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Changes in the P300 component of the tactile event-related potential following spinal cord injury

MJ Cohen[1,2,3], PA Ament[1], SL Schandler[1,4] and M Vulpe[1,2]

[1]*Department of Veterans Affairs Medical Center, Long Beach;* [2]*Department of Neurology, University of California, Irvine;* [3]*Department of Psychiatry and Human Behavior, University of California, Irvine; and* [4] *Division of Psychology, Chapman University, Orange, California, U.S.A.*

Previous studies have demonstrated that significant changes in action or behaviour (function) and morphology occur in the deafferentated and the adjacent somatosensory cortex after amputation or experimental spinal cord injury. These studies have shown changes in somatotopic mappings and somatosensory perception as well as altered evoked responses. The purpose of the present study was to examine the potential effect of these changes on cognitive processes using the tactile P300 event-related potential (ERP) in a spinal cord injured (SCI) population. The P300 ERP has been associated with more complex cognitive functioning such as selective attention, memory, and stimulus evaluation rather than earlier sensory processing of stimuli. Three groups consisting of healthy control, paraplegic, and tetraplegic subjects participated in a transcutaneous electrical stimulation 'oddball' task. Results indicate that all groups were successful in maintaining target counts and produced significantly larger P300 amplitudes with longer latencies to target trials compared to non-target trials. The SCI groups, however, produced P300 ERPs for both targets and non-targets that were significantly reduced in amplitude compared to the control group. In the case of the tetraplegia patients, the P300 was almost abolished. No differences in latency of the P300 was observed between any of the groups.

Keywords: spinal cord injuries; P300; event related potentials; somatosensory; cognition; paraplegia

Introduction

The central nervous system demonstrates significant plasticity to a variety of situations. Experiments showing changes in the cerebral cortex following peripheral injury,[1,2] sustained peripheral stimulation,[3] learning,[4,5] experimental amputation,[6,7] or experimental spinal cord injury in cats,[8,9] and in macaques[10] are of particular importance for understanding which changes may occur in various brain regions, particularly the somatosensory cortex, in spinal cord injured (SCI) humans.

We have attempted to assess the possible functional components of the cortical changes following the loss of ascending sensory pathways from supraspinal centers (central deafferentation) due to spinal cord injury in humans. We have previously used standard psychophysical techniques to determine if paraplegic patients with and without chronic dysesthetic pain syndrome (DPS) would show perceptual changes to tactile stimulation in intact somatic areas. The SCI pain patients exhibited more sensitivity to two-point discrimination tests (smaller distance between stimulation points) while the SCI no-pain patients exhibited less sensitivity compared to control subjects, particularly in spine and neck areas.[11] One possible interpretation of these results is that the reorganization found in brain mapping studies may have functional perceptual and cognitive consequences in the spinal cord injured. Obviously, there are other interpretations including reorganization at the spinal cord level.

Surprisingly little is known, however, regarding the impact on perception and cognition after central deafferentation in the SCI population. To measure attention-arousal mechanisms in paraplegic and tetraplegic humans, we manipulated intensity of auditory and visual stimuli and measured the effect on the event-related potential (ERP) measured at C3 and C4.[12] Overall, the SCI groups had attenuated cortical responding compared to a control group. Though the paraplegic and tetraplegia groups did not significantly differ from each other, the tetraplegic group had a flatter ERP. The difference among groups was most evident in the N100-P200 component which is hypothesized to reflect processing of the physical properties of the stimulus as well as selective attention processes.[13]

Correspondence: MJ Cohen

The current study was designed to further examine the extent of attenuated cortical ERP responding in SCI humans and to assess the potential effects of ERP attenuation on cognition, particularly selective attention processes as related to processing somatosensory stimuli. To achieve this, we used a tactile oddball paradigm to examine the later P300 component of the event-related potential in tetraplegic, paraplegic and control groups while ERP measures were made at Fz, Cz and Pz cortical locations. The P300 ERP is a particularly robust endogenous element associated with higher order cognitive processing, particularly selective attention, resource allocation and processing speed.[14] The oddball paradigm, during which the subject attends to a relatively infrequent target stimulus while ignoring a more frequently occurring non-target stimulus, is especially valuable for determining functional (action or behaviour) cognitive changes. To a large extent this paradigm examines cognitive stimulus evaluation processes that are separate and distinct from the normal perceptual processing of the physical characteristics of the stimulus. In healthy control populations, the P300 ERP is of higher amplitude and longer latency in response to the target stimuli compared to the non-targets. However, the effects of altered somatosensory perceptual processing due to SCI on the cognitive evaluation of those stimuli are unknown. Since the P300 reflects factors associated with cognitive evaluation rather than perceptual processing, it might be expected that the spinal cord injured groups will respond in a similar fashion to the control group.

Methods

Subjects

A total of 45 paid volunteers, four females and 41 males, participated in this study and consisted of 15 healthy controls, 15 with paraplegia, and 15 with tetraplegia. The paraplegic group consisted of eight individuals with complete spinal cord injuries (SCI). The level of injury for the paraplegic group ranged from T-6 to L-4, and for the tetraplegic subjects ranged from C-2 to C-7 and nine had incomplete injuries while six had complete injuries. Due to the nature of the tactile discrimination task, we did not select any complete tetraplegic subject with an injury level above C-4. Subjects ranged in age from 19 to 66 years, (M = 41.2, SD = 13.2).

Subjects in all groups were matched for age and were screened for the absence of any history of loss of consciousness, head injury, seizures, mental illness, or substance abuse. Additionally, all subjects were required to be free of any major medical illness, or any medication that is known to alter neurological activity. All SCI subjects were free of peripheral neuropathy, recurrent autonomic dysreflexia, cardiac or hepatic dysfunction, or renal insufficiency. The tetraplegic and paraplegic groups were recruited from inpatient and outpatient units in the spinal cord injury wards and clinics of a major medical centre with a large spinal cord injury inpatient and outpatient population. Controls were recruited from staff and volunteers of the medical centre and the student populations of two nearby university campuses.

Apparatus and recordings

The EEG was recorded from Fz, Cz, and Pz (International 10–20 system[15]) scalp sites from silver cup 10 mm electrodes and referenced to linked-earlobe A1-A2 sites using 7.5 mm Ag/AgCl electrodes. Electrode impedances were maintained below 10 k ohms. The electro-oculogram (EOG) was also recorded to identify eye movement artifact by positioning 3 mm Ag/AgCl electrodes in an oblique configuration with one electrode slightly inferior to the outer canthus and the other electrode positioned supraorbitally, superior to the inner canthus of the non-dominant eye. Pairs of 7 mm Ag/AgCl electrodes were also attached to central forehead and ventral foot sites in order to record electrodermal (skin conductance) responses although this data will not be reported here. One of the skin conductance electrodes served as subject ground. The EEG bandpass was set at 0.15–75 Hz and the EOG bandpass was set at 0.1–35 Hz

Transcutaneous tactile stimulation, just above threshold level, was delivered through two pairs of 32 mm diameter disk electrodes applied with adhesive collars having 10 mm diameter skin contact areas using Sol^{tm} electrode cream. Pairs of electrodes were positioned approximately 3 cm to the left and right respectively of the midline of the dorsal neck area midway between the inion and the seventh cervical process. In all cases the electrodes were positioned above the level of the sentient part of the injury. Stimulation was provided by a Grass^{tm} model S10DSCMA Constant Voltage Stimulator set to deliver a 0.2 ms width square-wave pulse through the S_1 lead. Pulses were directed through a Grass^{tm} model SIU8 Stimulus Isolation Unit. The output of the isolation unit was connected to computer controlled relays which then delivered the stimulus pulse to either the right or left electrode pair positioned on the dorsal neck. The use of the dorsal neck stimulation site was necessary due to the fact that this site is the lowest somatic region with intact sensory function for the complete tetraplegia subjects selected for this study. Very low-level transcutaneous stimulation (range 0.1 to 0.3 milliamperes) at this site was used to reduce the possibility of artifact contamination of the EEG, particularly at the Pz site. There were no differences in stimulus intensities among the groups.

Procedure

After explaining the tasks procedures and instructions, a signed informed consent was obtained from each subject. In the case of tetraplegic subjects whose injury prevented sufficient arm and hand function necessary to sign the consent form, a designated representative

signed the form in the presence of the subject and the experimenter. All Informed Consent procedures and forms had previously been approved by the Medical Center's Human Studies Sub-Committee.

A standard 'oddball' task was used for the experiment which consisted of two blocks of 100 trials each. The trials for each block consisted of 25 target stimulations and 75 non-target stimulations resulting in a total of 50 target events and 150 non-target events for the two blocks. For the first block, the 0.25 probability target stimulations were randomly assigned to either the right or the left dorsal neck site and the 0.75 probability non-target stimulations were assigned to the other side. Assignment of target side was counter-balanced for the two blocks, thus, if the right side was designated as the target side in block one, the left side was designated as the target side in block two. Stimulus type for each trial (either target or non-target) was determined for all subjects using a fixed-random order controlled by computer program.

For the task, subjects were instructed to close their eyes and to keep track silently to themselves the number of sensations that they felt on the target side (left or right) while ignoring all others on the other side. At the completion of each block, the subject was required to report how many sensations were felt on the target side. All subjects were within the range of 25 ± 2 correct responses for target stimuli for each block. A 5 min baseline period was used prior to the start of each block in the task in order to provide for adaptation to the recording environment prior to the start of the experiment and to provide a rest break prior to the start of the second block.

Data averaging and analyses

EEG and EOG data were digitized on-line at a rate of 400 Hz (2.5 ms per sample) at all recording sites for all stimuli. Each trial consisted of a 1075 ms epoch commencing 75 ms prior to stimulus onset and ending 1000 ms thereafter. Each trial epoch was then filtered off-line using a Blackman filter with lopass set at 30 Hz. Epochs associated with targets and non-targets were then averaged separately for the Fz, Cz, Pz, and EOG sites. A computer algorithm corrected for the effects of EOG artifact during averaging on a point by point basis. All artifact contaminated EEG points (greater than 100 μV in the EOG) were replaced with the mean of the non-contaminated corresponding points of the respective (target or non-target) EEG trials for that individual. Less than 10% of all data points required correction. Using this method, all trials were retained for analyses.

A standard scoring procedure for event-related potentials is to use a peak detection algorithm to determine the particular event task basis for individual subjects.[16] To identify the P300 for each trial, the algorithm selected the data point with the most positive value occurring between 250–500 ms after stimulus onset. Dependent measures consisted of amplitude and latency values of the P300 obtained from the data points for target and non-target stimuli. Amplitude values were baseline corrected by subtracting the average activity value for the 75 ms prestimulus period from the obtained amplitude value.

Results

P300 amplitude data

Grand average ERPs, and standard deviations for target and non-target trials at each recording site are presented in Figure 1 and Table 1 for each group separately. The data generally show increased P300 ERP amplitude to target stimuli compared to non-targets. Additionally, the SCI groups exhibited attenuated P300s at all sites for both targets and non-targets compared to the control group. The data were subjected to a three-factor repeated measures analysis of variance (ANOVA) with group (control, paraplegic, tetraplegic) as the between subject factor and site (Fz, Cz, Pz) along with type (target, non-target) as the within subject factors. This analysis allowed us to test for P300 differences among the groups, among the recording sites and between the target and non-target averages. In addition, the in interactions of groups, sites and type of stimulus

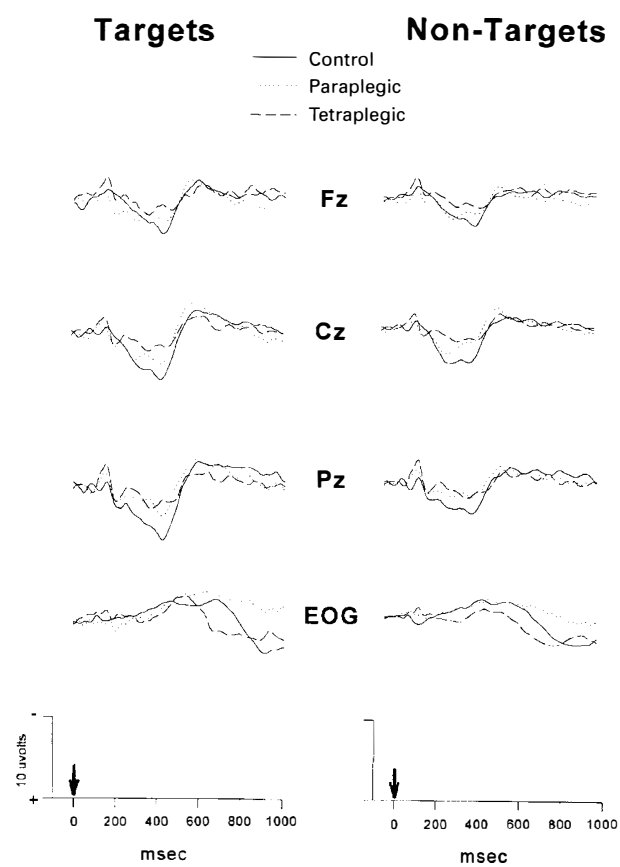

Figure 1 Grand average target and non-target ERPs for control, paraplegic, and tetraplegic groups at Fz, Cz, Pz and EOG sites. Arrow indicates stimulus onset

Table 1 Mean somatosensory P300 amplitude in uVolts at Fz, Cz and Pz for control, paraplegic and tetraplegic groups (SD in parentheses)

		Recording site mean P300 amplitude in uVolts SD in parentheses		
Group	*Type*	*Fz*	*Cz*	*Pz*
Control	Target	4.74	7.19	8.09
		(2.90)	(3.13)	(3.68)
	Non-target	3.96	5.37	4.65
		(2.29)	(3.42)	(2.52)
Paraplegic	Target	4.29	5.42	4.70
		(3.63)	(2.65)	(3.14)
	Non-target	2.94	3.12	2.84
		(2.30)	(2.39)	(2.18)
Tetraplegic	Target	2.65	3.20	4.21
		(3.31)	(2.32)	(2.34)
	Non-target	1.40	1.89	2.34
		(3.04)	(2.02)	(1.51)

(target and non-target) could be assessed. The 0.05 significance level was used for all comparisons and Huynh-Feldt corrections were applied to all repeated measures analyses.*

We found significant differences between groups, $F(2, 42) = 6.88$, $P = 0.003$; recording sites, $F(1.46, 61.24) = 7.05$, $P = 0.004$, and for stimulus type, $F(1, 42) = 58.58$, $P < 0.001$. The only two-way interaction that was significant was the site by type interaction, $F(1.9, 79.59) = 10.65$, $P = 0.002$. The three-way group by site by type interaction was also significant, $F(3.79, 79.59) = 4.21$, $P = 0.004$.

In order to understand the significant data points in the three-way interaction, the interaction was simplified according to the rules for analysing simple interactive effects.[17] The first step was to run separate two-factor ANOVAs (Groups X Recording Sites) on target and non-target trials separately. For the target trials, there were significant differences between groups, $F(2, 42)$, $P = 6.04$, $P = 0.005$, and recording sites, $F(1.26, 53.11) = 10.63$, $P = 0.001$. The group by recording site interaction for target trials approached significance, $F(2.53, 53.11) = 2.79$, $P = 0.058$. Newman-Keuls post-hoc analyses were calculated to determine exactly how the groups differed in amplitude of target trials. The tests showed that the control group produced significantly larger P300 amplitudes compared to the tetraplegic group, but the difference in P300 amplitude between the control group and the paraplegic group was not significant. The tetraplegic and paraplegic groups also did not differ from each other in P300 amplitude for the target trials. In terms of differences between recording sites for target trials, Newman-Keuls post-hoc analyses showed that the Fz site produced significantly smaller P300 amplitudes than did the Cz and Pz sites. There was no significant difference in P300 amplitude between the Cz and Pz sites.

A similar analysis for non-target trials resulted only in a significant group difference, $F(2, 42) = 6.44$, $P = 0.004$. Newman-Keuls analysis showed that the control group produced significantly larger P300 amplitudes compared to either the paraplegic or the tetraplegic groups. The two SCI groups did not differ in P300 amplitude from each other for non-target trials. The separate analyses for target and non-target trials showed, that in both cases, the control group had a significantly larger P300 than did the tetraplegic group. While the paraplegic group's P300 amplitude was between the control and tetraplegia group, the data were not statistically significant.

Previous studies have observed a linear increase in amplitude for the somatosensory P300 from anterior (Fz) sites to posterior (Pz) sites with maximal amplitude at the Pz recording site.[18,19] In view of this, the observation of reduced P300 amplitude at the Fz site relative to Cz and Pz for all groups in this study is not surprising. However, because the Pz and Cz recording sites did not differ significantly for the target trials in this study, we elected to further analyse the data from these two recording sites separately.

An ANOVA with group as the between subject factor and stimulus type (target *vs* non-target) as the within-subject factor was performed at the Cz recording site. We found a significant main effect for group, $F(2,42) = 8.03$, $P = 0.001$ and for stimulus type, $F(1,42) = 46.76$, $P < 0.001$. Newman-Keuls post-hoc analysis of the group main effect revealed that the control group produced significantly larger P300 amplitudes as compared to either the paraplegic or the tetraplegic, groups. The two SCI groups did not differ from each other. The significant main effect for type indicates that the P300 amplitudes for the target trials was significantly larger than those produced for the non-target trials at Cz for all groups.

A similar ANOVA procedure was also performed on the P300 amplitude data at the Pz site. Results showed significant effects for group, $F(2, 42) = 6.58$, $P = 0.003$; for type, $F(1, 42) = 84.95$, $P < 0.001$; and the group by stimulus type interaction, $F(2,42) = 4.13$, $P = 0.023$. Additional analysis indicated that the control group produced significantly larger P300 amplitudes to target trials compared to either the paraplegic group or the tetraplegic group. The two SCI groups did not differ from each other. Significant differences also emerged between groups for non-target trials at Pz, $F(2, 42) = 4.94$, $P = 0.0018$. Again, the control group again produced significantly larger P300 amplitudes for non-target trials at the Pz site compared to either the tetraplegic group or the paraplegic group. As with the target trials at Pz, the two SCI groups did not differ from each other for the non-target trials at Pz. We also found the target trials were significantly larger than the non-target trials for each of the groups;

*The Huynh-Feldt procedure corrects for certain assumptions of repeated measures analysis of variance. The correction makes it less likely to obtain a statistically significant outcome. The correction is automatically generated by the statistical program we used (BMDP).

Table 2 Mean somatosensory P300 latency in msec at Fz, Cz and Pz for control, paraplegic and tetraplegic groups (SD in parentheses)

		Recording site mean P300 latency in msec SD in parentheses		
Group	*Type*	*Fz*	*Cz*	*Pz*
Control	Target	328.1	319.7	338.4
		(47.8)	(57.3)	(55.1)
	Non-target	321.8	317.0	323.9
		(52.5)	(53.7)	(51.5)
Paraplegic	Target	309.4	313.5	327.4
		(46.8)	(38.8)	(34.6)
	Non-target	282.4	284.5	303.9
		(44.0)	(44.0)	(49.2)
Tetraplegic	Target	341.2	323.2	321.8
		(61.9)	(47.4)	(57.4)
	Non-target	334.3	322.5	326.7
		(61.6)	(52.3)	(51.1)

control, $F(1, 14) = 37.76$, $P < 0.001$; paraplegic, $F(1, 14) = 25.68$, $P < 0.001$; and tetraplegia, $F(1,14) = 22.28$, $P < 0.001$.

To summarize the results of the data at the primary Cz and Pz recording sites: all groups produced significantly larger somatosensory P300 amplitudes for target trials compared to non-target trials. In addition, the control group responded with significantly larger P300 amplitudes to both target and non-target stimuli as compared to either the paraplegic or the tetraplegic groups. The SCI groups did not differ from each other.

P300 latency data

Table 2 presents the means and standard deviations for the somatosensory P300 latencies for all groups at all sites for target and non-target trials. Analysis of variance revealed a significant main effect only for stimulus type, $F(1,42) = 6.08$, $P = 0.018$, indicating significantly longer latencies for target trials compared to non-target trials. It is very common to find that the P300 latency is longer to target stimuli. No other significant main or interaction effects emerged for the somatosensory P300 latency data.

Discussion

The primary findings in this study are that all groups maintained accurate target counts and produced larger amplitude P300 ERPs with longer latencies in response to target stimuli compared to non-target stimuli. Additionally, spinal cord injury patients produced significantly reduced P300 amplitudes compared to healthy controls. No significant latency differences among the groups were observed. Greater attenuation of the P300 was also apparent with higher injury levels (ie, P300 for those with tetraplegia is of smaller amplitude compared to those who were paraplegic).

The ability to maintain accurate target counts and to produce higher amplitude P300 ERPs with longer latencies in response to targets compared to non-targets (at least for the relatively easy task used in this study) indicate that spinal cord injured patients appear to retain intact selective attention and stimulus evaluation abilities. Reduced amplitude of the P300 in the SCI groups compared to the control group observed in this study at all recording sites is also in conformity with our previous orienting ERP study using auditory and visual stimuli which showed significantly reduced amplitude N1-P2 complexes in SCI groups.[12] We also have determined, that at least for auditory stimuli, sensory transmission, as measured by brain-stem auditory evoked potentials, is normal for the SCI population.[20]

The observation of reduced ERP amplitude in two separate tasks with two different sensory modalities suggests that central deafferentation due to spinal cord injury produces wide ranging effects involving more than localized somatosensory cortical changes. It is generally accepted that multiple brain regions and processes are responsible for the generation and propagation of the P300 ERP.[21] Although the exact generator sites have not been clearly identified, a number of different brain regions have been suggested and include subcortical and cortical brain regions such as hippocampus and amygdala,[22] various regions of the thalamus and basal ganglia,[23] and basal forebrain areas, particularly the nucleus basalis,[24] in addition to neocortex.[25] The observation in this study that all recording sites exhibited a uniformly reduced amplitude P300 in the SCI groups suggests that deafferentation due to SCI may be affecting fundamental cortical and/or subcortical P300 generator regions. We have established that the same P300 attenuation occurs in SCI groups in response to auditory stimulation in an 'oddball' paradigm[20] and preliminary analysis of data from an 'oddball' study of visual stimulation also indicates attenuated P300 ERPs. Such observations with multiple stimulus types supports the contention that a more globally acting process apart from somatosensory cortical changes, may be responsible for the reduced P300 ERP after SCI.

Although the SCI patients in this study were successful in maintaining accurate target counts and did produce higher P300 ERP amplitudes to target stimuli compared to non-targets, the observation of significantly reduced amplitude P300 ERPs in the SCI groups compared to controls in this study are also in agreement with prior behavioral studies that have shown a significant number of SCI patients exhibit memory deficits as well as problems with other cognitive functions.[26] Decreased memory functions in particular have been associated with lower P300 amplitude.[27] The potential association between specific cognitive deficits, including memory systems, and P300 changes in the SCI population remains to be investigated. An increased understanding of the neural systems responsible for the reduced amplitude P300 in the SCI population as well as ascertaining the

cognitive consequences of this reduction may lead to the development of enhanced or more effective rehabilitation programs for this population.

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