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The cruciform model of striate generation of the early VEP, re-illustrated, not revoked: A reply to Ales et al. (2013)

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ABSTRACT

Here we summarize the points raised in our dialog with Ales and colleagues on the cortical generators of the early visual evoked potential (VEP), and offer observations on the results of additional simulations that were run in response to our original comment. For small stimuli placed at locations in the upper and lower visual field for which the human VEP has been well characterized, simulated scalp projections of each of the visual areas V1, V2 and V3 invert in polarity. However, the empirically measured, earliest VEP component, "C1," matches the simulated V1 generators in terms of polarity and topography, but not the simulated V2 and V3 generators. We thus conclude that, 1) consistent with the title of Ales et al. (2010a), polarity inversion on its own is not a sufficient criterion for inferring neuroelectric sources in primary visual cortex; but 2) inconsistent with additional claims made in Ales et al. (2010a), the simulated topographies provide additional evidence for – not against – the tenet that the C1 component is generated in V1.

Introduction

In Ales et al. (2010a), scalp topographies resulting from activation of discrete visual areas V1, V2 and V3 were simulated based on retinotopic mapping data of 27 subjects. Consistent with the known projections of the lower visual field to the dorsal, mostly upward-facing division of V2/V3, and of the upper field to the ventral, mostly downward-facing division (Wandell et al., 2009), they found that simulated V2/V3 scalp topographies inverted in polarity for upper and lower locations. Upper–lower field polarity inversion is one of the more popularly known properties of the earliest component of the human visual evoked potential (VEP), "C1" (e.g. Di Russo et al., 2002; Martínez et al., 1999) and one of several properties comprising the classic "cruciform model" which proposes a primary visual cortical (V1) source for the C1 (Clark et al., 1995; Jeffreys and Axford, 1972a, 1972b). Combined with the results of constrained source modeling from another study indicating simultaneous onset of V1 and V2 (Ales et al., 2010b), Ales et al. (2010a) took this extrastriate polarity inversion as evidence that the C1 may be generated in V2 and/or V3 rather than in V1. In our original comment (Kelly et al., 2013) we contested this claim, specifically criticizing 1) their critically incomplete definition of the cruciform model, 2) their inappropriate use of large stimuli that blur V1-consistent topographical shifts, and 3) their neglect of intracranial findings in non-human primates. In their reply, Ales et al. (2013) contest the first issue on the basis of the neuroanatomical literature, and remedy the second and third issues by showing the results of new simulations of smaller appropriately-placed stimuli, and by reviewing the relevant human and non-human literature. In the following, we first examine the new simulation results with reference to empirical data for the same visual field locations (Di Russo et al., 2002); we then discuss the systematic within-quadrant topographical shifts that form a critical but neglected part of the unabridged cruciform model, and illustrate them using population-averaged VEP data and anatomical MRI; finally, we briefly address some of the conclusions made by Ales et al. (2013) on the non-human primate literature.

The Di Russo et al. locations: simulated versus measured

The results of the new simulations of Ales et al. (2013) replicate their previous finding that the scalp-projected potentials resulting from activation of V2 and V3 exhibit clear polarity inversion for stimuli in the

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upper and lower fields. This confirms that polarity inversion cannot be used as the sole criterion in inferring a V1 source, an error that Ales et al. claim was made in at least one previous study (Slotnick et al., 1999). Our issue was not with this finding, but rather with the additional finding that V1 projections *do not* polarity invert, and the consequent implication that the empirically observed, polarity-inverting C1 component might be generated in V2 and/or V3 *and not* V1. Ales et al. (2010a) specifically stated that only 3 out of 54 hemispheres showed polarity inversion for V1, although no quantitative criterion was specified for their classification. In their reply to our comment, Ales et al. (2013) have persisted in claiming that V1 responses do not exhibit polarity inversion. Since polarity inversion is the most well-known property of the C1, this directly implies that V1 is not the dominant generator of the C1. It is the latter implication that we examine further here.

Ales et al.'s (2013) new simulations on the first 10 subjects' data employ the exact same visual field locations as the study of Di Russo et al. (2002), a study in which the waveforms and topographies of the C1 are shown particularly clearly. A direct comparison can now be made between the simulated V1, V2 and V3 topographies and those of normative empirical data, allowing us to address the simple question: given the simulation results, is the empirically measured C1 best explained by a V1 source, a V2 source or a V3 source?

As we predicted, Ales et al.'s (2013, Fig. 1)new simulations in V1 show a much clearer polarity inversion for the Di Russo et al. locations, which are specifically aimed at the ceiling and floor of the calcarine sulcus in the average brain. Ales et al. (2013) variously state that these simulated topographies "do not fully" or more frankly, "do not" polarity invert, again without specifying any criterion. However, in a large midline scalp region where the C1 is typically measured for these locations, the simulated V1 responses most certainly do invert in polarity (see their Fig. 1). As Ales et al. (2013) correctly point out, the complementary positive and negative foci in the simulated topographies coincide more precisely for V2/V3 than for V1. We would further point out that the manner in which the positive and negative V1 foci do not precisely coincide closely parallels empirical C1 measurements (Di Russo et al., 2002; see also Clark et al., 1995 and Kelly et al., 2008 for locations of nearby polar angle). As detailed in Di Russo et al. (2002; see Table II, and Figs. 4, 5 and 6), the upper-field stimuli evoke a negative C1 focus that is slightly ipsilateral to the midline. This ipsilateral effect, mentioned in Jeffreys and Axford (1972a, 1972b) and observed on the individual subject level (Clark et al., 1995; Kelly et al., 2008), can be explained in the cruciform model by the fact that the activated section of cortical surface on the calcarine floor, if not perfectly horizontally-oriented, would naturally tend to face the medial direction on average (refer to coronal section in Fig. 2b). Consistent with the same principle, lower field stimuli in the Di Russo et al. configuration evoke a marked *contralateral*, positive scalp focus. In Ales et al.'s (2013) simulated responses to the Di Russo et al. locations, the V1 topographic foci follow this very pattern, while the simulated V2/V3 responses show very distinct distributions, with upper stimuli clearly projecting to contralateral rather than ipsilateral scalp sites (see summary Table 1).

More fundamental than these topographical lateralization effects is the fact that the simulated V2/V3 topographies are opposite in polarity with respect to the V1 topographies. The cruciform model not only predicts upper–lower polarity inversion, but more specifically maps the upper field to negative polarity and the lower field to positive polarity for V1 sources, following a surface-negative assumption for initial cortical activation. As we pointed out in our original comment, surface-negative activation of V2/V3 would result in positive scalp polarity for upper stimuli and negative scalp polarity for lower stimuli, which is opposite to the pattern seen for the empirically measured C1. In their Fig. 1, Ales et al. (2013) chose to simulate surface-positive cortical activation rather than surface-negative activation, so that the polarity on the scalp for V2/V3 activation matches the C1. However, surface-positive activation is inconsistent with available intracranial data in monkeys (e.g. Schroeder et al., 1991, 1998) and, as we demonstrate in the next section, the within-quadrant topographical shifts observed for the empirical C1 are uniquely consistent with surface-negative activation. If we accordingly assume surface-negative activation for Ales et al.'s (2013) Fig. 1, as was done in their Fig. 3 (note the opposite color of equivalent topographies in Figs. 1 and 3), the simulated scalp polarities would be as listed in Table 1. When considered alongside empirically measured C1 characteristics, these simulation outcomes suggest a very clear winner for the most likely dominant generator of the C1.

In their Fig. 3, Ales et al. (2013) simulate mixtures of V1 and V2 activity in order to make the point that the polarity of the C1 does not isolate V1 activity because it allows for a 50–50 mixture of V1 and V2. However, when one considers the full scalp distributions rather than just midline electrodes, a comparison between Ales et al.'s (2013) Fig. 3 and Di Russo et al.'s (2002) Fig. 5 (identical left visual field locations) is very revealing: the Di Russo et al. C1 topographies at 70–85 ms closely match the simulated 100%-V1 topographies, whereas the Di Russo et al. topographies at 95–115 ms bear a remarkable resemblance to the simulated 50–50 mixture of V1 and V2. Not having the data ourselves, we can only make these comparisons by eye; nevertheless, we would strongly encourage the reader to do the same. Though we agree that it is unlikely that V2 lies inactive for any more than a few milliseconds following the onset of V1 activation, these qualitative comparisons suggest, at least superficially, that V2's expression on the scalp may not come to be as strong as that of V1 until tens of milliseconds after VEP onset.

The full cruciform model includes within-quadrant topographical shifts and a surface-negative assumption

In our original comment, we complained that the definition of the cruciform model used by Ales et al. (2010a) was a critically truncated one, because it ignored systematic topographic shifts occurring within visual quadrants (Jeffreys and Axford, 1972a). In this section we illustrate why this is important. The full cruciform model describes a shift from a roughly vertical dipolar orientation on the floor or ceiling of the calcarine sulcus to a roughly horizontal orientation on emergence from the sulcus onto the medial-facing wall, which corresponds to visual locations closer to the vertical meridian (see Clark et al., 1995). As Ales et al. (2013) point out, the proportion of V1 lying outside the calcarine sulcus may not be 50%, as was falsely suggested by our casual expression, "as much outside the calcarine sulcus as inside," but rather somewhere between 33% (Hinds et al., 2008) and 45% (Aine et al., 1996). These proportions are still far from negligible, and as we demonstrate below, these medial-facing sections

Table 1
Salient characteristics of empirically measured C1 component topographies (Di Russo et al., 2002) listed alongside corresponding characteristics of the V1, V2 and V3 topographies simulated by Ales et al. (2013), assuming surface-negative cortical activation.

	Polarity on the scalp		Topographic focus	
	Upper field stimuli	Lower field stimuli	Upper field stimuli	Lower field stimuli
Empirical C1 (Di Russo et al., 2002)	Negative	Positive	Slightly ipsilateral	Contralateral
Simulated V1	Negative	Positive	Slightly ipsilateral	Contralateral
Simulated V2	Positive	Negative	Contralateral	Slightly contralateral
Simulated V3	Positive	Negative	Contralateral	Slightly contralateral

comprise a very salient part of the full cruciform model that clearly distinguishes V1 contributions from V2/V3 contributions.

To first illustrate the above-mentioned within-quadrant topographical shifts, Fig. 1 shows the scalp topographies of integrated amplitude in an early (75–85 ms) time interval of a pattern-pulse multifocal VEP (PPMVEP; James, 2003) averaged across 16 subjects. The PPMVEP was derived for each of 32 equal-sized radial segments of a large annular checkerboard pattern extending from 3 to 10° of eccentricity (see Vanegas et al., 2013). The main feature to note here is that in every quadrant, as one proceeds from the horizontal meridian toward the vertical meridian, the topography undergoes a shift in orientation consistent with the emergence from the calcarine sulcus, transitioning from a focus close to the midline, consistent with a vertically-oriented dipolar field, to a lateralized pattern consistent with a horizontally-oriented dipolar field. Can this be explained instead by a V2 or V3 source?

In Fig. 2 we illustrate how the predicted topographical shifts for polar angles nearing the vertical meridian differ for V1 and V2. We took an oblique slice through a population-averaged anatomical image (the MNI-152 brain at 0.5 mm resolution available with AFNI; Cox, 1996) which passes through the standard site POz (20% of the distance from inion to nasion on the scalp according to the 10–20 system), where the Di Russo et al. (2002) C1 components are maximal, and the point along the calcarine sulcus closest to fMRI activations reported in two studies using the same locations (Di Russo et al., 2002, 2007; we converted from Talairach to MNI coordinates using functions from http://www.brainmap.org/icbm2tal/). An outline of the outer surface of the cortex in this slice is rendered in Fig. 2b, resolving the calcarine sulcus but skipping over other sulci on the outer surface for simplicity. It should be echoed here that individual anatomy varies extremely widely about this average brain; the rounded surface is intended not to be representative of any individual but of the population-average cortical surface, which corresponds with the population-averaged VEP data on which our arguments are based. At this posterior location, the dorsal and ventral V1–V2 borders lie at medially facing sections within the interhemispheric fissure, whereas the V2–V3 borders lie on the outer dorsal or ventral surface. Based on the coincident but opposite-polarity topographies for simulated dorsal and ventral V2 (Ales et al., 2013), we can assume that the lower and upper Di Russo et al. locations must project to sections of V2 that are out on the dorsal and ventral surface, respectively, in the average brain. We illustrate the predicted topographical shifts for V1 and V2 using the upper right visual field quadrant as an example, but the logic applies equally well to all quadrants.

Ales et al. (2013) pointed out that while the available evidence in monkeys indicates that the initial cortical activation of both V1 and V2 results in negative potential deflections on the cortical surface, stimulus and species differences preclude the generalization of this finding to contrast-change stimuli in humans. Further, a constrained source modeling study indicated that V2 initially activates with a surface-positive deflection (Ales et al., 2010b; but see Hagler et al., 2009). Thus, the negative midline focus for the upper Di Russo et al. location (location A in Fig. 2c) could arise either from surface-negative electric fields in ventral V1 (dipole A in Fig. 2d), or, alternatively, from surface-positive electric fields in ventral V2 (dipole A in Fig. 2e). As Figs. 2d and e show, as one proceeds from the horizontal meridian to the vertical meridian (from location A to location B in Fig. 2c), a shift in dipolar orientation from vertical to horizontal would be predicted for V2 as well as for V1. However, the direction of dipole rotation is opposite for the V1 and V2 cases. In the V1 case, the dipole rotates clockwise, leading to a rightward shift of the negative scalp focus (Fig. 2f), which is indeed what is seen in empirical data (see Fig. 1 and Clark et al., 1995). If, instead, the negative upper-field C1 was generated by surface-positive activation in ventral V2, the dipole would rotate counterclockwise and thus the negative focus would shift toward the left on the scalp (Fig. 2g), moving in the direction opposite the empirical C1 data.

Thus, in terms of topographical shifts for locations proceeding toward the vertical meridian, the prediction for V2 generation is directly opposite to the prediction for V1, and the empirical data follow the latter. For area V3 and beyond, there are no reported systematic changes in cortical orientation within quadrant representations that could explain the empirical data. Again, we cannot claim that V2 and V3 are entirely inactive during the time frame of these topographies, but it is clear that the V1 contribution must dominate. The potential issue under discussion has been that V2 or V3 activity could potentially masquerade as V1 activity, and so effects on the C1, such as those resulting from attention, may not be on V1 at all. But as we

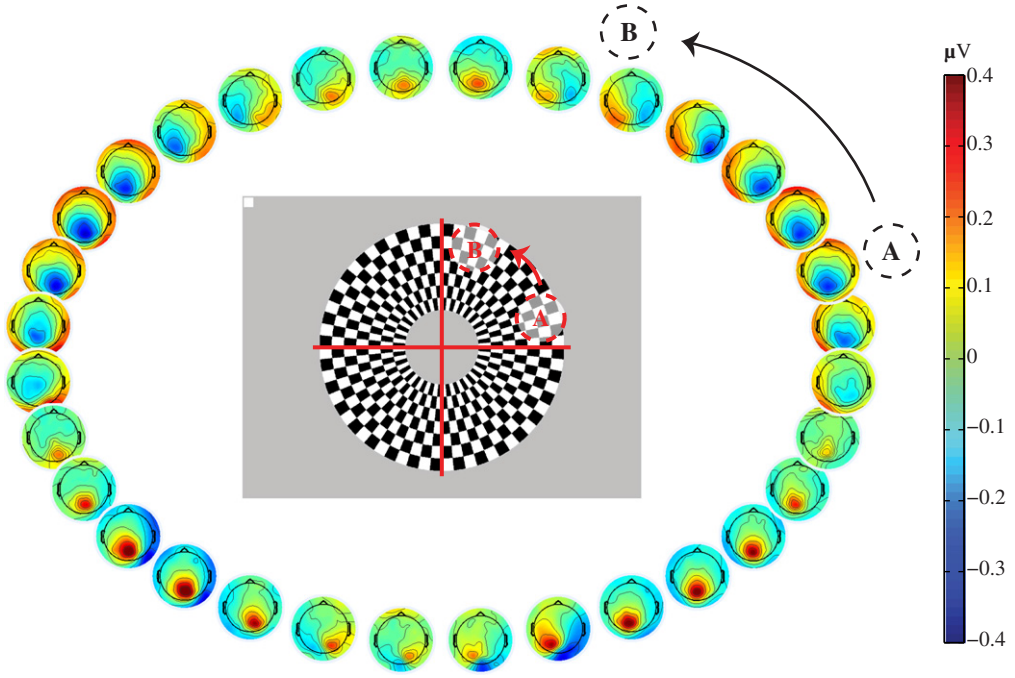

Fig. 1. Topographical distributions of the earliest potential deflection "C1" (75–85 ms) in a pattern-pulse multifocal VEP derived for 32 orthogonally pulsed, radial segments of a large annular checkerboard. Example locations 'A' and 'B' of Fig. 2 are labeled.

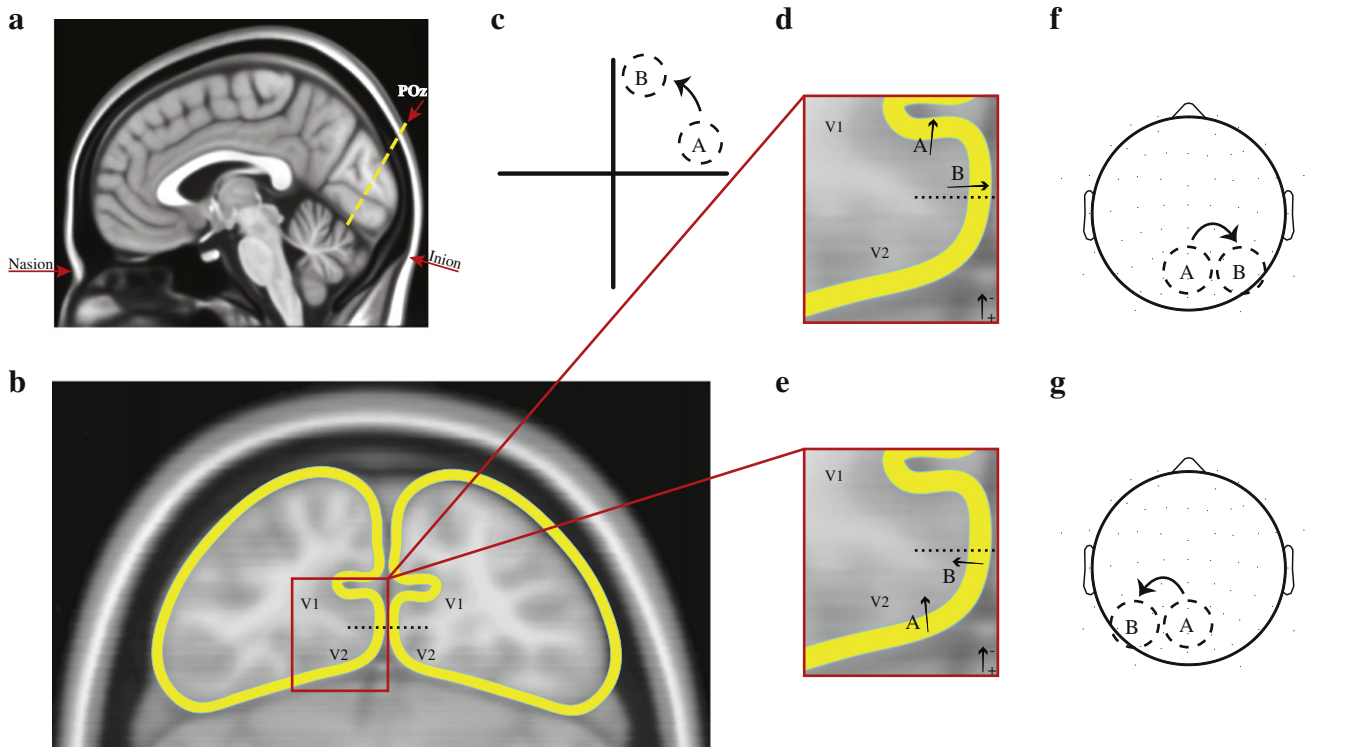

Fig. 2. a. Sagittal view of the oblique coronal slice in the MNI-152 brain passing through the scalp focus of the average C1 and the average locus of functional activation for the Di Russo et al. (2002) stimulus locations. b. Outline of cortical surface in this oblique coronal slice, marking the ventral V1/V2 border as mid-way down the ventral medial wall. Border location is not intended to be precise, but rather serves to illustrate orientation transitions for V1 and V2. c. Example locations A and B lying close to the horizontal and vertical meridian, respectively, in the upper right field. d. A zoomed portion of the ventral left-hemisphere section of areas V1 and V2, illustrating the dipole orientation that is required to explain the scalp polarity of the C1 for location A assuming generation in V1, along with the rotated orientation that must follow for location B. e. The same zoomed section, illustrating the dipole orientation that is required to explain the scalp polarity of the C1 for location A assuming generation in V2, along with the rotated orientation that must follow for location B. In both d and e, arrows represent electrical dipoles, with the head corresponding to the negative pole. f. Topographical shift of the negative scalp focus predicted by the hypothetical V1 generators depicted in d. g. Topographical shift of the negative scalp focus predicted by the hypothetical V2 generators depicted in e. The empirically observed shifts in Fig. 1 match the predictions for V1 in d, f.

have just seen, for a V2 activation to masquerade as a V1 activation, it would have to be both upside-down and come from a visual cortex that is turned inside-out.

Another visible feature in the empirical data of Fig. 1 is that the flip in polarity from negative to positive occurs some distance below the horizontal meridian. The distance in these data appears somewhat less than the 20° reported by Clark et al. (1995), but the 32 non-overlapping segments used in this experiment do not offer fine enough resolution to accurately judge. As Ales et al. (2013) point out, more work needs to be specifically aimed at this question to validate Clark et al.'s (1995) revision of the cruciform model whereby the horizontal meridian projects to a point along the ventral calcarine bank rather than precisely at the fundus. For the time being, we would point out that Ales et al. (2013) did not provide anatomical evidence that was inconsistent with this feature, they merely highlighted that there is a *lack* of evidence that is *consistent* with it, because no functional imaging studies have been specifically aimed at the question. We would further point to a recent study by Benson et al. (2012) that again does not specifically address this question, but nonetheless displays clear images that suggest a horizontal meridian projection to a point ventral to the fundus (see their supplementary Fig. 1).

To clarify our original position, we at no point claimed that V1 could be fully "isolated" by any means, whether by polarity inversion at certain locations or by timing. Our main point, which we believe is supported by the above arguments, was that the topographical variations in C1 as a function of polar angle are more consistent with a V1 source than a V2 or V3 source, and that even though it is unlikely that V1 is active for long in complete isolation, the evidence suggests that it is by far the dominant contributor to the C1.

Insights from intracranial neurophysiology

Ales et al. (2013) provide a literature review on the issues related to intracranial findings, which serves to highlight the uncertainty yet surrounding the inter-area timing, physiological generating mechanisms and scalp projection of early visual activity, and the impact of stimulus and inter-species differences. The authors quite correctly point out that more work needs to be done to resolve these issues. To clarify our original position, we at no point claimed that monkey intracranial data have closed the case on the sequence of activation of visual areas — we merely aired the reasonable complaint that this literature should not be ignored. Further, we did not assert that areas beyond V1 sat in complete silence for the duration of the initial afferent response in V1 — rather, we argued that in light of the current evidence on V1 versus V2 latency differences from intracranial recordings, the finding in human source analysis of simultaneous activation of V1 and V2 should be interpreted with caution.

In the accounting of interareal latency findings in monkey intracranial studies, a couple of critical factors must be considered. First, several studies recorded from anesthetized subjects, a factor which dramatically changes the entire brain response by generally depressing responses and significantly delaying them. Moreover, these effects are distinctive for many of the different anesthetics. This concern applies to numerous empirical as well as review papers; for example, Lamme and Roelfsema (2000) mixed across anesthetized/awake data in a meta-analysis. Second, as Ales et al. (2013) point out, stimulation conditions differ considerably across studies, and care must be taken in mixing these conditions in any meta-analysis.

Among the papers that we cited in our original comment, those that record latencies from the input to the superficial layers of V1 (Chen et al., 2007; Givre et al., 1995; Maunsell and Gibson, 1992; Schroeder et al., 1991; Schroeder et al., 1998) are consistent in showing a significant latency offset. The papers that examine latencies across areas (e.g., Chen et al., 2007; Schroeder et al., 1998) are consistent in showing an offset between areas V1 and V2; very fast responses in V2 due to the magnocellular pathway from the lateral geniculate nucleus (LGN) to 4cα of V1 to the thick CYTOX stripes of V2 do not seem to cause the mass of V2 to respond at a very short latency. The fact that a branch of this pathway does seem to cause a very fast response in the dorsal stream beginning at MT (Chen et al., 2007), and as well may trigger small early responses in V4 (Givre et al., 1994), does not seem relevant to the present dialog, as these areas do not have polarity-opposed upper-field and lower-field projections and thus could not contribute to the polarity inversion effect. Overall, the studies that have directly compared V1 to V2 have all shown a significant latency difference, despite the caveat that some of the studies show an overall latency increase due to anesthesia (spiking: Raiguel et al., 1989; Nowak et al., 1995; Schmolesky et al., 1998; LFP: Schroeder et al., 1998; Mehta et al., 2000). Nowak et al. (1999) state that, "Measurements of visual response latencies show that, on average, V2 neurons are activated 10 ms later than neurons in area V1 (Nowak et al., 1995; Raiguel et al., 1989)." Schmolesky et al. (1998) also showed a delay from V1 to V3, albeit a small one of 6–9 ms. On the whole, despite the stimulus differences, it seems reasonable to say that among the three visual areas identified as having dorsal and ventral sections of opposed orientation, V1, V2 and V3, the available evidence suggests that V1 responds earlier. We would also reiterate that relative response strength should be taken into account — to what degree are areas beyond V1 expressing their activation on the scalp compared to V1? The only studies that directly compare the postsynaptic electrical activation profiles for multiple visual areas in the same monkeys are those of Schroeder et al. (1998), and they show not only earlier, but much stronger (approximately 6×) initial activation in V1 than V2. Undoubtedly, extrastriate areas do not remain silent throughout the initial afferent V1 activation, but at the same time, the "substantial extrastriate contributions" found in human source modeling work (Ales et al., 2010b) may not be definitive.

A final point of Ales et al. (2013) that we are compelled to address is their assertion that response onset latencies for a given stimulus type are equal in humans and non-human primates, and therefore that the 3/5 rule for comparing latencies in monkeys and humans may not be generally applicable. We could not agree less with this assertion. That there is a considerable interspecies difference in neural response latency has been established in a long line of studies from the 60's to the 90's. The mean initial V1 response latencies to diffuse flash stimuli, quantified in both spiking and synaptic current flow/local field potentials in unanesthetized monkeys, are between 25 and 30 ms (Chen et al., 2007; Maunsell and Gibson, 1992; Schroeder et al., 1998). Ales et al. (2013) state that such very early (30 ms) onsets in humans have been found both extracranially (Odom et al., 2009) and intracranially (Ducati et al., 1988). However, neither of the cited studies were specifically aimed at the issue of response latency and accordingly do not even specify methods for computing latency. Odom et al. (2009) is a paper about clinical recording standards, which does not specify the stimulation and recording methods used for the example waveforms shown, let alone address common confounds associated with flash stimulus generation, such as early auditory responses to sounds emitted by the stimulation apparatus. Ducati et al. (1988) show response waveforms for both flash and pattern reversal stimuli but do not attempt to precisely measure or directly compare latencies across these stimulus conditions, presumably because non-stimulus evoked activity precludes a clear measurement of onset. An early component, P40 (onsetting around 30 ms), was indeed observed in early studies of the flash VEP, but this very small early deflection was believed to be of subcortical origin on the basis of comparisons between human and monkey recordings (Kraut et al., 1985; Vaughan, 1966; Vaughan and Hull, 1965). Indeed, Schroeder et al. (1992) showed that the early surface component, N25, in the monkey (onset 18–22 ms), could be explained by an intracranial component measured in the lateral geniculate nucleus (LGN). Thus, early-onset components of the human flash VEP can be seen to correspond to even earlier subcortical components in monkeys following the same 3/5 rule.

Ales et al. (2013) also claim that pattern-reversal response onsets are equal in human and monkey, on the basis of one human intracranial study reporting latencies of 45–55 ms in recordings made directly from the peri-calcarine region (Farrell et al., 2007). Neither Ales et al. (2013) nor Farrell et al. (2007) themselves specify whether this latency range refers to component onset or peak, or whether it was evoked by pattern onset, pattern reversal or flash. Farrell et al. (2007) do point to an N55 component, which they note is on very rare occasions observed as a positive "P55" on the scalp for pattern reversal stimulation. A similarly rare intracranial component "N40" has been reported in the V1 recordings of Schroeder et al. (1991), again consistent with the 3/5 rule. The 3/5 rule fits not only for the aforementioned early visual components but also the pattern-evoked P1 (peaks in monkey at ~60 ms, and in human at ~100 ms), as well as for initial auditory and somatosensory component comparisons (Peterson et al., 1995; Schroeder et al., 1995, 2004). Finally, we would reiterate that precise estimates of human V1 onset latencies based on noninvasive measures (Foxe and Simpson, 2002: Clark et al., 1995) come in at about 42–45 ms, consistent with a 3/5 simian/human rule. While the 3/5 principle could use further validation, we introduced it in our discussion in order to emphasize that the latency offsets between V1 and higher visual areas that have been well established in monkeys are likely to be an underestimate of those in humans, and that the overwhelming evidence for V1–V2 latency offsets simply cannot be ignored when interpreting human electrophysiological responses.

To conclude, we emphasize that we have not claimed to know how to isolate, or to have a better "diagnostic," of V1, nor have we asserted that the cruciform model is infallible. Our main point is that a demonstration of V2/V3 polarity inversion does not constitute strong evidence against the full cruciform model for primary visual cortical generation of the early VEP. The simulations of Ales et al. (2010a, 2013) have clarified a very important aspect of the cruciform model, which is that it is composed of several instances of polarity inversion and topographical shifts with polar angle, and no single instance should be used as a sole diagnostic for a V1 source. Our discussion centered on what this means for the tenet that the earliest component of the VEP is generated in V1, and we have contended that there is no more evidence to the contrary than there was before these simulations were run — in fact, comparisons with empirical data appear to favor the C1–V1 link.

More generally, our discussion should serve as a strong cautionary note in relation to the growing toolkit of the human neurophysiologist. In the present situation, the quantitative sophistication of modern source analysis algorithms has clearly not outweighed the fundamental logic underlying a qualitative model based on elementary geometry and empirical data. Combined EEG and fMRI approaches building on the remarkable innovations of Ales et al. (2010a, 2010b) and others (e.g. Hagler and Dale, 2013; Hagler et al., 2009) will undoubtedly be key in the future use of human visual evoked potentials in understanding visual processing. As we progress, however, it is important not to cast away existing qualitative models as "old notions," but rather incorporate them as logical constraints.

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Conflict of interest

The authors declare that they have no conflict of interest in the work described in this study, financial or otherwise.

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