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Comments and Controversies

What does polarity inversion of extrastriate activity tell us about striate contributions to the early VEP? A comment on Ales et al. (2010)

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ABSTRACT

Recently, a forward-model simulation study demonstrated that the upper and lower visual field projections to extrastriate visual cortical areas V2 and V3 have polarity-inverted electrical scalp projections, a property famously associated with potentials generated in primary visual cortex (V1) (Ales et al., 2010a). The authors use this finding, along with other findings from fMRI-constrained source modeling, to argue that the initial component “C1” of the human visual evoked potential may not be generated in V1 as has been widely believed, but may instead come from V2/V3. Here, we examine the validity of this claim with respect to the full set of anatomical and electrophysiological factors comprising the unabridged “cruciform” model linking C1 to V1. We find that the simulations in their current form do not present a valid test of the model, nor are their results inconsistent with it. We also review non-human primate neurophysiology findings that support the C1–V1 principle, and that can and should be taken into account in assessing the validity of constrained source models of human EEG in general.

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No less now than at the time of Hans Berger's original discoveries in 1924, the noninvasive measurement of scalp potentials—known as electroencephalography (EEG)—is our best means of studying the electrical activity of neural ensembles in the healthy and pathological human brain non-invasively. Despite the considerable challenges involved in interpreting this remote, spatially summated signal, the EEG-based visual evoked potential (VEP) has provided insight into the timecourse of cognitive and perceptual processes operating in vision. The component of the VEP that has arguably suffered least doubt as to its cortical origins is the so-called C1, the first component that appears after stimulus onset. For more than 40 years the C1 has been considered an index of initial afferent activity in primary visual cortex (V1), because of its early latency (50–70 ms) and the retinotopic specificity of its distribution on the scalp with reference to the geometry of human V1 (Clark et al., 1995; Jeffreys and Axford, 1972a,b). A recent paper has challenged this principle on the basis of neural source simulations (Ales et al., 2010a). Given the importance of having a human EEG marker of the most physiologically well-characterized sensory region of the brain, and the insight into cognitive influences on basic sensory processing that has been gained based on

the C1–V1 principle (e.g. Kelly et al., 2008; Martínez et al., 1999; see Rauss et al., 2011 for a review), the rejection of this principle is not to be taken lightly. Here we critically examine the evidence. We first review the cruciform hypothesis in its complete form. We then explain how its truncation in Ales et al. (2010a), in combination with their choice of simulation parameters and assumptions, nullifies the validity of the simulations as a test of the hypothesis. Finally, we review the findings of direct, invasive recordings of visual cortical potentials that were not taken into account, and discuss the abiding question mark over the validity of EEG source modeling in this context.

The origin and predictions of the cruciform model

Jeffreys and Axford (1972a,b) originally derived what came to be known as the “cruciform model” in their seminal work relating scalp potential distributions to the retinotopic organization of early visual cortex as understood from earlier lesion studies (Holmes, 1945). Their extensive study systematically examined both the transverse and longitudinal scalp distribution of the C1 (65–80 ms) and C2 (90–110 ms) as a function of the location of full-field, half-field, quadrant and octant stimuli, as well as annular stimuli of varying eccentric extent. Using a simple model of *surface-negative* dipole sheets, they demonstrated in exhaustive detail how the typical striate cortical organization could

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fully explain the topographical shifts in the C1 component for that diverse set of stimuli, whereas the characteristics of the C2 were consistent with extrastriate generators.

Jeffreys and Axford's conclusions were not merely based on any single instance of polarity inversion. Rather, they fully took into account the dependence of topography on stimulus location, particularly emphasizing the smallest stimuli spanning visual octants. They pointed out that V1 is unique in the way that the horizontal field octants project to the ceiling and floor of the calcarine sulcus, while the vertical field octants project chiefly to the medial surfaces outside the calcarine sulcus. This predicts roughly vertically oriented electrical source dipoles for the horizontal octants, of opposite polarity for the upper and lower fields, but it predicts horizontal dipoles of like polarity for the vertical octants.

Clark et al. (1995) later dug deeper into the acute sensitivity of the C1 to polar angle in the visual field, using higher density recordings and more comprehensively mapping the C1 with small stimuli presented at finely spaced locations around a ring of equal eccentricity. They compellingly demonstrated that only the C1 component exhibited the systematic changes in topography as a function of polar angle predicted by the cruciform model, including the dramatic shifts occurring within each visual quadrant corresponding to the sharp turn taken by V1 at the lip of the calcarine sulcus. Further, they showed that C1 polarity reversal did not occur precisely at the horizontal meridian but approximately 20 degrees of polar angle below it, in the lower visual field. This is highly consistent with histological analysis of the position of V1 relative to the calcarine sulcus, which has demonstrated that the calcarine fundus divides V1 rather dorsally so that more of V1 extends over the medial occipital wall below the calcarine than above it (Clark et al., 1995; Stensaas et al., 1974).

The data of Clark et al. (1995) enabled Di Russo et al. (2002, 2003, 2005, in press) to identify four circumscribed visual field locations that would, on average, target the upper and lower calcarine banks and generate C1 components that are easily dissociated from later extrastriate-generated potentials. These locations were precisely 25° of polar angle above and 45° below the horizontal meridian in the left and right hemifields, and elicited polarity-inverted C1 components at dorsal midline sites. Although the polarity inversion effect at those particular polar angles became widely associated with potentials fitting the cruciform model, it clearly represents only a sample of the retinotopic contingencies comprising the full cruciform model.

Simulated V2/V3 scalp projections and the cruciform model

In their paper, Ales et al. (2010a) construct models of electrical conductivity in the brains of 27 subjects based on segmentation of individual structural MRI and boundary-element modeling. In addition, they map the retinotopic projections to visual areas V1, V2 and V3 and the boundaries between them using retinotopic mapping in a functional scan. This enabled them to simulate the scalp-potential topographies that would result from the activation of each of these visual brain areas by stimuli of a given size and location. Up to now, histological (e.g. Amunts et al., 2000; Rademacher et al., 1993), lesion (e.g. Horton and Hoyt, 1991) and anatomical/functional imaging (e.g. Dougherty et al., 2003) studies have characterized the variability of early visual cortex in terms of shape, areal extent and location with respect to anatomical landmarks. The innovative approach of Ales et al. (2010a) addresses the variability of the surface orientation of retinotopically organized cortex with respect to the scalp, and thus makes a significant advance that is of particular interest for human EEG research.

Using these fMRI-constrained forward models, Ales et al. (2010a) were able to demonstrate that activation of the dorsal and ventral divisions of V2 and V3 by stimuli spanning whole visual quadrants leads to strong polarity reversal on the scalp. This, of course, is wholly unsurprising, as the dorsal and ventral extrastriate divisions lie on the upper and lower cortical surfaces of the brain, respectively, and would be oppositely-oriented. What seemed more surprising was that activation

of V1 by the same simulated stimuli show weak if any polarity reversal on the scalp in comparison to the V2/V3 distributions. The authors asserted that this comparison presents a serious challenge to the cruciform model, and concluded that the C1 component of the VEP may be generated in V2/V3 rather than V1. It is the latter conclusions we contest here.

As noted above, the full cruciform model incorporates systematic variations in scalp topography as a function of fine increments in polar angle around the full visual field (Clark et al., 1995). The simulated full-quadrant stimuli in Ales et al. (2010a) would collapse these systematic variations. Polarity inversion over midline scalp, in particular, is only seen for subsections of the upper and lower quadrants at discrete locations such as those used by Di Russo et al. (2002). The mere presence of polarity inversion, without accounting for the precise mapping of stimulus to scalp location, not to mention the critical factor of timing, does not constitute a sufficient test, “diagnostic” or “definitive marker” for striate cortical generators and to our knowledge has never been used as such. By extension, a finding of weak polarity inversion, especially when the sensitive factor of polar angle is ignored, does not directly challenge the cruciform model. To further stress this point, we note that Jeffreys and Axford (1972a,b) themselves showed clear polarity reversal of not only the C1 but also the later *extrastriate-generated* C2 (see their Figs. 2 and 3). For full-quadrant stimuli like those simulated in Ales et al. (2010a), their figures show little if any polarity inversion of the C1, whereas the extrastriate C2 exhibited striking polarity inversion across the whole transverse distribution (see e.g. their Fig. 5). Therefore, the main finding of Ales et al. (2010a) was already established by Jeffreys and Axford in 1972, and was not at all contrary to their model.

The lack of clear polarity inversion of simulated V1 activity in Ales et al. (2010a) can be readily explained by the projection of full quadrant stimuli predicted by the most fully developed version of the cruciform model (Clark et al., 1995). The cruciform cartoon of Ales et al.'s Fig. 1 fails to illustrate that the full primary visual cortical area extends as much outside the calcarine sulcus as inside, and the portions outside project roughly orthogonally to the portions inside, resulting in a highly diffuse scalp distribution for stimuli spanning whole quadrants. Further, because the horizontal meridian projects to a point somewhere along the ventral calcarine bank, lower-quadrant stimuli extending right up to the horizontal meridian would activate both the upper and lower banks to a fair extent, resulting in a closed field; meanwhile, the upper-field projection to ventral V1 would include only a minor portion of the lower calcarine bank and would be dominated by the medial wall section, thus explaining the general weakness of the V1 topographies.

It is thus clear that a more direct test of the polarity inversion effect as a critical case within the overall cruciform model, would have been to match the forward model simulation parameters to the stimulus parameters used in the study that was singled out for promoting the polarity inversion principle (Di Russo et al., 2002). Specifically, stimuli of 2° diameter lying at 4° eccentricity, +25° and –45° of polar angle relative the horizontal meridian, should be simulated. To complete the test, the simulated topographies of the respective V1, V2 and V3 activations for these circumscribed stimuli would be compared to individual C1 (65–80 ms) topographies for the same stimuli, measured from actual EEG data (such are available in the data of Ales et al., 2010b). But even if stronger polarity inversion were demonstrated for extrastriate cortex compared to striate cortex for those parameters, how much of a problem would it present to the tenet that C1 is generated in V1? It stands to reason that the relative response latency, relative response strength, and the polarity, of the initial afferent potentials on the cortical surface in V1, V2 and V3 are critical factors. Fortunately, there exist extensive data on these factors, owing to intracranial recordings in non-human primates.

Insights from non-human primate neurophysiology

Aside from the retinotopy-related factors discussed above, the fact that the C1 is the earliest onset potential in the VEP has been an

important factor in its wide acceptance as a component of striate origin. Latency was dismissed as a potential issue (Ales et al. (2010a) on the basis of a previous modeling study (Ales et al., 2010b), in which a functional localizer-constrained inverse solution was applied to real EEG data and the estimated V2 source waveform was found to onset simultaneously with the V1 waveform. However, the latter finding stands in stark contrast to the extensive studies on the relative timing of initial activation in early visual areas in the macaque (e.g., Chen et al., 2007; Givre et al., 1994; Givre et al., 1995; Maunsell and Gibson, 1992; Nowak et al., 1999; Raiguel et al., 1989; Schmolesky et al., 1998; Schroeder et al., 1998, 2004), all of which agree on the presence of significant latency offsets across ascending stages. While many of these studies were conducted in anesthetized monkeys, so that their estimates of absolute latency may not be considered to translate to human sensory processing, a subset of studies are highly relevant as they characterized both the timing and laminar distribution of transmembrane current flow underlying synaptic activity in multiple visual cortical areas of awake, behaving monkeys (Chen et al., 2007; Givre et al., 1994; Schroeder et al., 1991, 1995, 1998, 2004). Transmembrane current flow is the first order response to synaptic input, and thus, is a more sensitive response index than the action potential, as it reflects subthreshold excitatory and inhibitory activations, as well as those that cross the action potential threshold (Schroeder et al., 1998). More importantly, transmembrane current flow is the process that generates local field potentials (Mitzdorf, 1985; Schroeder et al., 1995), a subset of which summate and are volume-conducted to the scalp surface to produce ERPs (see e.g., recent discussion by Kajikawa and Schroeder, 2011). Using such signal measurements, the average onset of the response in V1 has been found to be approximately 26 ms, with the V2 response onset following 10 ms later (Schroeder et al., 1998). This latency difference likely underestimates that in humans; if a 3/5 timing ratio is assumed in extrapolating from monkey to human sensory response latencies (Schroeder et al., 1995, 2004), the V1–V2 lag is likely to be in excess of 15 ms in humans. This value is in good agreement with individual-by-individual analyses of high-density EEG recordings (Foxe and Simpson, 2002), and, interestingly, also with the results of source models (Hagler et al., 2009) using highly similar constraints and processing steps to Ales et al. (2010b).

In addition to timing, the intracranial field potential recordings of Schroeder et al. (1998) provide crucial information on the relative strength and polarity of initial electrophysiological responses on the visual cortical surface. First, the amplitude of the initial potential in V1 was far greater than in V2, where the average rectified waveform was mainly dominated by later (post-75 ms) activity. Second, whereas higher dorsal and ventral stream areas displayed a series of small-amplitude potentials reflecting the heterogeneity of transmission pathways from the retina, the initial granular layer depolarization in V1 and V2 was consistently marked by a negative component on the pial surface lasting approximately 25 ms. The negative polarity of the initial components on the surface of V1 and V2 supports an important component of Jeffreys and Axford's original model. Both their simple anatomical model as well as the MRIs of Ales et al. (2010a) highlight that the cortical surfaces (and hence the dipolar sources) of V1 and V2 tend to be oriented in an opposite fashion. This means that initial excitation of ventral V1 on the lower bank of the calcarine by a stimulus in the upper horizontal octant would cause a negative deflection on the midline scalp, whereas initial excitation of ventral V2 would cause a positive deflection. A positive potential generated in ventral V2 would thus tend to cancel the initial negativity projected from V1. Consistent with sequential onset of V1 and V2, and the stronger initial amplitude of the V1 response (Schroeder et al., 1998), experiments using this stimulus location demonstrate a midline VEP that is initially negative and shortly gives way to a positivity (e.g. Di Russo et al., 2002). Given the above points on polarity, timing and relative response strength, it is difficult to see how this negative midline C1 could be better explained by a V2 source than a V1 source.

What can constrained source modeling tell us about visual processing?

The phrasing of our final subheading echoes a prominent trend in neuroimaging research, particularly among studies aimed at determining the physiological basis of the BOLD signal (e.g. Heeger and Ress, 2002; Logothetis and Wandell, 2004). In general, strong concerted efforts have been made in that community to validate the BOLD signal as a reliable measure of neural population activity. Across the board, the approach to validating the signal has been to relate it in a principled, quantitative way to the neural signals recorded intracranially from non-human primates (see Boynton, 2011 for a recent review). Whether or not one believes in such a notion of a “gold standard,” it is troubling to note that this imperative of validation against intracranial data is not at all prominent in the domain of EEG source modeling. The discrepant findings of simultaneously-onsetting V1 and V2 responses of opposite cortical-surface polarity in source-estimated ERPs (Ales et al., 2010b) provide a salient example.

It is clear that in theory, the validity of solutions to the scalp EEG inverse problem increases with the application of well-grounded, physiology-based constraints. But at what point will their validity be sufficiently high to accept their results as definitive on a level anywhere near that associated with invasive recordings? While it is tempting to regard a modeling algorithm's validity as commensurate with its “sophistication” gauged by the number of constraints and processing steps applied, we know that the two are fundamentally separate. Constraints allow an underdetermined estimation problem to become overdetermined, but this in itself just means increased likelihood of converging on a solution that reduces residual variance to a minimum. The *accuracy and validity* of the solution is another thing altogether, and it depends on the degree to which the constraints reflect the reality, and the error contributed by each of the many processing steps, neither of which can be precisely quantified. In general, while source models often give the impression that the source signals are more accurate and higher resolution than the signals measured on the scalp, it is critical to acknowledge that the source waveforms are nevertheless fully derived from those same scalp signals.

The above considerations were directly acknowledged by Hagler et al. (2009), who used a similar retinotopic mapping-constrained source modeling approach as Ales et al. (2010b). They listed several potential sources of error that may limit the accuracy of their technique. For example, they limited the number of modeled visual areas to three, despite there being many more retinotopically organized regions of the visual system (Serenio et al., 1995, 2001; Silver and Kastner, 2009), and ignored known differences between upper and lower visual fields (Liu et al., 2006; Skrandies, 1987; Van Essen et al., 1984). The authors also pointed out sources of inaccuracy relating to dipole location and orientation, as well as in the forward model itself. Having acknowledged these limitations, Hagler et al. explored how more plausible source waveforms could be generated at the cost of increased residual error, and their simulated V1 and V2 waveforms display timing differences and initial polarities that are consistent with intracranial findings. By contrast, Ales et al. (2010b) focused on minimizing residual variance and used harsher constraints and assumptions (e.g., only two visual areas V1 and V2, and spherical head models rather than reconstructions of the subjects' actual head shapes) and found a significantly different pattern involving simultaneous V1 and V2 onsets. Clearly an important additional factor in establishing the validity of source modeling, before it may be considered to provide definitive information beyond that already available on the scalp, will be to account for such discrepancies observed across studies employing such ostensibly similar constrained modeling approaches.

As a final note we would emphasize again that it is not the constrained source modeling approach itself that we take issue with, but its use as a basis to reject the cruciform model without due

consideration of the full set of factors from which that model was derived, or information from intracranial data recorded directly from the areas in question. The approach taken by Ales et al. (2010a) in fact leads to many exciting possibilities. For example, V1 is so anatomically variable that often a C1 cannot be identified for a subject at all (see Kelly et al., 2008). Though perhaps not their intention, Ales et al. have in their paper highlighted a solid approach to determining optimal stimulus locations that will elicit a robust C1 potential in individual subjects. We would certainly like to see this innovative source modeling method developed in this way.

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