IMAGING THE GENETICS OF EXECUTIVE FUNCTION

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Abstract

Recent advances in neuroimaging technologies have allowed ever more detailed studies of the human brain. The combination of neuroimaging techniques with genetics may provide a more sensitive measure of the influence of genetic variants on cognitive function than behavioural measures alone. Here we present a review of functional magnetic resonance imaging (fMRI) studies of genetic links to executive functions, focusing on sustained attention, working memory and response inhibition. In addition to studies in the normal population, we also address findings from three clinical populations: schizophrenia, ADHD and Autism Spectrum Disorders. While the findings in the populations studied do not always converge, they all point to the usefulness of neuroimaging techniques such as fMRI as potential endophenotypes for parsing the genetic aetiology of executive function.

I. Introduction

The abilities to control and inhibit action and to use memory to guide future behaviour are fundamental aspects of human cognition that allow us to function successfully in complex environments. In evolutionary terms, the development of such "executive" capacities has in large part paralleled the development of the frontal lobe of the human brain. It is perhaps unsurprising that individual differences in executive capacity may be attributed, at least in part, to genetic variation (see Goldberg & Weinberger, 2004 for a review) Inroads to studying the genetic underpinnings of neuronal processes underlying executive functions have traditionally been made by investigating hereditary disorders characterised by deficits in these processes. Technological advances have meant that the effects of allelic variation in genes involved in neurotransmission can now be partially observed using neuroimaging techniques such as magnetic resonance imaging (MRI). This review draws on findings from both genetics and neuroimaging in an effort to elucidate our current understanding of the influence of genetic variants on the neuropsychology of healthy and psychiatric populations.

For the purposes of this review, we focus on three executive functions and their genetic and neurological correlates: sustained attention, working memory and response inhibition. We focus on studies of three heritable psychiatric disorders, namely attention deficit hyperactivity disorder (ADHD), autism and schizophrenia, and compare findings from these disorders with studies of normal populations in an attempt to clarify the genetics of executive function. Although a body of research has addressed the impact of genetic factors on morphological changes in these orders, the implications of these findings are beyond the scope of this review, and we limit ourselves to a discussion of functional MRI studies.

II. Disorders

Schizophrenia

Symptoms

Schizophrenia is characterised by a large variety of symptoms, usually subdivided into 'positive' (e.g. hallucinations, delusions) and 'negative' (e.g. flattening of affect, apathy, poverty of speech) symptoms (see Capuano *et al.*, 2002 for an overview).

Executive function deficits

Deficits in a broad range of executive functions are commonly seen in schizophrenia (Goldberg *et al.*, 2003). A large body of research has shown that participants with schizophrenia routinely perform poorly on the Wisconsin Card Sorting Test (WCST), one of the most common tests of executive function (see Heinrichs & Zakzanis, 1998 for a review). The performance of patients with schizophrenia in different aspects of executive function has been independently assessed, and deficits have been observed in tests of sustained attention (Heinrichs & Zakzanis, 1998), working memory (Heaton *et al.*, 2001), conflict resolution (Wang *et al.*, 2005) and response inhibition (Badcock *et al.*, 2002) .

Genetic evidence

Schizophrenia is known to be highly heritable, with estimates ranging from 68-89% (Jones and Cannon 1998; National Institute of Mental Health's Genetics Workgroup, 1998). The cognitive deficits of the disorder also appear to have a heritable component, with unaffected siblings of schizophrenic patients displaying inferior performance on the WCST compared with controls (Egan, Goldberg, Gscheidle *et al.*, 2001). A frequently expressed view is that schizophrenia is the result of specific variation in a large number of genes, each with small effect (Risch & Rao, 1990).

ADHD

Symptoms

Attention deficit hyperactivity disorder (ADHD) is a common childhood-onset psychiatric condition, characterised by age-inappropriate levels of behavioural impulsivity, hyperactivity and inattention (American Psychiatric Association, 1994). The disorder is relatively common, with estimates ranging around 3-5% of school age children (Buitelaar, 2002), persisting into adulthood in about 30-50% of cases (Weiss & Hechtman, 1993).

Executive function deficits

Individuals with ADHD typically show impairments of executive function, particularly in the domains of working memory (including spatial and verbal working memory), sustained attention and response inhibition, although the extent of these deficits varies from child to child (Nigg, 2005). Two reviews (Nigg, 2005; Willcutt *et al.*, 2005) found that case/control differences for these functions were associated with Cohen's d effect sizes between .46 and .75, suggesting that these executive functions discriminate reasonably well between individuals with and without ADHD.

Genetic evidence

ADHD has a strong genetic component, with additive effects of multiple genes explaining around 80% of an individual's susceptibility to ADHD (Thapar *et al.*, 1999). Studies looking at ADHD prevalence show siblings of an individual with ADHD to be three to five times more likely to be affected with ADHD than the general population (Faraone *et al.*, 1993), while monozygotic twins have a concordance of 50-80% compared with 33% for dizygotic twins (Bradley & Golden, 2001). Studies investigating the influence of candidate genes have mostly focused on the catecholamine system (specifically dopamine and noradrenaline), as well as genes associated with the indolamine serotonin (see Voeller, 2004 for an overview).

Autism Spectrum Disorders

Symptoms

Autism, high-functioning autism and Asperger's syndrome, grouped under the term autism spectrum disorders (ASDs), are neurodevelopmental disorders clinically defined by deficits in social behaviour, delayed onset of verbal and non-verbal communication and unusual patterns of restricted, repetitive behaviours and interest, before the age of three years (American Psychiatric Association, 1994).

Executive function deficits

Abnormalities in executive function in the ASDs include deficits in working memory (Silk *et al.*, 2006), planning (Ozonoff & Jensen, 1999), set shifting (Verte *et al.*, 2005), response inhibition (Johnson, Robertson *et al.*, 2007), and different aspects of attention, including orienting (Townsend *et al.*, 1996) and shifting (Rinehart *et al.*, 2006).

Genetic evidence

The ASDs have a strong genetic component to their aetiology (Bailey *et al.*, 1995) with heritability estimates of up to 90% (Ronald *et al.*, 2006). Each of the three core behaviours of the ASDs may have independent genetic origins (Ronald *et al.*, 2006). The genetic origins of the ASDs are complex; no one gene has been unequivocally identified as containing risk alleles for autism. In a recent review of the genome-wide linkage studies for autism and the ASDs, 94 loci were reported as potential candidate genes (Yang & Gill, 2007).

III. Endophenotypes

ADHD, the ASDs and Schizophrenia are representative of many complex psychiatric disorders, in that symptoms and aetiologies may vary widely among patients. This renders the detection of candidate genes highly problematic. A hypothesised solution to this problem is the application of *endophenotypes*, which are measurable quantitative

traits that lie intermediate between gene function and behaviour, and can be more clearly linked to genetic variation (Gottesman & Gould, 2003).

Neuroimaging technologies such as functional magnetic resonance imaging (fMRI) provide a sensitive measure of the efficiency of cognitive networks and may be a more suitable assay of underlying genetic influences than purely behavioural measures. The utility of fMRI may be particularly apparent in conditions where individual differences in behavioural measures are minimal due to either ceiling or floor effects on the neurocognitive task under study. Neuroimaging of cortical activity during performance of behavioural tests of sustained attention, response inhibition and working memory may therefore provide more sensitive endophenotypes for disorders of the executive system than behavioural testing alone.

IV. Functions

Sustained attention:

Sustained attention refers to the ability to maintain focus on a task without exogenous alerting (Robertson *et al.*, 1997). Heritability estimates for sustained attention vary considerably depending on the measure employed, ranging from around 20% to 70% (Boomsma, 1998; Heiser *et al.*, 2006).

A catecholamine (dopamine and noradrenaline) model of attention has been proposed which relies heavily on the activity of the right frontal and parietal cortices (Levy & Swanson, 2001; Posner & Peterson, 1990). Performance of sustained attention tasks has been consistently shown to activate a fronto-parietal cortical network, largely lateralised to the right hemisphere (Lawrence *et al.*, 2003), although left prefrontal cortex (Fassbender *et al.*, 2004) and subcortical regions including the thalamus and putamen (Kinomura *et al.*, 1996; Paus *et al.*, 1997) have also been implicated.

Sustained Attention in Normal Populations

Researchers have investigated the role of several dopaminergic genes in the modulation of attention. The COMT gene codes for the catechol-O-methyltransferase enzyme, responsible for the degradation of dopamine. The Met allele of a polymorphism at position 158 within this gene breaks down dopamine more slowly and results in higher levels of cortical dopamine (Lachman *et al.*, 1996) than the Val allele. While Blasi *et al.* (2005) found an association between COMT and attentional control, others (Fossella *et al.*, 2002; Stefanis *et al.*, 2004) found no association between COMT genotype and sustained attention in normal populations.

Two fMRI studies of attentional control (Blasi *et al.*, 2005; Heinz & Smolka, 2006) found lower activity levels in the anterior cingulate with increasing dose of the COMT Met allele. Combined with findings that the Met allele is associated with better performance of this task, this indicates that the Met allele produces a more focused response, and contributes towards a more efficient prefrontal attention network than the Val allele (also see Winterer *et al.*, 2006). In contrast with this interpretation, Fan *et al.* (2003) found that increased efficiency of the conflict network in the Attention Network Test (ANT) was associated with augmented activity in the anterior cingulate. In a study of the effects of the dopaminergic genes MAOA and DRD4 (coding for the dopamine D4 receptor) on attention networks, the authors found that the alleles of the two genes that were known to be associated with better performance on the task were associated with increased, not decreased cortical activity. Some association of a polymorphism in Exon III of DRD4 with attention problems in normally-developing children had previously been demonstrated (Auerbach *et al.*, 2001; Schmidt *et al.*, 2001), however no association was found between any variant of the DRD4 gene and the efficiency of the ANT alerting network (Fossella *et al.*, 2002). The alerting network is assayed by comparing response times under a condition in which participants must maintain response readiness in the absence of an alerting cue, compared to response times when this alerting cue is provided. Thus, the alerting network may be considered somewhat analogous to the

sustained attention network described above, as in both cases attention must be maintained without exogenous alerting.

Fossella and colleagues did however find the efficiency of the alerting network to be modulated by a 30bp promoter region polymorphism in the MAOA gene, responsible for the degradation of serotonin and noradrenaline. The neurotransmitter serotonin and its associated genes have traditionally been considered to play a role in affective and emotional regulation (see other articles within this special edition). In a different context, however, polymorphisms in the gene coding for the serotonin transporter (5HTT) have also been linked with differences in activation of the anterior cingulate during a Stroop-type task (Canli *et al.*, 2005).

Sustained Attention in Schizophrenia

Difficulties with sustained attention are a well known symptom of schizophrenia (Egeland *et al.*, 2003). Although patients with schizophrenia show significant deficits on tests of sustained attention relative to their unaffected relatives, the family members perform less well than control subjects (e.g. Cornblatt *et al.*, 1999), indicating a familial risk profile for sustained attention deficits in schizophrenia. Patients with schizophrenia have been reported to display lower levels of activation in anterior and posterior cingulate, right lateral frontal cortex and superior temporal gyrus during performance of tasks requiring sustained attention (Carter *et al.*, 1997; Kiehl & Liddle, 2001).

The nicotine system has been implicated in the modulation of attention in schizophrenia (Harris *et al.*, 2004), and one study reported an association between a polymorphism in Exon 5 of the CHRNA4 gene, coding for the nicotinic acetylcholine α4 subunit, and performance on an auditory oddball task measuring sustained attention (Winterer *et al.*, 2007). Variation at the CHRNA4 locus was also associated with the efficiency of attention networks in the anterior cingulate and parietal cortex.

Sustained attention difficulties in schizophrenia have also been related to variation in several other genes, including the serotonin 2A receptor gene (Ucok *et al.*, 2007), DISC1

(Liu *et al.*, 2006) and dysbindin (Donohoe et al., 2007), but not to COMT genotype (Smyrnis *et al.*, 2007).

Sustained attention in ADHD

Inferior target detection on tasks of sustained attention is reliably reported in children with ADHD compared to matched controls (e.g. Johnson, Kelly *et al.*, 2007a), although it has been suggested that the absence of robust time-on-task effects in ADHD argues against significant impairment in sustained attention (Stins *et al.*, 2005). More recent work within the cognitive neurosciences, however, shows that brief lapses of sustained attention, as measured by poor target detection, are preceded by momentary reductions of activity in frontal control regions (Weissman *et al.*, 2006). Sustained attention deficits in ADHD may thus be influenced by both a failure in the moment-to-moment control of attention as well as a more gradual diminution in arousal over time (Johnson, Kelly *et al.*, 2007a).

While we have found no studies relating specific candidate genes to functional brain differences in children with ADHD during sustained attention performance, a number of genes thought to modulate sustained attention in the disorder have been identified. A number of polymorphisms in the gene encoding the dopamine transporter (DAT1) have been tested for association with ADHD. A VNTR in the 3' untranslated region of the gene has been associated with a diagnosis of ADHD in many (e.g. Barkley *et al.*, 2006; Barr *et al.*, 2001; Gill *et al.*, 1997) but not all (e.g. Todd *et al.*, 2001) populations. An association between the 10-repeat allele of this marker and sustained attention deficits has been reported in ADHD (Bellgrove, Hawi, Kirley *et al.*, 2005).

In addition to this finding, the 7-repeat allele of the DRD4 gene has been associated with increased errors of commission in individuals with ADHD, when performing sustained attention tasks (Kieling *et al.*, 2006), but see Bellgrove, Hawi, Lowe *et al* (2005) for a contrasting result. In children with ADHD, performance on sustained attention tasks has also been linked to variation in the DBH gene (Bellgrove, Mattingley *et al.*, 2006). DBH codes for the dopamine β-hydroxylase enzyme which catalyses the conversion of

dopamine to noradrenaline. ADHD children with two copies of an allele that was previously associated with ADHD (A2 allele of an Intron 5 polymorphism) performed more poorly on a test of sustained attention than ADHD children possessing fewer copies of this allele (Bellgrove, Hawi *et al.*, 2006). The Val variant of the COMT gene has been associated with better performance on a sustained attention task, in children with ADHD (Bellgrove, Domschke *et al.*, 2005), contrary to what is typically found in the general population.

Sustained Attention in ASDs

Only a handful of studies have investigated sustained attention in children with ASD and most studies have reported intact sustained attention (for a review see Johnson, Robertson *et al.*, 2007). To date, there have been no functional neuroimaging studies of sustained attention in autism spectrum disorders, however given the neuroanatomical debate as to whether the parietal cortex is implicated in autism (for a review see Schmitz *et al.*, 2007), it would be valuable to examine the function of the frontal and parietal cortices during a sustained attention task in people with ASD (Sanders *et al.*, 2007). It may be the case that, as was found in other tests of executive function (Schmitz *et al.*, 2006), normal performance is achieved by a number of compensatory mechanisms which might be observed with fMRI.

We are not aware of any studies that have examined the impact of any candidate genes on brain function during sustained attention in ASD.

Working Memory:

The classical view of working memory (see Baddeley, 1992) maintains that it is a system for the short-term storage of information, composed of a central executive and two 'slave' systems, a phonological loop and a visuospatial sketchpad, which temporarily store auditory and visual information, respectively. This view accords with the common division of working memory processes into those dealing with storage or maintenance of information, and those dealing with manipulation of that same information. Working

memory appears to have a significant genetic component, with estimates of its heritability ranging from 33% to 49% (Ando *et al.*, 2001; Wright *et al.*, 2001).

The process of working memory is largely subserved by the prefrontal cortex (although the role of the dorsolateral prefrontal cortex (DLPFC) remains controversial; McCarthy *et al.*, 1994; Petrides, 1994) in conjunction with regions of the parietal cortex, and is known to be mediated by dopaminergic systems (Mehta *et al.*, 2001; Muller *et al.*, 1998). Dopamine is believed to have an inverted U-shaped dose/response curve for working memory whereby either too much or too little dopamine will result in sub-optimal performance (Vijayraghavan *et al.*, 2007). Noradrenaline has also been shown to be a key neurotransmitter for working memory (see Chamberlain *et al.*, 2006 for a review). Similarly to dopamine, an optimal level of noradrenaline appears critical for working memory.

Working Memory in Normal Populations

A number of studies have examined the impact of COMT genotype on working memory in healthy controls. While several studies found no significant differences in working memory performance among genotype groups (e.g. Bertolino, Blasi *et al.*, 2006; Bruder *et al.*, 2005; Stefanis *et al.*, 2004), those studies that did find differences converge to suggest that the less active Met allele is associated with better verbal or numerical working memory performance (e.g. Diamond *et al.*, 2004; Goldberg *et al.*, 2003).

The relevance of the COMT Val/Met polymorphism to working memory was demonstrated in an fMRI study. Amphetamine, which binds to the dopamine transporter and reduces reuptake of extrasynaptic dopamine, was administered to participants with differing COMT genotypes prior to performance of a working memory task. Amphetamine resulted in improvement in cortical efficiency and reaction time for Val/Val participants, while it reduced cortical efficiency and impaired performance in the most difficult task condition for Met/Met participants (Mattay *et al.*, 2003). The implication of this is that efficient performance of prefrontal-dependent tasks relies on the presence of an optimal level of extrasynaptic dopamine. The increase in dopamine

occasioned by the administration of amphetamine will therefore have differential effects on performance depending on the baseline dopamine levels produced by COMT genotype.

Two studies of the effects of this polymorphism on brain activation during performance of a non-spatial working memory n-back task found the Met allele to be associated with a more focused, efficient cortical response than the Val allele (Bertolino, Blasi *et al.*, 2006; Egan, Goldberg, Kolachana *et al.*, 2001). Bertolino and colleagues also assessed the impact of the 3' VNTR in the DAT1 gene on cortical activation during this task; not only was the 10-repeat allele associated with a more efficient cortical network, but homozygosity for both the DAT1 10-repeat allele and the COMT Met allele was linked with the most focused response of all, indicating an additive effect of these genes on the working memory cortical network. Similarly, Caldú et al. (2007) found homozygosity for both the DAT1 9-repeat allele and COMT Val allele to be associated with the highest level of activation during an n-back task. An association was also reported between variation in the DRD2 gene and working memory ability in normal participants. This association was strengthened when interaction with the COMT Val/Met polymorphism was investigated (Xu *et al.*, 2007).

An association of the G444A marker of the DBH gene with spatial working memory performance has been demonstrated. Increasing dosage of the high-activity G allele is associated with lower levels of the DβH in plasma and cerebrospinal fluid (Cubells *et al.*, 1998), and was found to be linked to greater accuracy on the more difficult conditions of a spatial working memory storage task, but not on a visuospatial attention task (Parasuraman *et al.*, 2005). The G444A marker has previously been shown to be in strong linkage disequilibrium with the main functional variant controlling plasma DβH levels, the C-1021T polymorphism (Zabetian *et al.*, 2003), however no links with spatial working memory have been demonstrated for this marker. The authors found no association of a polymorphism in the CHRNA4 gene, reported to be linked with visuospatial attention, with spatial working memory in this study. Research performed in other groups has indicated no association between working memory performance and

variation in the DAT1 (Bertolino, Blasi *et al.*, 2006), 5HTT (Hariri *et al.*, 2002), NET (Szöke *et al.*, 2006) or MAOA (Yu *et al.*, 2005) genes.

Working Memory in Schizophrenia

Working memory deficits are a core neuropsychological symptom of schizophrenia (Goldman-Rakic, 1991). The extent of these deficits is thought to be mediated by a number of genes, including COMT (Egan, Goldberg, Kolachana *et al.*, 2001), Reelin (Wedenoja *et al.*, 2007), Neureglin (Stefanis *et al.*, 2007), DISC1 (Burdick *et al.*, 2005), DAT1 (Rybakowski *et al.*, 2006) and several of the dopamine receptor genes (Rybakowski *et al.*, 2005; Szekeres *et al.*, 2004).

Abnormalities in prefrontal function during performance of working memory tasks are frequently reported in schizophrenia. Many of these studies indicate hypoactivation of lateral prefrontal cortex (e.g. Barch & Csernansky, 2007), while others describe either increased activation in those areas (Callicott *et al.*, 2000; Manoach *et al.*, 1999), or no apparent difference from control participants (Walter *et al.*, 2007). This has led to the suggestion that changes in cortical activation with increasing task demands or memory load may also follow an inverted-U shaped curve. This appears to be the case even after controlling for the effect of COMT genotype (Bertolino, Caforio *et al.*, 2006). Abnormalities in parietal activation are also common; schizophrenic patients appear to demonstrate decreased activation in dorsal and ventral inferior parietal cortex (Barch & Csernansky, 2007; Schneider *et al.*, 2007), however some contradictory results have also been reported (Mendrek *et al.*, 2005; Thermenos *et al.*, 2005).

A genetic link to the functional abnormalities observed in the brains of schizophrenic patients is supported by the discovery that the unaffected first degree relatives of patients display significantly greater DLPFC activation than controls during working memory tasks (e.g. Callicott *et al.*, 2003). The majority of genetic neuroimaging studies of working memory in schizophrenia address the impact of COMT genotype on cortical response. The consensus of these studies is that increasing gene dosage of the Met allele is associated with a more efficient prefrontal cortical response during performance of

working memory tasks (Bertolino, Caforio *et al.*, 2006; Egan, Goldberg, Kolachana *et al.*, 2001; Ho *et al.*, 2005). Further, improvement in both behavioural working memory performance and prefrontal efficiency following a course of the antipsychotic medication olanzapine is predicted by Met allele load (Bertolino *et al.*, 2004).

Cortical activity relating to working memory may be affected in schizophrenia by genes involved in other neurochemical systems; for example, a schizophrenia-associated polymorphism in the DISC1 gene has been shown to have an effect on hippocampal activation during working memory (Callicott *et al.*, 2005).

Working Memory in ADHD

A number of studies suggest that individuals with ADHD demonstrate problems with working memory. For example, medication-naïve children with ADHD were found to be impaired in spatial-working memory, compared with control children or children with ADHD on stimulant medication (Barnett *et al.*, 2001). Impairments in working memory in individuals with ADHD are associated with low levels of striatal dopamine (e.g. Frank *et al.*, 2007), and often respond well to stimulant medications that increase dopaminergic activity (for a review see Pietrzak *et al.*, 2006).

A growing number of studies have used functional imaging to investigate ADHD (see Fassbender & Schweitzer, 2006 for an overview). Based on the current evidence, they suggest that in individuals with ADHD the processing of executive functions such as sustained attention, response inhibition and working memory is often taken over by other (presumably unaffected) regions, while hypoactivity is observed in those (affected) regions that are typically engaged in processing the task. Individuals with ADHD show reduced activation in prefrontal areas (as well as other regions including cerebellum and occipital cortex) when engaged in a verbal working memory task (Valera *et al.*, 2005). Relatively few studies have imaged spatial working memory in ADHD, despite the robust effect sizes associated with behavioural measures of spatial working memory (see Martinussen *et al.*, 2005, pp. for a meta-analysis). Reductions in activity within the right parietal lobe, as well as occipital areas including the cuneus and precuneus, have been

observed during mental rotation, a process requiring the spatial storage of relations between objects (Silk *et al.*, 2005; Vance *et al.*, 2007).

Very few studies of genetic effects on working memory in ADHD have been published. A recent article by Levy (2007) reviewed the relationship between COMT polymorphisms and response to treatment medication in individuals with ADHD. Individuals possessing the more active Val variant typically perform better with stimulant medication on tests that assess working memory, unlike individuals homozygous for the Met variant whose performance decreases. A study by Dorval and colleagues (2007) found the GRIN2B gene to be associated with ADHD symptoms such as inattentiveness and hyperactivity, but not with either verbal working memory or short term memory (also see Adams *et al.*, 2004 for similar negative findings regarding the link between GRIN2A and working memory).

Working Memory in ASDs

People with ASD frequently demonstrate deficits in working memory (for a review see Russo *et al.*, 2007). A number of functional imaging studies have been conducted examining differences in cortical activation in participants with ASD during performance of working memory tasks. A study by Koshino and colleagues (2005) using an N-back working memory task with letter stimuli found that, despite the absence of any differences in performance, adults with ASD showed less activation in the left prefrontal regions than controls, especially in DLPFC, inferior frontal gyrus and posterior pre-central sulcus. The authors suggest that as verbal working memory is related to the left prefrontal cortex, and non-verbal working memory to the right, the adults with ASD may have been processing the letter stimuli as visual codes rather than verbal information. These participants also showed increased activation of the right parietal cortex and decreased activation of the left, again suggesting that the letter stimuli were processed as non-verbal, visual graphics rather than using a phonological code. A later study by the same group (Koshino *et al.*, 2007) found less activation in left prefrontal and right posterior temporal cortices during an N-back working memory task using facial stimuli. The implication here is that participants with ASD process faces purely as objects,

without the emotional element. Functional connectivity analyses suggested lower connectivity with the frontal areas but normal connectivity with the parietal cortices, indicating a fundamentally different cortical network for working memory processing in autism. This makes any extrapolation of findings to a normal population highly problematic.

Similar differences in cortical activation were observed in the performance of several other working memory tasks; on a mental rotation task, adolescents with ASD demonstrated less activation in the DLPFC, anterior cingulate, the lateral and medial premotor area and the caudate nucleus, but normal activation in the parietal cortices (Silk *et al.*, 2006), while on a spatial working memory task, adults with ASD showed less activation of the DLPFC and posterior cingulate cortex than controls (Luna *et al.*, 2002). Normal activation was shown in the anterior cingulate cortex, insula, basal ganglia, thalamus and lateral cerebellum.

Although we are aware of no studies examining the effects of specific candidate genes in working memory in ASDs, it appears that spatial working memory deficits, as measured by the delayed oculomotor response task, may have a genetic component. Parents of children with ASD demonstrated poorer spatial accuracy than a control group, but normal levels of premature saccades (eye movements towards a stimulus) and normal latency of remembered saccades, suggesting the parents of ASD probands exhibited spatial working memory deficits (Koczat *et al.*, 2002). We are aware of no functional imaging studies, however, addressing genetic links to working memory deficits in ASD.

Response Inhibition:

Response inhibition, the ability to withhold a prepotent response to a stimulus, is considered to be a critical measure of executive function (Chambers *et al.*, 2006; Dempster & Brainerd, 1995), and is often assessed by the use of Go/No-Go or Stop Signal tasks. Studies with the unaffected family members of clinical groups with response inhibition deficits have indicated that the ability to inhibit a response includes a

heritable component (e.g. Slaats-Willemse *et al.*, 2003). The extent of that heritability is however unclear, varying from 0 to 54% (Groot *et al.*, 2004; Heiser *et al.*, 2006).

In a similar fashion to sustained attention, correct inhibition of a prepotent response recruits a distributed cortical network largely lateralised to the right hemisphere (Garavan *et al.*, 1999), with heavy reliance on both parietal and ventral prefrontal cortices (Aron *et al.*, 2003; Chambers *et al.*, 2006; Menon *et al.*, 2001). The role of dopamine in response inhibition has been described in a number of studies (e.g. Mink, 2001; Roesch-Ely *et al.*, 2005). For example, one study administered the dopamine precursor levodopa to participants during performance of a Go/No-Go task (Hershey *et al.*, 2004). The resulting increase in cortical dopamine levels led to lower activation in right parietal and cerebellar regions in the absence of any difference in performance accuracy or reaction time. This implies more efficient response inhibition processing with increased dopamine levels.

Response Inhibition in Normal Populations

A number of genes of the dopaminergic system have been implicated in the process of response inhibition, although few studies have addressed this relationship in normal populations. In one study however, normal children homozygous for the 10 repeat allele of DAT1 were found to perform less well on a test of response inhibition than children with one copy of the allele (Cornish *et al.*, 2005), further highlighting the contribution of that allele to executive function. A more recent study has reported an interaction between polymorphisms of the DRD4 and DAT1 genes on response inhibition. Carriers of the 7-repeat DRD4 allele who were also homozygous for the 10-repeat DAT1 allele displayed poorer response inhibition on a stop-signal task (Congdon et al, 2007).

A body of evidence has indicated a role for the serotonin system in impulse control and response inhibition (Lucki, 1998). A logical progression of this was that a polymorphism in the serotonin transporter gene (5HTT), which leads to reduced gene transcription and diminished serotonin uptake (Lesch *et al.*, 1996), might be involved in these processes. Nevertheless, a number of studies (Clark *et al.*, 2005; Fallgatter *et al.*, 1999) failed to

demonstrate an association between the 5HTTLPR polymorphism and performance on either a CPT or stop signal reaction time task.

The TPH2 gene exercises control over tryptophan hydroxylase, a rate-limiting enzyme in the catalysis of serotonin from tryptophan (Grahame-Smith, 1964). Variation in this gene has been associated with increased error rates on the ANT conflict network measure, indicating decreased impulse control (Reuter *et al.*, 2007), and with reaction times in a Stop Task (Stoltenberg *et al.*, 2006), although this trend was only significant for male participants. Variation in this gene is known to influence amygdala reactivity, but we are not aware of any neuroimaging studies addressing disparity in any executive functions relating to this gene.

Some evidence has been provided for association between the serotonergic MAOA gene and response inhibition in normal populations (Passamonti *et al.*, 2006). Variation in a promoter-region polymorphism of this gene was not significantly associated with performance of a Go/No-Go task (although carriers of the high-activity allele tended to make more errors of commission), but differences in cortical activation during performance of the task were observed. Carriers of the less active allele, which would be expected to degrade noradrenaline and serotonin more slowly, displayed higher levels of cortical activity in bilateral extrastriate cortex and right superior parietal cortex, but lower activation levels in right ventrolateral prefrontal cortex than carriers of the high-activity allele.

Response Inhibition in Schizophrenia

Difficulty with response inhibition is representative of the general neuropsychological deficits seen in schizophrenia (Wykes *et al.*, 2000), and patients have been shown to demonstrate poor performance in response inhibition tasks relative to healthy controls (Thoma *et al.*, 2007). One of the most frequently reported neurocognitive markers of schizophrenia is difficulty with performance of antisaccades, that is, voluntary inhibition of automated ocular saccades towards a light stimulus (Crawford *et al.*, 1995; Fukushima

et al., 1988). Antisaccade performance has been closely linked with capacity for response inhibition (Donohoe *et al.*, 2006).

A commonly reported neurological sign of schizophrenia is frontal hypoactivity during performance of executive function tasks (Chua & McKenna, 1995), and patients have been shown to demonstrate reduced activity in the left anterior cingulate and DLPFC during response inhibition tasks (Rubia *et al.*, 2001). Schizophrenic patients and their healthy siblings both fail to show normal increases in striatal activation during preparation for response inhibition (Vink *et al.*, 2006).

Response inhibition in schizophrenia may be influenced by COMT genotype; one study found that participants homozygous for the Met allele outperformed those in possession of one or two copies of the Val allele on a Stroop test (Ehlis *et al.*, 2007). We are aware of no other studies addressing the effect of specific genes on response inhibition in schizophrenia, or on associated cortical activity.

Response Inhibition in ADHD

A recent review article by Wodka and colleagues (2007) suggests that response inhibition should be seen as one of the key deficits in ADHD, even when cognitive task demands are minimal (but see also Rommelse *et al.*, 2007). Deficiencies in response inhibition have been proposed as a valuable cognitive endophenotype for ADHD (Aron & Poldrack, 2005).

In a study with normal participants (Bellgrove *et al.*, 2004), behavioural differences such as increased response variability and an increase in commission errors (both of which have been observed in ADHD, see Johnson, Kelly *et al.*, 2007b; Wodka *et al.*, 2007), were shown to dissociate the brain regions used in a Go/No-Go task. Efficient response inhibition was associated with activity in regions including the middle frontal and inferior frontal gyri. These regions are often found to be affected in ADHD, being smaller in size and often displaying hypofunction (Durston *et al.*, 2004), suggesting that the poor

performance of people with ADHD on these tasks may be exacerbated by relying on compromised brain regions.

The 7-repeat allele of a VNTR in the DRD4 gene has been associated with an impulsive and inaccurate response style in children with ADHD, independent of symptom severity (Langley *et al.*, 2004). The 10-repeat polymorphism of the DAT1 gene has also been implicated in deficiencies in response inhibition in a population-based sample of boys who scored high on a measure of ADHD symptoms (Cornish *et al.*, 2005). This strongly implies a role for the DRD4 and DAT1 genes in particular, and the dopamine system in general, in the process of response inhibition.

Although response inhibition deficits have been observed in ADHD, and have been linked with a number of genetic markers, no studies to date have examined genetic effects on abnormalities in cortical activation observed during response inhibition in children with ADHD.

Response Inhibition in ASDs

The issue of whether or not children with ASDS display deficits on response inhibition tasks is contentious (Sanders *et al.*, 2007). Studies have demonstrated normal response inhibition abilities on tasks such as the Stroop test (Goldberg *et al.*, 2005; Ozonoff & Jensen, 1999), the stop signal paradigm (Ozonoff & Strayer, 1997), and inhibition in the neutral condition of a Go/No-Go task (Ozonoff & McEvoy, 1994). Other studies have shown deficits on the prepotent inhibition of a Go/No-Go task (Ozonoff & McEvoy, 1994), the Windows task (Ozonoff & McEvoy, 1994) , the random Sustained Attention to Response Task (SART; Johnson, Robertson *et al.*, 2007), oculomotor anti-saccade task (Luna *et al.*, 2007) and the Detour Reaching task (Hughes & Russell, 1993).

Despite normal behavioural performance on a Go/No-Go task, functional imaging showed increased activation of the frontal and parietal cortices in a group of adults with ASD, compared with controls (Schmitz *et al.*, 2006). Greater left hemisphere activity in

the inferior and orbitofrontal cortices may indicate an alternative, compensatory mechanism in these participants (Schmitz *et al.*, 2006). In another Go/No-Go task, adults with ASD showed normal behavioural performance but reduced brain activation in the right cingulate gyrus, right insula, right inferior frontal gyrus, right premotor cortex, but normal activation in the parietal cortices (Kana *et al.*, 2007). In a slightly more difficult condition of the task including a working memory component, participants with ASD displayed activation in the anterior cingulate and parietal cortex and increased activity in premotor regions, areas associated with processing cues in readiness to respond.

No specific candidate genes have as yet been associated with response inhibition deficits in autism.

V. Conclusions

Investigations into the genetic correlates of individual differences in executive control have to date produced disparate findings. Initial positive results are frequently not replicated in subsequent studies (see for example the often contradictory literature relating variation in the DRD4 gene to sustained attention in ADHD). These disparities can be partially attributed to small effect sizes of individual genes, and the fact that multiple genes may contribute to a single function. In addition, while the various executive functions may be relatively easily discriminated at the behavioural level, the distinctions between them are less clear cut at the genetic level, with similar genetic foundations appearing to support a wide variety of functions. Similarly, imaging studies reveal that the three executive functions discussed here display extensive overlap in the brain regions recruited; working memory, sustained attention, and response inhibition all activate functional networks involving prefrontal and parietal regions. To some extent this may reflect common components to these functions, allowing us to group them together under the name 'executive functions'. Careful manipulation of the task characteristics has, however, been shown to dissociate between partially overlapping and interacting functional networks in these regions (see e.g. Corbetta & Shulman, 2002; Lungu *et al.*, 2007; Wager & Smith, 2003). This again underpins the importance of using

cognitive endophenotypes which maximally dissociate the underlying function and associated brain regions.

The low power common to studies of this kind has led to the current trend for large scale consortia that can conduct genome-wide association studies of disorders or processes to give firm leads on candidate genes and to identify quantitative trait loci. This approach also has the potential to identify novel variants for which no a priori hypothesis for an association with executive control exists. To date, no genome-wide association studies of sustained attention, spatial working memory or response inhibition have been conducted. To some extent, imaging studies may be helpful in providing the power that is sought in genetic studies by acting as endophenotypes with higher signal-to-noise ratios. Cognitive neuroscience allows us to define cognitive-neuroanatomical models which can constrain linkages between a gene and a process based on what we know about where the gene is expressed and how a cognitive function is influenced by different neurotransmitters. For example, working memory is known to activate prefrontal regions, and to be heavily dependent on dopamine (Vijayraghavan *et al.*, 2007). The discovery that the dopamine transporter is sparse in prefrontal cortex led to an appreciation of the role of catechol-O-methyltransferase as the main vehicle for dopamine clearance in the prefrontal cortex, and provided a rationale for association studies of the COMT gene with working memory performance (Sesack *et al.*, 1998).

Furthermore, genetics may be used to test cognitive-neuroanatomical models of cognition. As yet, no studies of which we are aware have demonstrated a double dissociation between genetic links to the neurological correlates of two discrete executive functions, although studies of this nature have been conducted to discriminate genetic effects on cortical activation related to emotional processing from activation related to working memory (Hariri *et al.*, 2002; Heinz & Smolka, 2006). The scope for real discovery in this area is broad; it might, for example, be possible to find a dissociation between genes for spatial versus verbal working memory, or for sustained versus spatial attention. The current developments in neuroimaging and genetics are therefore

producing what may be one of the most informative lines of research in the field of executive function.

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