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Improvement In Arousal, Visual Neglect, And Perception Of Stimulus Intensity Following Cold Pressor Stimulation

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Abstract

The relationship between arousal, perception, and visual neglect was examined in this case study. Cold pressor stimulation (CPS: immersing the foot in iced water) was used to manipulate arousal and to determine its effects on contralesional neglect, perception of stimulus intensity (magnitude estimation), reaction time, and an electrophysiological correlate of ascending reticular activating system activity (i.e., the P50 potential). Measures that normalized from baseline following CPS included contralesional neglect on a clock drawing test, perception of stimulus magnitude, and P50 amplitude. The P50 amplitude returned to its abnormally low baseline level 20 minutes after CPS ended, indicating that CPS increased arousal.

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Introduction

Arousal deficits play a fundamental role in the neglect syndrome (Heilman, Watson, & Valenstein, 1985). Arousal is a construct that involves several physiological systems, in both cerebral hemispheres, that regulate wakefulness, alertness, and conscious perception (Fuller, Gooley, & Saper, 2006; Garcia-Rill, 2009). Several neuronal populations in the ascending reticular activating system (ARAS) modulate arousal and cortical synchronization, including the pedunculopontine nucleus (PPN), laterodorsal tegmental nucleus, locus coeruleus (LC), and raphe nucleus (RN). Ascending cholinergic (PPN) and monoaminergic (LC and RN) projections from the ARAS to the intralaminar thalamus can increase arousal both by activating the cortex and inhibiting neurons in the reticular nucleus of the thalamus (Steriade, McCormick, & Sejnowski, 1993). Cortical neurons return descending activity to thalamocortical neurons (Pare & Llinas, 1995), setting up recursive action. Simultaneous, recursive action of specific and nonspecific thalamocortical processes, at gamma frequencies, is thought to be the basis for conscious perception.

Neglect is defined as the failure to orient, report, or respond to stimuli located in space lying opposite brain injury (i.e., contralesional), when the deficit cannot be attributed to primary

sensory or motor impairment (Heilman et al., 1985). Contralesional neglect may result, in part, from decreased arousal following lesions of the ARAS or heteromodal association areas that project to the ARAS and the reticular nucleus of the thalamus (Heilman et al., 1985). Deficits in arousal have also been associated with impaired performance in neglect that is not strictly lateralized to one side of space. Such non-lateralized features of neglect (Husain & Rorden, 2003) include slow and inconsistent reaction times (Anderson, Mennemeier, & Chatterjee, 2000; Ladavas, 1987; Posner & Rafal, 1987; Robertson, 2001; Samuelsson, Hjelmquist, Jenson, Ekholm, & Blomstrand, 1998) and altered perception of stimulus intensity/deficits in magnitude estimation (Chatterjee, 1995; Chatterjee, Mennemeier, & Heilman, 1992; Mennemeier et al., 2005; Tegner & Levander, 1991). This study used a cold pressor test to manipulate arousal and behavior related to neglect in a patient with a chronic neglect following a right hemisphere stroke.

Cold water stimulation of the left ear canal, or caloric vestibular stimulation (CVS), is known to have a dramatic ameliorative effect on visual neglect that may be achieved, in part, by increasing arousal. Rubens (1985) originally attributed the CVS effect to a vestibular-mediated leftward shift of attention, but later studies (Cappa, Sterzi, Vallar, & Bisiach, 1987) attributed the effect to vestibular-mediated activation of the intact left-hemisphere. Storrie-Baker and colleagues (Storrie-Baker, Segalowitz, Black, McLean, & Sullivan, 1997), in a single case study of a patient with a right hemisphere stroke and visual neglect, found that CVS improved both neglect and reaction time. CVS also increased high frequency wave and decreased slow-wave EEG activity recorded over both cerebral hemispheres. However, the most pronounced increase occurred over the right hemisphere. As the conscious waking state is characterized by low amplitude, high frequency EEG oscillations, behavioral improvement following CVS was associated with a general increase in arousal level.

The case study in this report differed from the Storrie-Baker et al (1997) study in several ways that are theoretically important. First, this study used cold pressor stimulation to increase arousal (CPS: immersing the foot in iced water between 2 ° and 4 °C for 50 seconds) rather than CVS to avoid the effect of vestibular stimulation on shifts of spatial attention. If CPS improves neglect in a manner similar to CVS, then its effect can be more closely tied to changes in arousal. CPS is a reliable test of sympathetic activation in both normal subjects and stroke patients (Saab et al., 1993). Furthermore, the receptors and spinal cord pathways involved in cold stimulation activate the ARAS via the spinoreticular and spinomesencephalic tracts of the anterolateral system (Levine, 2000). Most of the fibers of these tracts synapse in the ARAS rather than synapsing directly in the specific sensory thalamic nuclei.

Secondly, this study recorded the midlatency auditory evoked P50 potential as an electrophysiological correlate of level of arousal, rather than the EEG. P50 potentials were recorded because of the P50's demonstrated relationship to processing within the ARAS. The P50 potential is a vertex recorded response to an auditory stimulus that has demonstrated sensitivity to altered states of arousal in a variety of human clinical populations (Garcia-Rill & Skinner, 2002a). The P50 potential diminishes and disappears with progressively deeper stages of slow-wave sleep and is blocked by scopolamine. P50 potential's reappearance during REM (rapid eye movement) sleep suggests that one generator is functionally related to states of arousal and modulated by cholinergic mesopontine cell groups (Buchwald, Rubenstein, Schwafel, & Strandburg, 1991; Erwin & Buchwald, 1986; Garcia-Rill, 1997).

Third, this study examined changes in magnitude estimation following CPS to determine its relationship to arousal. Magnitude estimation is a psychophysical method used to study conscious sensory perception wherein subjects use numbers to rate the intensity of supra-

threshold stimuli (Gescheider, 1997; Stevens, 1975). Estimates of stimulus intensity are expressed as power functions (log-log plots) of physical intensity. The power function slope (i.e., the exponent) and y-intercept (i.e., the constant) are convenient summary variables that can be compared both within and across subjects to measure changes in perception of stimulus intensity.

Methods

Case Description

The participant was a 63 year-old, right handed female with chronic left-sided visual neglect (i.e., 4 months post-stroke). A reading of her clinically obtained CT scan indicated a middle cerebral artery infarction of the fronto-temporo-parietal cortices in the right hemisphere. She had left-sided weakness of the upper and lower extremities (i.e., rated as a 4 out of 5 for both extremities according to the grading system for motor strength testing in the standard neurological exam where a 4 of 5 is defined as movement possible against some resistance by the examiner but less than normal and less than the noninvolved side of the body. A 5 of 5 would indicate normal strength and a 3 of 5 would indicate the ability to move against gravity, but not against added resistance.) She could stand and pivot with an ankle brace on her left leg. She could also walk short distances with assistance. She could detect tactile sensory stimulation on both sides of the body and she did not evidence extinction to double simultaneous stimulation. She spoke normally and completed manual tests with her dominant right hand. She did not evidence any visual field defects when tested in a standard confrontation exam. Neglect was assessed formally using the six conventional tests of the Behavioural Inattention Test (BITC: Wilson, Cockburn, & Halligan, 1987). Her subtest scores on the BITC were as follows: line crossing 31/36; letter cancellation 38/40; star cancellation 42/54; figure and shape copy 3/4; line bisection 5/9; & representational drawing 1/3. Her total BITC score was 120 (below the cutoff for neglect = 129) and she was below the cut-off score for five of the conventional tests indicating a severe level of neglect. Behavioral and electrophysiological data obtained from the participant were compared to that obtained from two reference groups that are described in the data analysis section. All subjects signed an Institutional Review Board (IRB) approved written informed consent prior to participating in these studies.

Stimuli, Design, & Apparatus

Cold Pressor Stimulation (CPS)—The participant's right foot was immersed in iced water for 50 seconds and then removed and wrapped in a dry towel. The right foot was stimulated to avoid any potential confounds due to contralateral sensory impairment following stroke. Approximately 10.2 cm of water was placed in an oval pan that measured 60.96 cm by 30.48 cm. Crushed ice was floated on top of the water for 10 minutes prior to stimulation and allowed to remain in the pan. Water temperature was not measured for our patient; however, it was recorded for control subjects using a digital thermometer with a sensor placed in the water and found to range between 2 and 4 degrees Celsius. The following measures were performed immediately before and after CPS with the goal of completing all measures within 8 minutes after stimulation ended. Previous studies in our laboratory indicated that the behavioral effects of CPS on neglect last approximately 10 minutes (Woods et al., 2004).

Visual Neglect—The Clock Face Drawing subtest of the BITC was used to assess visual neglect following CPS because this test provided the strongest evidence of contralesional neglect at baseline. Other tests of the BITC were not repeated because they could not be finished, along with tests of magnitude estimation, within 8 minutes.

Estimates of stimulus intensity—The participant was instructed to use numbers between 10 (least) and 99 (greatest) to rate the intensity of two types of stimuli – the visual area of black squares printed on 24 x 24 cm sheets of white paper and the height of wooden blocks inserted between the thumb and index finger of the right hand (i.e., a proprioceptive finger span test). Both tests were shown in previous studies to discriminate patients with right hemisphere lesions and neglect from normal subjects and patients with left hemisphere injury (Mennemeier, Murphy, Kretzmer, Jewell, & Nunn, 2003). A blindfold was used to prevent visual inspection during the finger span. There were 8 intensities for each type of stimulation. Area stimuli were 1, 2.99, 6.05, 15.37, 28.94, 68.89, 125.89, and 200 cm^2, respectively. Finger span stimuli were 0.4, 0.8, 1.4, 2.4, 3.4, 4.4, 5.4, and 6.3 cm in height, respectively. Each stimulus was presented three times (24 trials per stimulus type) in random order.

Reaction Time—Reaction time was measured using the Psychomotor Vigilance Test (PVT; (Dinges, 1985). The PVT measured simple reaction time to a 1 KHz auditory stimulus of 90 dB. The interstimulus interval varied from 2–10 sec. The task was two minutes in duration and yielded approximately 20 RTs per task.

Arousal – P50 Amplitude—Detailed techniques for recording and analyzing the P50 potential have been published (Garcia-Rill & Skinner, 2002b). To summarize, the participant listened to auditory click sounds via ear buds (i.e., 0.1 msec in duration, set at least 50 dB above hearing threshold and generated with a Grass Instruments auditory stimulator STM10) and silently counted the number of tones heard to ensure attention to the tones. Recordings were made using gold-plated surface electrodes with a water-soluble conducting paste. Electrode resistance was maintained at <5 Kohm. The P50 potential was recorded at the vertex (Cz) with reference to a frontal electrode (Fz), as this yields a clearer waveform than reference to linked mastoid electrodes. Artifacts due to eye and jaw movements were measured using diagonally placed canthal electrodes and a lead over the masseter muscle referred to the chin, respectively. A subclavicular ground was also used. EEG signals that contain interference from EOG or EMG leads were excluded. Each channel was led to a Grass Instruments 5P11 amplifier with a high resistance input stage. The gain and bandpass were as follows: P50 potential ×100 K and 3 Hz–1 KHz; EOG ×20 K and 3 Hz–1 KHz; and EMG ×10 K and 30 Hz–3 KHz, with a 60 Hz notch filter on each amplifier. Fast Fourier Transform analysis has shown that the P50 potential is not degraded by the notch filter. Testing sessions of 6–8 min in duration consisted of paired click stimuli at a 250 msec interstimulus intervals (ISI). Pairs of clicks were delivered once every 5 seconds (previous studies have shown that stimulation at faster frequencies can lead to a decrement in the P50 potential amplitude) until 64 pairs of evoked potentials are acquired, averaged, and stored. Using paired click stimuli allows for the examining of habituation of P50 amplitude to a second stimulus. At an ISI of 250 msecs, the average percent habituation to the second auditory click is similar for males and females; it ranges from approximately 15 to 40% in normal subjects, but may be much higher for adolescents than adults (Rasco, Skinner, & Garcia-Rill, 2000). Habituation of P50 amplitude to a second stimulus may also be unreliable at longer ISIs (Smith, Boutros, & Schwarzkopf, 1994). Amplified signals were displayed on an oscilloscope for visual monitoring, digitized using a GW Instruments I/O module, averaged using Superscope software (GW Instruments), and stored on computer disk. The P50 potential was identified as the largest amplitude positive wave occurring at 40–70 msec latency following the primary auditory cortical evoked potential (Pa), at 25–40 msec latency. The amplitude from the preceding negativity (Nb), or from the preceding baseline if Nb is absent was measured.

Procedures

Testing was performed in two sessions separated by one week. During the first session, tests of neglect and magnitude estimation (fingers span and area judgment) were completed immediately before and immediately following CPS. All tests were completed in less than 10 minutes. A therapy appointment precluded retesting 20 minutes after CPS. Reaction time and P50 recordings were completed during a second test session, before, immediately after, and 20 minutes following CPS.

Data Analysis

Clock drawings completed before and immediately after CPS are provided in Figure 1 for visual inspection. Power function parameters (i.e., the slope (exponent), y-intercept (constant), and r^2) for the magnitude estimates of finger span and area judgment were referenced to 95% confidence intervals established by right handed, normal control subjects (Magnitude Estimation Reference Group; n= 39, mean age = 58 years, SD = 16 years) who performed the same tasks in a separate study (see Table 1). Both the objective and subjective estimates (i.e., ratings) of stimulus intensity were log-transformed and the estimated values were regressed on the objective values to yield a power function. The exponent, constant, and an r^2 value of these power functions were compared to those for normal controls. The participant's P50 and PVT data before, immediately, and 20 minutes after CPS are displayed graphically in Figures 2 and 3, respectively. Finally, data were obtained from 11 age appropriate female subjects, with a minimum of 12 years formal education, (mean age = 53.6 years, SE = 2.1; range = 46 to 66 years) who completed the P50, PVT, and finger span test of magnitude estimation before, immediately, and 20 minutes after CPS of the right foot under conditions identical to our patient (see Table 2).

Results

Visual Neglect

Left visual neglect was obvious on the clock face drawing subtest of the BITC prior to CPS, but resolved completely and dramatically immediately following CPS (Figure 1).

Magnitude estimation

At baseline, the patient's power function parameters for estimates of finger span and area judgment fell outside the 95% confidence interval established by the magnitude estimation reference group (Table 1). After CPS, all power function parameters for finger span normalized, but those for area judgment did not. For control subjects (n = 11), the r^2 value significantly increased from baseline to the CPS and post CPS conditions ($F_{(2, 20)} = 8.8$, $p < .002$), but the exponent and constant did not change across CPS conditions (Table 2).

Reaction time

The participant's mean reaction time (RT) fell above 95% confidence intervals established by the control group across all CPS conditions. In contrast, mean RTs for the control group decreased significantly across CPS conditions ($F_{(2, 20)} = 4.86$, $p < .02$) and significantly from baseline (mean = 275.39, SD = 68.59) to post cps (mean = 226.23, SD = 47.57).

Arousal

The participant's P50 potential amplitude was absent (0μV) prior to CPS (control group mean = 2.25 μV). P50 potential amplitude increased to 1.72μV immediately following CPS and fell within 95% confidence limits for the control group (mean = 2.19 μV; 95% CI = 1.2 – 3.1). However, P50 potential amplitude fell to 0.6μV twenty minutes after CPS, which was below 95% confidence limits for the control group (mean = 2.26 μV; 95% CI = 1.3 – 3.1).

The main effect of CPS on the P50 potential amplitude was not significant for the control group.

Discussion

This is the first report, to our knowledge, that visual neglect and related deficits in magnitude estimation can be ameliorated by immersing the subject's foot in cold water (CPS), similar to the way that CVS improves neglect. Performance on both the clock face drawing and the test of magnitude estimates for finger span estimation normalized immediately after CPS. Changes in the P50 potential amplitude after CPS indicate that the effect of CPS on neglect and magnitude estimations is mediated, at least in part, by increased arousal. The P50 amplitude was absent prior to stimulation; it normalized immediately following CPS and fell below normal limits 20 minutes after CPS ended. These findings are consistent with the effect of CVS on EEG indicators of arousal in a patient with neglect who was reported by Storrie-Baker et al (1997). Additionally, the relative absence of any CPS-induced changes in the responses of control subjects further suggests that CPS may have helped the patient overcome a deficit of arousal. In general, control subject did not evidence changes in magnitude estimation or P50 amplitude following CPS. The increase in r^2 from baseline to CPS observed in control subjects and the decrease in mean RT from baseline to post CPS both appear to represent improvement due to practice rather than change due to CPS. Unlike the Storrie-Baker et al (1997) study, we did not observe a significant effect of CPS on RT for the case participant. Significant effects might have occurred if the duration of the RT test was longer (e.g., 10 minutes rather than 2); however, the study design necessitated a shorter RT task.

A limitation of the study design is that more tests for neglect were not attempted following CPS because we were trying to complete all measures before the effect of CPS dissipated. In fact, magnitude estimates of visual area may not have normalized, like those for finger span, because the test was performed last, when the effect of CPS may have been waning. Alternatively, visual area could simply be less sensitive to changes in arousal than finger span. For example, previous studies indicate that the effect size to distinguish patients with neglect from those without neglect is much larger for finger span than visual area test (Mennemeier et al., 2003). It would be better in future studies to use more of the conventional tests of the BITC to assess neglect following CPS. Another possible limitation of the present study could involve potential variability in water temperature for CPS (between 2–4 degrees C), baseline body temperature, and ambient room temperature, which were not controlled in this study. We do not know whether or how our results might have been influenced by this variance; however, our procedures are consistent with most studies using CPS (delivering it between 0 and 7 degrees C) (Mitchell, MacDonald, & Brodie, 2004). Whereas case studies often raise more questions than they answer; the pervasive effect of CPS on clock drawing, finger span, and the P50 amplitude indicates that chronic neglect can be improved by increasing arousal. This finding also suggests another interpretation of the CVS effect on neglect.

Rubens (1985) attributed temporary improvement of left neglect following CVS to a vestibular-mediated leftward shift of attention. Because CPS can have a similar effect without stimulating the vestibular system, it is interesting to speculate that the CVS effect on neglect may have more to do with increasing arousal than altering spatial attention. CPS is well known to activate sympathetic systems (Saab et al., 1993). CPS triggers vasoconstriction (Mizushima et al., 1998) with heart rate and blood pressure elevated within 20 seconds of CPS and returning to normal after stimulation ends (Findlay et al., 1988; McLaren et al., 2005; Mizushima et al., 1998; Northcote & Cooke, 1987; Waters et al., 1983). Second, CPS activates the ARAS. Thermal stimulation is slowly conducted to the

spinal cord along C-fibers and sensory transmission of thermal stimulation within the spinal cord occurs along the adrenergic, spinoreticular, and spinomesencephalic tracts of the anterolateral system. Most of the fibers from these tracts synapse in the ARAS upon reaching the brain stem, rather than synapsing directly in the specific sensory nuclei in the thalamus (Levine, 2000).

As further evidence of the beneficial effect of increasing arousal on neglect and related behaviors, we reported in a previous case study that the stimulant modafinil (Provigil) ameliorated neglect and deficits in magnitude estimation (Woods et al., 2006). Provigil is a stimulant medication approved for use in narcoleptic patients to decrease excessive daytime sleepiness. The P50 potential amplitude is markedly decreased in patients with narcolepsy compared to normal control subjects (Boop, Garcia-Rill, Dykman, & Skinner, 1994). Modafinil increased both the P50 potential amplitude in human subjects and increased the amplitude of the analogue of the P50 potential in rodents, the P13 potential (Garcia-Rill et al., 2008). Modafinil could be beneficial for treating visual neglect in those patients who show a capacity for improvement such as a positive response to CPS or CVS.

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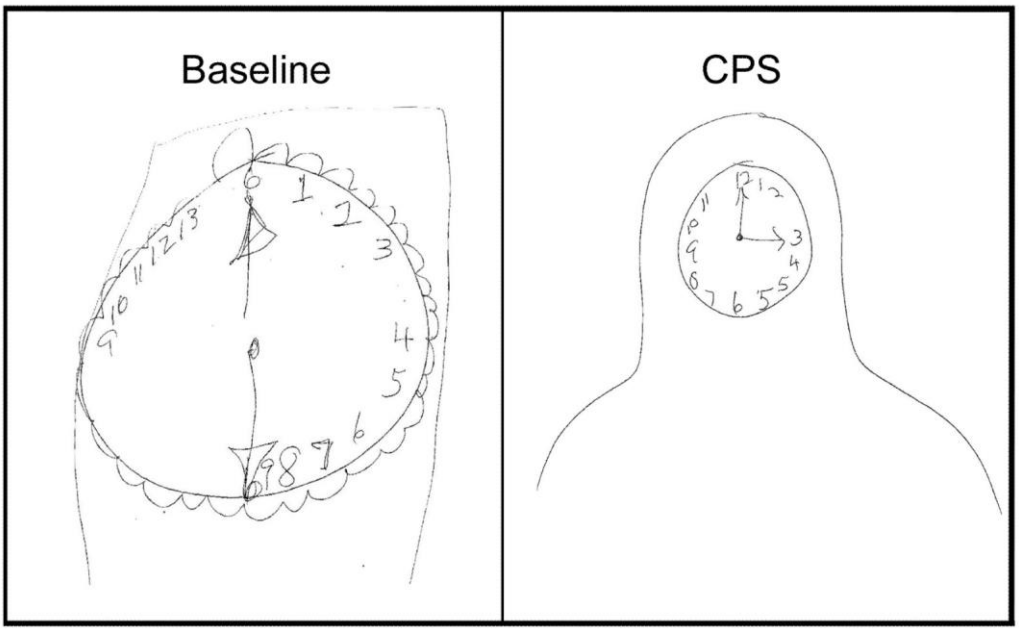

Figure 1.
Clock drawing performance a) Pre-CPS and b) immediately following CPS.

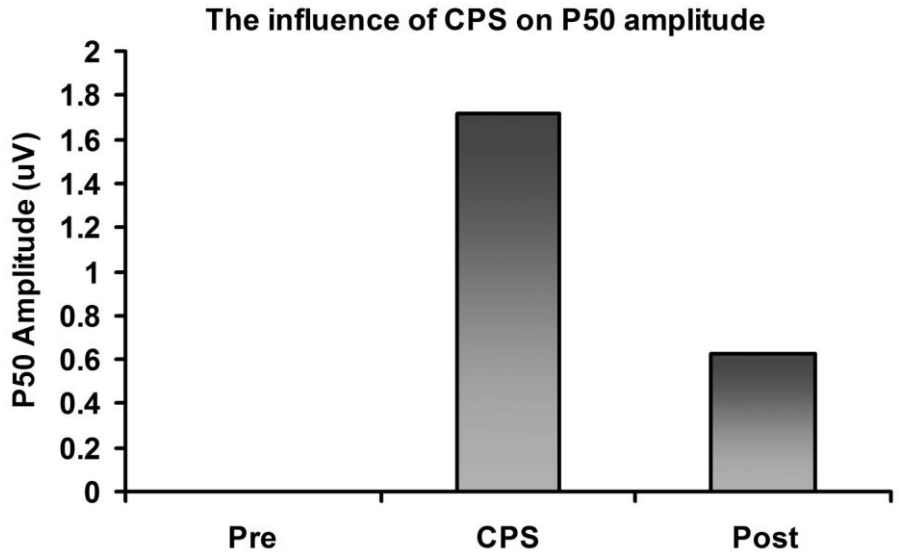

Figure 2.
Reaction time performance on the PVT before (Pre), immediately after cessation of CPS (CPS), and 20 minutes after CPS (Post).

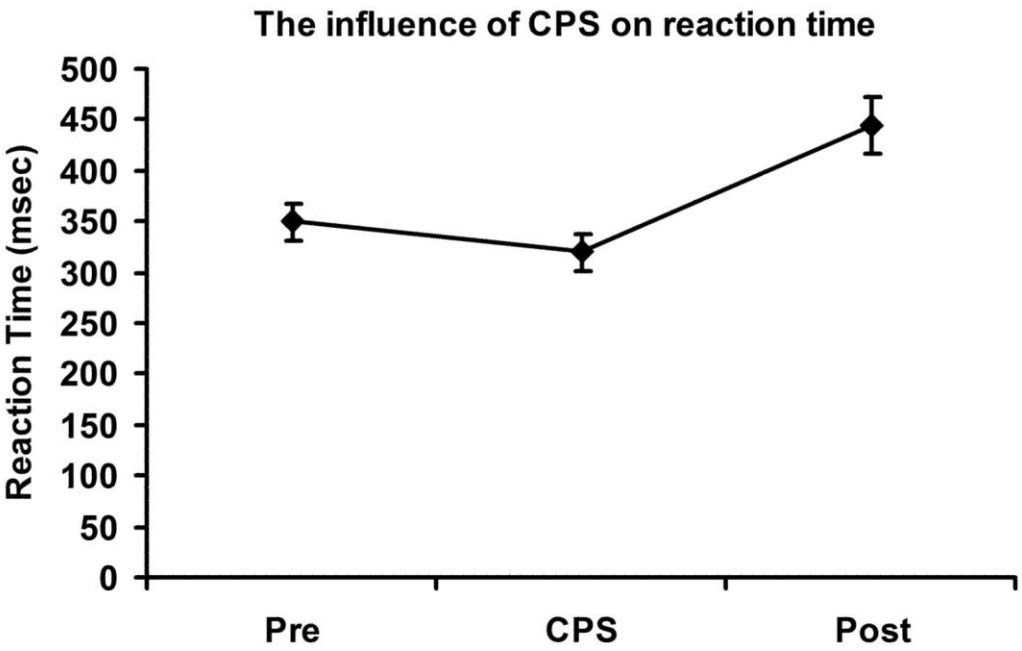

Figure 3.
P50 potential amplitude before (Pre), immediately after cessation of CPS (CPS), and 20 minutes after CPS (Post). Normal P50 range = 1.0 – 3.5μV.

Table 1

Measures of Magnitude Estimation

Variables	Patient		Reference Group
	Pre CPS	CPS	95% CI [a]
FS r^2	.79	.93*	.83–.88
FS exponent	.39	.64*	.67–.76
FS constant	5.9	3.5*	3.0–4.2
Area r^2	.76	.82	.85–.91
Area exponent	.25	.26	.34–.38
Area constant	15.4	13.0	8.4–9.4

FS = Finger span, CI = confidence interval,

* Normalized power function

[a] 95% CI established by the magnitude estimation reference group.

Table 2

Patient and control data before and after CPS

Variables	Patient			Controls		
	Pre CPS	CPS	Post CPS	Pre CPS	CPS	Post CPS
FS r^2	.79	.93	na	.83 (.78–.88)	.88 (.83–.92)	.88 (.83–.93)
FS exponent	.39	.64	na	.71 (.62–.80)	.71 (.61–.81)	.70 (.61–.80)
FS constant	5.9	3.5	na	4.9 (3.8–5.7)	4.9 (3.9–5.7)	4.9 (4.0–5.8)
Mean RT	349	319	444	275 (226–324)	238 (206–270)	226 (192–260)
P50 amplitude	0	1.72	.60	2.25 (1.6–2.8)	2.19 (1.2–3.1)	2.26 (1.3–3.1)

FS = Finger span, RT = reaction time, na = not available, parentheses indicate 95% confidence limits.