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Neuropsychologia 43 (2005) 1838–1844

NEUROPSYCHOLOGIA

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Can whole brain nerve conduction velocity be derived from surface-recorded visual evoked potentials? A re-examination of Reed, Vernon, and Johnson (2004)

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Received 5 November 2004; received in revised form 11 February 2005; accepted 28 February 2005
Available online 24 March 2005

Abstract

Reed, Vernon, and Johnson [Reed, T. E., Vernon, P. A., & Johnson, A. M. (2004). Sex difference in brain nerve conduction velocity in normal humans. *Neuropsychologia*, *42*, 1709–1714] reported that "nerve conduction velocity" (NCV) of visual transmission from retina to the primary visual area (V1) is significantly faster in males than females. The authors estimated the NCV by dividing head length (nasion-to-inion distance) by the latency of the well-known P100 component of the visual evoked potential (VEP). Here, we critically examine these metrics and we contend that knowledge of the underlying physiology of neural transmission across the initial stages of the visual processing hierarchy dictates that a number of their assumptions cannot be reasonably upheld. Alternative, and we believe, more parsimonious interpretations of the data are also proposed.

Keywords: Visual evoked potential; Neural transmission; Timing; Reaction time; Gender; Human

This paper evaluates Reed, Vernon, & Johnson (2004) recent contention that there are sex-differences in neural conductivity within the human brain. These authors, using the visual evoked potential (VEP) method, an especially powerful tool for assessing functionality and integrity within the visual processing pathways, report that "nerve conduction velocity" (NCV) of visual inputs from retina to primary visual cortex is significantly faster in males than females. As their primary metric, they estimated speed of neural transmission by dividing head length (i.e. the sagittal distance between the nasion and inion) by the latency of the well-known P100 component of the VEP, a robust positive-going waveform that emerges over occipital scalp at about 100 ms after stimulus onset. In addition, Reed et al. claim that the faster NCVs found in males are in accordance with the fact that males have faster reaction times (RT) across a variety of tasks.

Three major conditions need to be satisfied to allow for the determination of the retino-thalamo-cortical NCV from the VEP according to the methods of Reed et al. First, the P100 peak latency must correspond directly to the transmission time from the retina to the primary visual cortex (Brodmann's area 17 or V1), excluding delays related to retinal and cortical integration. Second, the processing represented by P100 must be generated solely in area V1. Third, the physical pathway length from the optic nerve head to V1 must be known for each subject, and used with that subject's conduction time measurements to calculate that subject's "NCV." Here, we

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doi:10.1016/j.neuropsychologia.2005.02.010

critically examine these conditions based on the extant literature and the metrics used by the authors according to the following points: (1) the timing of visual transmission; (2) the sources of the VEP components; (3) the different stages ("compartments") of visual processing from retina to cortex; (4) the putative correlation between VEP and reaction time; (5) alternative explanations and conclusions. We contend that knowledge of the underlying physiology of neural transmission across the initial stages of the visual processing hierarchy dictates that a number of the assumptions made by Reed et al. cannot be upheld.

1. Information flow through the visual system

Reed et al. contend that it takes about 50 ms for information to reach thalamus from the retina and that another 50 ms is accounted for by flow through the optic radiations. The assumption that 100 ms is a realistic timeframe for transmission of inputs from retina to cortex, and implicitly that P100 represents the initial input to primary visual cortex is simply not supported by the literature. In fact, it is remarkable just how much processing the brain can actually achieve in just the first 100 ms of activity after visual stimulus onset. This includes, for example, figure-ground segregation within the visual system (Bach & Meigen, 1998; Lamme, 1995; Murray et al., 2002), binocular integration (Fukai, 1985; Regan & Spekreijse, 1970; Saint-Amour, Lepore, Lassonde, & Guillemot, 2004), substantial cortical interaction between visual and other sensory modalities (Fort, Delpuech, Pernier, & Giard, 2002; Giard & Peronnet, 1999; Molholm et al., 2002; Schroeder & Foxe, 2002; Schroeder, Lindsley, et al., 2001; Schroeder, Mehta, et al., 2001), integration of visual information across both hemifields (Murray, Foxe, Higgins, Javitt, & Schroeder, 2001) and even the initiation of motor output activity (~105 ms) associated with fast RTs (Saron, Foxe, Simpson, et al., 2003). Intracranial recordings in awake macaques show that latencies for both parvocellar and magnocellular retinal inputs to the thalamic relay nucleus, the lateral geniculate nucleus (LGN), are in the range of 13–18 ms (Schroeder, Mehta, et al., 2001). In fact, less than 30 ms are necessary for retinal inputs to reach the primary visual cortex (Givre, Schroeder, & Arezzo, 1994; Maunsell & Gibson, 1992; Schroeder, Mehta, & Givre, 1998; Schroeder, Tenke, Givre, Arezzo, & Vaughan, 1990, 1991), although the fastest magnocellular inputs to V1 can be seen as early as 15–20 ms post-stimulation. The visual system, from the primary visual cortex to high-level extrastriate areas of the infero-temporal (IT) cortex, becomes activated within just 30 ms of the initial afferent input to area V1 (Mehta, Ulbert, & Schroeder, 2000a, 2000b; Schroeder et al., 1998; Schroeder, Mehta, et al., 2001; see Lamme & Roelfsema, 2000 for a exhaustive review of the VEP latencies in macaque). The dorsal visual stream activation, by virtue of its dominant magnocellular input, is even faster than the ventral stream, so that essentially the entire parietal pathway is activated with less than 15 ms lag from the initial activation of V1. For example, inputs to the intraparietal sulcus occur at an average onset latency of 28 ms with the earliest inputs seen even earlier (22 ms).

Human scalp-recordings indicate similar conclusions. Of course, latencies in the human are somewhat longer than those in a macaque, but a scaling factor of 3/5 is quite reliable to draw correspondence between human and monkey component latencies (Schroeder, Molholm, Lakatos, Ritter, & Foxe, 2004). Regions of the human frontal cortex are activated by visual stimuli within just 30–40 ms of initial V1 activation, which begins by 40–50 ms after stimulus onset (Clark & Hillyard, 1996; Foxe & Simpson, 2002; Saron, Schroeder, Foxe, & Vaughan, 2001). For example, Foxe & Simpson (2002) showed stimulus-driven frontal activity at just 85 ms and intracranial recordings in epileptic patients showed quite similar timing (Blanke et al., 1999). From the above brief overview of timing information derived directly from monkey and human recordings, it is absolutely clear that a component peak at 100 ms cannot represent anything approximating the initial input to primary visual cortex. Indeed, this is some 50–60 ms later than the initial afferent input.

2. Input to primary visual cortex is indexed by the onset of the "C1" component

Typical checkerboard VEPs are characterized by a distinct negative component preceding P100, often called the N70 or the N75. Surprisingly, Reed et al. do not describe this component and do not show any waveforms in their report. Yet, the description of the N70/N75 could be helpful for the interpretation of the data since the onset of this component is certainly more directly related to the transmission time between retina and V1 than the P100. Jeffreys & Axford (1972a) are credited with first describing this component of the flash-pattern VEP, which they termed the C1. Depending on stimulus parameters, this component onsets between 40 and 70 ms and peaks considerably before 100 ms. Because C1 reverses in polarity if the stimulation is presented in the upper or in the lower visual field, they suggested that only the unique hardwired retino-topic organisation of the calcarine fissure (striate cortex) could account for the origin of the C1 (Butler et al., 1987; Clark, Fan, & Hillyard, 1995; Jeffreys & Axford, 1972a, 1972b; Mangun, 1995; Simpson, Foxe et al., 1995; Tzelepi, Ioannides, & Poghosyan, 2001). Although the origin of neural generators of the early components of the VEP is not yet fully understood and we still have only a rather basic knowledge of the nature of processing that is occurring over successive epochs, there is a general consensus in the human literature that the initial C1 component represents striate cortex activity. The generation of the corresponding component in monkeys further supports this hypothesis. Indeed, the N40 for flash VEP and N50 for pattern VEP reflect excitatory post-synaptic potentials of stellate cells in primary visual cortex layer 4C driven directly by the primary thala-

mic afferents (Givre, Arezzo, & Schroeder, 1995; Givre et al., 1994; Schroeder et al., 1998, 1991). On the other hand, several studies in humans have shown that the ensuing P1 (peaking between approximately 90–130 ms) and N1 components (a negative component peaking between approximately 130 and 180 ms) represent subsequent extrastriate activation (Clark et al., 1995; Clark & Hillyard, 1996; Di Russo, Martinez, Sereno, Pitzalis, & Hillyard, 2001; Foxe, Murray, & Javitt, in press; Gomez Gonzalez, Clark, Fan, Luck, & Hillyard, 1994; Heinze et al., 1994). As proposed by Foxe & Simpson (2002), the "early" ERP components such as P1 and N1 are likely to reflect relatively late processing involving top–down influences from parietal and frontal regions after the initial volley of sensory afference through the visual system.

The C1 (or the N70/N75) is therefore the best estimate of the onset of the initial response in human V1. Despite this, the estimation of the latency of the C1 (or any other component) can be equivocal because the generation of the component starts before the waveform "peak", which is commonly used as a latency point of reference. The use of the C1 peak is, in fact, highly likely to overestimate the time needed for retinal inputs to reach V1. Although the C1 is associated with the activation of striate cortex, it has been proposed that only the initial portion of the C1 component (the first 10–15 ms) is likely to represent predominantly V1 activity. Given the timing described above, the latter portion of the C1 waveform almost certainly reflects extrastriate processing as well (Foxe & Simpson, 2002).

Although the neural generators of the pattern-onset VEP have been repeatedly modelled based on combined functional magnetic resonance imaging (fMRI) and source-modelling of high-density scalp-recordings (e.g. Clark et al., 1995; Clark et al., 1996; Di Russo et al., 2001; Gomez Gonzalez et al., 1994; Heinze et al., 1994; Simpson, Foxe, et al., 1995; Simpson, Pflieger et al., 1995), it was only very recently that these techniques were applied to the pattern-reversal VEP (Di Russo et al., 2005). As expected, these authors found a V1 source for the N70/N75 component, which almost certainly corresponds to the C1 component. They also found both striate and extrastriate generators during the timeframe of the P1. Striate cortex has been implicated as one of the active generators during the pattern-reversal P1 by many authors (e.g. Biersdorf, 1987; Bonmassar et al., 2001; Brecelj, Kakigi, Koyama, & Hoshiyama, 1998; Hoeppner, Bergen, & Morrell, 1984; Nakamura, Kakigi, Okusa, Hoshiyama, & Watanabe, 2000), but a considerable number of studies have also found extrastriate generators (V2–V3–V4) to be more prominent during the P1 (Lehmann, Darcey, & Skrandies, 1982; Onofrj et al., 1993; Onofrj, Fulgente, Thomas, Curatola, et al., 1995; Onofrj, Fulgente, Thomas, Malatesta, et al., 1995; Schroeder et al., 1995; Vanni, Tanskanen, Seppa, Uutela, & Hari, 2001). As such, it appears clear that both striate and extrastriate generators contribute to the P1, whereas the preceding component (N70/N75 or C1) is a better index of early V1 activation.

3. Necessity of "compartmentalizing" in derivation of a brain NCV measurement

Using the peripheral NCV as a conceptual model is inappropriate. The computation of a median nerve CV, for example, involves two measurements. The first is the conduction time from the stimulation point at the wrist to the onset of the compound action potential response at a more proximal location (e.g. the elbow or at Erb's point). The second is the length of the pathway from the wrist to the measuring point in the popliteal fossa or brachial plexus (easily indexed with a tape measure). On the other hand, there are at least five "compartments" that contribute to the latency of a V1 response: (1) retinal integration time (receptor depolarization, intraretinal conduction, ganglion cell integration and discharge); (2) conduction time from the optic nerve head (the point at which most ganglion cells are myelinated) to the lateral geniculate nucleus, which corresponds to the empirical NCV, i.e. the real conduction time over the real distance; (3) peri-synaptic time in the lateral geniculate nucleus (retino-geniculate axon terminal invasion time, synaptic delay, post-synaptic integration time); (4) conduction time in the optic radiations (NCV plus distance); (5) Peri-synaptic time in V1. Direct study of the first three compartments in non-human animal subjects (Schroeder, Salinger, & Garraghty, 1986) illustrates both the difficulty of accurate reliable measurements, and the necessity of obtaining them.

As discussed above, the examination in humans of the time required for subcortical visual processing can be accomplished, in a gross sense, using C1 onset. Getting beyond this stage, that is determining how the various post-retinal elements of the primary visual pathways contribute to conduction/processing time in the pre-cortical portion of the pathway, will be difficult. The effort must first acknowledge the potential sources of variance in the measure (i.e. the compartments). Once this is done, the magnitude of the task becomes apparent. For example, we already know that retinal processing time accounts for the bulk of time involved in cortical onset latency (Schroeder, Tenke, Arezzo, & Vaughan, 1989; Schroeder et al., 1986), and even isolating this compartment requires deriving a valid and reliable non-invasive index of the onset of retinal output, and this is a non-trivial problem. Isolating the other compartments with non-invasive methods is, at present, impractical. As such, macroscopic measurements of visual processing (scalp-recording over Oz) and retino-geniculate pathway (nasion-to-inion distance) make the assessment of brain NCV impossible.

4. Correlations between VEP components and reaction time

On the other hand, one can question the interpretation from Reed et al. regarding RT and visual transmission time. Since males showed faster reaction times, they concluded that such performance should be related to their faster NCV.

This RT conclusion is, again, based on indirect evidence. To claim such a relationship, the authors should minimally have demonstrated a correlation between the VEP latency (or the 'NCV') and RT; they did not. In fact, the existence of such correlation is unlikely. The stimulation used by Reed et al. to test RT (Cognometer battery test^{TM}) was different from those used for their VEPs (checkerboard), and both measures were not performed simultaneously. Studies, which have compared the VEP and motor RT, suggest that their relationship varies depending on the stimulus parameters (Baedeker & Wolf, 1987; Hartwell & Cowan, 1993; Musselwhite & Jeffreys, 1985). While a linear relationship between the VEP and RT is possible for contrast variation (Hartwell & Cowan, 1993) only partial or no correspondence has been found over a limited range of luminance or spatial frequencies, respectively (Hartwell et al., 1993; McKerral, Lachapelle, & Benoit, 1992). For example, McKerral, Lepore, & Lachapelle (2001) have shown that the peak time of the pattern VEP demonstrates spatial frequency selectivity while RT does not. Absence of correlation between RT and VEP measures has also been reported for motion detection (Kubova, Kremlacek, Szanyi, Chlubnova, & Kuba, 2002) and for interhemispheric transfer time (Hoptman, Davidson, Gudmundsson, Schreiber, & Ershler, 1996; Saron & Davidson, 1989; Saron, Foxe, Schroeder, et al., 2003; Saron, Foxe, Simpson, et al., 2003).

It is therefore clear that the relationship between VEP and RT is not straightforward and certainly not causal. The comparison of these measures between males and females is probably even more problematic. In addition to this issue, one might also ask how gender-differences in latency ranging from 1 to 3 ms (or 0.077–0.082 m/s in NCV) could be linked to gender-differences in RT ranging from 16 to 128 ms? In other words, how does the highest male/female ratio of NCV (1.044, i.e. 4.4% faster for males) account for the highest ratio of RT (1.18, i.e. 18% faster for males)? In addition to any putative anatomical determinants, many other factors such as practice (manual abilities, video gaming history, etc.), attention and/or cognitive strategies could account for the faster RT commonly found in males (e.g. Adam et al., 1999; Donchin, Ritter, & McCallum, 1978).

5. Alternative interpretations of Reed et al. findings

It is commonly assumed that head size reflects brain volume. However, the relationship between the actual brain size and the cranial measures is quite questionable (Peters et al., 1998). For instance, Simmons (1942) showed that the brain volumes of human subjects (males) with identical length, breadth and height measurements of the cranium could differ by more than 225 cm^3 in brain volume. Conversely, he also showed that similar cranial capacity measures were obtained for skulls with very different external measurements. Similar discrepancies have been observed by Friedman, Wiechers, Cerny, Schulz, & Buckley (2000) based on more sophisticated statistical analyses. The authors found that external measures of the head were correlated with the cranial capacity, but they accounted for, at most, only 60% of the variance. Additional studies have shown that the magnitude of the relationship between brain size and head size is even weaker in females than in males (e.g. Ivanovic et al., 2004; Peters et al., 1998). Obviously, cerebral tissues and spaces (e.g. skull, sinus, muscles, fat, epidermal layers) contribute to head size independently of brain size.

The lack of convergence for a clear relation between brain size and head measures – in addition to the issues regarding the latency measurement – strongly discredits the NCV gender-difference reported by Reed et al. The whole point of their paper is to demonstrate that there is a sex-difference in the NCV. Yet, nowhere do they demonstrate that their P100 latency is at all responsive to head length independent of sex. There is no simple regression analysis of head length by latency. For example, Guthkelch, Bursick, & Sclabassi (1987) found a better correlation of P100 latency with head circumference (interestingly, no significant correlation was found between P100 and head length) than with gender. Using head circumference as a predictor of the latency of the P100, the addition of gender to the regression equation did not improve the prediction. These results suggest that a major determinant of differences in the latency of the P100 in adults may well be head size rather than gender.

How can we then account for the results of Reed et al.? The difference in P100 latency between males and females, namely a slight advantage for females (100.6 ms versus 102.1 ms in average), is in agreement with previous findings (e.g. Celesia, Kaufman, & Cone, 1987; Emmerson-Hanover, Shearer, Creel, & Dustman, 1994). However, the nature of this difference is unclear. One explanation might be found in the actual brain volume (which cannot be reliably estimated from cranial measures as detailed above). Indeed, the average female brain weighs approximately 100–150 grams (about 10–12%) less than the male brain (see Peters, 1991; Peters et al., 1998). Based on the assumption that any pathway of the brain varies in length as the cube root of the brain volume (Schmidt-Nielsen, 1975), one can speculate that the putative shorter visual pathway length in the female brain could account for shorter latencies in the VEP (Allison, Wood, & Goff, 1983). Another complementary possibility is the fluctuation of the VEP latency in females as a function of hormonal levels (La Marche, Dobson, Cohn, & Dustman, 1986; Shushtarian & Yahyavi, 1999; Yilmaz, Erkin, Mavioglu, & Sungurtekin, 1998). It has been suggested that estrogen facilitates synaptic transmission along the optic pathways (Yilmaz et al., 1998). As such, the faster visual transmission time observed in females during the ovulatory phase can be attributable to the high concentration of estrogen during that period (Shushtarian & Yahyavi, 1999; Yilmaz et al., 1998). Interestingly, the corollary is that the putative male/female difference for latency would disappear during other phases.

The data of Reed et al. show that the head size varies systematically by sex (11 mm or 5.9% different, $p < 0.0001$),

which is also in accordance with the literature. As a consequence, the ratio head length/P100 latency will systematically vary by sex even if there is weak or no difference in P100 latency (the actual observed latency sex-difference was 1.6 ms or an average of 1.5%). As such, the gender-difference found by the NCV calculation is largely attributable to the head length size per se, i.e. to the numerator of the ratio, and not to the latency of P1. Since the idea by which the latency of the P100 is directly related to the length of the visual pathway is false, the findings of Reed et al. cannot be linked together and have to be considered separately: On the one hand, there is a significant difference between males and females for head size, and on the other hand, there is a significant difference in the latency of P100.

6. Conclusions

We believe that the NCV measure is an oversimplification and ultimately a misleading concept to account for visual transmission in the human brain. We contend that such a calculation cannot reasonably be performed from human scalp-recordings. Considering the limitations of the visual NCV measure discussed above, it is not surprising that reports of NCV data have not been common in the literature to date, with the exception of the studies by Reed et al. (2004) and Reed & Jensen (1992). The extant literature provides a very clear picture indicating that the P100 component does not reflect primary visual cortical processing, but instead is an index of relatively late processing stages resulting from synchronization and reverberations (re-entrant processing) throughout the cerebral cortex. The processing represented by the early VEP components involves many visual structures and has a time latency window long enough to allow considerable intersensory computations. The fact that, on the one hand, the P100 reflects much more than just the transmission time from retina to V1, and on the other hand, head length does not represent the actual visual path length, seriously challenges the NCV measure. The NCV as conceptualized and presented by Reed et al. could thus constitute another *Mismeasure of Man* (Gould, 1981) or woman, of course.

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