treatment as usual; NFMHS: National Forensic Mental Health Service. CMH: Central Mental Hospital. SCID: Structured Clinical Interview for the Diagnostic and Statistical Manual IV (SCID). DUNDRUM-1: Dangerousness, Understanding, Recovery and Urgency Manual (The Dundrum Quartet); Historical Clinical Risk Management, Version 2: HCR-20; SPSS: Statistical Package for the Social Sciences; CONSORT: Consolidated Standards of Reporting Trials; CPZeq: chlorpromazine equivalent; ACB: anticholinergic burden; MSCEIT: Mayer-Salovey-Caruso Emotional Intelligence Test; SOFAS: The social and occupational functioning assessment scale; PANSS: positive and negative syndrome scale; ITT: intention to treat; ANOVA: analysis of variance: 95 % CI: 95 percent confidence interval.

Declarations

Ethics approval and consent to participate

This study was approved by the research ethics and effectiveness committee of the NFMHS (AREE/290814, 29th August 2014) and Faculty of Health Sciences Research Ethics committee Trinity College Dublin (8th September 2014). The study complied with the Helsinki Declaration of 1975, revised in 2008. All participants were assessed by their treating consultant psychiatrists as having the capacity to consent to the research study. All participants were supplied with a written letter of information concerning the study. After a period of seven days, all gave written, informed, and competent consent in keeping with the approval of the research ethics committees.

Consent for publication: This manuscript does not contain any individual person's data which could be readily identifiable in any form (including any

individual details, images or videos) i.e. no individually identifiable material was included. And all patients gave consent to publish the studies findings.

Availability of data and material

Because of the sensitive nature of the patients' situation, data is not publicly available but is available from the first author on reasonable request.

Competing interests: All authors declare that they have no financial involvement (including employment, fees, share ownership) or affiliation with any organization whose financial interests may be affected by material in the manuscript, or which might potentially bias it. HGK is a member of the editorial board of BMC Psychiatry but has had no editorial involvement with the publication of this article.

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each author has agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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6. Chapter 6: Conclusion and Future Directions

This final chapter reviews the thesis in its entirety presenting a summary of the findings and highlighting how they make unique contributions to the fields of forensic mental health and mental health more generally. Each study is linked with existing theories and knowledge thus explaining how they progress the field. The strengths and limitations of each study are also reviewed. Taking a prophetic glance to the future this chapter outlines the many ways that a focus on cognition will lead to changes in care and treatment for forensic patients with schizophrenia or schizoaffective disorder. The chapter concludes by listing some of the innovations concerning care and treatment, which have occurred at Ireland's National Forensic Mental Health Service and at our Central Mental Hospital, arising out of this PhD thesis.

The overall aim of this thesis was to determine the importance of cognitive impairment for forensic mental health patients with schizophrenia or schizoaffective disorder. Within academic mainstream psychiatric literature, it has been known for some time that the cognitive impairments experienced by patients with schizophrenia or schizoaffective disorder are important for functional outcomes (Green et al., 2003; Kahn and Keefe, 2013). However, even within the general psychiatric field the importance of cognitive impairments for those suffering with schizophrenia or schizoaffective disorder appears to have been underappreciated (Kahn and Keefe, 2013). It is now known that cognitive impairment is a risk factor for schizophrenia and schizoaffective disorder, and that cognitive impairment can be observed many years prior to the onset of psychosis, and that cognitive impairment contributes to more of the variance of 'real world' functional outcome when compared to psychiatric symptoms – perhaps because symptoms can be treated with anti-psychotic medication (Kahn and Keefe, 2013). The importance of these impairments in information processing, which are resistant to anti-psychotic medication, has led to a call for schizophrenia to be reclassified or reconceptualised as a cognitive rather than psychotic disorder (Kahn and

Keefe, 2013). Moreover, it has been argued that the scientific and clinical communities' continued emphasis on psychotic symptoms over cognitive impairments explains the lack of progress in the treatment of schizophrenia for the past fifty years (Kahn and Keefe, 2013).

In contrast to the general academic psychiatric literature, within the field of forensic mental health the importance of cognitive impairment experienced by patients with schizophrenia or schizoaffective disorder has scarcely been examined. At the time of the publication of the empirical studies contained within this thesis very little work had been done in this area. In addition to the lack of scientific research on the topic, the cognitive impairments experienced by patients with schizophrenia or schizoaffective disorder are often masked by preserved verbal intelligence causing clinicians, managers and policy makers to grossly underappreciate their importance (Keefe, 1995; Aylward et al. 1984). Understanding the role played by cognitive impairment experienced by patients with schizophrenia or schizoaffective disorder and whether the magnitude of impairment can at least be partially ameliorated, is of crucial importance given the rise of forensic beds internationally (de Tribolet-Hardy and Habermeyer, 2016). Unless the problem of cognitive impairment can be acknowledged and addressed it is likely that asylums of the past will become the forensic hospitals of the future, although governed by more robust human rights legislation.

This PhD thesis facilitates the understanding of cognitive impairment experienced by forensic patients with schizophrenia or schizoaffective disorder in two ways. First, by investigating the prevalence of cognitive impairments within a national forensic cohort, in addition to determining the relevance of cognitive impairment for violence risk, 'real world' functioning, and treatment progression. Second, the thesis explored what could be done to potentially improve the cognitive impairments experienced by this population, which included recognising the possible iatrogenic role played by anticholinergic burden and participating in cognitive remediation training (CRT). Moreover, the effectiveness of CRT in a 'real world' setting was robustly evaluated using

an intention to treat (ITT) randomised controlled trial (RCT). To date only two randomised controlled trials of CRT have occurred within a forensic mental health setting, one of which mixed forensic with non-forensic patients thus potentially obscuring the benefit for forensic patients, whilst the second was a pilot study focusing on social cognition (Taylor et al., 2015; Ahmed et al., 2015).

In collaboration with my supervisors, Professor Gary Donohoe (School of psychology, National University of Ireland Galway, who at the time of commencement was employed by the Department of Psychiatry, Trinity College Dublin), and Professor Harry Kennedy (Department of Psychiatry, Trinity College Dublin and Executive Clinical Director of the National Forensic Mental Health Service), I designed the studies, selected appropriate tests for the assessment batteries, sought ethical approval, registered the RCT, researched and developed the therapy content – or principles of cognitive remediation, supervised the delivery of the therapy, and carried out coding and statistical analysis for all empirical studies, and wrote the first and final draft of all articles.

This PhD project consists of four main components – 1) a twelve month prospective cohort study investigating the relationship between neurocognition, social cognition and violence for a national forensic cohort of patients with schizophrenia or schizoaffective disorder – 2) a three year prospective cohort study examining the association between anticholinergic burden, cognitive impairment and ability to benefit from psychosocial treatment programmes associated with treatment progression within a forensic hospital – 3) a study protocol describing the rationale for delivering a cognitive remediation study for forensic mental health patients with schizophrenia or schizoaffective disorder, in addition to describing the principles informing the CRT intervention and also the intention to treat (ITT) RCT design – 4) the RCT which occurred over a two year period evaluating the effectiveness of CRT. Each empirical study therefore evaluated several original research questions which will now be summarised.

6.1 Chapter Two: Empirical paper 1: Prospective cohort study of the relationship between neuro-cognition, social cognition and violence in forensic patients with schizophrenia and schizoaffective disorder

This study's aim was to clarify the mean level of cognitive impairment experienced by forensic patients and to establish if cognitive impairment was a determinant of reactive unplanned violence. Although not a core diagnostic feature of schizophrenia or schizoaffective disorder (American Psychiatric Association, 2013; WHO, 1993) many patients experience cognitive impairment (Kahn and Keefe, 2013). Both neuro-cognitive and social cognitive impairments are a major source of disability for patients with schizophrenia and schizoaffective disorder and account for more of the variance of functional outcome than symptoms such as delusions and hallucinations (Kahn and Keefe, 2013). The cognitive impairments associated with these disorders may be relevant for some kinds of violence carried out by some patients (Foster, et al., 1993; Krakowski and Czobor, 2012; Nazmie et al., 2013; O'Reilly et al., 2015). Crucially, the violence acts carried out by patients with schizophrenia or schizoaffective disorder are associated with the same risk factors for violence in general (Tengstrom et al., 2001; Erb et al., 2001; Large et al., 2009). Violence risk assessment schemes take advantage of this and include many equally weighted items not specific to psychotic disorders but are associated with sub-optimal functioning (Webster et al., 1997; Risk management authority of Scotland, 2008). It is likely that the cognitive impairments experienced by many patients with schizophrenia or schizoaffective disorder underpin some of the functional difficulties associated with violence risk.

Cognitive impairment has also been found to be associated with violence in a range of other populations including those with brain injury, delinquency, and intellectual disability (Fazel et al, 2011; Farrington and Welch, 2007; Holland et al., 2002). Findings from the schizophrenia and violence literature however are harder to interpret and the field has produced some contradictory or conflicting findings with some studies suggesting a relationship whereas others

do not (Witt et al., 2013). For mental disorders like schizophrenia or schizoaffective disorder the role played by cognitive impairments for acts of violence may be obscured by focusing on the presence of symptoms such as delusions (Taylor, 1985; Taylor, 1993; Taylor, 1998; Appelbaum et al., 2000), without considering a person's reasoning and judgment within the psychotic state. It is therefore possible that there may be an interaction between untreated delusions and cognitive impairment, which would be consistent with the hypothesis that forensic patients are more cognitively impaired or incapacitated (O'Reilly et al. 2019). Also, violent acts carried out by patients with schizophrenia or schizoaffective disorder may be of different kinds and have discrete causal factors (Naudts and Hodgins, 2005), which to a greater or lesser extent may involve cognitive impairment. For example, some patients are violent at a young age prior to the onset of psychosis, whereas others become chronically violent after the onset of psychosis even when receiving antipsychotic medication, and there are those patients that carry out a single act of violence during their lifetime (Hodgins, 2002; Fazel et al., 2009).

The role played by cognitive impairments for acts of violence for patients with schizophrenia and schizoaffective disorder may also be obscured by whether violent acts are instrumental or planned versus those that are reactive and unplanned. Although acts of violence may have both instrumental and reactive components the distinction is relevant due to the management and treatment difficulties associated with ego-syntonic instrumental violence. The cognitive impairments experienced by patients are likely to be particularly relevant to acts of reactive unplanned violence, which is executively simple when compared to instrumental violence which is often executively complex. We therefore chose to examine prospectively the role played by cognitive impairment for acts of reactive unplanned violence within an inpatient forensic hospital setting. We were interested in examining whether the cognitive impairment experienced by patients with schizophrenia and schizoaffective disorder that is thought to occur prior to the onset of psychosis, creates the

foundation for a range of risk factors, and impairments of function, which are causally related to violence.

We hypothesised that:

- Neurocognitive and social cognitive impairments would be determinants of violence.
- That the relationship between neurocognitive impairments and violence would be mediated by risk factors such as deficits in social reasoning, increased symptoms, impaired social functioning, and increased violence proneness.

A total of eighty-nine patients met inclusion criteria and consented to participate in the study. A key finding of the study was that the mean level of cognitive impairment within this national forensic cohort as assessed by the MATRICS Consensus Cognitive Battery (MCCB) was more than 3SD lower than the nonclinical population mean. When comparing those patients that were violent to those that were not over the twelve months follow up period, cognition accounted for 34% of the variance of violent incidents using multivariate analysis. The mean cognitive impairment for the non-violent group was a t-score of 20.9 (t scores have a mean of 50 and a standard deviation of 10), the mean t-score for violent group was a t-score of 12.8.

When the influence of neuro-cognition on violence was explored using mediation analysis, neuro-cognition emerged as a distal risk factor, whose effect on violence occurred through more proximal risk factors, such as social cognition (MSCEIT), violence proneness (HCR-20 Total score), psychiatric symptoms (PANSS), and social functioning (SOFAS). The neurocognitive impairment experienced by patients with schizophrenia and schizoaffective disorder appears to be a distal risk factor for violence mediated by a range of more proximal factors. In contrast to neuro-cognition, social cognition as assessed by a social reasoning test involving a specified problem and goal state (MSCEIT; understanding and managing emotions), had a direct effect on

violence even when controlling for violence proneness (HCR-20 Total score) and produced an effect size of 1.14 (Cohen's d) as a predictor of violent acts. However, although impaired social cognition (MSCEIT) was associated with violence during the twelve months follow up period, less impaired social cognition (MSCEIT) was positively associated with the 'seriousness of violence' at the time of patients' index offence which led to hospitalisation (DUNDRUM item 1; $r = .254$; $p = .016$). The discrepancy in the direction of the correlation between social cognition and violence may suggest that those with less impaired social cognition have the potential to be more dangerous, but that those with more impaired social-cognition are more likely to carry out unplanned or reactive violence. Again, as a group this national forensic cohort were very cognitively impaired overall scoring more than 3SD lower than the nonclinical population mean.

Patients' cognitive ability as assessed by the MCCB composite was also significantly correlated with independently assessed social functioning (SOFAS; $r = .556$), negatively correlated with violence proneness (HCR-20 Total score; $r = -.343$) and negatively correlated with psychiatric symptoms (PANSS; $r = -.405$) demonstrating the validity of the measurement of cognition with this group of forensic patients. This also highlights the relationship between cognitive impairments and suboptimal functioning (SOFAS). These consistencies also help to answer scepticism about the validity of neuropsychological tests within a forensic setting where patients may be motivated to feign cognitive impairment.

The results of this study are in keeping with the broader literature showing that impaired cognition, including impaired neurocognition and social cognition, is a risk factor for violence in many diagnostic groups (Fazel et al., 2011; Farrington et al., 2007; Holland et al., 2002). A recent study involving 88,145 US prisoners from the state of Ohio found that verbal and math ability assessed at the point of entry to the prison estate predicted the frequency of prison misconduct over a five and ½ year period (Silver and Nedelec, 2018). Research on the relationship between mental disorders and violence may find it useful to

make distinctions between proximal and distal risk factors, as well as different typologies of violence such as unplanned or reactive violence and planned or instrumental violence. Meta-analysis and systematic reviews should also make use of this distinction to advance knowledge within the field. To date no meta-analysis within the field of forensic mental health has focused on the distinction between instrumental or reactive violence as disparate outcomes, which may stymie progress in understanding, managing, treating, and predicting the violence carried out by patients with schizophrenia or schizoaffective disorder.

This study had several limitations and strengths. This study took place within a forensic setting which may limit the generalisability to non-forensic or community patients. Those patients who are at risk of being violent are best identified with reliable and valid risk assessments. This study used one such risk assessment the HCR-20, which was significantly negatively correlated with cognitive ability. In other words, those patients with higher risk scores on the HCR-20 were more cognitively impaired. Strengths of the study included the use of a consensus measure of cognitive impairment in schizophrenia the MCCB, the independence of all ratings, and the sample which consisted of a national forensic cohort.

To our knowledge this is the first study to quantify the mean level of cognitive impairment experienced by a national forensic cohort of patients with schizophrenia or schizoaffective disorder. In keeping with the non-forensic literature, this study highlights the importance of cognition for functional outcomes for forensic patients with schizophrenia or schizoaffective disorder, where reactive unplanned violence may be regarded as evidence of impaired functioning. The findings of this study are important as they suggest that cognitive impairment is a risk factor for reactive violence, in addition to impaired functioning. It may follow that evidence-based interventions to improve cognitive impairment may reduce violent and other adverse events and improve functional outcomes for forensic patients with schizophrenia or schizoaffective disorder.

6.2 Chapter Three: Empirical paper 2: Anticholinergic burden in schizophrenia and ability to benefit from psychosocial treatment programmes: a 3-year prospective cohort study

Pharmacological agents have currently been unsuccessful for treating the cognitive impairments associated with schizophrenia or schizoaffective disorder (Harvie and Bowie, 2012). Therefore, psychosocial treatments are generally used to address the functional disability arising in part out of cognitive impairment (Grant et al., 2011; Kahn and Keefe, 2013). Also, there is evidence that whilst maintenance pharmacotherapy improves symptoms such as delusions and hallucinations it may lead to poorer functional outcomes over time (Wunderink et al., 2013). One way that pharmacotherapy may negatively affect the cognitive impairments is via anti-cholinergic cognitive burden (Nebers et al., 2005; Campbell et al., 2009). Most anti-psychotics contain anti-cholinergic properties (Chew et al., 2008), also approximately 50% of patients with schizophrenia have other psychiatric or general medical conditions which require treatment (Green et al., 2003; Jones et al., 2004). Pharmacological treatments when aggregated may create a considerable anti-cholinergic burden that may affect patients with schizophrenia or schizoaffective disorders of cognition, 'real world' functioning, and their ability to benefit from psychosocial treatments. Only one study has investigated whether anti-cholinergic burden moderates the effectiveness of behavioural treatment, which in this case was cognitive remediation (Vinogradov et al., 2009). No study has investigated whether anti-cholinergic burden influences the effectiveness of functional outcomes like ability to benefit from psychosocial treatments via cognitive impairment. This study sought to investigate whether anti-cholinergic burden was associated with greater cognitive impairment and reduced ability to benefit from psychosocial treatment within a forensic hospital over a three-year period.

We hypothesised that:

- The relationship between anti-cholinergic burden and the ability to benefit from psychosocial treatment programmes would be mediated by cognitive ability, age, gender, baseline performance on psychosocial treatment programmes, total antipsychotic dose and symptoms.
- That the mediation relationship between medication, cognition, and programme completion would be specific to anti-cholinergic burden, and not total anti-psychotic dose, and that the mediation would be specific to cognition, not to symptoms or functioning when cognition is controlled for.

The findings of this study were that anti-cholinergic burden was associated with greater cognitive impairment, which in turn was associated with reduced ability to benefit from psychosocial treatment programmes, over a three-year period, even when controlling for a range of confounding variables including age, gender, anti-psychotic dose, and symptom severity. The effect of anti-cholinergic burden on ability to benefit from psychosocial treatment programmes was mediated by cognitive impairment. There was also evidence that greater cognitive impairment was specific to anti-cholinergic burden and not to total anti-psychotic dose. Moreover, symptom severity did not mediate the effect of anticholinergic burden on ability to benefit from psychosocial treatment programmes. Clinicians' ratings of patients' 'real world' functioning also did not mediate the relationship between anti-cholinergic burden and patients' ability to benefit from psychosocial treatment programmes when cognition was controlled. In other words, the effect of anti-cholinergic burden on ability to benefit from psychosocial treatment programmes appears specific to cognition and not 'real world' functioning as assessed by the SOFAS.

The primary strengths of this study were that the participants consisted of most of a national forensic cohort of patients with schizophrenia and schizoaffective disorder, followed up for a three-year period, and the use of independently assessed measures. The weaknesses include that the sample was cross-sectional rather than an incident series of new admissions. However, to achieve

an incident sample of sufficient size would require a very prolonged study or a multi-centre study. This study paves the way for a range of studies to be carried out within forensic hospitals including a prospective study involving an incident series of new admissions and an interventionist study perhaps using a randomised controlled trial methodology.

6.3. Chapter Four, Study Protocol: A randomised controlled trial of cognitive remediation for a national cohort of forensic mental health patients with schizophrenia or schizoaffective disorder

The fourth chapter describes a protocol for a registered intention to treat (ITT) randomised controlled trial of cognitive remediation training with most of a national cohort of forensic patients with schizophrenia or schizoaffective disorder. The protocol provides a detailed review of the importance of cognitive impairments for patients with schizophrenia or schizoaffective disorder, in addition to a review of meta-analyses of randomised controlled trials of cognitive remediation involving non-forensic participants, which have occurred outside of forensic mental health settings. In contrast, within forensic mental health settings, only a small number of randomised controlled trials have been carried out and the evidence base for psychological interventions within this setting is weak (Cullen et al., 2012; Rees-Jones et al., 2012; Lindqvist et al., 2000a; Lindqvist et al., 2000b; Blackburn et al., 2004; Seppenan et al., 2018). Of the randomised controlled trials that have been carried out, two have been CRT interventions. The first of these studies (Ahmed et al., 2015) mixed forensic patients with general mental health patients who were less cognitively impaired thus obscuring the applicability of the intervention for forensic patients, the second was a feasibility study investigated the possibility of improving social cognition (Taylor et al., 2016).

This chapter makes a crucial distinction between ‘help seeking’ and ‘help receiving patients’ and argues that in contrast to most non-forensic patients, forensic patients are involuntarily detained and consequently may not occupy

the role of ‘customer’ thus necessitating the use of RCT methodologies for determining the effectiveness of psychological interventions within this setting. The protocol chapter also provides a description of the CRT intervention, the outcome measures for evaluating the RCT, and the study design. Our CRT intervention is based on principles rather than a tightly manualised format in keeping with the common factors model of psychological therapies (Wampold et al., 2015; Gastonguay and Beutler, 2006), to be sensitive to working with forensic patients who have variable levels of ability and unique problems and needs.

6.4. Chapter 5: Empirical paper 3: A randomised controlled trial of cognitive remediation for a national cohort of forensic patients with schizophrenia or schizoaffective disorder.

The fifth chapter provides the findings of the RCT of cognitive remediation training for most of a national forensic cohort of patients with schizophrenia or schizoaffective disorder.

We hypothesised that:

- That patients allocated to CRT would improve on the primary outcome measure, cognition at the end of treatment, and at eight months follow up.
- That patients allocated to CRT would improve on specific neurocognitive and social cognitive domains at end of treatment and eight months follow up.
- That patients allocated to CRT would experience improvements in negative and disorganised symptoms.
- That patients allocated to CRT would experience improvements in real world functioning, net moves to lower level of security, and that patients’ functional improvements or moves to lower levels of security would be mediated by cognitive gains.

- That patients would experience CRT as a satisfactory and efficacious intervention.

Patients with schizophrenia and schizoaffective disorder who participated in CRT obtained significant improvements in the primary outcome measure, a composite score of the MCCB both at end of treatment and at eight months follow up. There were significant improvements in specific cognitive domains including working and visual memory, but not social cognition. There were no significant differences in symptoms (PANSS) apart from a difference in favour of the control group in the PANSS excitement factor. There were no significant differences between CRT and TAU on routine measures of ‘real world’ functioning ascertained by the multidisciplinary team (SOFAS), or for net positive moves. However, mediation analysis revealed that those who benefited neurocognitively from CRT had related improvement in functioning at the end of treatment (SOFAS); and more net positive therapeutic moves at follow up; there were meaningful functional gains associated with CRT, but these gains were predicated on having improved measures of cognitive function. Conversely, those who received CRT but did not have improved cognitive function failed to make ‘real world’ functional gains. The patients who were randomly assigned to CRT appeared to value the intervention. Ninety-six percent reported that their subjective neurocognitive ability had improved because of participating in CRT and that the cognitive gains they achieved had positively affected their daily lives.

One of the strengths of this study was its ecological validity. Of the sixty-nine patients who met the inclusion criteria in this national service, 65 agreed to take part representing a 94% uptake of those eligible to participate. This study also casts light on the mechanism of action of CRT using mediation analysis. Cognitive improvements associated with CRT were also associated with ‘real world’ functional improvements such as being moving to a unit with a lower level of security.

The weaknesses of this study included the numbers of forensic patients available nationally, and the lack of an active control group. In keeping with existing studies, CRT appeared to be an effective intervention for forensic mental health patients (Ahmed et al., 2015; Taylor et al., 2016) The patients who received CRT demonstrated improved global cognitive performance at the end of treatment and follow up. The high uptake of patients willing to participate, and the positive feedback received suggests that patients' regarded CRT as an acceptable and valued intervention for forensic mental health patients with schizophrenia or schizoaffective disorder.

6.5 Future Directions and Associated Studies

This PhD thesis presents three empirical studies demonstrating: a) the mean level of cognitive impairment amongst a national forensic cohort of patients with schizophrenia or schizoaffective disorder, b) the importance of these impairments for functional outcomes like reactive unplanned violence, and the ability to benefit from psychosocial treatment programmes, c) the potential value of pharmacological interventions, namely reducing anticholinergic burden, and d) the utility of psychological interventions like cognitive remediation training, for reducing these impairments.

A focus on cognitive impairments has the potential to influence the care and treatment experienced by forensic patients with schizophrenia or schizoaffective disorder in a myriad of additional ways. For example, we have also published a study highlighting the importance of 'moral cognition' for homicide carried out by forensic patients with schizophrenia or schizoaffective disorder (O'Reilly et al. 2017). Paradoxically those forensic patients who scored higher on a trait measure of moral cognition the Moral Foundations Questionnaire (MFQ-30; Graham et al., 2011), were more likely to have carried out a homicide than those that did not. Overall the five dimensions of the MFQ-30, care, fairness, loyalty, authority, and purity could account for 47% of the variance of homicide within this sample of patients found Not

Guilty by Reason of Insanity (NGRI). Presumably those patients who held more strongly endorsed moralistic attitudes were capable of justifying extreme violence. Furthermore, high scores for specific trait dimensions of moral cognition associated with homicide, namely ‘authority vs disrespect’ and ‘loyalty vs betrayal’, were also linked to cognitive impairment. Those patients who were more cognitively impaired endorsed more extreme moral cognitions concerning the importance of ‘authority’ and ‘loyalty’, which in turn were associated with homicide (O’Reilly et al., 2017). The moral cognitions experienced by patients may therefore explain why some patients with schizophrenia or schizoaffective disorder act on their delusions whereas others do not. Should strongly endorsed moral cognition prove to be a determinant of delusionally driven violence this may lead to new ways of conceptualising violence risk in addition to new forms of psychological intervention.

The cognitive impairments experienced by forensic patients also appear relevant for patients’ functional capacity, namely their ability to make and communicate decisions in an autonomous fashion (Moynahan et al., 2018). Using a measure of functional capacity, the DUNDRUM Capacity Ladders, we recently found that the MCCB composite correlated significantly with three separate domains of decision making pertinent to evaluation of functional mental capacity: finances ($r = .60$), welfare ($r = .63$), and medical treatment ($r = .65$), (Moynahan et al., 2018). The size of these correlations highlights the fundamental relationship between functional mental capacity in the areas of appreciation, understanding, reasoning, and decision making, and cognitive impairment specific to schizophrenia as measured by the MCCB. This finding suggests that although functional mental capacity is typically considered to be a dynamic construct varying across situations etc, it may not be as separable from cognitive ability, typically considered to be a static construct as has previously been believed (Moynahan et al., 2018).

Finally, it is likely that cognitive impairments play an important role in the formation and maintenance of delusions (Bell et al., 2006) in addition to the ability to benefit from psychological interventions (Richter et al., 2018). Two

specific cognitive factors which may maintain delusions. These are the ability to ask ‘useful or sceptical questions’ and the ability to update beliefs in light of new information (Bell et al, 2006). Deficits within these areas are likely to be distinct from the concept of ‘bias’, (Dudley et al., 2016), which has permeated the literature of cognitive behavioural therapy for psychosis. One problem with the concept of ‘bias’ is that it is more suggestive of an attentional glitch than a stable and independent impairment, which can be quantified and compared to the non-clinical population mean. Clarifying the role played by cognitive impairment for maintaining delusions is important as it may identify those patients, who are more likely to be helped by cognitive behavioural therapy (CBT) and anti-psychotic medication, in addition to those patients who are vulnerable to relapse. Understanding the mechanisms responsible for maintaining delusions may also lead to new psychological and pharmacological approaches for targeting these areas, or more specific inclusion criteria within clinical trials of cognitive behavioural therapy. CBT for psychosis is currently thought to produce only a small effect on the symptoms of schizophrenia (Jauhar et al., 2014). However, inclusion criteria within these trials of CBT for psychosis are based in part on using measures of verbal intelligence, which is relatively preserved by the illness, rather than measures of cognitive impairment specific to schizophrenia like the MCCB, or cognitive impairment relevant to delusions like the ability to ask ‘useful or sceptical questions’ or update beliefs. Those patients who have considerable cognitive impairments may therefore benefit from CRT prior to commencement of specific psychological therapies for targeting delusions, or alternatively may be deemed unsuitable for CBT due to a pronounced and generalised neuropsychological deficit in the ability to ask sceptical questions or update beliefs in response to new information.

6.6 Links to Existing Literature and Theories

This thesis presents evidence for the importance of cognitive impairments for patients with schizophrenia or schizoaffective disorder hospitalised within a forensic setting. This has been a neglected area of enquiry within forensic mental health services (FMHS). Two fundamental properties of a good scientific theory are that it has explanatory reach and is hard to vary (Deutsch, 2011). The theory that cognitive impairment is an important feature of these disorders has explanatory reach, namely it can account for a range of outcomes including but not limited to, quality of life, ‘real world’ functioning, mental capacity, reactive violence, moral cognition, delusions, in addition to ability to respond to psychosocial treatments (Kahn and Keefe, 2013; Moynahan et al., 2018; O’Reilly et al., 2017; Bell et al, 2006; Richter et al., 2018). The theory that cognitive impairment is an important feature of schizophrenia and schizoaffective disorder is also functionally linked in specific ways to each of these outcomes, for example greater impairments of cognitive functions such as processing, attention, memory, and executive abilities are associated with anti-cholinergic burden, and predict reduced ability to benefit from psychosocial treatment, even when considering ‘real world’ functioning and psychiatric symptoms. The theory is also consistent with modern biological hypotheses like synaptic pruning, which explain the delayed onset of schizophrenia a highly heritable condition (Keshavan et al., 1994; Sekar et al., 2016). A focus on cognitive impairment may therefore be the key to understanding and treating schizophrenia (Kahn and Keefe, 2013). Crucially, should forensic mental health services wish to claim that they have patients’ and societies best interests at heart, they can no longer afford to ignore these important theoretical developments and their associated practical applications.

6.7. Service implications of this PhD thesis

At a service level this PhD thesis has had several practical effects that have transformed service delivery. These innovations should be seen within the

context that there are known barriers to implementing change within psychiatric services (Spaulding and Sullivan, 2016) specifically concerning the translation of new science into effective practice. Disappointingly, dissemination of evidence-based assessment techniques and evidence-based therapies frequently does not make it beyond academic research centres (Dicherson and Leheman, 2011; Ballas and Boran, 2000). In part this dissemination problem has been attributed to conflict between the professional and organisation structures of traditional disciplines and practices, and new approaches to psychiatric rehabilitation (Spaulding and Sullivan, 2016). The studies contributing to this PhD, in addition to associated studies, have changed clinical practices at Ireland's National Forensic Mental Health Service and the Central Mental Hospital, Dundrum, Dublin 14. The changes included but are not limited to the following:

- A realisation amongst clinicians working within Ireland's National Forensic Mental Health Service and at Ireland's Central Mental Hospital that cognitive problems are a key feature of schizophrenia and schizoaffective disorder.
- A realisation amongst clinicians that cognitive problems like difficulties with memory and attention may be hidden by intact verbal intelligence amongst forensic patients with schizophrenia or schizoaffective disorder.
- A realisation amongst clinicians that forensic patients with schizophrenia or schizoaffective disorder also experience impairments in social cognition or difficulties reasoning with social information, which are relevant to their violence risk.
- The adoption of the MATRICS Consensus Cognitive Battery (MCCB) as a routine measure for assessing patients' cognitive ability at the point of admission to the Central Mental Hospital, so that improvement or deterioration in cognitive functioning can be observed during repeated testing.

- A greater awareness that anti-cholinergic burden when aggregated across all physical and psychiatric medications may negatively affect patient's cognitive capability.
- A greater awareness of how cognitive problems may affect patient's ability to participate, engage and benefit from psychosocial treatment programmes.
- A realisation that it is possible to carry out randomised controlled trials within a forensic mental health service to establish an evidence base for this group who may not readily assume the position of 'customer'.
- An awareness amongst patients and clinicians that cognitive remediation training may help improve cognitive functioning.
- Finally, our intense cognitive remediation training programme (4 sessions a week over a 14-week period: 56 sessions in total) has become part of treatment as usual (TAU) at the Central Mental Hospital and is being offered under our Seven Pillars of Care (Kennedy et al., 2010; DUNDRUM toolkit).

6.8. Conclusion

This PhD thesis draws attention to the mean level of cognitive impairment experienced by forensic patients with schizophrenia and schizoaffective disorder, as well as the relevance of these impairments for outcomes such as 'real world' functioning, reactive violence, and ability to benefit from psychosocial treatment programmes. For this national cohort the mean composite score on a neuropsychological battery specific to the cognitive impairments experienced by patients with schizophrenia and schizoaffective disorder was more than three standard deviations (SD) lower than the nonclinical population mean. A score of three SD lower than the nonclinical population mean is comparable to the abilities of those with a moderate intellectual disability (American Psychiatric Association, 2013).

Having clarified the extent of the problem, two of the empirical studies seek to address the important issue of remediation. We found that anticholinergic burden arising from polypharmacy was associated with the magnitude of cognitive at baseline (i.e. the higher the ACB the greater the cognitive impairment), which in turn was related to the ability to benefit from psychosocial treatment programmes via these cognitive impairments. This finding suggests that it may be possible to reduce cognitive impairment by minimising anticholinergic burden however this remains to be demonstrated. Cognitive remediation training (CRT) also appears to be a viable approach for reducing the cognitive impairments experienced by patients with schizophrenia or schizoaffective disorder. The patients participating in the trial also experienced CRT as an acceptable and valued intervention for addressing their cognitive difficulties.

Our randomised controlled trial is one of a handful of randomised trials carried out within a forensic mental health setting (Lindqvist and Skipworth, 2000a; Lindqvist and Skipworth, 2000b; Cure and Adams, 2000; Cullen et al., 2012; Williams et al., 2014; Taylor et al., 2015; Ahmed et al., 2015). Furthermore, some authors have suggested that randomised controlled trials are not necessary within a forensic mental health setting, despite their prominence within other areas of medicine (Lindqvist and Skipworth, 2000a; Cure and Adams, 2000; Lindqvist and Skipworth, 2000b). The argument in part rests on the difficulty in conducting such studies for forensic patients (Lindqvist and Skipworth, 2000a; Cure and Adams, 2000; Lindqvist and Skipworth, 2000b). Our RCT of CRT demonstrated that it is both possible and feasible to conduct a trial within a forensic mental health setting and thus contributes to the forensic literature more generally regarding the need to generate a robust evidence base. Moreover, the process of conducting an RCT has many practical benefits as was the case with the research more generally.

In addition to their academic contributions, all three empirical studies had meaningful and practical effects, which have directly or indirectly benefited patients and patient care at Ireland's National Forensic Mental Health Service.

This PhD thesis has therefore made important contributions to the culture of Ireland's forensic mental health services. It is my sincere hope that these service contributions, in addition to the internationally disseminated academic publications, will create a ripple within the forensic mental health network, which in time will become a wave, leading to sweeping and wide-reaching changes in the care and treatment of patients with schizophrenia or schizoaffective disorder.

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RESEARCH ARTICLE

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Prospective cohort study of the relationship between neuro-cognition, social cognition and violence in forensic patients with schizophrenia and schizoaffective disorder

Ken O'Reilly^{1,2}, Gary Donohoe¹, Ciaran Coyle², Danny O'Sullivan², Arann Rowe², Mairead Losty², Tracey McDonagh², Lasairiona McGuinness², Yvette Ennis², Elizabeth Watts², Louise Brennan², Elizabeth Owens², Mary Davoren^{1,2}, Ronan Mullaney^{1,2}, Zareena Abidin² and Harry G Kennedy^{1,2*}

Abstract

Background: There is a broad literature suggesting that cognitive difficulties are associated with violence across a variety of groups. Although neurocognitive and social cognitive deficits are core features of schizophrenia, evidence of a relationship between cognitive impairments and violence within this patient population has been mixed.

Methods: We prospectively examined whether neurocognition and social cognition predicted inpatient violence amongst patients with schizophrenia and schizoaffective disorder ($n = 89$; 10 violent) over a 12 month period. Neurocognition and social cognition were assessed using the MATRICS Consensus Cognitive Battery (MCCB).

Results: Using multivariate analysis neurocognition and social cognition variables could account for 34 % of the variance in violent incidents after controlling for age and gender. Scores on a social cognitive reasoning task (MSCEIT) were significantly lower for the violent compared to nonviolent group and produced the largest effect size. Mediation analysis showed that the relationship between neurocognition and violence was completely mediated by each of the following variables independently: social cognition (MSCEIT), symptoms (PANSS Total Score), social functioning (SOFAS) and violence proneness (HCR-20 Total Score). There was no evidence of a serial pathway between neurocognition and multiple mediators and violence, and only social cognition and violence proneness operated in parallel as significant mediators accounting for 46 % of the variance in violent incidents. There was also no evidence that neurocognition mediated the relationship between any of these variables and violence.

Conclusions: Of all the predictors examined, neurocognition was the only variable whose effects on violence consistently showed evidence of mediation. Neurocognition operates as a distal risk factor mediated through more proximal factors. Social cognition in contrast has a direct effect on violence independent of neurocognition, violence proneness and symptom severity. The neurocognitive impairment experienced by patients with schizophrenia spectrum disorders may create the foundation for the emergence of a range of risk factors for violence including deficits in social reasoning, symptoms, social functioning, and HCR-20 risk items, which in turn are causally related to violence.

Keywords: Schizophrenia, Violence, Mediation, MATRICS, MSCEIT, Neurocognition, Social cognition, Reasoning HCR-20, Function

* Correspondence: kennedh@tcd.ie

¹Department of Psychiatry, Trinity College Dublin, Dublin, Ireland

²National Forensic Mental Health Service, Central Mental Hospital, Dundrum, Dublin 14, Ireland



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Background

Most patients diagnosed with schizophrenia are never violent. However there is a small but significant association between schizophrenia and violence and with homicide in particular [1–3]. The relationship between violence and schizophrenia is thought to arise primarily from active symptoms such as delusions and co-morbid problems particularly substance misuse [1, 4]. But there is a link between schizophrenia and vulnerability to substance misuse and an increased risk of violence remains even when substance misuse is taken into account [4, 5]. Also violent acts carried out by people with schizophrenia are complex and cannot always be explained by psychotic symptoms alone. Some people with schizophrenia can become violent at a young age prior to the onset of psychosis, whereas others become chronically violent after the first psychotic episode even when receiving medication, and there are those who commit only a single act of violence during their lifetime [1, 3, 6]. Furthermore the violent acts carried out by people with schizophrenia appear to be driven by some of the same risk factors as violence in general [6–9]. Violence risk prediction schemes such as the Historical-Clinical-Risk-20 (HCR-20) [10, 11] take advantage of this and assess violence proneness by including a large number of equally weighted items [12] that are not specific to schizophrenia or mental disorder but are associated with suboptimal functioning. For example, substance misuse, homelessness, employment problems, relationship problems, lack of social support, history of victimisation and criminal history, are all risk factors for violence [13–15]. Many of these difficulties are likely to be underpinned by the cognitive decline experienced by patients with schizophrenia [16–20]. Neurocognitive impairments may therefore represent a common or distal risk factor whose influence on violence is mediated by a range of more proximal risk factors.

Impaired neurocognition and social cognition in schizophrenia

Although not a core diagnostic feature in DSM-5 [21] or ICD-10 [22], cognitive impairment has always been associated with schizophrenia [17, 23, 24]. Contemporary research has quantified this association using a range of neuropsychological tasks. On these measures patients with schizophrenia perform worse than healthy controls by as much as 2 standard deviations [17]. These impairments are thought to occur prior to the onset of psychosis [17]. Crucially the problems also occur in medication naïve patients [17]. Standardised batteries have been developed to assess the cognitive problems experienced by patients with schizophrenia, of which the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) is one

example [25]. The cognitive tasks on which patients perform poorly include not only neuropsychological or neurocognitive tests of memory, attention, and executive functioning, but also tests of social cognition such as perception of affect, emotional awareness, theory of mind, context sensitive processing, and emotional reasoning. [26]. Like neurocognitive deficits, many of these social cognitive problems are thought to be stable across phases of illness and linked to suboptimal functioning [17, 27]. For example, three tests - emotional reasoning (using the Mayer-Salovey-Caruso Emotional Intelligence Test MSCEIT), theory of mind and social relationship perception all predicted real world functioning at twelve months for patients experiencing first episode psychosis [28]. Social cognitive problems appear to account for additional variance of real world social functioning even when controlling for neurocognition [29]. Recent evidence also suggests that deficits in social cognition may mediate the relationship between neurocognitive impairments and positive symptoms, which have traditionally been seen as two separate domains [27, 30]. Because of the importance of the construct of social cognition for real world functioning and because of its strong psychometric properties, the managing emotion branch of the MSCEIT was included as a separate domain within the MCCB [25]. Finally both neurocognitive and social cognitive problems represent a major source of disability for patients with schizophrenia, accounting for more of the variance in functional outcome than symptoms [17, 29]. Patients with severe cognitive impairments have difficulties functioning day to day, finding meaningful employment and living independently [17].

Impaired neurocognition and violence in schizophrenia

An association between neurocognition and violence has been documented in meta-analyses and reviews concerning brain injury, delinquency, and intellectual disability even when controlling for genetic and socioeconomic factors [31–33]. In contrast findings from the schizophrenia and violence literature are contradictory and harder to interpret. One recent meta-analysis failed to support a relationship between psychosis, neurocognition and violence [15]. The analysis examined a variety of cognitive factors including lower total scores on the full scale Wechsler Adult Intelligence Scale (WAIS), lower scores on the verbal subscale of the WAIS, lower scores on the performance subscale of the WAIS, lower total scores on the National Adult Reading Test (NART), and poorer executive functioning (higher perseverative errors on the Wisconsin Card Sorting Test). However, Witt et al. [15] advised caution in ruling out a relationship between cognition and violence because of the large amount of case studies suggesting a link and also because other systematic reviews have identified that theory of mind, insight and

attitudinal cognition may be risk factors for violence [14]. In addition, two other recent literature reviews exploring the relationship between cognition and violence produced equivocal findings [3, 34]. None of the studies reviewed assessed the range of neurocognitive deficits associated with schizophrenia as outlined in the MATRICS consensus battery.

Impaired social cognition and violence in schizophrenia

In comparison with neurocognitive deficits, problems with social cognition are likely to be particularly relevant to violence risk [14]. But because social cognition is also a multidimensional construct a variety of measures have been developed to measure these processes [35]. Social cognitive processes are also thought to occur in an informational processing stream with perception of affect and emotional awareness occurring before more abstract processes such as emotional reasoning [26]. Many of the constructs which fall under the social cognitive umbrella have their own historical roots and have grown out of a variety of literatures. For example it is possible to make distinctions between the constructs of theory of mind, mentalisation and empathy [36–38]. Theory of mind, the ability to attribute mental states to oneself and to others and the realisation that others have mental states different from one's own is primarily associated with the field of autism research. Mentalisation, the ability to understand mental states when one's attachment system is activated has its roots within the psychodynamic, borderline personality disorder and attachment literature. Empathy undoubtedly involves theory of mind but also includes the ability to experience a compassionate emotional response in relation to another's suffering, and is primarily associated with developmental and social psychology. Theory of mind, mentalisation and empathy have all been related to violence in schizophrenia [39]. However because research on social cognition and schizophrenia is in its infancy there have been difficulties developing psychometrically sound and agreed upon instruments for measuring different components of social cognition [25]. In particular it has been challenging to measure empathy in schizophrenia in part due to the limitations of self-report questionnaires [40]. It was for this reason the managing emotions branch of the MSCEIT was the only social cognitive measure to be selected for use within the consensus battery of cognitive deficits in schizophrenia [25].

Instrumental and reactive violence in schizophrenia

Few of the studies exploring the relationship between cognition and violence in schizophrenia have included measures of social reasoning or made a distinction between instrumental and reactive violence. Instrumental violence is predatory, goal directed and complex requiring forethought and sequential planning, whereas reactive violence

is impulsive, defensive and executively simple [41–44]. Cognitive scientists have argued that reason, judgement, and decision making are not adequately measured by intelligence tests and are distinct domains of ability [45]. Impaired ability to foresee potential outcomes and to weigh up the pros and cons of social consequences is likely to contribute to reactive and less sophisticated forms of instrumental violence. Also it is noteworthy that mankind's ability to reason has been credited as the primary factor responsible for the historical decline of violence [46]. The faculty of reason as defined by our knowledge of the world and our ability to use this knowledge in the pursuit of goals has allowed mankind to perceive conflict as a problem to be solved, to develop cultural institutions to deter violence, and to think through the social consequences of our actions [46]. Social reasoning from this perspective is in part social knowledge, innate social cognitive ability, and also acquired skill. The distinction between instrumental and reactive violence may also help account for some of the discrepancies observed in the literature regarding the relationship between cognition and violence. For instance, Naudts and Hodgins [3] found that people with schizophrenia who have a long history of aggressive behaviour have better executive functioning than those who become violent after illness onset. But the study failed to make a distinction between instrumental and reactive violence and it may be that those with long histories of aggressive behaviour were primarily committing instrumental acts of instrumental violence thus requiring higher levels of executive functioning.

Paradigms for measuring violence in schizophrenia

There is much to recommend the study of inpatient violence for the purpose of disentangling the relationship between neurocognition and violence. The accurate measurement of violence in the community is beset by several methodological challenges such as reliance on self-report, or information being documented in police files concerning arrest or conviction. All of these may be incomplete. Violence in the community however is likely to be a more realistic test of risk assessment and prediction. In contrast, measures of staff-observed inpatient violence are likely to be more objective and complete, though the number of actual incidents of violence is likely to be reduced by intensive nursing care and de-escalation. Both inpatient and outpatient violence occur in instrumental and reactive varieties. Also meta-analytic reviews have found that the strength and direction of violence risk factors are the same for inpatient and outpatient violence [1, 14, 15]. To date only a few inpatient prospective studies have been carried out to explore the relationship between neurocognitive deficits and violence [47–49]. All of these studies have found a positive relationship in samples of patients with schizophrenia.

None of these studies examined neurocognitive deficits as a distal risk factor for violence or 'root cause' whose effect is mediated through more proximal risk factors such as social cognitive deficits, psychiatric symptoms, day to day social functioning and violence risk. Similarly no study has focused on emotional and social reasoning whilst controlling for other risk factors.

Aims

We hypothesised that for forensic patients with schizophrenia or schizoaffective disorder that a) neurocognitive and social cognitive deficits would be determinants of violence and b) that the relationship between neurocognitive deficits and violence would be mediated by risk factors such as deficits in social reasoning, increased symptoms, impaired social functioning and increased violence proneness.

Method

Study design

This is a naturalistic 12 month prospective observational cohort study of cognitive ability (neurocognition and social cognition) as a determinant of violence amongst patients with schizophrenia and schizoaffective disorder in a forensic hospital. Data were gathered from 2012–2013. All assessments for each individual were completed on average over a one month time period. Patients were followed up from the point of assessment for 12 months or until discharge to observe if they had been involved in a violent incident. The assessment consisted of the MATRICS Consensus Cognitive Battery (MCCB) an assessment of neurocognition and social cognition [22], The Social and Occupational Functioning Assessment Scale (SOFAS) [50], an assessment of 'real world' social functioning and the Positive and Negative Symptom Scale (PANSS) [51] an assessment of symptom severity. The Historical Clinical and Risk 20 (HCR-20) was used as an assessment of violence proneness or 'risk' [10–12]. Each of these domains was assessed by researchers who were blind to the results of the other assessments. Several patients who consented and participated in the cognitive assessment refused to take part in an assessment of symptoms.

Participants and setting

The study was approved by the National Forensic Mental Health Service Research and Audit Ethics and Effectiveness committee. All participants gave written informed consent.

The National Forensic Mental Health Service for Ireland provides specialised care for adults who have a mental disorder and are at risk of harming themselves or others. All patients are detained under forensic mental health legislation or special parts of the Mental Health Act, or are conditionally discharged to supervised community places

under forensic mental health legislation. At the time of the study the National Forensic Mental Health Service (NFMHS) for Ireland had 94 secure inpatient beds at high, medium and low levels of therapeutic security [52] located on a single campus, the Central Mental Hospital (CMH), and 13 supervised community beds for those discharged subject to conditions [53]. The CMH is the only secure forensic psychiatric hospital for the Republic of Ireland, a population of 4.6 million.

In total 123 patients were deemed eligible to participate during the recruitment phase. Of these, 8 patients declined to take part, 9 were discharged before they could complete the assessment, 1 patient was judged to be feigning during the assessment, and 1 patient did not complete the cognitive assessment.

All participants were diagnosed independently of other assessments by a consultant forensic psychiatrist using the Structured Clinical Interview for DSM-IV-TR [54]. Participants were selected if they met DSM-IV-TR criteria for schizophrenia or schizoaffective disorder. A total of 89 participants (76 with schizophrenia, 13 with schizoaffective disorder) met the inclusion criteria and consented to participate in the study. A further 15 with other diagnoses were excluded. Of the 89 participants, 8 were being supervised in the community for part of the follow-up period and 81 were hospital in-patients throughout.

Five (5.6 %) of the 89 were female. The average age of the 89 patients who participated in the study was 40 years. The mean length of stay was 7.5 years (SD 9.5), median 4.7 years, and mode 5.2 years.

Cognitive assessment

Patients were assessed using the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus assessment battery of cognitive deficits in schizophrenia [25], and also the Test of Premorbid Functioning TOPF-UK [55]. These assessments were carried out at the same time by masters' level Assistant Psychologists.

The MATRICS battery covers seven cognitive domains: Processing speed; Attention/ vigilance; Working memory; Verbal learning; Visual learning; Reasoning and problem solving; Social Cognition assessed using social reasoning tasks for managing emotions taken from the Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT) [56, 57]. The Managing Emotions subtest of the MSCEIT is a social reasoning test. The test comprises of vignettes of various situations, specified goals, and options for coping with the emotions and social situations depicted in these vignettes. Participants are required to indicate the effectiveness of each solution ranging from one (very ineffective) to five (very effective). We will refer to the sub-test of the MSCEIT used within the MCCB throughout this paper as a measure of social

cognition, while acknowledging that there are other measures and other constructs. In validation studies, and in antipsychotic trials of stable patients, the MATRICS demonstrated excellent reliability, minimal practice effects and significant correlations with measures of functional capacity with test-retest reliability of 0.9 for the overall composite score in the original validation study [57]. This value has been consistently found in multisite clinical trials. For example, the reliability was 0.88 in the 29-site study mentioned above [58].

There is evidence that the six neurocognitive sub-scales of the MATRICS can be expressed as three factors [59] but only by excluding the MSCEIT social cognition sub-scale, with an associated loss of sensitivity to social function [59]. Fett et al. [29] have found in a meta-analysis that social cognition is more closely related to social outcomes than is neurocognition. There is also a growing awareness that non-social and social cognition are separable dimensions. Therefore the MCCB scoring system now provides an option for a neurocognitive composite that does not include the social cognition sub-scale [60]. We believe it shows greater fidelity to the design of the MATRICS to first analyse all sub-scales including the social cognition scale separately, and to give the results also for the MATRICS composite score. We have therefore presented results for all seven subscales, and we have combined the six neurocognitive sub-scales into a single neurocognitive composite scale. To analyse neurocognition separately from social cognition a composite neurocognition score was calculated from the mean t-score for the first six items of the MATRICS battery (excluding social cognition) not correcting for age, gender, and education. This method of calculating a composite measure of neurocognition without being contaminated by the social cognitive domain has been widely used within the literature [61].

Scores for estimated pre-morbid intelligence (TOPF-UK) were not adjusted for education as an estimate of premorbid ability because the symptoms associated with mental disorder can affect educational attainment. A small number of patients (12 of 89) could not complete the TOPF-UK because of literacy problems. The mean estimated premorbid IQ was 96.

Functional performance

The SOFAS [50] was completed by a member of the multidisciplinary team responsible for the care of the patient, who was blind to the other assessments including the cognitive assessment. Functioning assessments were obtained for 86 of the 89 participants.

Symptom assessment

A PANSS [51] assessment was completed on 77 of the 89 patients. The PANSS assessments were completed

independently of the cognitive assessments by a psychiatric registrar and an assistant psychologist trained in its use. The PANSS is designed to be scored for positive, negative and general symptoms, and a total symptom score. Because symptoms may overlap with personality traits relevant to violence such as impulse control, affect regulation, narcissism, and paranoid cognitive personality style [62], the total symptom score may be as good or better a predictor of violence than the positive symptom score alone.

Assessment of violence risk and need for therapeutic security

The HCR-20 [10], a measure of risk of violence was assessed by forensic psychiatry higher trainees (equivalent to US fellow) who were blind to the other assessments (MD and ZA). The HCR-20 is amongst the most extensively validated risk assessment schemes for use within forensic mental health settings [11]. The historical scale contains ten 'static' items: previous violence, young age at first violent incident, relationship instability, employment problems, substance misuse problems, history of major mental illness, psychopathy, childhood maladjustment, personality disorder, and prior supervision failure. The psychopathy item was omitted because it is not routinely assessed. The clinical scale contains five 'current' items sensitive to change including lack of insight, negative attitudes, active symptoms of major mental illness, impulsivity and unresponsiveness to treatment. The risk scale contains five 'future' items: plans lack feasibility, exposure to destabilisers, lack of personal support, noncompliance with remediation attempts and stress. All items are given equal weight [12]. We have previously described the extent to which the HCR-20 and its individual items when measured at baseline do or do not predict subsequent violence in this population [13]. In the present study the HCR-20 is taken as the means of controlling for violence proneness at baseline.

The DUNDRUM-1 triage security instrument [63] is a static assessment of the need for therapeutic security. It is used as a means of comparing the patients in this forensic hospital with those in forensic hospitals elsewhere. The DUNDRUM-1 triage security instrument includes eleven items rating the seriousness of violence, need for specialist treatments and other indicators of need for high, medium or low levels of therapeutic security. A mean item score of between 3 and 4 indicates a need for high security, between 2 and 3 for medium security, 2 for low security, 1 for open hospital or community settings [64]. Item 1 rates the severity of the most serious violent act, ranging from 0 for none to 4 for fatal or potentially fatal violence.

Assessment of violence

A psychiatric trainee (EW) who was blind to the scores on other assessments reviewed the incident report forms,

patient's clinical notes and legal forms recording incidents of restraint or seclusion, as well as a separate log of incidents kept in the nursing operational management office. This process identified all violent incidents from multiple cross-referenced sources, following the assessments up to the date of discharge or twelve months follow-up. The 8 patients in supervised community residences for part of the follow-up period were monitored in the same way. An individual was classified as violent if they were the clear instigator or co-aggressor, and if the incident involved harm to staff or other patients. The first violent incident was taken as a means of defining violence as a binary outcome. This outcome measure lends itself to both the receiver operating characteristic (ROC) area under the curve analysis (AUC) and to binary logistic regression and so this has become the recommended way of studying factors predicting violence and other discrete outcomes [11, 65]. Very few patients were violent more than once in the follow-up period so that frequency of violence can be studied only in very large samples.

Violence was further classified into reactive and instrumental violence using Woodward and Porter's coding scheme [42].

Medication

A chlorpromazine equivalent (CPZeq) was calculated for each participant as a measure of his/her relative daily dose of antipsychotic medications [66–68].

Data analysis

All data were analysed using SPSS-22 [69]. Demographics and differences between violent and nonviolent groups are presented in Table 1.

To correct for multiple hypothesis testing for the seven cognitive domains comprising the MATRICS battery group differences across all subtests and the neurocognitive and MATRICS composites were analysed using multivariate analysis of variance, with age and gender entered as co-variables. Group differences across cognitive domains and composite scores were analysed using one way ANOVAs. Bonferroni correction was applied as a conservative check on multiple hypothesis testing. Similarly for the PANSS and HCR-20 all subscales including the total scales were analysed using multivariate analysis of variance, with age and gender as co-variables.

The ability of baseline measures to discriminate those who during the follow-up period committed violent incidents was analysed using the receiver operating characteristic (ROC) area under the curve (AUC). An association was deemed significant if the lower limit of the 95 % confidence interval of the AUC was greater than 0.5, the line of random information.

Correlations were calculated using Spearman's non-parametric method as violence is a binary variable.

SPSS PROCESS macro model 4 [70] was used to analyse mediation relationships between antecedent factors such as neurocognition, social cognition, and the dichotomous outcome violence (Fig. 1). Age and gender were entered as co-variants in all mediation analysis. SPSS PROCESS macro is a computational tool for path analysis-based moderation and mediation analysis. Various measures of effect size for indirect effects are generated in mediation models. Effect sizes were calculated as regression coefficients in the first instance and later as odds ratios to facilitate interpretation. Bootstrapping was used to estimate indirect effects, and 95 % bias-corrected confidence intervals were used for the indirect effects using 1,000 bootstrap samples. A confidence interval for an odds ratio that does not contain a score of one indicates statistically significant mediation.

Mediation effects were in each case examined for all combinations to determine the direction of the causal effect. If a relationship between an antecedent factor, a mediating factor and violence does not hold true when the order of antecedent and mediating factors is switched this has been taken as support for preferring one pathway (an ordering of factors) over another.

We also tested more complex mediation models involving two or more mediators employed SPSS PROCESS macro models 4 (parallel) (Fig. 2) and model 6 (Fig. 3) (serial) [70]. These models were regarded as exploratory.

Results

The mean follow-up period ($n = 89$) was 1.22 years (SD 0.44). There were 107.4 person-years at risk. During the follow-up period, 10 of the 89 patients with schizophrenia-schizoaffective disorders committed violent acts (base rate 9.7/100 person-years at risk). Note that only the first violent incident for each person was counted. All violent incidents were coded [42] as reactive violence, with two rated as also having a minor instrumental element. On the DUNDRUM-1 item 1 measure of seriousness of violence (scored 0 to 4 where '4' is fatal or life threatening) eight violent incidents were rated '2' and the remaining two were rated '1'.

A relationship between gender and violence did not reach statistical significance, as 2/10 who were violent were female, compared to 3/79 who were not violent, Fisher's exact test = 4.39, $p = 0.095$.

All of the participants had a history of past violence as recorded by the HCR-20 and DUNDRUM-1 triage security instrument. On item 1 of the DUNDRUM-1 triage security instrument, 62 patients scored '4', indicating a history of homicide or life threatening violence to others and 20 scored '3' indicating other serious violence. On the HCR-20 item 1, 86 scored '2' indicating a history of serious or repetitive violence to others.

The mean score on the DUNDRUM-1 eleven item scale was 29.5 (SD 5.0) and for the DUNDRUM-1 nine

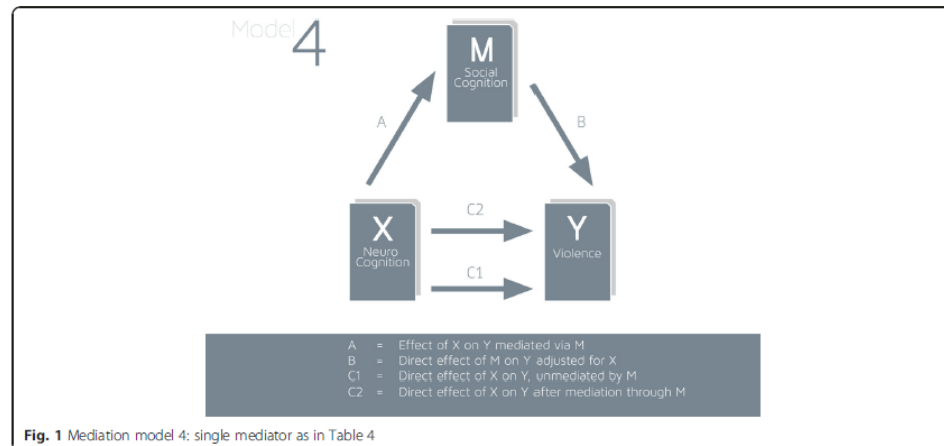
Table 1 Mean (SD) comparisons between violent and non-violent groups after controlling for age and gender as co-variants. Effect sizes and AUC for receiver operator characteristics (ROC)

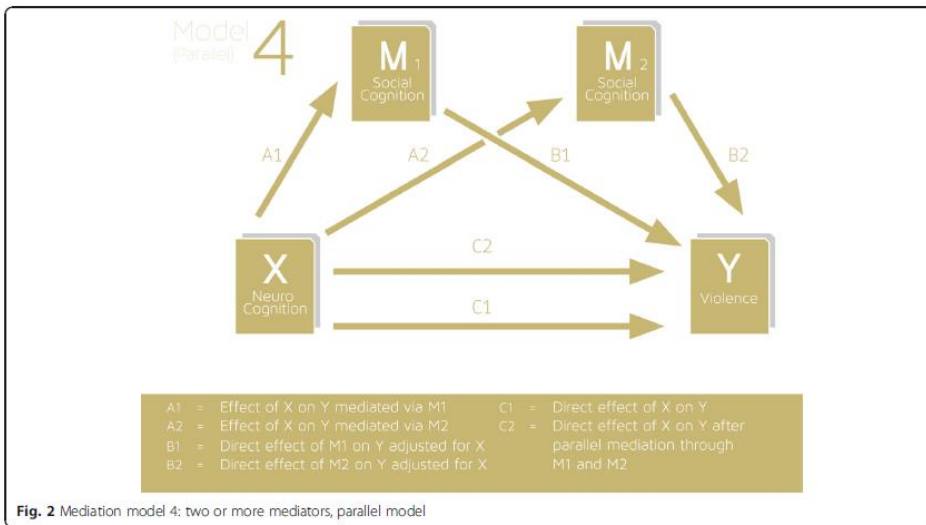
	ANOVA						Effect size		Receiver operating characteristic				
	Non-violent n = 79		Violent n = 10		F-statistic (df 1,87)	P value	Partial Eta squared	95 % CI		95 % CI			
	mean	S.D.	mean	S.D.				d	lower	upper	AUC	lower	upper
Age	40.9	12.7	36.1	9.4	1.342	0.250	-	0.38	-0.27	1.04	0.62	0.45	0.80
Length of stay (years)	8.0	9.7	3.0	5.0	2.243	0.13	-	0.50	-0.16	1.16	0.73	0.54	0.91
Chlorpromazine equivalents	538	366	772	397	3.6	0.063	-	0.64	-0.03	1.30	0.67	0.46	0.88
Pre-morbid IQ (TOPF-UK)	96.0	12.6	96.8	8.1	0.023	0.879	-	0.06	-0.72	0.84	.49	0.31	0.67
PANSS total	62.5	20.0	90.1	19.4	12.2	0.001	.157	1.38	0.58	2.19	0.84	0.71	0.97
PANSS positive	13.7	7.0	21.6	8.7	9.32	0.003	.113	1.21	0.41	2.01	0.79	0.65	0.93
PANSS negative	18.9	7.9	25.0	6.5	6.175	0.111	.078	0.98	0.19	1.78	0.71	0.55	0.87
PANSS general	29.02	10.3	43.6	10.4	14.202	.000	.163	1.49	0.68	2.31	0.86	0.73	0.99
HCR-20 total score	20.8	5.7	28.2	8.0	14.04	0.000	.142	1.26	0.57	1.94	0.78	0.59	0.96
HCR-20 Historical	12.9	2.7	15.2	4.5	5.178	.025	.057	0.763	0.09	1.43	0.75	0.55	0.95
HCR-20 Current	4.50	2.63	7.2	2.78	12.59	.001	.129	1.91	0.51	1.87	0.76	0.59	0.94
HCR-20 Risk	3.39	2.12	5.80	2.29	10.06	.002	.106	1.064	0.39	1.74	0.77	0.62	0.71
SOFAS	59.2	17.2	35.6	18.9	14.9	0.001	-	1.29	0.61	1.98	0.83	0.66	0.99
DUNDRUM-1 (11 item)	29.54	5.01	27.40	7.1	.994	0.322	.012	0.334	-0.33	0.99	0.44	0.21	0.66
DUNDRUM-1 (9 item)	27.08	3.93	23.90	6.93	3.275	0.074	.037	0.607	-0.06	1.27	0.38	0.16	0.60

item scale omitting self-harm items, the mean score was 27.1 (SD 3.9), a mean score per item of 3.0 (SD 0.4). The mean for the Total HCR-20 In was 20.8 (SD 5.7), median 21.0, mode 17.

The mean t-score of the MATRICS composite score for all patients was 17.9 (SD 13.2, range -11.0 to 51.0). The published population norm is a t-score of 50 (SD

10). This group of forensic hospital patients with schizophrenia is therefore more than three standard deviations below the population norm. Table 2 shows that for the group who were not violent during follow-up the MATRICS composite represented as a mean t-score was 20.9 (SD 14.0). The violent group was even more impaired (12.8, SD 9.1).





Differences in cognitive ability between violent and nonviolent groups

One-way MANOVA showed that violent patients had significantly worse neurocognitive and social cognitive abilities than non-violent patients (Pillai's Trace $V = 0.339$,

$F(8, 78) = 5.008, p < 0.001$, Partial Eta squared = 0.339) after controlling for age and gender.

Violent patients performed significantly worse than non-violent patients on the MATRICS domains of processing speed, verbal learning, social cognition and the

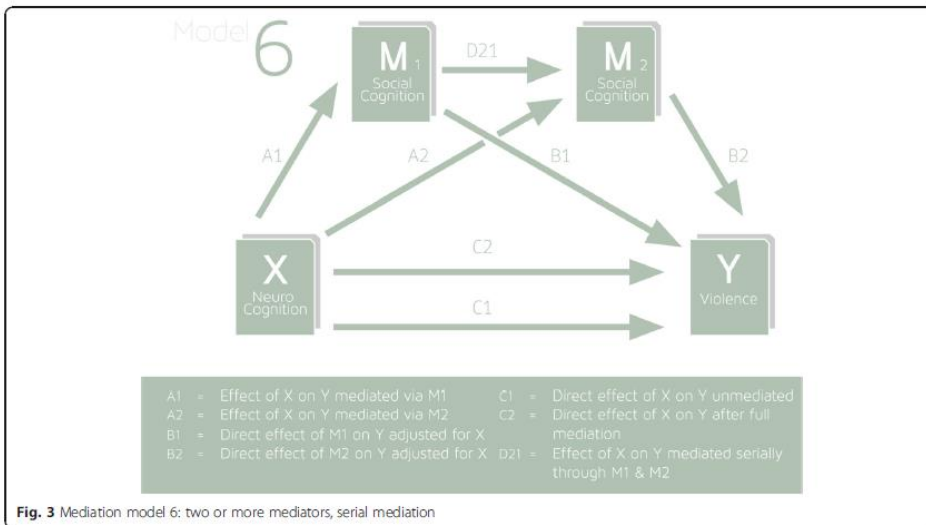


Table 2 Mean (SD) comparisons for t-scores on MATRICS domains and composites, comparing violent and non-violent groups after controlling for age and gender as co-variants. Effect sizes and AUC for receiver operator characteristics (ROC)

MATRICS Domains and Composites	ANOVA						Effect Size d			Receiver operating characteristic			
	Non-violent n = 79		Violent n = 10		F-statistic (df 1,87)	P value	Partial Eta squared	d		AUC	95 % CI		
	Mean	S.D	mean	S.D				lower	upper		lower	upper	
Processing Speed	24.82	15.5	18.50	10.2	5.242	0.025	0.058	0.76	0.10	1.43	0.65	0.51	0.79
Attention	28.4	11.1	23.8	10.4	2.43	0.122	0.028	0.52	-0.13	1.18	0.62	0.43	0.81
Working Memory	31.3	12.7	32.8	8.4	0.053	0.818	0.001	0.24	-0.41	0.90	0.45	0.30	0.60
Verbal Learning	33.9	7.6	28.4	4.5	7.56	0.007*	0.082	0.92	0.25	1.59	0.72	0.58	0.86
Visual Learning	32.7	12.6	26.5	11.9	2.57	0.11	0.029	0.53	-0.12	1.20	0.64	0.46	0.82
Reasoning	35.9	7.4	35	5.4	0.808	0.371	0.009	0.30	-0.35	0.96	0.51	0.33	0.68
Social Cognition	35.7	11.0	24.4	6.3	11.57	0.001*	0.12	1.14	0.46	1.82	0.81	0.71	0.90
Neuro-cognitive composite	31.1	9.3	27.5	6.7	3.05	0.084	0.035	0.58	-0.07	1.24	0.61	0.45	0.76
MATRICS Total Composite	20.9	14.0	12.8	9.1	5.720	0.019	0.063	0.80	0.13	1.47	0.67	0.53	0.81

*Is significant following Bonferroni Correction

MATRICS total composite (Table 2). Following Bonferroni correction for multiple testing the violent and non-violent groups differed only on the verbal learning domain and the social cognitive domain. The magnitudes of the differences between violent and nonviolent groups are also presented as effect sizes (Cohen's d) in Tables 1 and 2.

For PANSS scores, one-way MANOVA showed that violent patients had significantly higher levels of psychopathology (Pillai's Trace $V = 0.172$, $F(4, 70) = 3.639$, $p < 0.009$, Partial Eta squared = 0.172) (Table 1).

One-way MANOVA showed that HCR-20 total scores for risk of violence were higher for violent patients (Pillai's Trace $V = 0.149$, $F(3, 83) = 4.839$, $p < .004$, Partial Eta squared = 0.149) (Table 1).

Predicting violence

Three of the seven neurocognitive domains of the MATRICS - processing speed, verbal learning, and social cognition had AUCs significantly greater than random. The MATRICS composite was also significantly better than random (Table 2). The social cognitive domain of the MATRICS had the highest AUC. Although the MATRICS composite was predictive of violence the Neurocognitive composite without the addition of the Social Cognitive Domain was not.

The total HCR-20 score, PANSS positive, PANSS negative, PANSS general and PANSS total scores all had ROC AUC scores that were significantly better than random.

Correlations between cognition, real world functioning, violence risk and violence

Table 3 depicts non-parametric Spearman correlations between cognition (both neurocognition and social cognition), social functioning using the SOFAS, proneness to

violence (risk of violence) using the HCR-20 total score, past history of homicide or lethal violence (DUNDRUM-1 item 1) and actual violence during the follow-up period. These can be summarised as showing that social cognition and neurocognition correlated positively with each other and with social function (SOFAS). They correlated negatively with symptom severity (PANSS total), violence proneness (HCR-20 total score), and subsequent actual violent acts. It is notable that neurocognition did not correlate directly with PANSS positive symptoms, though it did correlate negatively with PANSS negative symptoms and PANSS general symptoms. Social cognition (MSCEIT/MATRICS) tended to have the strongest correlations with all symptom measures and with subsequent violence, while neurocognition had stronger correlations with the HCR-20 and SOFAS scores. An incidental finding was that less impaired social cognition was associated with a past history of lethal or life-threatening violence (a score of '4' on DUNDRUM-1 item 1).

Mediation between neurocognition, social cognition and violence

The relationship between neurocognition and violence was completely mediated by the social cognitive domain of the MATRICS, after co-varying for age and gender (Table 4).

Figure 1 shows the mediation model in schematic form. Table 4 shows these effects expressed as odds ratios.

Neurocognition appears to have no influence on violence independent of its effect on social cognition (Table 4). There was no evidence that neurocognition mediated the relationship between social cognition and violence. In total the effect of neurocognition, social cognition, and age and gender could account for 35 % (Nagelkerke R^2) of the variance in incidence of violence.

Table 3 Spearman correlations. Each column is divided into three cells per row. These are the Spearman correlation coefficient, p value and number of subjects for each row

	1	2	3	4	5	6	7	8	9	10	11
1 Social Cognition	-										
2 Neuro-cognition Composite	0.397 .001 89	-									
3 MATRICS Composite (includes neuro-cognition and social cognition)	0.541 .001 89	0.984 .001 89	-								
4 PANSS Total	-0.461 .001 77	-0.338 .003 77	-0.405 .001 77	-							
5 PANSS Positive	-0.361 .007 77	-0.149 .195 77	-0.217 .058 77	0.773 .000 77	-						
6 PANSS Negative	-0.398 .001 77	-0.359 .001 77	-0.406 .001 77	0.729 .001 77	0.323 .004 77	-					
7 PANSS General	-0.473 .001 77	-0.298 .009 77	-0.371 .001 77	0.917 .001 77	0.735 .001 77	0.571 .001 77	-				
8 HCR-20 Total In	-0.252 .017 89	-0.314 .003 89	-0.343 .001 89	-0.666 .001 77	0.567 .001 77	0.543 .001 77	0.614 .001 77	-			
9 SOFAS	0.411 .001 86	0.521 .001 86	0.556 .001 86	-0.617 .001 77	-0.438 .001 77	-0.499 .001 77	-0.542 .001 77	-0.616 .001 86	-		
10 History of Homicide or lethal violence D1 Item 1	0.254 .016 89	-0.021 .848 89	0.028 .759 89	-0.210 .067 77	-0.145 .207 77	-0.197 .087 77	-0.092 .425 77	-0.215 .043 89	0.082 .453 86	-	
11 Violence	-0.340 .001 89	-0.122 .255 89	-0.194 .069 89	0.343 .002 77	0.293 .010 77	0.214 .062 77	0.362 .001 77	0.308 .003 89	-0.351 .001 86	-0.288 .006 89	-

PANSS Total score as a mediator between neuro-cognition and violence

The PANSS total score completely mediated the relationship between neurocognition and violence. The indirect effect of neurocognition on violence as mediated by the PANSS total score was OR = 0.94. There was no evidence that neurocognition mediated the relationship between psychiatric symptoms (PANSS total) and violence (Table 4). In total the effect of neurocognition, symptoms, and age and gender could account for 48 % (Nagelkerke R^2) of the variance in the incidence of violence.

Social functioning as a mediator between neurocognition and violence

Social functioning (SOFAS) completely mediated the relationship between neurocognition and violence after controlling for age and gender. The indirect effect of Neurocognition on Violence as mediated by the SOFAS score was OR = 0.91. There was no evidence that neurocognition mediated the relationship between social functioning and violence. In total the effect of neurocognition, social functioning, and age and gender could account for 34 % (Nagelkerke R^2) of the variance of violent incidents.

Table 4 In all cases, the outcome (Y) is 'violent act'. X is the hypothesised determinant factor and M is the hypothesised mediating factor. See also Additional file 1 for figures representing these effects and pathways

M	C1: Direct effect X on Y before mediation			C2: Direct effect X on Y after mediation			A: Mediated effect X on Y via M		B: Direct effect M on Y adjusted for X			
	OR	95 % CI		OR	95 % CI		OR	95 % CI		OR	95 % CI	
		lower	Upper		lower	Upper		lower	upper		Lower	upper
X = Neurocognitive composite	0.929	0.850	1.016									
social cognition				0.989	0.893	1.095	0.932	0.849	0.976	0.869	0.779	0.970
PANSS				0.955	0.836	1.092	0.947	0.821	0.994	1.069	1.016	1.125
SOFAS				1.008	0.904	1.124	0.916	0.788	0.997	0.931	0.882	0.982
HCR-20				0.972	0.881	1.072	0.950	0.831	0.997	1.214	1.058	1.393
X = social cognition	0.864	0.781	0.957									
neurocognition				0.869	0.779	0.970	0.997	0.934	1.031	0.989	0.893	1.095
PANSS				0.886	0.774	0.986	0.958	0.791	1.034	1.054	0.997	1.114
SOFAS				0.906	0.811	1.012	0.964	0.817	1.052	0.953	0.901	1.007
HCR-20				0.890	0.803	0.987	0.973	0.870	1.065	1.187	1.025	1.374
X = symptoms (PANSS total score)	1.067	1.017	1.120									
neurocognition				1.069	1.015	1.126	1.006	0.985	1.126	0.955	0.836	1.092
Social cognition				1.054	0.997	1.114	1.029	0.995	1.107	0.886	0.774	1.014
SOFAS				1.042	0.986	1.102	1.037	0.909	1.136	0.935	0.867	1.009
HCR-20				1.032	0.969	1.099	1.043	0.915	1.165	1.170	0.953	1.436
X = social function (SOFAS)	0.931	0.887	0.978									
Neurocognition				0.930	0.881	0.982	1.002	0.958	1.046	1.008	0.904	1.124
Social cognition				0.953	0.901	1.007	0.973	0.913	1.005	0.906	0.811	1.012
PANSS				0.935	0.867	1.009	0.972	0.866	1.092	1.042	0.986	2.633
HCR-20				0.971	0.920	1.024	0.942	0.753	1.008	1.320	1.095	1.614
X = violence proneness (HCR-20 total score)	1.228	1.075	1.403									
Neurocognition				1.214	1.058	1.393	1.012	0.956	1.085	0.972	0.881	1.072
Social cognition				1.187	1.027	1.371	1.055	1.000	1.166	0.890	0.797	0.987
PANSS				1.170	0.953	1.436	1.102	0.817	2.175	1.032	0.984	1.107
SOFAS				1.320	1.088	1.601	1.058	0.759	1.392	0.971	0.917	1.022

Age and Gender as covariates. C1, C2, A and B refer to the labelling in Fig. 1. Confidence intervals underlined and in bold are significant

HCR-20 Violence risk as a mediator between neuro-cognition and violence

Violence proneness (risk of violence) as measured by the HCR-20 total score completely mediated the relationship between neurocognition and violence. The indirect effect of neurocognition on violence as mediated by the HCR-20 total was OR = 0.95. There was no evidence that neurocognition mediated the relationship between violence risk and violence. In total the effect of neurocognition, HCR-20, and age and gender could account for 35 % (Nagelkerke R²) of the variance of violent incidences.

Neurocognition as the foundation for the emergence of violence risk factors

In addition to the consistent evidence of mediation between neurocognition and violence (Table 4), there was

evidence that the relationship between social cognition and violence was mediated in part by social functioning (SOFAS), and the relationship between social functioning (SOFAS) and violence was mediated in part by violence proneness (HCR-20 violence risk). To test the hypothesis that neurocognitive impairments represent the foundation for the emergence of a range of risk factors for violence such as social cognitive deficits, increased symptoms, impaired functioning and HCR-20 violence risk we constructed a serial mediation model (Fig. 3, model 6 of the PROCESS macro [70]). When all four mediating factors were entered into a serial mediation model between neurocognition and violence, there was no evidence of serial mediation from neurocognition, to social cognition, to psychiatric symptoms, to social functioning, to HCR-20 violence proneness. Nor was there

evidence of serial mediation between any three of the four mediating variables. Also there no evidence of serial mediation between any two of the four mediating variables.

When all four mediating variables are entered into a parallel mediation model (Fig. 2, model 4 of the PROCESS macro [70]) there is no evidence of an indirect mediated effect between neurocognition and violence. When every combination of three out of the four mediating variables is entered into the parallel mediation model (Model 4) there was again no evidence for an indirect mediated effect between neurocognition and violence. When each possible pair of the four mediating variables was entered in the parallel model (model 4) there was evidence that the total indirect effect between neurocognition and violence was significant, completely mediated by social cognition and HCR-20 violence risk as two parallel pathways from neurocognition to violence (total indirect effect expressed as odds ratio 0.896, 95 % CI 0.730 – 0.971). Altogether this model could account for 46 % of the variance of violent incidents. There were no other robust effects mediated by any other pair of mediating factors.

Social cognition and symptoms as a mediator between neurocognition and violence

Although psychiatric symptoms did not mediate the relationship between social cognition and violence (Table 4), because of the link between delusions and violence [1, 14, 15] and the association between social cognition and symptoms (Table 3), we wanted to investigate whether there would be evidence of serial mediation between neurocognition and violence when social cognition and symptoms were added to the model (Process Macros Model 6). We omitted the measure of violence proneness or risk (HCR-20) because of likely overlap in content between some items in the HCR-20 and the measure of symptom severity (PANSS). As set out above, there was no evidence that social cognition and symptoms mediated the relationship between neurocognition and violence, either serially or in parallel.

Discussion

Main findings

In this prospective cohort study of forensic hospital patients with schizophrenia and schizoaffective disorder we found a robust association between cognitive (neurocognitive and social cognitive) deficits and violence. Using multivariate analysis the cognitive domains measured by the MCCB could account for 34 % of the variance in violent incidents after controlling for age and gender during a 12 month follow up. Both nonviolent and violent patients had significant impairments in neurocognition and social cognition. The mean MCCB composite was three standard deviations below a nonclinical mean.

Also even though these forensic patients were admitted because of a prior history of violence, most were not violent during the period of study. Of all the MCCB domains, performance on the social reasoning test (MSCEIT) produced the largest effect size.

When the influence of neurocognition on violence was explored using mediation analysis, neurocognition emerged as a distal risk factor whose effect on violence occurred through more proximal risk factors. The relationship between neurocognition and violence was completely mediated by social cognition (MSCEIT), violence proneness (HCR-20 Total), psychiatric symptoms (PANSS total), and social functioning (SOFAS). There was also evidence of parallel mediation from neurocognition through social cognition and through violence proneness (violence risk, HCR-20) to violence. This may cast some light on why risk factors within the HCR-20 such as employment problems and prior supervision failure that ought to operate mainly in the community, none-the-less remain predictive in hospital. These risk items may be markers of general dysfunction underpinned by cognitive impairment. In contrast to neurocognition, social cognition as measured by a social reasoning task (MSCEIT) had a direct effect on violence even when controlling for violence proneness (HCR-20 Total Score), psychiatric symptoms (PANSS), and neurocognition. The direct effect of social cognition on violence was however attenuated to insignificance by mediation through a measure of general social function (SOFAS).

Differences between violent and nonviolent group during 12 month follow up

The greatest difference between violent and nonviolent groups was on the MATRICS social cognition domain, a social and emotional reasoning task assessing patients' ability to manage emotions. Significant differences were also observed for the neurocognitive measures of verbal learning and processing speed. There was no significant difference between chlorpromazine equivalents of antipsychotic medication between violent and nonviolent groups. In this prospective study of violent outcomes, social cognition measured at baseline produced ROC AUCs comparable with the HCR-20, one of the most widely used violence risk assessment and management schemes. Impaired emotional and social reasoning ability as measured by the MSCEIT appeared to be a determinant of reactive, impulsive violent behaviour.

Mediation analysis

These findings were further explored using mediation analysis. There was no evidence that neurocognition had an effect on violence independent of social cognition. The composite measure of neurocognition was only related to violence in so far as it affected social and emotional reasoning. Using this model, neurocognitive difficulties

amongst people with schizophrenia spectrum disorders in a forensic hospital did not have a direct effect on violence but neurocognitive problems leading to difficulties with social and emotional reasoning did.

For patients with schizophrenia and schizoaffective disorder the relationship between neurocognition and violence was also completely mediated by symptoms (PANSS total score), by social functioning (SOFAS) and by violence proneness (HCR 20 violence risk). Although neurocognitive impairments are thought to occur before the onset of psychosis and to underpin functional impairment to be sure of the causal direction we tested all possible combinations of factors. There was no evidence that neurocognition mediated the relationship between any of the described variables and violence. Of all of the variables examined, neurocognition was the only independent variable whose effects on violence consistently showed evidence of mediation. Neurocognition therefore appears to be a distal risk factor for violence whose influence only becomes manifest through more proximal risk factors such as social cognition, symptoms, functioning and the risk factors contained within the HCR-20.

There was a significant indirect effect of neurocognition on violence that was mediated by social cognition and violence proneness (HCR-20) in parallel. This was the only higher order mediation found, though this may reflect the size of the sample. The effect of social cognition on violence was independent of violence proneness and symptoms.

Strengths

This study contained a number of methodological strengths. First to our knowledge this is the only prospective cohort study of patients with schizophrenia and schizoaffective disorder that has examined the relationship between cognition (neurocognition and social cognition) and violence using the MATRICS Consensus Cognitive Battery (MCCB). The MCCB demonstrated its value within a forensic setting. There was evidence of concurrent validity including large and moderate correlations with independently rated measures of social functioning, psychiatric symptoms and violence proneness (violence risk).

Second, for the most part violence is not a homogenous entity. This difficulty was overcome by using an established coding scheme for classifying instrumental and reactive violence. All violent acts in this study were reactive. Violent acts often contain instrumental and reactive elements and those prone to premeditated or instrumental violence also often act violently on impulse or reactively. However it is less common for those who are mainly prone to reactive violence to be instrumentally violent [43]. The association between cognitive impairment (neurocognition and social cognition) and violence observed in this prospective study is strictly speaking an association

with reactive acts of violence. However Table 3 shows a retrospective association between the seriousness of the violence leading to admission to the forensic hospital and the MSCEIT measure of social cognition in the MCCB that is positive, the more socially competent, the more serious was the past violence (Pearson $r = 0.246$, $p = 0.020$, $n = 89$). These acts were usually delusionally driven and were not always reactive. There is some evidence for differing developmental origins of schizophrenia that may be associated with different patterns of violence [3, 71, 72]. Clarifying this relationship will require further study.

Third, this study is one of a small number of prospective cohort studies of patients with schizophrenia and schizoaffective disorder evaluating cognitive (neurocognitive and social cognitive) determinants of violence against persons [47–49] and therefore satisfies the temporal and association criteria for causal inference.

Limitations

This study took place within a secure forensic setting which may limit the generalisability of the findings for non-forensic or community settings or in prisons. However within any setting whether community or forensic, patients with schizophrenia who are at risk of violent behaviour are best identified using a reliable and valid risk assessment instrument. This study assessed violence proneness in forensic patients using the range of violence risk factors captured by the HCR-20 which has been validated in many settings [11].

The patients in this study were predominantly male. It is possible that different processes mediate violence in women patients. It has also been suggested that inpatient and outpatient violence are not comparable and that the structured routine, close observation and proximity to others within inpatient settings may be a determinant of violence. However, more recent research suggests that the risk factors predictive of outpatient violence are also predictive for inpatient violence. A history of substance abuse for example is a robust risk factor for violence amongst psychiatric patients in outpatient settings, but is also a risk factor for violent behaviour within inpatient settings, even where substance abuse prior to violent behaviour can be ruled out [13]. Similarly within forensic settings (hospital and community residences) medication adherence is carefully monitored and controlled but this risk factor remains predictive [13].

Although it was not possible to assess psychiatric symptoms concurrently with violent acts in this study, there were significant baseline differences between violent and nonviolent groups on the PANSS total score. Because the neurocognitive cognitive decline observed amongst patients with schizophrenia is thought to occur before the onset of psychosis [16, 17] as does the

impairment in social cognition [27] it would be reasonable to infer that cognition (neurocognition and social cognition) influences symptoms rather than the other way round. However because the PANSS data was assessed at baseline only, it is not possible to be more definitive concerning whether psychiatric symptoms immediately preceded violent incidents. Although mediation effects between neurocognition, social cognition, symptoms, social functioning, violence proneness (risk) and violence worked only one way, causal statements about the relationship between neurocognition, psychiatric symptoms and violent behaviour therefore must be qualified.

We did not find evidence for serial or higher order parallel mediation pathways involving psychiatric symptoms, but this may be due to the size of the cohort. Further studies with larger numbers would be helpful.

Implications

These results are in keeping with the wider literature suggesting that cognitive difficulties (neurocognitive and social cognitive difficulties) are a risk factor for violence in many diagnostic groups [31–33, 48]. The nature of social cognition is itself a matter for continuing research and debate, although it is already recognised that deficits in social cognition occur in a range of mental disorders including autism and schizophrenia [35]. Recent genetic research has demonstrated an overlap amongst the many single nucleotide polymorphisms for schizophrenia, bi-polar affective disorder, attention deficit hyperactivity disorder and autism [73]. An overlap symptom profile or phenotype has been described for patients with schizophrenia and patients with autism spectrum disorder, consisting of selected symptoms from the PANSS negative and general symptom scales [74]. A recent empirical review has shown that the relationship between neurocognition and functioning in schizophrenia is significantly mediated by social cognition so that neurocognition influences social cognition which in turn influences functioning [30, 75]. More specifically the finding that social cognitive difficulties as measured by the MATRICS/MSCEIT were directly related to violence is also in keeping with social cognitive theories of violence and with evolving social reasoning being credited for the historical decline of violence [46].

The indirect influence of neurocognition on violence may also help explain some of the discrepancies observed within the literature; where some studies have found a relationship between cognition and violence whereas others have not. Also although much work has been done identifying risk factors for violence in people with schizophrenia and schizoaffective disorder the relationships amongst risk factors have been scarcely studied. One cross-sectional study has reported that in patients with schizophrenia, mentalisation, defined as

the ability to attribute mental states to others, mediates the relation between psychopathy and type of aggression. This mediation is facilitated by a specific mentalising profile characterised by the presence of intact cognitive and deficient emotional mentalising capacities associated with deliberate aggression [76]. Deficits in mentalisation have also been associated with self-reported aggression in cross-sectional studies [77]. The current study sheds light on the relationship between a range of variables and subsequent actual violence.

Research on related constructs such as mentalisation and metacognition may help guide future research on treatment. Mediation analysis may help elucidate the relationship between a range of variables which could be targeted by psychological intervention. Deficits in mentalisation for example may mediate attachment styles and the expression of personality traits or personality clusters [77]. Also although measures of metacognition have not been found to distinguish between forensic and non-forensic patients with schizophrenia [78] metacognition may mediate symptom severity and social dysfunction [79]. Evidence of the relationship between delusions and violence in schizophrenia that is mediated through anger and confirmed by temporal proximity may represent an experimental confirmation of this concept [80, 81]. The relationship between delusions, anger and violence [82, 83] has at times been referred to as 'affect-logic' [83–85].

Recently several psychotherapeutic approaches have been developed to improve various neurocognitive and social cognitive domains in schizophrenia including cognitive remediation therapy [86–88], metacognitive approaches [89, 90] and mentalisation-based treatment [90, 91], all of which may prove useful for reducing violence risk for patients with schizophrenia. Improvements in social and emotional reasoning on an ability test such as the MSCEIT may be a useful intermediary marker regarding the effectiveness of these programmes. This study formed part of the preliminary work for a study of cognitive remediation therapy in schizophrenia and schizoaffective disorder. We believe there is now a need for a range of studies of means to improve neurocognition and social cognition in patients with schizophrenia in order to improve social function and reduce risk factors for violence and other adverse outcomes.

The findings of this study may also have implications for understanding mental capacity amongst patients with schizophrenia. The current legal model that distinguishes between dynamic impairments of mental capacity supposedly due to psychiatric symptoms and fixed impairments of mental capacity due to intellectual disability may prove to be a false dichotomy. The legal model assumes that when symptoms of schizophrenia spectrum disorders resolve, general and function specific mental incapacities

will also resolve. This may also prove to be a false assumption. However there is some tentative evidence that the metacognitive therapy of Moritz et al. [89] may enhance functional mental capacities relevant to competence and legal status [92].

Conclusions

Research in schizophrenia should concentrate on functional outcomes. Violence is itself evidence of impaired social function, as well as a cause of stigma. In this study, impairments of neurocognition and social cognition experienced by forensic patients with schizophrenia and schizoaffective disorder accounted for a large portion of the variance of subsequent violent behaviour. However the link is nuanced and indirect. Deficits in social reasoning may be more important than other neurocognitive abilities. Neurocognition appears to be linked to violence insofar as it affects higher level social reasoning processes, psychiatric symptoms, social functioning, and violence proneness as measured by the HCR-20 violence risk scores. The neurocognitive difficulties experienced by forensic patients with schizophrenia and schizoaffective disorder may therefore create the foundation for a range of risk factors and impairments of function, which in turn are causally related to violence.

Additional file

Additional file 1: Mediation effects demonstrated.

Abbreviations

HCR-20: Historical-clinical-risk management-20; DSM-5: Diagnostic and statistical manual of mental disorders, 5th edition; ICD-10: International classification of diseases, 10th edition; MATRICS: Measurement and treatment research to improve cognition in schizophrenia; MCCB: MATRICS Consensus cognitive battery; MSCEIT: Mayer-Salovey-Caruso Emotional Intelligence Test; WAIS: Wechsler adult intelligence scale; NART: National adult reading test; SOPAS: The social and occupational functioning assessment scale; PANSS: Positive and negative symptom scale; NFMHS: National forensic mental health service; CMH: Central Mental Hospital; DSM-IV-TR: Diagnostic and statistical manual of mental disorders fourth edition text revision; TOPF-UK: Test of premorbid functioning; DUNDRUM: Dangerousness, understanding, recovery and urgency manual; ROC: Receiver operating characteristic; AUC: Area under the curve; CPZeq: Chlorpromazine equivalents; SPSS-22: Statistical package for the social sciences, version 22; ANOVA: Analysis of variance; SD: Standard deviation; 95 % CI: 95 percent confidence interval; MANOVA: Multivariate analysis of variance; OR: Odds ratio.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

KOR originated the conception and design of the study and the analysis and interpretation of the data, with substantial involvement also of GD and HGK. CC, DO'S, AR, ML, TMD, LMcG, YE, EW, LB, EQ, RM, MD and ZA all contributed substantially to the acquisition of data and all met the guidelines for authorship. All authors have read and approved the final manuscript.

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Anticholinergic burden in schizophrenia and ability to benefit from psychosocial treatment programmes: a 3-year prospective cohort study

K. O'Reilly^{1,2}, P. O'Connell^{1,2}, G. Donohoe³, C. Coyle¹, D. O'Sullivan¹, Z. Azvee¹, C. Maddock¹, K. Sharma¹, H. Sadi¹, M. McMahon¹ and H. G. Kennedy^{1,2*}

¹National Forensic Mental Health Service, Central Mental Hospital, Dundrum, Dublin, Ireland

²Department of Psychiatry, Trinity College Dublin, Ireland

³Department of Psychology, National University of Ireland, Galway, Ireland

Background. Many medications administered to patients with schizophrenia possess anticholinergic properties. When aggregated, pharmacological treatments may result in a considerable anticholinergic burden. The extent to which anticholinergic burden has a deleterious effect on cognition and impairs ability to participate in and benefit from psychosocial treatments is unknown.

Method. Seventy patients were followed for approximately 3 years. The MATRICS consensus cognitive battery (MCCB) was administered at baseline. Anticholinergic burden was measured with the Anticholinergic Cognitive Burden (ACB) scale. Ability to benefit from psychosocial programmes was measured using the DUNDRUM-3 Programme Completion Scale (D-3) at baseline and follow-up. Psychiatric symptoms were measured using the PANSS. Total antipsychotic dose was measured using chlorpromazine equivalents. Functioning was measured using the Social and Occupational Functioning Assessment Scale (SOFAS).

Results. Mediation analysis found that the influence of anticholinergic burden on ability to participate and benefit from psychosocial programmes was completely mediated by the MCCB. For every 1-unit increase on the ACB scale, change scores for DUNDRUM-3 decreased by -0.27 points. This relationship appears specific to anticholinergic burden and not total antipsychotic dose. Moreover, mediation appears to be specific to cognition and not psychopathology. Baseline functioning also acted as mediator but only when MCCB was not controlled for.

Conclusions. Anticholinergic burden has a significant impact on patients' ability to participate in and benefit from psychosocial treatment programmes. Physicians need to be mindful of the cumulative effect that medications can have on patient cognition, functional capacity and ability to benefit from psychosocial treatments.

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Key words: Anticholinergic burden, cognition, MCCB, psychosocial treatments, schizophrenia.

Introduction

The neurocognitive theory of schizophrenia has demonstrated explanatory reach (Deutsch, 2011; Kahn & Keefe 2013). Cognitive impairment accounts for a range of outcomes including ability to live independently, employment, quality of life and reactive violence in addition to response to antipsychotic medication (Kim *et al.* 2008; Chang *et al.* 2013; Kahn & Keefe, 2013; O'Reilly *et al.* 2015). Although pharmacotherapy is the primary treatment for the symptoms of schizophrenia (Leucht *et al.* 2012) such as delusions and hallucinations, it is less effective for negative symptoms

like lack of motivation, nor is it effective for cognitive impairment (Harvey & Bowie, 2012; Nielsen *et al.* 2015). Only one in seven patients achieve recovery when defined as clinical and social adaptation sustained over time (Jääskeläinen *et al.* 2013). Psychosocial treatments are generally used to address the functional disability that characterizes schizophrenia (Grant *et al.* 2011). Unfortunately cognitive problems may also interfere with the effectiveness of these interventions (Green *et al.* 2000; Kurtz, 2011; O'Reilly *et al.* 2016).

To facilitate the development of cognitive enhancing agents the US National Institute of Mental Health devised a neuropsychological battery for treatment studies, the MATRICS consensus cognitive battery (MCCB; Nuechterlein *et al.* 2008). The US Food and Drug Administration (FDA) requires that cognitive enhancing agents be supported by both evidence of

* Address for correspondence: Professor H. G. Kennedy, Central Mental Hospital, Dundrum, Dublin, Ireland.
(Email: kennedh@tcd.ie)

change in cognitive performance and improvements in 'real world' functioning (Buchanan *et al.* 2005). Currently pharmacological attempts to enhance cognition among patients with schizophrenia have been unsuccessful (Harvey & Bowie, 2012). The reason for this is unclear. Excessive synaptic pruning may limit the potential for improving cognition via neurotransmitters (Keshavan *et al.* 1994; Harvey & Bowie, 2012; Sekar *et al.* 2016). But the use and dose of concurrent medications may also be important (Harvey & Bowie, 2012). One mechanism through which a deleterious effect of concurrent medications might occur is via the cholinergic system (Nebes *et al.* 2005; Campbell *et al.* 2009). The cholinergic system is a series of pathways from the basal forebrain radiating throughout the cerebral cortex and involved in regulating attention and memory (Chudasama *et al.* 2004; Sarter *et al.* 2005).

Most antipsychotic medications administered to patients with schizophrenia possess anticholinergic properties (Chew *et al.* 2008). The side-effect profile of antipsychotic medication is also sometimes treated with anticholinergic agents. In recognition of this the FDA-NIMH-MATRICS Guidelines for Clinical Trial Design of Cognitive-Enhancing Drugs require that first-generation antipsychotics can be utilized in clinical trials but only with no additional anticholinergic agents (Buchanan *et al.* 2011). Over 50% of people with schizophrenia also have other psychiatric or general medical conditions which require treatment (Green *et al.* 2003; Jones *et al.* 2004). Many medications for treating these non-psychiatric problems have anticholinergic properties. Pharmacological treatments when aggregated may create a considerable anticholinergic burden that impairs cognition, functional capacity and ability to benefit from psychosocial treatments amongst a group of patients who are already cognitively impaired (Vinogradov *et al.* 2009; O'Reilly *et al.* 2015).

To our knowledge only one study has investigated whether anticholinergic burden moderates the effectiveness of behavioural treatments (Vinogradov *et al.* 2009). Serum anticholinergic activity uniquely accounted for 20% of the variance in change of global cognition following a programme of cognitive remediation therapy, independent of age, IQ or symptom severity. A limitation of this study was that it consisted of patients who were treatment responsive and who volunteered to participate in 50 hours of intensive therapy. Moreover, the study was limited to cognitive outcome and did not examine the effect of anticholinergic burden on functional status. Because cognitive impairment in schizophrenia is an important goal of treatment and because cognitive deficits are known to affect patients' ability to benefit from psychosocial programmes it is necessary

to examine whether anticholinergic burden affects patients' ability to benefit from treatments.

- (1) We hypothesized that the relationship between anticholinergic burden and ability to benefit from psychosocial treatment programmes would be mediated by cognitive ability, when controlling for age, gender, baseline performance on psychosocial treatment programmes, total antipsychotic dose, and symptoms.
- (2) We hypothesized that the mediation relationship between medication, cognition, and programme completion would be specific to anticholinergic burden and not total antipsychotic dose; and that the mediation would be specific to cognition, not to symptoms or functioning when cognition is controlled for.

Method

This was a naturalistic 3 year prospective observational cohort study of anticholinergic burden, cognitive ability and patient benefit from psychosocial treatment programmes. Data were gathered from 2012 to 2015. Baseline data was gathered in 2012. Follow up data was gathered until the end of 2015. All of the assessments were completed by assessors who were blind to the results of the other assessments

Participants and setting

The National Forensic Mental Health Service (NFMHS) for Ireland provides specialized care for adults who have a mental disorder and are at risk of harming themselves or others. At the time of the study the NFMHS had 94 secure inpatient beds located on a single campus, the Central Mental Hospital (CMH), and 13 supervised community beds for those discharged subject to conditions. The CMH is the only secure forensic psychiatric hospital for the Republic of Ireland.

Inclusion criteria were having a diagnosis of schizophrenia or schizoaffective disorder and being judged to be able to provide informed consent. A total of 123 patients were invited to participate during 2012. Of these eight patients declined to take part and 15 did not have a diagnosis of schizophrenia or schizoaffective disorder as assessed by a consultant psychiatrist using the Structured Clinical Interview for DSM-IV (SCID; First *et al.* 2002). Of the 100 remaining, 19 patients were discharged and one patient died before they could complete the programme completion assessment at follow-up, one patient was judged to be feigning during the assessment, and one patient did not complete the cognitive assessment, while eight patients did not complete the Positive and

Table 1. Demographics and sample characteristics

	<i>n</i> = 70	Median	s.d.
	Mean (range)		
Age (years)	39.5	37.5	11.1
Gender	66 male, 4 female		
Length of stay at baseline (years)	7.73	5.79	8.07
Length of follow up period (years)	2.94	3.24	0.84
Baseline D-3	16.54	17	6.63
Follow up D-3	15.01	13	7.36
Change score D-3	1.52 (range 29)	1	5.22
Estimate of Premorbid Intelligence TOPF-UK (standard score)	96.8	98	11.9
MCCB Composite (<i>t</i> score)	21.3	21.5	14.25
SOFAS	56.64	59	19.72
PANSS Total score	64.12	60	21.67
CPZeq (mg/day)	529.15	471	339.45
ACB score	4.40 (range 14)	3	2.80

D-3, DUNDRUM-3 Programme Completion Scale; TOPF, Test of Premorbid Functioning; MCCB, Matrices consensus cognitive battery; SOFAS, Social and Occupational Functioning Assessment Scale; PANSS, Positive and Negative Symptom Scale; CPZeq, chlorpromazine equivalent; ACB, Anticholinergic Cognitive Burden scale.

Negative Syndrome Scale (PANSS; Kay *et al.* 1987) assessment. Of the 70 patients that remained in the study 59 patients has a SCID diagnosis of schizophrenia and 11 a diagnosis of schizoaffective disorder. There were 66 male (94.3%) and four female (5.7%) patients. The mean age of patients in the study was 39 years (s.d.=11.1).

The mean length of stay at baseline for the 70 patients was 7.73 years (s.d.=8.07), median 5.79. Of the 70 patients included in the study 62 (88%) remained in the study until 2015. Seven patients were discharged during the 3-year follow-up and one patient died. As assessments were carried out every 6 months, the last assessment was taken. Demographic details and sample characteristics are presented in Table 1.

Cognitive assessment

Patients were assessed using the Measurement and Treatment to Improve Cognition in Schizophrenia (MATRICS) Consensus assessment battery of cognitive deficits in schizophrenia (MCCB), and also the Test of Premorbid Functioning (TOPF-UK; Wechsler, 2011). The mean MCCB composite score was 21.32 (s.d.=14).

Scores for estimated pre-morbid intelligence (TOPF-UK) were not adjusted for education as an estimate of premorbid ability because the symptoms associated with mental disorder can affect educational

attainment. A small number of patients (*n* = 7) could not complete the TOPF-UK because of literacy problems. The mean estimated premorbid IQ was 96.8 (s.d.=12.0).

Functional performance

The Social and Occupational Functioning Assessment Scale (SOFAS) was completed by a member of the multidisciplinary team responsible for the care of the patient, who was blind to the other assessments including the cognitive assessment (Rybarczyk, 2011). The mean score on the SOFAS was 57 (s.d.=20).

Programme completion

The DUNDRUM-3 Programme Completion Scale (D-3) is a structured clinical judgement instrument taken from the DUNDRUM toolkit which assesses whether patients have participated in, engaged and benefited from psychosocial programmes (Kennedy *et al.* 2010). An independent review found that the scale met requirements for routine outcome measures examining functioning, recovery, risk and placement pathways within forensic mental health populations (Shinkfield & Ogloff, 2014). The D-3 has also been shown to distinguish significantly between groups of patients at different levels of therapeutic security within a forensic setting (Davoren *et al.* 2012); and it has been shown

to predict moves between levels of therapeutic security and to predict conditional discharge from a secure hospital (Davoren et al. 2013).

The D-3 has seven items measuring outcomes for programmes concerning physical health, mental health, drugs and alcohol, problem behaviours, self-care and activities of daily living, education occupation and creativity, and family and social networks. These items are intended to cover the domains of health defined by the WHO (1986), which holds that health is 'a resource for everyday life, not the objective of living. Health is a positive concept emphasizing social and personal resources, as well as physical capacities.' Each item is rated on a 5-point scale with lower scores representing a higher level of participation, sustained engagement and change. Engagement is demonstrated through more than simply having attended all sessions of a programme. This battery of assessments encompasses the range of interventions typically offered for patients with schizophrenia in a modern forensic hospital over a time scale of years rather than months. Annual audits during the period of this study showed that patients achieved a target of 25 h a week of timetabled therapeutic activity and represents 'treatment as usual'.

The mean D-3 score at baseline was 16.5 (s.d.=6.63) which is the total score for all seven items. The mean D-3 at follow up was 15.0 (s.d.=7.36). D-3 change scores were calculated by subtracting the D-3 score at follow-up from the D-3 at baseline to estimate the strength of the anticholinergic effect. The mean change in D-3 score over the follow-up period was 1.52 (s.d.=5.22).

Symptom assessment

The PANSS was completed on all 70 patients who remained in the study. The PANSS assessments were completed by a psychiatric registrar and an assistant psychologist trained in its use, who were blind to the cognitive assessments. The mean PANSS Total score at baseline was 64 (s.d.=22).

Medication

A recent review indicated that evidence is not sufficiently robust for any one of a number of methods of calculating dose equivalence for different antipsychotic medications to be considered as a gold standard, and justification should be offered for the method chosen in any particular study (Patel et al. 2013). A chlorpromazine equivalent (CPZeq) was calculated for each participant as a measure of his/her relative daily dose of antipsychotic medications (Taylor et al. 1994; Woods, 2003; Haddad et al. 2010). CPZeq was selected for calculating antipsychotic dose as it is a widely used and coherent method, appeared to have the best face validity for the purposes of this study and produces

similar results to other approaches such as the British National Formula percentage maximum dose and defined daily dose (Sweileh et al. 2014). The mean CPZeq score at baseline was 529.15 mg/day (s.d.=339.45).

Anticholinergic burden

Anticholinergic burden was assessed using the Anticholinergic Cognitive Burden (ACB) scale (Boustani et al. 2008). The ACB scale was developed by a multidisciplinary expert panel based on a systematic review of medications with known anticholinergic activity likely to have an effect on cognition. The ACB scale contains 88 listed medications. Each listed medication can be rated on a 4-point scale (0-3): 0 = no anticholinergic activity, 1 = mild anticholinergic activity, 2 = moderate anticholinergic activity, and 3 = severe anticholinergic activity. The total anticholinergic burden is then calculated by aggregating the score for each listed medication. The ACB scale has been validated in a range of studies (Salahudeen et al. 2015).

The ACB scale was scored from prescription charts by a consultant psychiatrist (P.O.C.) the week prior to the baseline cognitive assessment. The mean ACB score at baseline was 4.40 (s.d.=2.80), mode 3; 75% of the sample had an ACB score <6. Table 2 shows that many of the medications contributing to ACB score were non-psychiatric. No benzodiazepines were prescribed.

Statistical analysis

Distributions of all measures were screened for outliers and evaluated for normality. One case was assessed as being an outlier on the ACB scale using an outlier labelling method and visual inspection of plots. This case was winsorized to the value of the next highest case not considered an outlier. Four cases were determined to be outliers for the change score on the D-3. These cases were also winsorized to the next highest or lowest case not considered to be an outlier. Following the removal of outliers both the ACB score and the D-3 change scores were normally distributed. The variables age, baseline 2012 D-3 and CPZeq were not normally distributed and were transformed using log₁₀ and Srt transformation. The PANSS Total score and the MCCB Total score met criteria for a normal distribution and did not require any transformations.

A paired sample *t* test was used to calculate whether there was a significant difference between patients' performance on the D-3 at baseline and 3 years follow-up. Morris & DeShon's (2002) within-group effect-size formula was used to calculate the magnitude of the effect size over a 3-year period.

Table 2. Medications contributing to the anticholinergic cognitive burden (ACB) scale score

Score of 1	No.	Score of 2	No.	Score of 3	No
Atenolol	10	Carbamazepine	1	Chlorpromazine	3
Captopril	1			Clomipramine	2
Ranitidine	1			Clozapine	46
Codeine	1			Olanzapine	34
Frusemide	1			Oxybutynin	3
Haloperidol	7			Paroxetine	1
Methodone	2			Procyclidine	21
Prednisolone	2			Promethazine	1
Quinidine	1			Quetiapine	3
Risperidone	9			Scopalomine	19
				Tolterodine	2

Numbers (No.) are the numbers of patients receiving each medication. Note also that no patients were prescribed benzodiazepines.

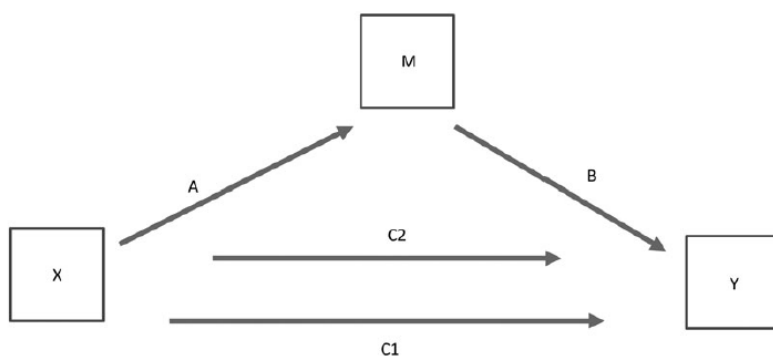


Fig. 1. C1, Direct effect of X on Y, before mediation via M; C2, direct effect of X on Y after mediation via M; A, indirect effect of X on Y mediated via M; B, direct effect of M on Y, adjusted for X.

SPSS PROCESS macro model 4 (Hayes, 2013) was used to analyse mediation relationships between anticholinergic burden measured by the ACB scale and change of D-3 scores over a 3-year period in scores on the D-3. Unstandardized effect sizes were generated for the mediation models using 10000 bootstrap samples and 95% bias-corrected confidence intervals were calculated. Age and gender were entered as covariants for all coefficients (Fig. 1).

Six specific mediation analyses were carried out to test the specificity of the relationship between anticholinergic burden, cognition, and patients' ability to participate in and benefit from treatment programmes (change in D-3 score). First, we examined whether cognitive ability as measured by the MCCB Total score would mediate the relationship between anticholinergic burden and change in D-3 score, when controlling

for age, gender, baseline performance on the D-3, psychiatric symptoms as measured by the PANSS Total score, and antipsychotic dose. Second, we examined whether MCCB also mediated an effect of dose (CPZeq) on change in D-3 score as an alternative to a specific effect of ACB. Third, we examined whether psychiatric symptoms as measured by the PANSS Total score would mediate the relationship between anticholinergic burden and change in D-3 score, controlling for age, gender, cognition as measured by the MCCB Total score, antipsychotic dose and baseline performance on the D-3. Fourth, we examined whether baseline functioning as measured by the SOFAS would mediate the relationship between anticholinergic burden and change in D-3 score, when controlling for age, gender, baseline performance on the D-3, cognition as measured by the MCCB Total score,

Table 3. Pearson correlations ($n = 70$) and significance (p) values

	ACB	MCCB Total	Change scores D-3	Baseline D-3	3 years D-3	PANSS Total	CPZEqv	Baseline SOFAS
ACB	–							
MCCB Total	–0.547 0.000	–						
Change scores D-3	–0.167 0.168	0.290 0.015	–					
Baseline D-3	0.340 0.004	–0.429 0.000	0.176 0.145	–				
3 Years follow-up D-3	0.414 0.000	–0.578 0.000	–0.516 0.000	0.735 0.000	–			
PANSS Total	0.384 0.001	–0.403 0.001	–0.228 0.058	0.617 0.000	0.700 0.000	–		
CPZEq	0.402 0.001	–0.250 0.037	–0.049 0.686	0.348 0.003	0.294 0.013	0.419 0.000	–	
Baseline SOFAS	–0.523 0.000	0.603 0.000	0.235 0.050	–0.719 0.000	–0.790 0.000	–0.631 0.000	–0.342 0.004	–

ACB, Anticholinergic Cognitive Burden scale; MCCB, Matrics consensus cognitive battery; Change scores D-3, DUNDRUM-3 Programme Completion Change Scale scores; Baseline D-3, DUNDRUM-3 Programme Completion Scale scores at baseline; 3 years follow-up D-3, DUNDRUM-3 Programme Completion Scale score at follow-up; PANSS, Positive and Negative symptom Scale; CPZEq, chlorpromazine equivalent; SOFAS, Social and Occupational Functioning Assessment Scale.

antipsychotic dose, and psychiatric symptoms. Fifth, we examined whether cognition (MCCB Total score) would act as mediator when additionally controlling for baseline functioning (SOFAS), and whether baseline functioning (SOFAS) would act as a mediator when cognition (MCCB) was not controlled.

Ethical standards

This study was approved by the research ethics and effectiveness committee of the NFMHS and complied with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All participants gave written informed consent.

Results

Magnitude of change over a 3-year period within a forensic mental health service

The mean follow-up period ($n = 70$) was 2.94 years (s.d.=0.840). The mean change in D-3 score was -1.528 units s.d. 5.22. This was a significant change [paired $t = 2.448$, $df = 69$, $p < 0.017$; 95% confidence interval (CI) 2.77–0.28]. The Pearson correlation between baseline programme completion and programme completion at 3-year follow-up was $r = 0.726$.

The magnitude of effect of 3 years of treatment in a forensic mental health service using D-3 was 0.295 (Cohen's d).

Anticholinergic burden and change in programme completion scores over 3 years

The MCCB Total score completely mediated the relationship between anticholinergic burden (ACB) and the change in D-3 scores, when controlling for age, gender, baseline programme completion, total antipsychotic dose (CPZEq), and total psychopathology (PANSS). The unstandardized indirect effect of anticholinergic burden as measured by the ACB scale through cognition as measured using the MCCB Total score was -0.27 (95% CI -0.58 to -0.0545) (Table 3) which can be read that for every 1-point increase on the ACB scale changes on the D-3 decrease by -0.27 points.

Cognition as a mediator between CPZeqs and change in programme completion score

To test the hypothesis that anticholinergic burden and not total antipsychotic dose had a specific effect on cognition which in turn influenced the functional outcome of programme completion we constructed a mediation model where CPZEq was the independent variable and controlled for anticholinergic burden,

age, gender, psychopathology, and baseline programme completion. There was no evidence of a direct effect or an indirect effect via cognition for CPZeq on programme completion, when controlling for ACB and other variables.

Total psychopathology as a mediator between anticholinergic burden and change scores for 3 years and programme completion

To test the hypothesis that the effects of anticholinergic burden were specific to cognition and not psychopathology in general we constructed a model where PANSS Total score was the proposed mediator controlling for age, gender, baseline programme completion, CPZeq, and the MCCB Total score. There was no evidence of an indirect effect of PANSS Total score on change in D-3 score when controlling for other variables.

SOFAS as a mediator between anticholinergic burden and change in programme completion scores over 3 years

To test the hypothesis that the effect of anticholinergic burden was specific to cognition we constructed a mediation model where the effect of anticholinergic burden on change in D-3 score was mediated by social and occupational functioning (SOFAS) controlling for age, gender, baseline programme completion, MCCB Total Score, CPZeq, and PANSS Total score. Social and occupational functioning as measured by the SOFAS significantly mediated the relationship between ACB and change in programme completion but only when MCCB Total score was removed from the model.

Cognition as a mediator between anticholinergic burden and change in programme completion scores when controlling for social and occupational functioning

When controlling for social and occupational functioning at baseline the MCCB Total score no longer mediated ACB and change in D-3 scores (Table 4).

Post-hoc analysis

A *post-hoc* analysis exploring the mediation relationship between ACB, cognition (MCCB Total score) and disability or functioning (SOFAS) was also conducted, controlling for age, gender, psychopathology (PANSS Total) and medication (CPZeq). This analysis again used PROCESS and 10 000 bootstrapped samples. In total the model accounted for 59% of the variance of functioning (SOFAS). The direct effect of ACB on functioning (SOFAS) was not significant (-0.7657 , 95% CI -2.4759 to 0.9445). However, the mediated

effect via cognition (MCCB) was significant (-1.4651 , 95% CI -2.5479 to -0.6905). For every 1-point increase in anticholinergic burden score, functioning (SOFAS) declined by 1.4651 points.

This effect was specific to cognition being fully mediated by MCCB score. Psychopathology (PANSS Total) did not mediate the relationship between ACB and functioning when cognition was controlled for (-0.4508 , 95% CI -1.558 to 0.4978). Further, the effect was specific to anticholinergic burden and not total antipsychotic dose. CPZeq did not affect functioning (SOFAS) via cognition, when ACB was controlled for (0.0028 , 95% CI -0.0026 to 0.0089).

Discussion

This is the first study to demonstrate that anticholinergic burden has a negative impact on the outcomes of psychosocial treatment programmes for patients with schizophrenia or schizoaffective disorder. It is noteworthy that many of the medications contributing to the ACB score were non-psychiatric. This adverse effect on psychosocial treatments appears to be mediated specifically through impaired cognitive capacity. The patients within this prospective cohort were cognitively impaired at baseline and had a mean MCCB *t* score composite of 21.3, which is almost 3 s.d. below the non-clinical mean. A score of this size approximates the cognitive abilities of individuals with a moderate intellectual disability. The cognitive ability of patients within this sample is especially marked given that their estimated premorbid IQ was found to be in the average range. Anticholinergic burden in part appeared to be a determinant of cognitive ability and psychosocial treatment outcomes. Within this study for every 1-unit increase on the ACB scale, patients change in D-3 scores, a scale measuring participation and benefit from psychosocial treatment programmes, decreased by -0.27 points. This decrease needs to be taken in context that the mean change score on the D-3 was 1.52 over the 3-year period (Cohen's $d=0.29$). The range of change in D-3 score was, however, very wide (Table 1). Anticholinergic burden impairs cognition, which in turn impairs the ability to benefit from treatment programmes, even when controlling for a range of confounding variables including age, gender, antipsychotic dose and symptom severity.

These findings appear to be specific to anticholinergic burden and cognition. The effect of total antipsychotic dose on change in programme completion score was not mediated by cognition. Since no benzodiazepines were prescribed, these could not have contributed to slowed processing speed. Moreover, total psychopathology (PANSS) did not mediate the effect of anticholinergic burden on change in programme

Table 4. Regression and mediation coefficients

Mediator (N = 70)	Change in programme completion		C1: direct effect of X on Y before mediation		C2: direct effect of X on Y after mediation		A: indirect effect of X on Y mediated via M		B: direct effect of M on Y adjusted for X	
	R ²	p	Unstandardized effect size	95% CI	Unstandardized effect size	95% CI	Unstandardized effect size	95% CI	Unstandardized effect size	95% CI
Model 1										
X - ACB	0.33	0.000	-0.3653	-0.8555 to 0.1250						
M - MCCB					-0.0908	-0.6214 to 0.4397	-0.2744	-0.5897 to -0.0545	0.1104	0.0148 to 0.2060
Model 2										
X - CPZeq	0.33	0.000	1.2032	-3.8297 to 6.2362						
M - MCCB					0.7165	-4.1716 to 5.6046	0.4867	-0.6244 to 2.4977	0.1104	0.0148 to 0.2060
Model 3										
X - ACB	0.33	0.000	-0.2236	-0.7837 to 0.3364						
M - PANSS					-0.0908	-0.6214 to 0.4397	-0.1328	-0.4043 to 0.0624	-0.0989	-0.1612 to -0.0365
Model 4										
X - ACB	0.41	0.000	-0.0908	-0.6214 to 0.4397						
M - SOFAS					0.0529	-0.4555 to 0.5612	-0.1437	-0.4033 to 0.0244	0.1242	0.0416 to 0.2067
Model 5										
X - ACB	0.41	0.000	-0.0761	-0.5538 to 0.4017						
M - MCCB					0.0529	-0.4555 to 0.5612	-0.1289	-0.3904 to 0.0308	0.0666	-0.0280 to 0.1611
Model 6										
X - ACB	0.34	0.0002	-0.3653	-0.8555 to 0.1250						
M - SOFAS					-0.0761	-0.5538 to 0.4017	-0.2892	-0.6079 to -0.0674	0.1421	0.0630 to 0.2212

CI, Confidence interval; ACB, Anticholinergic Cognitive Burden scale; MCCB, Matrix consensus cognitive battery; CPZeq, chlorpromazine equivalent; PANSS, Positive and Negative Symptom Scale; SOFAS, Social and Occupational Functioning Assessment Scale.

In all cases, the outcome (Y) is 'Change in DUNDRUM-3 Programme Completion Scale scores'. X is the hypothesized determinant factor and M is the hypothesized mediating factor. Total sample n = 70.

Models 1, 2, 3 include age, gender, DUNDRUM-3 Programme Completion Scale (D-3) baseline scores; PANSS Total, MCCB Total, and CPZeq. Models 4 and 5 also include SOFAS in addition to age, gender, D-3 Baseline, PANSS Total, MCCB Total and CPZeq. Model 6 does not include or control for MCCB and contains ACB, SOFAS, age, gender, PANSS Total, and CPZeq. In each case the dependent variable (Y) is change scores on the D-3.

completion scores. Clinicians' ratings of patients' psychosocial and occupational functioning (SOFAS) also did not mediate the relationship between anticholinergic burden and change in programme completion when cognition was controlled for. But SOFAS did mediate the relationship between anticholinergic burden and programme completion when cognitive ability was removed from the model, presumably because functioning is in part dependent on cognitive capacity.

Our *post-hoc* analysis demonstrates that anticholinergic burden may impact on patient disability as measured by the SOFAS. This effect again is specific to cognition as demonstrated by mediation analysis. Mediation analysis also shows that the effect of ACB on SOFAS is specific to anticholinergic burden and not total antipsychotic dose (CPZeq). This may have implications for rehabilitation in schizophrenia.

The findings of this study may go some way to explaining why Wunderink *et al.* (2013) found that dose reduction of antipsychotic medication was linked with superior functional but not symptomatic remission in comparison to maintenance treatment at 7 years follow-up. Reductions in anticholinergic burden may have been the mechanism responsible for this improved psychosocial functioning. It has been suggested that treatments like CBT may not be as helpful for patients with schizophrenia as for some other problems (Jauhar *et al.* 2014). But psychological interventions have a robust evidence base for a range of disorders (Carr, 2009). One reason for reduced efficacy in schizophrenia may be that cognitive impairments affect patients' ability to attend to, process, store, and use the information offered during psychological interventions (Green *et al.* 2000; Kurtz, 2011). This study illuminates a possible iatrogenic effect that pharmacotherapy can have on cognition and functioning, which in turn affects the outcome of psychosocial treatment. Cognitive ability and anticholinergic burden should therefore routinely be considered as moderators in clinical trials of psychological therapy for patients with schizophrenia.

We do not propose that anticholinergic burden is the sole cause of cognitive impairments amongst patients with schizophrenia or even the major cause, because these difficulties have been observed in medication naïve patients (Kahn & Keefe, 2013). However our findings do suggest that anticholinergic burden may have adverse effects for patients with schizophrenia. There are studies suggesting that there is a widespread decrease in muscarinic receptors in the brains of people with schizophrenia (Scarr *et al.* 2013) including post-mortem studies (Mancama *et al.* 2003; Zavitsanou *et al.* 2004; Newell *et al.* 2007; Gibbons *et al.* 2013) and a brain-imaging study (Raedler *et al.* 2003). Similar to older patients, or those with dementia, people with

schizophrenia are likely to have a vulnerable brain with a paucity of cholinergic neurons (Tune, 2001; Campbell *et al.* 2009; van Haren *et al.* 2011; Harvey & Bowie, 2012; Kahn *et al.* 2015; Gray *et al.* 2015; Kubota *et al.* 2015). Physicians are therefore required to conduct careful risk benefit decisions and collaborate with patients regarding the medications they prescribe. The ACB scale may be a useful clinical tool for helping physicians and patients make these decisions. Because verbal intelligence in people with schizophrenia is largely intact (Michel *et al.* 2013), it may be particularly challenging for physicians to identify declines or impairments in other cognitive domains. Also cognitive screening instruments may not be helpful as they do not take account of a patient's premorbid intellectual ability or have enough sensitivity to change (Lezak *et al.* 2012). Therefore comprehensive neuropsychological assessment using psychometrically robust and functionally relevant instruments may be important in the planning of care and treatment for people with schizophrenia.

This study has a number of methodological strengths as well as limitations. Strengths include a sample made up of most of a national cohort of forensic patients diagnosed with schizophrenia or schizoaffective disorder. This sample was followed up over a 3-year period. The use of the MCCB measure for assessing cognitive problems in schizophrenia and controlling for a range of confounders including psychopathology and antipsychotic dose are also strengths. Furthermore, all measurements were conducted independently of each other.

Limitations in this study include the specialist sample consisting entirely of forensic patients which may raise questions regarding the generalizability of the results to other samples of patients with schizophrenia. Patient participation and benefit from psychosocial treatment programmes was measured using the D-3 which has been specifically developed and recommended for this patient group. This scale takes account of the wide range of psychosocial interventions provided for hospitalized patients over a 3-year period. Because no attempt is made here to distinguish between treatment responses to different treatment programmes, the overall effect measured is a measure of 'treatment as usual' with multi-disciplinary delivery of programmes. The sample in this study was cross-sectional rather than an incident series of new admissions. To achieve an incident sample of sufficient size, a very prolonged study over as much as a decade would have been required, or a multi-centre study.

This study supports the validity of the ACB scale given its correlations with the MCCB, SOFAS, and D-3. However it is important to point out that a number of criticisms have been levelled at anticholinergic burden scales. There is no consensus for how to

calculate anticholinergic burden. Although a bioassay of serum anticholinergic activity has in the past been considered the gold standard it is only a marker of anticholinergic activity in serum, and not in the brain (Hori et al. 2014). Also dosage is not considered within clinical scales such as the ACB and medications are unlikely to have a simple 0:1:2:3 ratio in relation to dose or in relation to each other. However, a number of studies have found that unit weighting as used in the ACB scale is quite robust for making predictions (Dawes, 1979). Unit weighting performs particularly well where the criterion (in this case central anticholinergic effect) cannot be quantified and this is precisely the case regarding anticholinergic burden (Dawes, 1979). Unit weighting also performs well when there is not a straightforward relationship between the predictor variables and the criterion (Dawes, 1979), and there is considerable individual variation in absorption, distribution, rate of metabolism, formation, and excretion of pharmacologically active metabolites (Pollock, 2000). A third criticism of anticholinergic scales is that there is variability in the quantification of anticholinergic burden across different instruments. However, unit weighting is also viable when it is difficult to develop a regression model because of a larger number of predictors. There are more than 600 medications that have anticholinergic activity (Chew et al. 2008). Finally, because medications with anticholinergic properties do not have a straightforward relationship with cognitive decline the correlation between scales may be a better measure of construct validity than the kappa coefficient (Lertxundi et al. 2013).

Although a number of confounding factors were controlled for there was no attempt to manipulate any variable and therefore the study only approximates a causal design. The value of this study is that it establishes a case for an intervention study using meaningful outcome measures concerning treatment engagement and response, and real world functional outcomes. A number of studies have suggested that discontinuing anticholinergic treatments had a positive effect on cognition among patients with schizophrenia (Baker et al. 1983; Mori et al. 2002; Drimer et al. 2004; Ogino et al. 2011; Desmarais et al. 2014). But no study has yet examined whether improvements in cognition following reduction in anticholinergic burden have in turn affected real-world functioning.

Conclusion

Anticholinergic burden as measured by the ACB scale had a significant impact on patient ability to participate and benefit from psychosocial treatments within a forensic hospital as measured by change in D-3 score. Anticholinergic burden appears to impair

cognitive ability and real-world functioning, which in turn affects patient ability to participate in and benefit from psychosocial programmes. Physicians need to be mindful of the cumulative effect that psychiatric and other medications can have on cognitive ability, functional capacity, and ability to participate and benefit from psychosocial treatments.

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Declaration of Interest

None.

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STUDY PROTOCOL

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Study protocol: a randomised controlled trial of cognitive remediation for a national cohort of forensic mental health patients with schizophrenia or schizoaffective disorder

Ken O'Reilly^{1,2}, Gary Donohoe¹, Danny O'Sullivan², Ciaran Coyle², Ronan Mullaney^{1,2}, Paul O'Connell^{1,2}, Catherine Maddock², Andrea Nulty², Padraic O'Flynn², Carina O'Connell² and Harry G Kennedy^{1,2*}

Abstract

Background: Evidence is accumulating that cognitive remediation therapy (CRT) is an effective intervention for patients with schizophrenia or schizoaffective disorder. To date there has been no randomised controlled trial (RCT) cohort study of cognitive remediation within a forensic hospital. The goal of this study is to examine the effectiveness of a trial of cognitive remediation for forensic mental health patients with schizophrenia or schizoaffective disorder.

Methods: An estimated sixty patients will be enrolled in the study. Participants will be randomised to one of two conditions: CRT with treatment as usual (TAU), or TAU. CRT will consist of 42 individual sessions and 14 group sessions. The primary outcome measure for this study is change in cognitive functioning using the MATRICS Consensus Cognitive Battery (MCCB). Secondary outcomes include change in social and occupational functioning, disorganised symptoms, negative symptoms, violence, participation in psychosocial treatment and recovery. In addition to these effectiveness measures, we will examine patient satisfaction.

Discussion: Cognitive difficulties experienced by schizophrenia spectrum patients are associated with general functioning, ability to benefit from psychosocial interventions and quality of life. Research into the treatment of cognitive difficulties within a forensic setting is therefore an important priority. The results of the proposed study will help answer the question whether cognitive remediation improves functional outcomes in forensic mental health patients with schizophrenia or schizoaffective disorder. Forensic mental health patients are detained for the dual purpose of receiving treatment and for public protection. There can be conflict between these two roles perhaps causing forensic services to have an increased length of stay compared to general psychiatric admissions. Ultimately a focus on emphasising cognition and general functioning over symptoms may decrease tension between the core responsibilities of forensic mental health services.

Trial Registration: ClinicalTrials.gov Identifier: NCT02360813. Trial registered Feb 4th 2015 and last updated May 1st 2015.

Keywords: Schizophrenia, Forensic mental health, Cognitive remediation, CRT, Neurocognition, Effectiveness, Clinical trial

* Correspondence: kennedh@tcd.ie

¹Department of Psychiatry, Trinity College Dublin, Dublin, Ireland

²National Forensic Mental Health Service, Central Mental Hospital, Dundrum, Dublin 14, Ireland



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Background

Forensic Mental Health Services (FMHS) provide treatment for a minority of people with mental illnesses such as schizophrenia who come into contact with law enforcement agencies as a consequence of their mental disorder, or who cannot be safely managed within another service and require specialised therapeutically safe and secure care and treatment for a period of time [1, 2]. The offences carried out by mental health patients are heterogeneous and range from public order offences to homicide. It is possible to divert mentally ill patients charged with less serious offences to general psychiatric services especially when detention in prison would be detrimental to their health [3]. Forensic patients are often judged to have lacked mental capacity to form a criminal intent at the time of the offence. These patients are deemed to be not responsible or diminished in responsibility for what they have done due to deficits in comprehension, reasoning, and judgment [4]. The 'insanity defence' available in some jurisdictions is a special example of a loss of capacity within the context of criminal charges such as homicide or serious assault. Patients facing criminal charges and who receive a verdict of not guilty by reason of insanity are admitted to a forensic hospital so that they can receive treatment and to ameliorate the risk of future violence [2]. Frequently the dual role of providing treatment and public protection is codified in law as is the case for the Republic of Ireland's Criminal Law (Insanity) Act (2006) section 11(2) [5]. In these circumstances independent tribunals tasked with reviewing patients' detention are asked to consider the welfare and safety of the person and also the public interest (Criminal Law Insanity Act 2010). Forensic mental health services therefore have the dual role of treating and caring for the patient and representing their interests, whilst simultaneously protecting the public from further harm through involuntary detention and risk management [6, 7].

Length of stay within Forensic Mental Health

Forensic mental health patients are typically hospitalised for longer periods than their non-forensic counterparts [7–12]. International comparisons of length of stay are difficult to establish because they are hampered by differences in patient groups and criminal law [7]. For the Republic of Ireland the vast majority of forensic mental health patients have a diagnosis of schizophrenia or schizoaffective disorder with a small minority having bipolar or depressive disorder. A diagnosis of personality disorder would not ordinarily meet the criteria of mental disorder under Irish law and would thus not qualify to receive compulsory mental health care in either the civil or forensic services (Mental Health Act 2001 and Criminal Law (Insanity) Act 2006). Even when acknowledging

differences in patient populations it would not be unusual for patients to be detained within a European context for periods greater than five years [12]. It is likely that the dual role played by forensic mental health services regarding the needs of the patient on the one hand and society on the other is a contributing factor to lengthy admissions [6].

Limitations of pharmacotherapy for treating schizophrenia

The primary treatment strategy for patients with schizophrenia or schizoaffective disorder is pharmacotherapy using antipsychotic medication, a proven and efficacious intervention for the positive symptoms of schizophrenia i.e. delusions and hallucinations [13]. Following initial gains however, pharmacotherapy has limited efficacy for improving patient functioning. Antipsychotics are not effective for treating the neurocognitive deficits associated with schizophrenia such as problems with attention, memory and executive functioning; nor do they have efficacy for treating stable, trait-like social cognitive deficits such as emotional perception, theory of mind, context sensitive processing, or emotional reasoning [14]. Antipsychotics have also limited efficacy for treating negative symptoms such as avolition, anhedonia, apathy, blunted affect, asociality, and alogia [15, 16]. It is the neurocognitive impairment, social cognitive impairment, and negative symptoms experienced by patients with schizophrenia that are the strongest contributors to functional outcome [17–20]. Meta-analyses consistently demonstrate that both neurocognitive and social cognitive deficits in addition to negative symptoms account for more of the variance of suboptimal functioning than positive symptoms [17–26]. Specifically neurocognitive and social cognitive difficulties affect the ability to live independently, to engage in meaningful work and to benefit from psychosocial treatment programs. Ultimately these impairments impact on patients' quality of life [27, 28]. Also negative symptoms are probably partially attributable to cognitive impairments [29]. Because of the centrality of neurocognitive problems for patient functioning and because neurocognitive and social cognitive deficits occur prior to the onset of psychotic symptoms it has been argued that schizophrenia should be reconceptualised as a cognitive rather than a psychotic disorder [27]. Moreover it has been suggested that the development of new therapies for improving functional outcomes for patients with schizophrenia has been impeded by emphasising the psychotic features of the disorder [27].

Limitations of psychological and occupational interventions within forensic mental health

To address patients' suboptimal functioning and violence risk factors, forensic mental health services use an

eclectic mix of occupational therapy and psychosocial treatment programmes. Many of these interventions have a limited evidence base within forensic mental health practice [30–35]. But some specific programmes such as 'reasoning and rehabilitation' have been formally assessed, using violent behaviour and attitudes as outcome measures [36, 37]. Also concern has been expressed that patients with schizophrenia and other psychotic disorders may not be able to benefit from such programmes due to their negative symptoms and cognitive deficits [19, 28]. Recently we found that a nationally representative cohort of forensic mental health patients with schizophrenia and schizoaffective disorder scored more than three standard deviations below the population mean on the MATRICS Consensus Battery for cognitive deficits in schizophrenia [38]. Amongst patients with schizophrenia difficulties can occur at any point of the informational processing stream [39, 40]. Therefore forensic mental health patients with schizophrenia may not possess the necessary motivation and basic cognitive abilities to attend to the information being presented, store the information within their memory and utilise the information when presented with future problems and challenges. But because psychological interventions have a robust evidence base for a variety of mental disorders [41], it is probable that patients with schizophrenia could benefit from such interventions if their cognitive abilities could be partially remediated, or if their self-efficacy and intrinsic motivation were enhanced.

Cognitive remediation therapy

One approach that has shown potential to improve patients' cognitive and motivational difficulties in non-forensic settings is cognitive remediation therapy [42–44]. Cognitive remediation therapy is a behaviourally based training approach designed to help patients improve their cognitive abilities and real world functioning. A variety of therapies exist under the cognitive remediation umbrella but most aim to either strengthen patients basic cognitive capacities through a process of drill and practice, or to teach patients more effective ways to deploy cognitive resources using meta-cognitive strategies. Cognitive remediation is a nonthreatening activity which patients enjoy and focuses on success and mastery experiences and therefore has the potential to increase self-efficacy [45]. A recent meta-analysis by Wykes has demonstrated that cognitive remediation is an effective intervention for patients with schizophrenia [42]. Within the Wykes meta-analysis, the average patient with schizophrenia or schizoaffective disorder who received cognitive remediation improved performance on cognitive tasks by an effect size of about .5 (Cohens *d*) and .42 on patient functioning. Also cognitive remediation therapy has been shown to produce durable improvements in cognition and functioning [42]. And

there is evidence that cognitive remediation can optimise patients' responses to psychosocial rehabilitation [46].

But the evidence base for cognitive remediation within a forensic mental health setting is limited. To date only two randomised trials have been conducted. One study investigated the feasibility of improving social cognition amongst forensic mental health patients [47]. The second study mixed forensic mental health patients with general mental health patients. Mixing general mental health patients with forensic patients may undermine the confidence with which the findings can be generalised to forensic mental health patients as a whole [48]. Of note within this study the forensic mental health patients were significantly more cognitively impaired on working memory and verbal learning than the general mental health patients. However both studies produced positive outcomes on a range of measures including recognising emotion, neurocognition, aspects of patient functioning and patient satisfaction. Cognitive remediation therefore may be a promising intervention for forensic mental health patients. In theory cognitive remediation approaches have the potential not only to improve patients' cognitive abilities and day to day functioning, but also contribute to patients' ability to benefit from additional psychosocial and violence risk reduction programmes, thereby enhancing recovery and perhaps reducing length of stay.

Functional capacity and public protection

The separation between patient care and treatment, and public protection may be a false dichotomy. Although the link between violence and schizophrenia is typically attributed to psychotic symptoms such as delusions and hallucinations, many violence risk factors within this population concern suboptimal functioning [49–51]. Violence risk prediction or violence proneness schemes take advantage of this and place the same weight on items concerning suboptimal functioning as on items concerning psychotic symptoms or other risk factors [51]. Homelessness, employment problems, relationship difficulties, substance misuse, stress etc. are all risk factors for violence [50]. Many of the violence risk factors associated with suboptimal functioning are probably related to the cognitive difficulties experienced by patients with schizophrenia. It may also be that forensic patients are more functionally impaired than their non-forensic counterparts thus increasing their violence proneness and creating the circumstances for them to come into contact with law enforcement agencies [38]. Using a prospective cohort design, we have recently demonstrated that deficits in neurocognition and social cognition accounted for a large portion of the variance of reactive violence carried out by forensic hospital patients with schizophrenia [38]. We also found that neurocognitive deficits act as a distal risk factor whose effects on reactive violence were mediated by more

proximal factors such as problems with social reasoning, impaired functioning, symptoms and violence proneness [38].

Prioritising patient functioning over symptoms

Improving and where possible restoring patient functioning is central to psychiatric care. But services may be prone to emphasising the medical treatment of symptoms over interventions designed to restore patient functioning. For instance, a recent investigation by the Schizophrenia Commission into the provision of care for people with psychosis in England found inpatient settings to be “anti-therapeutic” with medication being prioritised over psychological interventions [52]. Concerning community care and treatment, one retrospective longitudinal study examining 25,000 Swedish patients with schizophrenia found an increase in the rate of adverse outcomes from 1972 to 2009. Amongst this cohort there was an increase in premature death, violent crime, and suicide [53]. The increase in the number of adverse outcomes was notably associated with a decrease in the numbers of inpatient beds and an increase of patients living in the community [53]. This finding may be explained by pressure to discharge patients who do not possess the necessary functional capacity to cope in the community, but have received antipsychotic medication. Clearly patients with low levels of functioning need high levels of support delivered in either an appropriately resourced community or hospital setting. But by placing greater emphasis on treating and managing the cognitive difficulties that underpin functional impairments, it may also be possible to reduce violence and other adverse outcomes. Although forensic mental health services have a dual responsibility to provide care, in addition to managing and decreasing violence risk, these are not necessarily conflicting roles. The prioritisation of cognition and function over symptoms may resolve the conflict between treatment and public protection. Any conflict that does occur between care and public protection is more likely to be a by-product of the limitations of particular treatment approaches and conceptual paradigms. Because a focus on the cognitive and functional deficits experienced by forensic mental health patients has the potential to bring the twin goals of patient care and public protection into alignment, evaluating the effectiveness of cognitive remediation is an important research priority.

Current study

To date there has been no randomised controlled cohort study evaluating cognitive remediation therapy within a forensic hospital although there have been feasibility and mixed studies [47, 48]. Therefore an important objective is to conduct a trial of cognitive remediation therapy examining the effectiveness, functional outcomes and

patient satisfaction for a nationally representative cohort of forensic mental health patients. We do not know whether cognitive remediation is an effective rehabilitation approach within this setting for improving cognition, reducing negative symptoms and improving general functioning. Equally it is not clear whether cognitive remediation has the ability to synergistically combine with routine psychosocial and violence risk management programs and to enhance patients’ ability to benefit from these interventions. Finally, it is not clear whether forensic mental health patients would find it acceptable to participate in an intensive programme of cognitive remediation.

Hypotheses

The current study will aim 1) to test the efficacy of cognitive remediation therapy for improving patient cognition, symptoms and functioning, where functioning includes measures of participation in psychosocial treatment programmes, recovery, and dynamic violence risk; 2) to establish patient satisfaction with cognitive remediation therapy within a forensic setting.

Method

The method was informed by the Clinical Trials Assessment Measure for psychological treatments, which is an instrument designed to assess the quality of psychological trials [54]. The Clinical Trials Assessment Measure covers the domains of sample characteristics; allocation to treatment (including allocation concealment, blinding, and randomisation); comparison treatments; outcome assessment (including standardised outcomes and blinding of participants); treatment description (including protocol and fidelity assessment); and appropriate analysis (such as intention-to-treat analysis). The validity measures for adherence to the protocol will include rate of enrolment, rate of retention, tests of the success of blinding, and the number of patients who complete the primary outcome measures.

This is a single centre randomised controlled trial.

Ethics, consent and permissions

The study was approved by the Research, Ethics and Audit Committee of the National Forensic Mental Health Service (NFMHS) and the School of Medicine Ethics Committee, Trinity College Dublin. All patients participating in the study will provide informed signed consent.

Setting

The NFMHS provides specialised care for adults who have a mental disorder and are at risk of harming themselves or others. At the time of the study the NFMHS had 94 secure inpatient beds located on a single campus (The Central Mental Hospital, CMH), and 13

community beds. The CMH is the only secure forensic psychiatric hospital for the Republic of Ireland, a population of 4.6 million.

Participants

Approximately sixty patients under the care of the Central Mental Hospital will be recruited to participate in this study. Inclusion criteria are having a diagnosis of schizophrenia or schizoaffective disorder established using the Structured Clinical Interview for the Diagnostic and Statistical Manual IV (SCID) [55] and being proficient in English. Exclusion criteria are being acutely psychotic, being judged too dangerous to participate in treatment (positive symptoms combined with aggressive or self-harming behaviour in the last month) or being over 65 years of age. Inclusion criteria are broad and exclusion criteria are minimal because we are primarily interested in investigating whether CRT will be effective for a nationally representative cohort of forensic mental health patients.

Randomisation and treatment allocation

Upon enrolment in the study participants will be randomised to cognitive remediation and a waiting list control group receiving treatment as usual (TAU) by the clinical director of the Central Mental Hospital using 'select cases' 'random samples' (select cases random number generator) function in SPSS V21 [56]. Fig. 1 is a CONSORT diagram outlining patient allocation. Patients randomised to receiving TAU will be offered the intervention upon completion of the study. The clinicians conducting the therapy sessions will be different from the research team carrying out the assessments. The sequence of randomisation will be concealed from the research team carrying out the baseline and outcome assessments i.e. blinded assessment. All participants will be trained not to reveal their study condition prior to each follow up assessment. Should the blind be broken this will be noted. Furthermore all assessors will be asked to guess whether participants were receiving TAU or CRT for each of the follow up assessments to see if they perform at a chance level of accuracy. Patient participation in CRT will be shared with their treating psychiatrist. The socio-demographic characteristics of the cognitive remediation group and the waiting list control group will then be compared on a range of measures e.g. age, sex, dose of antipsychotic medication (expressed as chlorpromazine equivalents) [57–59], pre-morbid IQ (estimated from TOPF^{uk}) [60], MATRICS global composite scores, MATRICS domain scores, Social Cognitive Scores [60–62], real world functioning (SOFAS), psychiatric symptoms (PANSS), negative symptoms (CAINS) and violence proneness (HCR-20) [63–66].

Cognitive remediation therapy

Cognitive remediation therapy is a behaviourally based training programme designed to improve cognitive problems associated with schizophrenia and schizoaffective disorder [42–44]. Patients allocated to cognitive remediation will receive three individual sessions a week and one group session for approximately 14 weeks, 56 sessions in total.

The focus of the individual sessions is to enhance patients' basic cognitive abilities through drill and practice and to introduce patients to a variety of meta-cognitive strategies to compensate for reduced performance according to need [44]. Meta-cognitive strategies may be distinct for particular cognitive domains e.g. the strategies of problem identification, breaking problems into parts, brainstorming, sequencing, monitoring, reflecting may be particularly useful for problem solving. Whereas strategies such as visualisation, chunking, association, rehearsal etc. may be helpful to compensate for memory difficulties. And strategies like self-verbalisation may be useful to enhance attentional abilities.

The focus of the group sessions is to help patients normalise and develop insight into their cognitive difficulties, to receive support and encouragement, and to generalise gains [67]. A detailed manual has been developed to guide the delivery of the CRT support group.

Cognitive remediation operationalised by nine treatment principles

Our cognitive remediation therapy is a principle driven intervention consisting of nine treatment principles (Table 1) and is in keeping with the recommendations of a task force on Principles of Therapeutic Change that Work, sponsored by the American Psychological Association and the North American Society for Psychotherapy Research [68]. In addition to the CRT literature the approach is also influenced by the success of multi-systemic therapy (MST), an empirically supported treatment for conduct disorder. Multi-systemic therapy is a flexible intervention operationalised by treatment principles rather than a prescriptive session format [69]. Conduct disorder, like schizophrenia is a heterogeneous disorder and also has a history of being considered refractory to psychological interventions. In contrast to manualised protocols, principle driven interventions like MST aim to provide clinicians with flexible heuristics rather than a set of tightly defined procedures prescribed at specific times in therapy. The emphasis on broad treatment principles rather than a scripted session format is therefore to facilitate a patient centred approach, which is responsive to each patient's own unique strengths and vulnerabilities.

Our cognitive remediation programme also aims to align the goals of forensic mental health services with

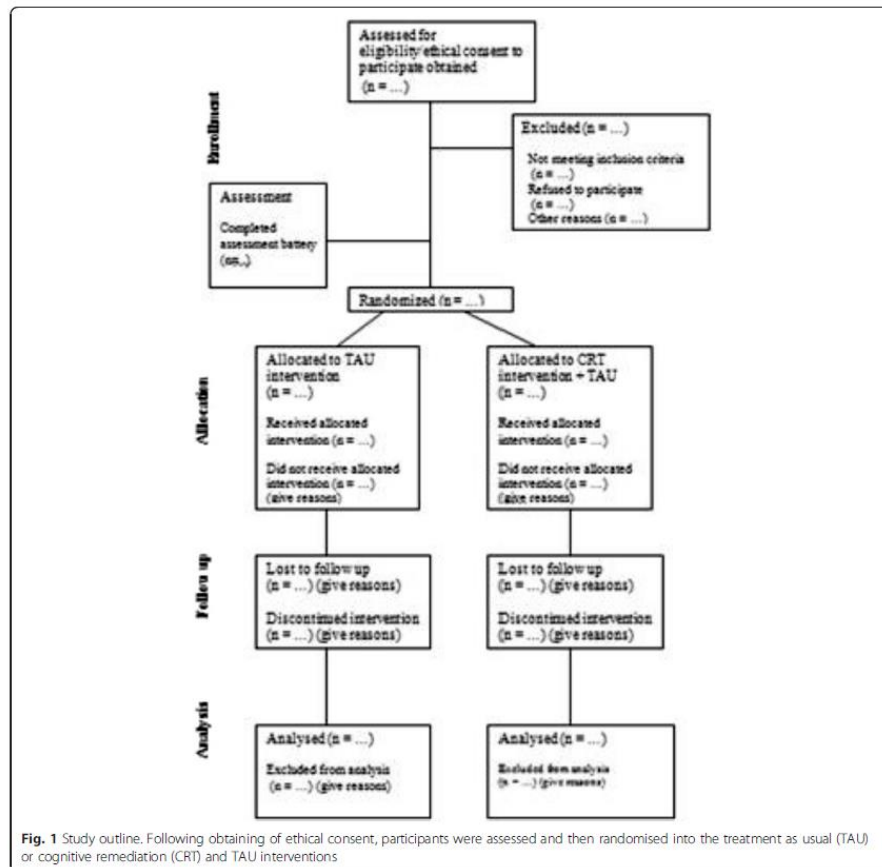


Fig. 1 Study outline. Following obtaining of ethical consent, participants were assessed and then randomised into the treatment as usual (TAU) or cognitive remediation (CRT) and TAU interventions

the goals of individual patients. For example, forensic mental health services may have a number of goals for their patients concerning physical health, mental health, substance misuse, harmful behaviour and occupational and recreational functioning [70]. These goals may vary in their level of explicitness, consist in a number of sub-goals, and vary in the extent to which they are communicated to patients. Also in some cases the patients may not share the service's goals but rather be a passive participant in the rehabilitative process. For instance, they may not agree that they have a substance misuse problem, have a mental illness or be at a high risk of violence. In these cases, the service, psychiatrist, key-worker, multidisciplinary team and

other parties are the customers of the intervention and not the patient. In contrast the starting point of our cognitive remediation intervention is to help patients to clearly and explicitly articulate their goals. Explicit links are then drawn between cognitive difficulties and patient aspirations and cognitive remediation is then offered as a vehicle which can help actualise goals. Every attempt is made to facilitate the patient to take on the role of the customer. We agree with Lindqvist and Skipworth who argue that it is the hopes of the patient which are decisive for recovery [33, 34].

Like MST our nine treatment principles are general statements that can be easily remembered and applied, which

Table 1 Principles guiding cognitive remediation intervention

Principle 1, Relationship Building: A major focus of each session is to prioritise the development of a strong therapeutic relationship. The therapeutic relationship will be strengthened by providing a credible rationale for participation, explicitly linking the cognitive remediation to patients' goals, promoting success experiences, making participation enjoyable, providing positive reinforcement, and managing ruptures, which may occur during the course of the intervention.

Principle 2, Collaborative Goal Setting: So as to promote 'buy in' patients will be encouraged to develop a series of short term, medium term, and long term goals. Patients neuropsychological and risk assessments e.g. HCR-20, Durrum toolkit, will be shared with patients to create a platform to develop goals. An explicit connection will also be drawn between cognitive difficulties and patients' aspirations. Short term goals may include having the concentration required to watch a TV programme or to read a book. Medium term goals may include patients' ability to self-medicate or move to a less secure unit. Long term goals may include returning to work, and developing relationships outside the hospital.

Principle 3, Session Structure: Each session will begin with a mood check to establish rapport or identify problems followed by agenda setting, implementation of the agenda items, and summaries before moving on to the next agenda item. The session will end by giving patients the opportunity to provide feedback.

Principle 4, Content of the sessions: The sequencing of interventions will be informed both by patients goals and their unique strengths and vulnerabilities as documented by neuropsychological assessment. Cognitive domains at the start of the informational processing stream e.g. attention and vigilance, working memory etc will typically be prioritised over those occurring later e.g. comprehension and social problem solving. This is because difficulties associated with higher level cognitive processes may be a result of problems with more basic processes such as attention and memory. As patients demonstrate some improvement in core cognitive skills, higher level domains will be targeted. Clinical judgement will be required to determine if patients achieve a basic level of mastery in certain cognitive domains of if a ceiling has been reached before progressing to more complex domains. CRT therapists should carefully assess whether patients are improving on core domains e.g. verbal memory etc, and if these improvements are being maintained over time.

Principle 5, Pacing: Therapists are encouraged to avoid trying to squeeze too much into each session or to work on too many problems simultaneously because it takes time to consolidate skills. In other words, patients need opportunities to repeat tasks again and again to improve performance, which is referred to as massed practice. Throughout the intervention each session should build on the next and be targeted at concrete goals. Patients should be provided with feedback on their progress towards goals. Newly acquired skills should not be abandoned once developed but refreshed during future sessions. Patients may also need breaks between tasks. This down time is a good opportunity to ask patients about their lives and to strengthen the therapeutic relationship.

Principle 6, Errorless Learning and Scaffolding: Task difficulty should be set so that patients obtain a high level of success on each task to avoid faulty learning and to enhance morale. Patients will be required to obtain a success rate of 80 % before the cognitive demands of the task are increased. Where problems are encountered therapists should provide scaffolding and model successful completion of tasks.

Principle 7, Meta cognitive Strategies: A major focus of each session will be to explicitly teach patients meta-cognitive strategies which are somewhat independent of basic cognitive ability and can be flexibly applied across situations. Examples of meta-cognitive strategies include goal setting, visualisation, focusing on one thing at a time, self-verbalisation, planning, breaking problems into parts, sequencing, chunking, advantage disadvantage analysis, perspective taking, monitoring performance, reflecting on performance etc. It is particularly important to explicitly model the effective use of meta cognitive strategies for patients. The effectiveness of strategies should be carefully assessed using a behavioural experiment framework. The use of particular strategies should be consolidated as evidenced by generalisation before additional meta-cognitive strategies are introduced. When mastery of basic strategies has been consolidated patients can be encouraged to simultaneously use multiple strategies.

Principle 8, Generalisation: Patients will be encouraged to utilise their cognitive skills outside of remediation sessions by participating in a support group. The focus of the support group will be helping patients to develop a shared understanding of the cognitive deficits associated with schizophrenia, to develop an awareness of how these deficits affect their lives, to identify situations where they can apply their cognitive skills, to obtain encouragement and support from other members of the group on how to implement these skills, to strengthen narratives where success has been achieved. In addition to the above positive group participation in and of itself may enhance cognitive processes as it requires patients to monitor their thoughts, reframe from interruptions, structure their contributions, and reflect on feedback.

Principle 9, Managing Ambivalence: Patients ambivalence towards participating should be met in a non-defensive empathic manner. Advantages and disadvantages of participating should be listed using pen and paper to ease the burden on working memory and to model effective problem solving. Patients should be gently reminded of their goals and their initial commitment to participate for the duration of the intervention. Ways of making the cognitive remediation more relevant or enjoyable should be actively explored.

identify relational conditions, therapist behaviours, and classes of interventions likely to lead to change. The treatment principles attempt to integrate the specific theories and techniques advocated by the CRT literature e.g. self-verbalisation or monitoring, errorless learning, scaffolding etc. combined with research into what makes psychological interventions effective in general e.g. emphasising the therapeutic relationship, offering a credible rationale for treatment, and routinely evaluating progress [41, 71].

Wykes defines self-monitoring, errorless learning and scaffolding as follows [43]. Self-monitoring is a technique for rehearsal of both the task instructions as well as task completion and can be accomplished by using verbalisation either overtly or covertly. Errorless learning is a technique whereby the therapist minimises opportunities for the participant to make errors. For example, individuals only attempt tasks where they have an 80 % success rate.

Finally scaffolding is a technique whereby the therapist challenges the participant to complete difficult tasks but with the assistance and guidance of the therapist. Our nine treatment principles are also in keeping with recent developments within the CRT literature, where it has been found that the therapeutic relationship, emotional state, and the motivation of participants, in addition to an emphasis on skills transfer, all play an important role in treatment success [42, 72–75]. For example, working alliance contributes to the success of CRT [72]; positive mood facilitates creative problem solving [73]; intrinsic motivation can be enhanced by providing a personalised context that links treatment with everyday life, and also by tailoring the intervention to the learning goals of each participant [74, 75]; and functioning outcomes are best achieved by combining CRT with other rehabilitation programmes [44].

It is also hoped that the nine treatment principles will form a bridge between abstract theoretical models and the concrete interventions carried out during sessions. Our approach combines models of cognitive remediation such as drill and practice aiming to strengthen cognitive performance as well as teaching meta-cognitive strategies aiming to compensate for cognitive function, whilst at the same time emphasising the process of therapy e.g. relationship building, goal setting, managing ambivalence etc.

In practical terms each session will involve practicing discrete cognitive functions identified by the MATRICS consensus cognitive battery [63] e.g. attention, working memory, verbal memory, visual memory, comprehension, problem solving and social cognition. A variety of pen and paper materials will be used to achieve this aim. A free open source version of the Dual N-back computer programme (<http://brainworkshop.sourceforge.net>) will also be used to help patients develop and modulate their attentional resources in addition to their working memory (visual and spatial) and processing speed. Over the course of the intervention as patients make progress the cognitive remediation procedures will gradually increase in difficulty.

The cognitive remediation will be delivered by Masters' level assistant psychologists and the cognitive remediation support group will be delivered by multidisciplinary professionals including psychiatric registrars, occupational therapists and psychiatric nurses. All therapists contributing to the cognitive remediation programme will attend a three day training course prior to delivering the intervention. All therapists will attend weekly supervision sessions where fidelity to the treatment principles will be actively monitored. Fidelity to the treatment will also be assessed by observing adherence to the nine treatment principles during randomly selected individual and group treatment sessions.

Treatment as usual

Participants in both conditions will receive treatment as usual from hospital clinicians. At a minimum, this will consist of antipsychotic pharmacotherapy and a therapeutically safe and secure environment appropriate to the individual patient's needs [76–78] however most patients are expected to be involved in a range of therapies provided by multidisciplinary team members, including psychiatrists, clinical psychologists, psychiatric nurses, occupational therapists and social workers [78].

Medication will be managed separately by the consultant psychiatrists responsible for the patients' care and may change over the duration of the study as required. Both antipsychotic dose and anticholinergic burden will be measured at each assessment point as these may be important treatment moderators [79].

The number of routine therapeutic hours each patient receives in the treatment as usual (control) and the cognitive remediation group will be recorded from patient's progress notes/ medical charts each week. A narrow definition of therapeutic activity will be applied to prevent over inclusion: a therapy will be defined as any activity that is occurring on a consistent or regular basis targeting specific goals and designed to address patients' forensic mental health needs. From this perspective regular occupational therapy, cognitive behavioural work, psycho-education, harmful behaviour programmes, substance misuse interventions, group programmes etc. would be defined as therapeutic activities, in contrast multidisciplinary team meetings, general interviews or assessments, physical exercise and general vocational or educational work will not be seen as therapies.

Assessment battery

All assessors will complete a training programme prior to administering study related assessments. For assessments that require clinical judgment (e.g. symptom severity measures), assessors will observe a number of interviews carried out by an experienced consultant psychiatrist whilst simultaneously rating patients' performance. The inter-rater reliability of assessors will also be measured as part of the training programme for assessors. Primary and secondary outcome measures are presented in Table 2.

Primary outcome measure: change in global cognitive functioning

Cognitive functioning among study participants will be assessed at baseline, end of treatment (approximately 6 months) and 8 month follow up using the MATRICS Consensus Cognitive Battery (MCCB) global composite score [61]. The MATRICS battery covers seven cognitive domains: processing speed; attention/ vigilance; working memory; verbal learning; visual learning; reasoning and problem solving; social cognition assessed using social reasoning tasks for understanding and managing emotions taken from the Managing emotions subtest of the Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT) which is a social reasoning test. The test comprises of vignettes of various situations, and options for coping with the emotions depicted in these vignettes [80, 81]. Participants are required to indicate the effectiveness of each solution ranging from one (very ineffective) to five (very effective). In validation studies, and in antipsychotic trials of stable patients, the MATRICS demonstrated excellent reliability, minimal practice effects and significant correlations with measures of functional capacity. It is hypothesised that there will be a group by time interaction (CRT vs TAU) on the total score of the MATRICS battery at the end of treatment approximately 6 months and at 8 months follow up.

Table 2 Outcome Measures

Primary Outcome Measure	MATRICES Consensus Cognitive Battery Composite Score (MCCB)
Secondary Outcome Measure	MCCB Domain Scores Social cognitive assessments <ul style="list-style-type: none"> • The Reading the Mind in the Eyes Test • The Faux Pas Recognition Test • The MSCEIT Social and Occupational Functioning Assessment Scale (SOFAS) Positive and Negative Syndrome Scale (PANSS) – negative and disorganised scales Clinical assessment interview for negative symptoms (CAINS) Historical Clinical Risk -20 (HCR-20) DUNDRUM-3 Programme Completion Scale DUNDRUM-4 Recovery Scale
Validity Checks	Rate of enrolment, rate of retention, rate of completion of primary outcome measures, success of blinding.
Patient satisfaction survey	Service user developed interview.

Secondary outcome measures**Change in specific cognitive domains**

The MATRICES battery will also be used to assess change in specific cognitive domains for study participants. The processing speed, attention/ vigilance, working memory, visual learning, verbal learning, reasoning/ problem solving and social cognitive domains of the MATRICES battery will all be used as secondary outcome measures. It is hypothesised that there will be a group (CRT vs TAU) by time interaction on the MATRICES domain scores at the end of treatment and eight month follow up [61]

Social cognitive measures

Changes in social cognition will be assessed using The Reading the Mind in the Eyes Test [62], the Faux Pas Recognition Test [63] and the Managing Emotions sub-test of the Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT). It is hoped that each of these tests will tap into different components of the emotional processing stream [40]. The Reading the Eyes of the Mind Test will measure emotional perception as well as theory of mind, the Faux Pas Recognition Test will measure the participants awareness of emotional context or social sensitivity, and finally the MSCEIT is a measure of social as well as emotional reasoning.

Real world functioning

Secondary outcome measures will include the Social and Occupational Functioning Assessment Scale (SOFAS) [64]. The SOFAS is a continuous scale (0–100) with verbal

tethers so that higher scores represent superior functioning. It is similar to the Global Assessment of Functioning Scale however it does not include the severity of psychiatric symptoms. Again it is hypothesised that there will be a group (CRT vs TAU) by time interaction at the end of treatment and eight month follow up.

Psychiatric symptoms

Secondary outcome measures will also include the scores on the disorganised and negative symptoms scales from the five factor Positive and Negative Syndrome Scale (PANSS) and the total score from the Clinical Assessment Interview for Negative Symptoms (CAINS) [67, 68]. The PANSS contains 30 items measuring psychopathology associated with schizophrenia, 7 items assess positive symptoms, seven items assessing negative symptoms and 16 items assess general psychopathology. A five factor model of the PANSS will be used to evaluate outcomes because CRT is thought to have a specific impact on negative and disorganised symptoms [82]. The CAINS is a 13 item interview for measuring negative symptoms associated with schizophrenia. It contains 9 items for assessing problems with motivation and pleasure and 4 items for assessing problems with emotional expression. Again it is hypothesised that there will be a group (CRT vs TAU) by time interaction at the end of treatment and eight month follow up.

Violence risk

Violence risk will be assessed with the Historical and Clinical Risk Management Scale 20 (HCR-20) a measure of violence risk, sometimes referred to as violence proneness [51]. The HCR-20 is among the most widely used violence risk assessment schemes. The HCR-20 contains ten historical or static items, five current or clinical items and five future risk items. Both the clinical and risk items are thought to be dynamic in nature in that they can change over time and are amenable to therapeutic intervention. Because the historical items are static in nature only the dynamic items will be used as a secondary outcome measurement. Violence risk will only be measured at baseline and eight month follow up. Again it is hypothesised that there will be a group (CRT vs TAU) by time interaction. The HCR-20 will be rated approximately every six months by the treating multi-disciplinary team and researchers.

Programme completion and recovery

It is hoped that there will be differences between participants receiving CRT compared to TAU on their ability to benefit from additional psychosocial treatment programmes offered. Participant ability to benefit from additional psychosocial treatment will be assessed with the Dundrum-3 Programme Completion scale rated by

psychiatric registrars and by patients' multidisciplinary teams blind to the intervention [78]. The Dundrum-3 is a structured clinical judgment instrument which assesses whether patients have participated in, engaged and benefited from psychosocial programmes and consists of seven items: physical health, mental health, drugs and alcohol, problem behaviours, self-care and activities of daily living, education occupation and creativity and family and social networks. Each item is rated on a five point scale with lower scores representing a higher level of participation and engagement. Patient ability to recover within a forensic setting will be assessed with the Dundrum-4 Recovery Scales [78]. The Dundrum 4 contains six items: stability, insight, therapeutic rapport, leave, dynamic risk and victim sensitivity. Similar to the DUNDRUM-3 Programme Completion Scale, each item of the DUNDRUM-3 is also rated on a five point scale with lower scores representing greater progress towards recovery. The Dundrum-3 Programme Completion Scale has been shown to significantly distinguish between levels of security within a forensic setting and the Dundrum-4 Recovery Scale has been shown to distinguish those given unaccompanied leave outside of a secure forensic setting. Programme completion and recovery will only be measured at baseline and eight month follow up. Again it is hypothesised that there will be a group (CRT vs TAU) by time interaction.

Patient satisfaction measure

An interview developed by service users will be used to explore patient satisfaction with cognitive remediation [45]. The interview will inquire about the following areas: 1) task difficulty, 2) experience of sessions, 3) relationship with therapist and 4) impact of CRT on daily life. The interview will be administered by a social worker who will be independent of treatment and assessment teams, to the intervention and to other assessments. Patients will be reassured that their responses will be anonymously recorded i.e. that their names will not be connected with the feedback they provide.

Proposed analysis

Data analysis will be carried out using an intention to treat methodology [83]. Data from all enrolled participants will therefore be used in the analysis regardless of their level of participation in the study. Missing data will be estimated using multiple imputation [84]

The interaction between time i.e. baseline vs. 6 month and treatment condition (CRT vs TAU) on our primary outcome variable (MCCB composite cognition score) will be examined rather than between group differences, because tests of group difference average Time 1 (baseline) and Time 2 (6 month) assessments across the groups and consequently will be less sensitive to change.

The interaction between time and treatment condition will be assessed using a repeated measure ANOVA with age and gender entered as covariates. This analysis will also be repeated at follow up using all three data points.

An a priori estimate of statistical power was completed using G*Power 3.1 [85]. Assuming a correlation greater than or equal to .5 between baseline and 6 month MCCB composite and a medium effect size (i.e. $f = .25$), the power to detect a statistically significant interaction between time and treatment conditions (i.e. CRT vs TAU) is adequately powered i.e. greater than or equal to .80. Should we find a statistically significant time X treatment condition interaction, post-hoc probing of the interaction will be completed with Bonferroni corrections applied where appropriate to maintain an alpha of 0.05.

SPSS PROCESS Macro Model 4 will be used to explore mechanisms of action should we find a positive impact of CRT. For example, whether change in cognition leads to a change in functioning, or whether a change in negative symptoms leads to a change in functioning etc. Change score will be calculated by subtracting the scores at baseline from the scores following the intervention. Age and gender will be entered as covariates in all mediation analysis. Bootstrapping will be used to estimate indirect effects, and 95 % bias-corrected confidence intervals using 1,000 bootstrap samples will be applied. A confidence interval that does not contain zero indicates statistically significant mediation ($p < 0.05$).

Discussion

Forensic mental health services have a dual role in treating and caring for patients with mental disorders while also protecting the public from recidivist acts of violence. This study aims to address both of these goals by attempting to alleviate or ameliorate the likely common underlying deficits leading to functional impairment and violence.

Recently there has been a shift in emphasis within the field of schizophrenia research from focusing on positive symptoms such as delusions and hallucinations to patients' cognitive abilities and functional outcomes [86]. Positive symptoms can be fairly successfully treated with medication however to date there is a lack of effective pharmacological treatments for cognitive difficulties and negative symptoms [13, 14]. It is these difficulties which are associated with patients' ability to function day to day [14]. Also many risk factors for violence for mentally disordered patients concern suboptimal functioning.

CRT appears to be an effective intervention for community patients with schizophrenia for improving cognitive deficits [42]. There is also evidence that the cognitive improvements brought about by CRT lead to improvements in patient functioning. Because forensic

mental health patients tend to be hospitalised for a longer duration than those in the community there is an unrealised opportunity to improve cognition and restore functioning within forensic services [8].

The results of the proposed study will help to answer the question whether cognitive remediation therapy is an effective intervention strategy for forensic mental health patients. Specifically it will test whether a nationally representative cohort of forensic mental health patients with schizophrenia or schizoaffective disorder benefit from cognitive remediation and whether patients are satisfied with the intervention.

A focus on cognition as a primary treatment target also has the potential to reduce violence risk in two ways. First it could help patients who are cognitively impaired benefit from specialised psychosocial programmes targeting the risk of violence. Second it could improve general functional ability. By placing the emphasis on cognition and functional ability over symptoms any conflict between the two roles played by forensic mental health services could be reduced thus improving recovery and decreasing patients' length of stay.

Limitations

The protocol has some limitations. A weakness of the study is the lack of an active control group beyond treatment as usual (TAU). An additional weakness is that it will not be possible to keep medication constant for the duration of the study. The confined environment of a forensic hospital may also present fewer opportunities for practicing and applying cognitive skills. In a non-quantitative narrative review of over 100 psychological intervention studies it was estimated that extra-therapeutic factors such as the persons' social environment accounted for approximately 40 % of the variance of the outcome of interventions [87]. Forensic services almost by definition limit patients' freedom. And there can be conflict within forensic mental health services between safety and security on the one hand, and the provision of a therapeutic environment on the other. However these disadvantages will be offset by the consistency of the daily milieu for the intervention and TAU groups, a consistency that cannot be achieved for groups living in the community.

Strengths

A major strength of the study is that CRT is being offered to a nationally representative cohort of forensic mental health patients with schizophrenia or schizoaffective disorder. The findings regarding efficacy and patient satisfaction will therefore inform whether CRT could or should be rolled out in forensic mental health services across other jurisdictions. A second strength of the study is the large battery of outcome measures for assessing the efficacy of the intervention, evaluating domains of

cognition, functioning, symptoms, programme completion, recovery and violence risk. Finally the patients themselves will also play a role in assessing the usefulness of the intervention by participating in a confidential interview.

Trial status

The trial is currently enrolling by invitation. Trial Registration: ClinicalTrials.gov Identifier: NCT02360813. First received: February 4, 2015.

Abbreviations

CRT: cognitive remediation therapy; HCR-20: Historical-Clinical-Risk Management-20; TOPF: test of premorbid functioning; MATRICS: measurement and treatment research to improve cognition in schizophrenia; MCCB: MATRICS consensus cognitive battery; MSCIEIT: Mayer-Salovey-Caruso emotional intelligence test; SOFAS: the social and occupational functioning assessment scale; PANSS: positive and negative syndrome scale; CAINS: clinical assessment interview for negative symptoms; MST: multi-systemic treatment; NFMHS: national forensic mental health service; CMH: Central Mental Hospital; CPZeq: chlorpromazine equivalents; SPSS-22: statistical package for the social sciences, version 22.

Competing interests

All of the authors declare that they have no competing interests.

Authors' contributions

KOR originated the conception and design of the study and will perform the analysis and interpretation of the data, with substantial involvement also of GD and HGK. DO'S, CC, RM, P O'C,CM, AN, P OF, CO'C, all met the guidelines for authorship. All authors have read and approved the manuscript.

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RESEARCH ARTICLE

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A randomized controlled trial of cognitive remediation for a national cohort of forensic patients with schizophrenia or schizoaffective disorder



Ken O'Reilly^{1,2}, Gary Donohoe³, Danny O'Sullivan², Ciaran Coyle², Aiden Corvin¹, Padraic O'Flynn², Muireann O'Donnell², Toni Galligan², Paul O'Connell^{1,2} and Harry G. Kennedy^{1,2*}

Abstract

Background: Evidence is accumulating that Cognitive Remediation Training (CRT) is effective for ameliorating cognitive deficits experienced by patients with schizophrenia and accompanying functional impairment. There has been no randomized controlled trial of CRT using a nationally representative population of forensic patients, despite the significant cognitive deficits frequently present within this group.

Methods: Sixty-five patients with schizophrenia or schizoaffective disorder were enrolled in a single blind randomized controlled trial of CRT versus treatment as usual (TAU); representing 94% of those eligible within a national forensic cohort. The primary outcome measure was the composite score of the MATRICS Consensus Cognitive Battery (MCCB). Secondary outcome measures included neurocognitive and social cognitive domains, symptoms, and 'real world' functioning. Patient satisfaction was examined using an exit interview. Participants were reassessed at 8 months follow up. All data were analyzed using an intention to treat design (ITT).

Results: For the primary outcome measure, the MCCB composite score, there were significant differences between those who participated in CRT and those receiving TAU at both end of treatment and 8 months follow up (Cohen's $d = 0.34$). Significant improvements were observed in visual and working memory. Mediation analysis found that those who cognitively benefited from CRT had corresponding improved functioning, and more net positive therapeutic moves i.e. moves to units with lower security within the hospital. Ninety-six percent believed their cognitive gains positively affected their daily lives.

Conclusions: CRT may be an acceptable and efficacious intervention for forensic patients with schizophrenia or schizoaffective disorder.

Trial registration: ClinicalTrials.gov Identifier: [NCT02360813](https://clinicaltrials.gov/ct2/show/study/NCT02360813). Trial registered Feb 4th 2015, last updated May 1st 2015.

Keywords: Schizophrenia, Forensic mental health, Cognitive remediation training, CRT, Neurocognition, Effectiveness, Clinical trial

* Correspondence: kennedh@tcd.ie

¹Department of Psychiatry Trinity College Dublin, the University of Dublin, Dublin, Ireland

²The Central Mental Hospital, National Forensic Mental Health Service Ireland, Dublin, Ireland

Full list of author information is available at the end of the article



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Background

Only one in seven patients with schizophrenia achieves functional and symptomatic remission sustained over time [1]. One explanation for the rate of recovery is the degree of cognitive impairment associated with the disorder [2]. Approximately 85% of patients with schizophrenia experience cognitive impairment [3]. The magnitude of cognitive impairment is particularly pronounced when measured using composite scores derived from instruments like the MATRICS Consensus Cognitive Battery (MCCB), which aggregate deficits across cognitive domains affected by the illness [2, 4]. The development of the MCCB has also facilitated direct comparisons of groups of patients regarding the extent of their cognitive impairments [5, 6]. Within a sample of 2616 stable patients participating in North American clinical trials the mean score on the MCCB was approximately 2.5 SD below the nonclinical mean [7]. However, there may be groups of patients who are even more impaired. Forensic patients are detained under mental health legislation with histories of social dysfunction including violence and are often excluded from mainstream research on schizophrenia [8]. Amongst a national cohort of forensic patients, we found that the mean MCCB composite was more than 3 standard deviations (SD) below the nonclinical mean i.e. a level traditionally associated with moderate intellectual disability [6]. In line with systematic reviews of cognitive difficulties experienced by non-forensic patients, the cognitive impairments experienced by forensic patients are also associated with difficulties in 'real-life' functioning and impaired ability to benefit from psychosocial treatment programs [9–11]. Addressing the cognitive impairments experienced by forensic patients is therefore an important objective [8].

Cognitive remediation training (CRT) is a behaviorally based treatment for the cognitive deficits associated with schizophrenia. CRT purports to take advantage of 'neuroplasticity' through a process of learning known as 'drill and practice', in addition to explicitly teaching meta-cognitive strategies [8]. For community patients, there is evidence that CRT is effective for ameliorating cognitive impairment and the associated functional difficulties. A meta-analysis of randomized controlled trials involving 2104 participants found evidence of an effect size (Cohen's *d*) of 0.44 on a composite measure of cognition and an effect size of 0.42 for 'real world' functioning [12]. There is also evidence that internet delivered cognitive training may be effective for some patients [13]. In keeping with stage-based theories of illness, forensic patients may require different interventions due to the magnitude of their cognitive impairment and social dysfunction, and because of the forensic context

in which treatment is offered [8, 14]. However, a modified form of CRT could be particularly useful for this population. Specifically, within a forensic setting CRT may facilitate patients to assume the role of 'customer', in line with both research on the importance of goal consensus for the outcome of psychotherapy, and recovery theory [8, 15]. In contrast to many patients' limited insight into their symptoms and violence risk [16], patients with schizophrenia often have an awareness of their cognitive impairments and are willing to engage in treatment [17]. Following successful completion of CRT forensic patients may be more likely to engage in programs targeting insight, substance misuse, and violence risk.

To date there has been limited investigation of the effectiveness of CRT for forensic patients [8]. Only two randomised controlled trials have been conducted [18, 19]. One study [18] investigated the feasibility of improving social cognition; the second study [19] mixed forensic patients with general mental health patients who were less cognitively impaired. Both trials reported cognitive gains. Neither of these studies adopted the use of a consensus measure of cognitive deficits such as the MCCB. Consequently, it is difficult to estimate the overall degree of cognitive impairment experienced by the participants. It is therefore unknown whether existing studies generalise to forensic patients who may be more severely impaired [8]. This study seeks to address these gaps by testing the efficacy of CRT using a national representative cohort of forensic patients with schizophrenia or schizoaffective disorder. This study may be regarded as an effectiveness study and a robust evaluation of the transportability of CRT to a 'real-world' setting [20, 21]. Our model of CRT is outlined in detail within our study protocol and has been specifically developed for forensic patients [8]. We operationalized CRT using nine treatment principles (Table 1). We chose to adopt flexible principles rather than a tightly manualized format in keeping with the common factors model of psychological therapies [8, 15, 22–24] in order to be sensitive to working with forensic patients who have variable levels of ability and unique problems and needs.

Hypotheses

- 1) That patients allocated to CRT would improve on the primary outcome measure, cognition at the end of treatment, and at 8 months follow up.
- 2) That patients allocated to CRT would improve on specific neurocognitive and social cognitive domains at end of treatment and 8 months follow up.

Table 1 Principles guiding cognitive remediation intervention

Principle 1, Relationship Building: A major focus of each session is to prioritise the development of a strong therapeutic relationship. The therapeutic relationship will be strengthened by providing a credible rationale for participation, explicitly linking the cognitive remediation to patients' goals, promoting success experiences, making participation enjoyable, providing positive reinforcement, and managing ruptures, which may occur during the course of the intervention.

Principle 2, Collaborative Goal Setting: So as to promote buy in/ patients will be encouraged to develop a series of short term, medium term, and long-term goals. Patients neuropsychological and risk assessments e.g. HCIR-20, DUNDRUM toolkit, will be shared with patients to create a platform to develop goals. An explicit connection will also be drawn between cognitive difficulties and patients' aspirations. Short term goals may include having the concentration required to watch a TV programme or to read a book. Medium term goals may include patients' ability to self-medicate or move to a less secure unit. Long term goals may include returning to work, and developing relationships outside the hospital.

Principle 3, Session Structure: Each session will begin with a mood check to establish rapport or identify problems followed by agenda setting, implementation of the agenda items, and summaries before moving to the next agenda item. The session will end by giving patients the opportunity to provide feedback.

Principle 4, Content of the sessions: The sequencing of interventions will be informed both by patients' goals and their unique strengths and vulnerabilities as documented by neuropsychological assessment. Cognitive domains at the start of the informational processing stream e.g. attention and vigilance, working memory etc. will typically be prioritised over those occurring later e.g. comprehension and social problem solving. This is because difficulties associated with higher level cognitive processes may be a result of problems with more basic processes such as attention and memory. As patients demonstrate some improvement in core cognitive skills higher level domains will be targeted. Clinical judgement will be required to determine if patients achieve a basic level of mastery in certain cognitive domains or if a ceiling has been reached before progressing to more complex domains. CRT therapists should carefully assess whether patients are improving on core domains e.g. verbal memory etc., and if these improvements are being maintained over time.

Principle 5, Pacing: Therapists are encouraged to avoid trying to squeeze too much into each session or to work on too many problems simultaneously because it takes time to consolidate skills. In other words, patients need opportunities to repeat tasks again and again to improve performance, which is referred to as massed practice.

Throughout the intervention each session should build on the next and be targeted at concrete goals. Patients should be provided with feedback on their progress towards goals. Newly acquired skills should not be abandoned once developed but refreshed during future sessions. Patients may also need breaks between tasks. This down time is a good opportunity to ask patients about their lives and to strengthen the therapeutic relationship.

Principle 6, Errorless Learning and Scaffolding: Task difficulty should be set so that patients obtain a high level of success on each task to avoid faulty learning and to enhance moral. Patients will be required to obtain a success rate of 80% before the cognitive demands of the task are increased. Where problems are encountered therapists should provide scaffolding and model successful completion of tasks.

Principle 7, Meta cognitive Strategies: A major focus of each session will be to explicitly teach patients meta-cognitive strategies which are some what independent of basic cognitive ability and can be flexibly applied across situations. Examples of meta-cognitive strategies include goal setting, visualisation, focusing on one thing at a time, self-verbalisation, planning, breaking problems into parts, sequencing, chunking, advantage/disadvantage analysis, perspective taking, monitoring performance, reflecting on performance etc. It is particularly important to explicitly model the effective use of meta cognitive strategies for

Table 1 Principles guiding cognitive remediation intervention (Continued)

patients. The effectiveness of strategies should be carefully assessed using a behavioural experiment framework. The use of particular strategies should be consolidated as evidenced by generalisation before additional meta-cognitive strategies are introduced. When mastery of basic strategies has been consolidated patients can be encouraged to simultaneously use multiple strategies.

Principle 8 Generalisation: Patients will be encouraged to utilise their cognitive skills outside of remediation sessions by participating in a support group. The focus of the support group will be helping patients to develop a shared understanding of the cognitive deficits associated with schizophrenia, to develop an awareness of how these deficits affect their lives, to identify situations where they can apply their cognitive skills, to obtain encouragement and support from other members of the group on how to implement these skills, to strengthen narratives where success has been achieved. In addition to the above positive group participation in and of itself may enhance cognitive processes as it requires patients to monitor their thoughts, reframe from interruptions, structure their contributions, and reflect on feedback.

Principle 9 Managing Ambivalence: Patients' ambivalence towards participating should be met in a non-defensive empathic manner. Advantages and disadvantages of participating should be listed using pen and paper to ease the burden on working memory and to model effective problem solving. Patients should be gently reminded of their goals and their initial commitment to participate for the duration of the intervention. Ways of making the cognitive remediation more relevant or enjoyable should be actively explored.

- 3) That patients allocated to CRT would experience improvements in negative and disorganised symptoms.
- 4) That patients allocated to CRT would experience improvements in real world functioning, net moves to lower level of security, and that patients' functional improvements or moves to lower levels of security would be mediated by cognitive gains.
- 5) That patients would experience CRT as a satisfactory and efficacious intervention.

Methods

Aim

This study aims to test the efficacy of cognitive remediation training (CRT) using a nationally representative cohort of forensic patients with schizophrenia or schizoaffective disorder.

Design

This study is a single blind randomized controlled trial of CRT versus treatment as usual (TAU) within a forensic setting.

Setting

The Republic of Ireland's National Forensic Mental Health Service (NFMHS) provides care and treatment for adults who have a mental disorder and are at risk of harming themselves or others. At the time of the study the NFMHS had 94 secure inpatient beds located on a single campus (The Central Mental Hospital, CMH).

The CMH is the only medium and high secure forensic hospital for the Republic of Ireland, a population of 4.7 million [25].

Participants

Criteria for inclusion in the trial were being a forensic inpatient with schizophrenia or schizoaffective disorder. The diagnosis of schizophrenia or schizoaffective disorder was established by a consultant psychiatrist using the Structured Clinical Interview for the Diagnostic and Statistical Manual IV (SCID-I) for axis I. Exclusion criteria were: being cared for on an acute unit, lacking capacity to consent, being too dangerous to participate in treatment (positive symptoms combined with aggressive or self-harming behavior in the last month), or being over 65 years of age. Capacity to consent to participation was assessed by the treating consultant psychiatrist. Inclusion criteria were broad and exclusion criteria were minimal because we were primarily interested in investigating the effectiveness of CRT for a nationally representative cohort of forensic patients with schizophrenia or

schizoaffective disorder. Sixty-nine patients met inclusion criteria, of whom 65 (95%) provided consent. The Test of Pre-morbid Functioning UK Edition (TOPF-UK) [26] was used in combination with a developmental and educational history. None had a pre-morbid diagnosis of developmental intellectual disability and mean TOPF was within the normal range. All 65 patients who chose to participate had a history of violence and 46% had a history of homicide. Schizophrenia was the diagnosis for 50 (76%) and schizoaffective disorder for 15 (24%). DUNDRUM-1 mean item score was 2.9 (SD 0.46, range 2.2 to 3.8) in keeping with a medium secure level of need [27]. The DUNDRUM-1 triage security instrument is a static assessment of the need for therapeutic security at the time of admission. Socio-demographic and baseline characteristics of all participants are presented in Table 2. Of note, this sample was particularly cognitively impaired with a mean MCCB t-score of 21, 3 SD lower than a nonclinical population mean. The mean Historical Clinical Risk Management version 2 score [28] (HCR-20) for the total sample was 26, SD 5.7.

Table 2 Sample characteristics at baseline

	TAU (N = 33)		CRT (N = 32)		T	df	p
	Mean	SD	Mean	SD			
Male/ female	27/6		28/4				
Age	39.30	9.51	42.68	9.74	-1.41	63	0.16
NGRI/ other	18/15		19/13				
CPZeq	472.15	313.52	505.31	362.14	-0.39	63	0.69
ACB	4.09	2.59	3.40	2.49	1.08	63	0.28
MCCB Modified	31.97	9.53	33.19	8.33	-0.54	63	0.58
MCCB	20.30	14.80	22.18	13.61	-0.53	63	0.59
Speed of processing	25.45	14.31	25.65	13.47	-0.05	63	0.95
Working memory	32.09	12.70	32.68	13.96	-0.18	63	0.85
Verbal learning	34.69	7.93	35.71	7.89	-0.52	63	0.60
Visual learning	29.42	12.98	33.65	11.50	-1.38	63	0.17
Problem solving	33.21	8.64	36.43	8.90	-1.48	63	0.14
Social cognition (MSCIT)	36.96	15.32	35.00	10.93	0.59	63	0.55
Eyes of the mind	20.56	7.62	20.96	5.10	-0.24	54.42	0.80
Faux Pas	38.84	17.25	46.34	11.65	-2.00	54.71	0.05
SOFAS	58.36	13.66	61.06	10.94	-0.87	63	0.38
PANSS Positive symptoms	9.90	5.03	9.65	4.51	0.21	63	0.83
PANSS Negative symptoms	17.09	6.55	15.37	5.54	1.13	63	0.25
PANSS Disorganization	10	4.37	9.68	4.11	0.29	63	0.76
PANSS Excitement	7.30	2.74	7.00	3.6	0.38	63	0.70
PANSS Emotional dysfunction	7.84	2.46	8.53	3.48	-0.91	63	0.36
DUNDRUM-1	2.84	0.52	3.02	0.40	-1.49	59.87	0.14
HCR-20	27.45	5.66	25.12	5.63	1.66	63	0.10

Male/ female Chi square 0.40, df = 1, $p = 0.52$, Age/ gender Chi square 0.15, df = 1, $p = 0.69$

Randomization and treatment allocation

Following enrolment participants were randomized using SPSS V21 to CRT or a waiting list control group receiving treatment as usual (TAU). Figure 1 outlines patient allocation (CONSORT diagram). The research team was blinded to group allocation. The clinicians conducting the therapy sessions were different from the research team carrying out the assessments. All patients participating in the study were trained not to reveal their study condition prior to each assessment. Evaluators were tested for ability to 'see through' blinding at the end of the study and follow-up. For clinical reasons patient participation in CRT was shared with their treating psychiatrist.

After randomization, 29 (88%) of 33 patients in the control group met criteria for schizophrenia and 4 (12%) for schizoaffective disorder, while in the intervention group 21 (66%) met criteria for schizophrenia and 11 (34%) for schizoaffective disorder. However the two groups did not differ significantly for any measure of

neurocognitive or social cognitive ability, symptom severity or functional ability (Table 2). A further sensitivity analysis showed that two groups defined by diagnosis (schizophrenia and schizoaffective disorder) did not differ significantly in any of the variables shown in Table 2.

Cognitive remediation training

CRT is designed to improve cognitive problems associated with schizophrenia and schizoaffective disorder [12]. Our cognitive remediation training is a principle driven intervention consisting of nine treatment principles, which are flexibly applied during delivery of the intervention ([8]; Table 1). Principle driven approaches are in keeping with the recommendations of a task force on Principles of Therapeutic Change that Work, sponsored by the American Psychological Association and the North American Society for Psychotherapy Research [22] and are also in keeping with a review of effectiveness and common factors [15]. Psychotherapy principle driven approaches integrate research concerning empirically supported treatments (EST)

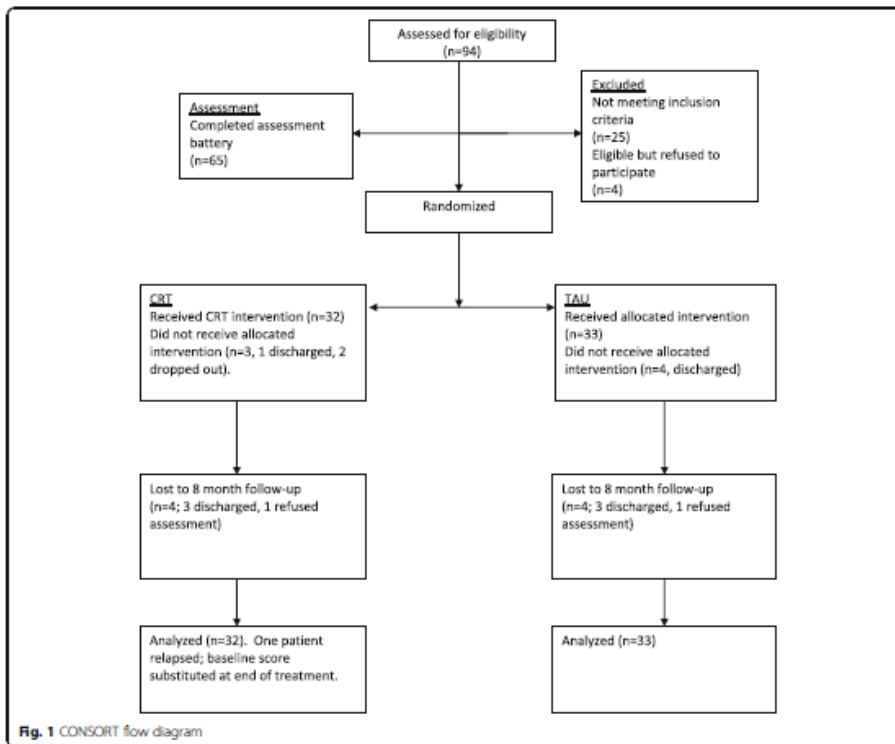


Fig. 1 CONSORT flow diagram

with research concerning the moderating influence of the therapeutic relationship [15, 22, 24]. Patients allocated to CRT received three individual sessions a week and one group session for approximately 14 weeks, 56 sessions in total. Most therapists were masters level psychologists, two therapists were psychiatrists, and another was an occupational therapist. Our CRT program has been extensively described in the study protocol and consisted of a combination of pen and paper and computerized materials [8]. Fidelity to the CRT principles was routinely assessed by randomly observing CRT therapists and by weekly supervision.

Treatment as usual TAU

Participants in both conditions received TAU from hospital clinicians. At a minimum, this consisted of antipsychotic pharmacotherapy and a therapeutically safe and secure environment appropriate to the individual patient's needs [11, 25, 27, 29, 30]. The system for delivering 'treatment as usual' has been described and shown to be effective in reducing a measure of violence proneness, the HCR-20 [11]. This draws on principles of multi-modal treatment [23] and multi-systemic treatment [24]. Most patients were expected to be involved in a range of therapies. These interventions are organized under seven pillars of care that may be regarded as treatment as usual within a forensic setting: physical health, mental health, drugs and alcohol, problem behaviors, independent living, education-occupation-creativity, and family relationships [27, 30]. Medication was managed by psychiatrists responsible for the patients' care. Antipsychotic dose CPZeq and anticholinergic burden ACB were measured at each assessment point [8].

Primary outcome measure: change in global cognitive functioning at end of treatment

Cognitive functioning among study participants was assessed at baseline and end of treatment using the MATRICS Consensus Cognitive Battery (MCCB) global composite score [5]. The MATRICS battery covers seven cognitive domains: processing speed; attention/ vigilance; working memory; verbal learning; visual learning; reasoning and problem solving; and social cognition. Like other cognitive remediation trials, we had trouble with the attentional-vigilance domain of the MCCB which is measured using a Continuous Performance Test [31]. The Continuous Performance Test is administered via computer and because of technical difficulties during the trial we excluded this task from our composite score. Consequently, the MCCB composite was created by averaging the scores over all other domains. In keeping with the recommendations in the MCCB manual we used age and gender corrected scores [5].

Secondary outcome measures

Cognitive functioning was also assessed at 8 months follow up using the MCCB composite.

Change in specific cognitive domains

The processing speed, working memory, visual learning, verbal learning, reasoning/ problem solving and social cognitive domains of the MCCB were used as secondary outcome measures.

Social cognitive measures

Changes in social cognition were assessed using the Managing Emotions subtests of the Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT) contained within the MCCB [32]. This was supplemented with the Reading the Mind in the Eyes Test [33] and the Faux Pas Recognition Test [34].

Psychiatric symptoms

A five-factor model of the Positive and Negative Syndrome Scale (PANSS) [35] consisting of positive, negative, disorganized, excitement and emotional dysfunction was used to evaluate outcomes because CRT is thought to have a specific impact on negative and disorganized symptoms [36].

Real world functioning

The Social and Occupational Functioning Assessment Scale (SOFAS) was used to assess real world functioning [37] (DSM-IV-TR 2000, 4th ed). Higher scores represent superior functioning. The SOFAS was completed by a member of the treating MDT as they were judged best placed to rate the patients functioning.

Positive moves from more secure to less secure units or discharge to community services

Patients at the CMH are stratified according to level of therapeutic security [29, 38]. Patients are moved from more secure wards to less secure wards and eventually to the community as they progress along the recovery pathway. The placements correspond to levels of risk, symptom severity, and the patient's overall level of functioning. A positive move represented transfer from a higher to a lower level of security. A negative move represented a transfer from a lower to higher level of security. The net number of positive moves that occurred during the trial was summed for each patient over the duration of the study i.e. at 8 months follow up. For the male patients five positive moves separate the acute unit from living in the community. For female patients who reside on a single ward with acute and stable patients one positive move separates them from the community.

Patient satisfaction measure

A service-user developed interview for evaluating patient experience of CRT was used to explore patient satisfaction with the intervention [39]. The interview was administered at the end of treatment by a social worker who was independent of treatment and assessment teams and blind to the intervention and to other assessments. Patients were reassured that all responses were anonymously recorded i.e. that their names were not connected with the feedback they provided.

Statistical analysis

Data analysis was carried out using intention to treat methodology (ITT) [40]. Data from all enrolled participants were used in the analysis regardless of participants' level of participation in the study using last observation carried forward. The ITT methodology was also utilized at the 8 months follow up to detect whether patients continued to benefit from participating in CRT. All data were analyzed using SPSS V 21. One patient who participated in CRT relapsed at the end of treatment. A decision was made to substitute this patient's data from baseline for the patient's end of treatment analysis in keeping with the ITT methodology.

ANOVA and chi-squared tests were used to examine baseline differences between CRT and TAU groups following randomization. At the end of treatment and at 8 months follow up ANCOVAs were carried out in which performance for the outcome of interest i.e. primary and secondary outcomes, was entered as the dependent variable, group (CRT or TAU) as independent variable, and baseline performance on the dependent variable was entered as covariate.

Three mediation analyses were also carried out in line with the study protocol. This was to clarify whether changes in cognition associated with CRT were linked to 'real world' functional outcomes including being moved to a unit with a lower level of security i.e. whether changes in cognition were associated with functional change. Mediation analyses were conducted using Hayes's SPSS PROCESS Macro Model 4 [41]. Bootstrapping (10,000 bootstrap samples) was used with 95% bias corrected confidence intervals applied. In the first mediation analysis, (Table 4 model A) the dichotomous variable CRT vs TAU was the independent variable, real world functioning (SOFAS at end of treatment) was the dependent variable, and neurocognitive functioning (MCCB composite at end of treatment; primary outcome) was the mediating variable. For the second mediation analysis CRT vs TAU was the independent variable, MCCB at 8 months follow up (secondary outcome) was the mediator, and real world functioning (SOFAS at 8 month follow up), was the dependent variable (Table 4, model B). Baseline MCCB and baseline

SOFAS were entered as covariates for both analyses. For the third mediation analysis (Table 4 model C) CRT vs TAU was the independent variable, net positive moves over the course of the study i.e. at 8 months follow up, was the dependent variable and neurocognitive functioning (MCCB composite at end of treatment; primary outcome) was the mediation variable to explore the impact that CRT vs TAU had on net positive moves over the course of the study. Because moves occurred throughout the study the MCCB at the end of treatment was entered at the mediator rather than the MCCB at 8 months follow up. Baseline MCCB and gender were entered as covariates for mediation analyses.

Results

At the end of treatment 29 patients remained in the CRT group (90%) and 28 patients remained in the TAU group (85%). At 8 months follow up 25 patients remained in both groups (78 and 76%). Table 3.

Primary cognitive outcome measures at end of treatment, and outcome at 8 months follow up

Differences in MCCB composite scores were compared between the CRT and TAU groups at both end of treatment (primary outcome) and 8-month follow up, using ANCOVAs co-varying for baseline MCCB composite performance. A significant difference in favor of CRT was observed on the MCCB composite at end of treatment (Cohen's $d = 0.34$). This difference in favor of CRT for the MCCB composite remained significant at 8 months follow up (Cohen's $d = 0.34$) (Table 3).

Secondary cognitive outcome measures at end of treatment and 8 months follow up

Significant differences were found between CRT and TAU for the MCCB domains of working memory and visual memory at end of treatment; cognitive improvements were not solely attributable to change in the MCCB composite. At 8 months follow up the difference between CRT and TAU was at trend level for working memory, however, the significant difference for visual learning was maintained. There were no significant differences between the other neurocognitive domains at end of treatment or at 8 months follow up (Table 3).

Social cognitive outcome measures at end of treatment and 8 months follow up

There were no significant differences in the MCCB social cognition task at end of treatment or 8 months follow up. The general cognitive differences that were observed occurred in the absence of any changes in social cognition.

Table 3 Outcome measures comparing three time points, baseline, end of treatment period and 8 months follow-up after treatment

Outcome measures	TAU (N = 33)						CRT (N = 32)						Post			Follow up (8 months)		
	Baseline		Post		Follow up		Baseline		Post		Follow up		F	p	d	F	p	d
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD						
MCCB modified	31.97	9.53	33.00	9.84	33.14	10.25	33.19	8.33	36.10	8.23	36.35	8.13	4.78	0.03	0.34	4.04	0.04	0.34
Speed of processing	25.45	14.31	26.72	14.11	28.93	17.01	25.65	13.47	28.93	14.17	31.21	14.67	1.49	0.22	0.15	1.41	0.29	0.14
Working memory	32.09	12.70	32	12.9	32.45	13.20	32.68	13.96	36.43	14.5	36.53	12.57	6.67	0.01	0.32	3.90	0.05	0.31
Verbal learning	34.69	7.93	34.33	8.38	35.24	7.98	35.71	7.89	36.53	8.78	38.25	8.22	0.82	0.36	0.25	2.24	0.13	0.37
Visual learning	29.42	12.98	31.63	14.15	30.18	12.26	33.65	11.50	41.25	11.37	37.78	11.91	8.82	0.00	0.79	4.61	0.03	0.62
Problem solving	33.21	8.64	35.03	9.06	34.93	9.15	36.43	8.90	35.75	8.82	36.71	7.98	0.93	0.33	0.08	0.01	0.86	0.20
Social cognition (MSCEIT)	36.96	15.32	38.30	12.81	37.09	14.79	35.00	10.93	37.71	10.77	37.56	10.85	0.06	0.80	0.04	0.95	0.33	0.03
Reading the mind in the eyes test	20.56	7.62	21.59	7.10	21.77	7.68	20.96	5.10	22.36	5.36	22.03	5.06	0.23	0.63	0.12	0.08	0.77	0.01
Faux pas recognition test	38.84	17.25	41.12	14.90	42.48	15.39	46.34	11.65	48.10	12.44	48.62	10.14	0.84	0.36	0.50	0.50	0.48	0.47
SOFAS	58.36	13.66	60.45	14.96	61.81	14.52	61.06	10.94	62.62	12.49	62.03	11.87	0.01	0.90	0.16	0.36	0.54	0.01
Net positive moves	-	-	-	-	.515	.939	-	-	-	-	0.59	0.75	-	-	-	0.10	0.74	0.09
PANSS positive	9.90	5.03	9.42	4.28	9.39	4.77	9.65	4.51	9.15	4.75	8.43	4.92	0.01	0.90	0.05	0.91	0.34	0.19
PANSS Negative	17.09	6.55	15.45	6.09	14.48	6.10	15.37	5.54	15.50	7.24	14.65	7.11	1.34	0.25	0.00	1.03	0.31	0.02
PANSS disorganisation	10.00	4.37	9.24	3.45	9.12	3.28	9.68	4.11	9.03	4.03	9.03	3.76	0.00	0.99	0.05	0.02	0.87	0.02
PANSS excitement	7.30	2.74	6.60	2.96	6.21	2.79	7.00	3.6	7.40	3.61	7.18	3.43	3.29	0.07	0.24	4.09	0.04	0.31
PANSS negative emotions	17.09	6.55	8.18	4.41	7.27	2.41	15.37	5.54	7.78	2.76	7.68	2.65	1.09	0.29	0.10	0.12	0.72	0.16

Symptom measures

There was no significant difference in any of the PANSS factors at end of treatment. At 8 months follow up a significant difference was found in favor of the TAU group for the PANSS excitement factor. There were no significant differences between the CRT and TAU groups for any other PANSS factors.

Functioning measures

There were no significant overall differences in the SOFAS scores at end of treatment or 8 months follow up, before mediation analysis.

Positive moves from more secure to less secure units or discharge to community services

There was no overall significant difference before mediation analysis in the number of net positive moves for the CRT group compared to the TAU group at 8 months follow up (Table 3).

Mediation analyses

In model A, neurocognitive function (MCCB composite at end of treatment) mediated the relationship between CRT and 'real-world' functioning (SOFAS) at end of treatment (Table 4) when controlling for baseline MCCB and baseline SOFAS. Improved cognition associated with CRT was associated with improved 'real world' functioning. For every one-unit increase in MCCB score associated with participating in CRT there was an increase of 1.60 points on the SOFAS. However, this association did not reach statistical significance at 8 months follow up (Model B) (Table 4).

Participating in CRT and the net number of positive therapeutic moves by end of the study i.e. the 8 months follow up period, was also mediated by neurocognitive function as measured by the MCCB at the end of

treatment, when controlling for baseline MCCB and gender (Model C). Those patients who participated in CRT and who benefited cognitively made more positive moves to lower levels of security within the hospital. For every one-unit increase in cognition associated with CRT there was an increase of 0.15 for the number of positive moves through the hospital (Table 4).

Patient experience of CRT

Twenty-seven of twenty-eight patients who remained in CRT participated in an anonymous interview evaluating patients' experience of CRT [38]. One refused to participate, and one was discharged. Nearly all reported subjective improvements in cognition (96%) with most feeling the change was maintained at follow up (85%). Twenty-eight percent believed the change would last, 24% said it would change over time, and 24% said that if they did not practice their skills improvements would deteriorate. Ninety-six percent believed the cognitive gains they experienced had positively affected their daily lives. Subjective improvements were noted in a) social interaction, for example decreased interruptions and improving conversational skills; b) engagement in activities, for example participating in other psychosocial treatments; c) working with clinicians, for example remembering the content of multidisciplinary meetings; d) community functioning. Ninety-six percent said that participating had led to positive feelings about themselves and a sense of achievement or confidence. Patients reported that their experience of the relationship with the CRT therapists was important to them (89%). A minority noted aspects that they disliked. Seven mentioned disliking specific tasks (26%). A small number reported anxiety during tasks (7%), some disliked the repetitive nature of sessions (7%). One (4%) disliked the time commitment and tiredness they experienced after

Table 4 Hayes process mediation model 4: regression and mediation coefficients

n = 69	Change in Y		C1: direct effect of X on Y before mediation		C2: direct effect of X on Y after mediation		A: indirect effect of X on Y mediated via M		B: direct effect of M on Y adjusted for X	
	R ²	p	Unstandardized effect size	95% CI	Unstandardized effect size	95% CI	Unstandardized effect size	95% CI	Unstandardized effect size	95% CI
Model A										
X = Group	0.49	.000	0.49	-4.69, 5.68	-1.10	-6.27, 4.05	1.60	0.12, 4.21	0.88	0.16, 1.60
M = MCCBT1										
Model B										
X = Group	0.45	.000	-1.81	-6.83, 3.20	-2.39	-7.55, 2.77	0.55	-0.23, 2.63	0.30	-0.32, 0.93
M = MCCBT2										
Model C										
X = Group	0.12	0.04	0.06	-0.36, 0.48	-0.08	-0.50, 0.33	0.15	0.02, 0.38	0.07	0.02, 0.13
M = MCCBT1										

Models A and B controlled for baseline MCCB and baseline SOFAS. Model C controlled for baseline MCCB and gender
 Model A: Y = SOFAS at end of treatment. Model B: Y = SOFAS at 8 months follow up. Model C: Y = number of net positive moves; Results in bold are statistically significant
 CI Confidence interval

sessions. Most said that participating made them aware of their limitations and provided them with insight into their cognitive difficulties (89%). Finally, 26% reported a sense of loss when CRT ended.

Discussion

The primary aim of this study was to test the effectiveness of CRT within a 'real world' population of forensic mental health patients experiencing severe cognitive impairment. The mean score for the forensic patients who enrolled in this study was approximately three standard deviations lower than a nonclinical mean as assessed using the MCCB composite. We were also interested in the acceptability of CRT and patients' experience of the intervention. Five main outcomes were observed. First, patients who participated in CRT obtained significant improvements in the primary outcome measure, a composite score of the MCCB both at end of treatment and at 8 months follow up. Second, there were significant improvements in specific cognitive domains including working and visual memory, but not social cognition. Third, there were no significant differences in symptoms (PANSS) apart from a difference in favor of the control group in the PANSS excitement factor. Fourth, there were no significant differences between CRT and TAU on routine measures of real world functioning ascertained by the multidisciplinary team (SOFAS) or net positive moves. However, mediation analysis revealed that those who benefited neurocognitively from CRT had related improvement in functioning at the end of treatment (SOFAS); and more net positive therapeutic moves at follow up; there were meaningful functional gains associated with CRT but these gains were predicated on having improved measures of cognitive function. Conversely, those who received CRT but did not have improved cognitive function failed to make 'real world' functional gains. Fifth, the patients who were randomly assigned to CRT appeared to value the intervention. Ninety-six percent reported that their subjective neurocognitive ability had improved because of participating in CRT. Importantly 96% percent reported that the cognitive gains they achieved had positively affected their daily lives.

This study contributes to a body of work suggesting that CRT is an effective intervention for patients with schizophrenia or schizoaffective disorder, improving both cognitive and functional outcomes [12, 18, 19]. Although over 40 studies have been conducted, this study overcomes a potential weakness associated with randomized controlled trials namely selection bias [20, 21]. Those who participate in trials may not always be representative of the general population of patients. We be-

group, and of the 69 patients who met the inclusion criteria in this national service, 65 agreed to take part representing a 94% uptake of those eligible to participate. This study also casts light on the mechanism of action of CRT using mediation analysis. Cognitive improvements associated with CRT were also associated with 'real world' functional improvements such as being moving to a unit with a lower level of security. CRT may have the potential to reduce length of stay in secure settings and create savings for services [42].

We controlled for baseline cognition and baseline SOFAS and showed non-the-less that improved cognition associated with CRT was associated with improved real world function (SOFAS). We also showed that when controlling for baseline MCCB and for gender, positive moves were non-the-less associated with improved neurocognition associated with CRT. It may be taken from this that baseline MCCB, SOFAS and gender were not predictors of response to CRT. To clarify the predictors of positive response however would require formal dismantling studies [43, 44].

To date there has only been a small number of RCTs evaluating the effectiveness of psychological interventions within forensic mental health settings [8, 45], and there has been an even smaller number evaluating CRT [18, 19]. This may arise from the misconception that interventions which are efficacious in community settings will be equally effective within forensic settings despite patients being legally detained and potentially more impaired [6, 8]. Forensic services typically have a legally defined dual role requiring care and treatment and in addition public protection [8]. Both roles may not always be aligned and in these cases, it is society and not the patient who is the 'customer', which is likely to affect engagement [8]. This study demonstrates that CRT has the potential to improve cognitive functioning for forensic patients in addition to helping patients adopt the role of 'customer' [8]. The forensic patients' response to participating in CRT is particularly striking with the majority of patients regarding the intervention positively. Patients' positive attitudes towards CRT are likely to be a result of our nine treatment principles, which emphasise the therapeutic relationship, and common factors associated with psychological interventions [15]. CRT may therefore play a useful role by engaging patients to participate in challenging psychological interventions like working on refractory symptoms, violence risk, substance misuse difficulties and pro-social attitudes.

There are limitations and strengths associated with this study. The primary limitation was the numbers of forensic patients available nationally. A robust evaluation of the effectiveness of CRT within forensic services will

way for such initiatives. Additional limitations were that medication could not be kept constant during the study, and the absence of an active control group. Additional strengths include having an appropriate dose of therapy [11, 12], the wide range of secondary outcome measures, and the ITT design.

Conclusion

CRT is an effective intervention for patient groups with schizophrenia experiencing severe cognitive impairments. Those who received CRT demonstrated improved global cognitive performance at the end of treatment and follow up. The high uptake of patients willing to participate, and the positive feedback received suggests that patients' regarded CRT as an acceptable and valued intervention.

Abbreviations

95% CI 95 percent confidence interval; ACB: Anticholinergic burden; ANOVA: Analysis of variance; CMH: Central Mental Hospital; CONSORT: Consolidated Standards of Reporting Trials; CPZeq: Chlorpromazine equivalent; CRT: Cognitive remediation training; DUNDRUM-1: Dangerousness, Understanding, Recovery and Urgency Manual (The Dundrum Quartet); HCR-20: Historical Clinical Risk Management, Version 2; ITT: Intention to treat; MCCB: MATRICS Consensus Cognitive Battery; MSCEIT: Mayer-Salovey-Caruso Emotional Intelligence Test; NFMHS: National Forensic Mental Health Service; PANSS: Positive and negative syndrome scale; SCID: Structured Clinical Interview for the Diagnostic and Statistical Manual IV (SCID); SD: Standard deviation; SOFAS: The social and occupational functioning assessment scale; SPSS: Statistical package for the social sciences; TAU: Treatment as usual

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Availability of data and materials

Because of the sensitive nature of the patients' situation, data is not publicly available but is available from the first author on reasonable request.

Authors' contributions

KOR is the lead author and this work forms a substantive part of his PhD thesis. All authors (KOR, GD, DOS, CC, AC, POF, MOD, TG, POIC, HGK) contributed to and have approved the final manuscript. All authors made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; all authors have been involved in drafting the manuscript or revising it critically for important intellectual content; and all authors have given their final approval of the version to be published. Each author has participated sufficiently in the work to take public responsibility for appropriate portions of the content; and each author has agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics approval and consent to participate

This study was approved by the research ethics and effectiveness committee of the NFMHS (AREE/290814, 29th August 2014) and Faculty of Health Sciences Research Ethics committee Trinity College Dublin (8th September 2014). The study complied with the Helsinki Declaration of 1975, revised in 2008. All participants were assessed by their treating consultant psychiatrists

as having the capacity to consent to the research study. All participants were supplied with a written letter of information concerning the study. After a period of 7 days, all gave written, informed, and competent consent in keeping with the approval of the research ethics committees.

Consent for publication

This manuscript does not contain any individual person's data which could be readily identifiable in any form (including any individual details, images or videos) i.e. no individually identifiable material was included. And all patients gave consent to publish the study's findings.

Competing interests

All authors declare that they have no financial involvement (including employment, fees, share ownership) or affiliation with any organization whose financial interests may be affected by material in the manuscript, or which might potentially bias it. HGK is a member of the editorial board of *BMC Psychiatry* but has had no editorial involvement with the publication of this article.

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Author details

¹Department of Psychiatry Trinity College Dublin, the University of Dublin, Dublin, Ireland. ²The Central Mental Hospital, National Forensic Mental Health Service Ireland, Dublin, Ireland. ³School of Psychology, National University of Ireland Galway, Galway, Ireland.

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