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Preattentive Sensory Processing as Indexed by the MMN and P3a Brain Responses is Associated with Cognitive and Psychosocial Functioning in Healthy Adults

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Abstract

Understanding the basic neural processes that underlie complex higher order cognitive operations and psychosocial functioning is a fundamental goal of cognitive neuroscience. Event-related potentials allow investigators to probe the earliest stages of information processing. Mismatch negativity (MMN) and P3a are auditory event-related potential components that reflect automatic sensory discrimination. The aim of the present study was to determine if MMN and P3a are associated with higher order cognitive operations and psychosocial functioning in clinically normal healthy subjects. Twenty adults were assessed using standardized clinical, cognitive, and psychosocial functional instruments. All individuals were within the normal range on cognitive tests and functional ratings. Participants were also tested on a duration-deviant MMN/P3a paradigm (50-msec standard tones, $p = .90$; 100-msec deviant tones, $p = .10$; stimulus onset asynchrony [SOA] = 505 msec). Across fronto-central electrode regions, significant correlations were observed between psychosocial functioning and MMN ($r = -.62$, $p < .01$) and P3a ($r = .63$, $p < .01$) amplitudes. P3a amplitude was also highly associated with immediate and delayed recall of verbal information with robust correlations widely distributed across fronto-central recording areas (e.g., $r = .72$, $p < .001$). The latency of the P3a response was significantly associated with both working memory performance ($r = -.53$, $p < .05$) and functional ratings ($r = -.48$, $p < .05$). Neurophysiological measures of relatively automatic auditory sensory information processing are associated with higher order cognitive abilities and psychosocial functioning in normal subjects. Efficiency at elementary levels of information processing may underlie the successful encoding, retrieval, and discrimination of task-relevant information, which, in turn, facilitates the iterative and responsive processing necessary for adaptive cognitive and social functioning.

INTRODUCTION

Understanding the basic neural processes that underlie complex higher order cognitive operations and functional domains is a fundamental goal of cognitive neuroscience. Event-related potentials (ERPs) allow investigators to probe sensory, perceptual, and cognitive processing with millisecond precision. This high temporal resolution lends itself to the study of the earliest stages of information processing and the subsequent transitions from sensory-based perceptual processing to the higher cognitive operations that are necessary to successfully navigate through the complex stimulus-laden environment of everyday life. Mismatch negativity (MMN) is an ERP component that reflects a largely automatic and preattentive form of sensory processing. The MMN wave is automatically generated when a sequence of “standard” repetitive stimuli (e.g., $p = .90$) is interrupted by infrequent (e.g., $p = .$

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10), deviant, “oddball” stimuli (e.g., stimuli that differ in duration or pitch from the more frequently presented “standard” stimuli). The MMN response onset occurs as early as 50 msec after oddball stimuli and peaks after an additional 100 to 150 msec. Physiologically, MMN is the first measurable brain response that differentiates deviant versus standard stimuli (Näätänen, Paavilainen, Alho, Reinikainen, & Sams, et al., 1989). MMN is not under subject control, requires no overt behavioral responses, can be elicited while subjects perform other mental activities in parallel without apparent interaction or interference, and is to a large extent unaffected by top-down information processing (Sussman, Winkler, & Wang, 2003; Rinne, Antila, & Winkler, 2001; Näätänen, 1992). Indeed, the mismatch response is evoked regardless of whether subjects are even remotely aware of subtle task-irrelevant deviant stimuli in the environment. In this context, it is striking that well-defined MMN waveforms can be obtained from fetuses using magnetoencephalography (Draganova et al., 2005), as well as from sleeping infants (Huotilainen et al., 2003; Cheour-Luhtanen et al., 1996; Alho, Sainio, Sajaniemi, Reinikainen, & Näätänen, 1990) and adults (Sabri & Campbell, 2002; Nashida et al., 2000), patients with severe brain injuries (Kaipio et al., 2001; Woods, Knight, & Scabini, 1993), and even comatose individuals who ultimately regain consciousness (Morlet, Bouchet, & Fischer, 2000; Fischer et al., 1999; Kane et al., 1996). Because MMN occurs even in the absence of conscious and effortful attention, it appears to index a preattentive form of sensory memory (Näätänen, 1992) that may “govern” some higher order physiological and behavioral cognitive operations in normal subjects (Tiitinen, May, Reinikainen, & Näätänen, 1994). A variety of complex MMN paradigms have also been developed to assess higher cognitive processes beyond simple auditory change detection (e.g., discrimination of abstract sound patterns, sorting of multichannel input into sources, temporal grouping, anticipation of sounds; cf., Näätänen, Tervaniemi, Sussman, Paavilainen, & Winkler, 2001).

At fronto-central electrodes, the MMN wave is often followed by a positive-going ERP component that peaks at 250 to 300 msec. This P3a component is thought to reflect an automatic reorienting or shifting of attention. Typically, the P3a is elicited in response to occasional “distractor” stimuli when the subject is actively trying to detect in-frequent target stimuli (e.g., of a different pitch) embedded in a stream of frequently presented standard stimuli (Turetsky et al., 2007; Polich & Criado, 2006; Rinne, Sarkka, Degerman, Schroger, & Alho, 2006; Dien, Spencer, & Donchin, 2004; Katayama & Polich, 1998; Näätänen, 1992; Grillon, Courchesne, Ameli, Geyer, & Braff, 1990; Braff, Callaway, & Naylor, 1977; Squires, Squires, & Hillyard, 1975). Unfortunately, the corresponding cognitive process associated with the P3a waveform is not as well understood in the context of a traditional passive MMN experiment where attention is commonly directed away to some other task such as watching a silent video.

MMN has many uses for basic cognitive neuroscience and clinical science (Näätänen, 2003; Michie, 2001; Gene-Cos, Ring, Pottinger, & Barrett, 1999). First, MMN can be rapidly assessed and is highly stable over time (Light & Braff, 2005b; Kujala, Kallio, Tervaniemi, & Näätänen, 2001; Kathmann, Frodl-Bauch, & Hegerl, 1999; Pekkonen, Rinne, & Näätänen, 1995). Second, because the mismatch response appears to reflect a predominantly automatic process, it allows investigators to interrogate the earliest stages of information processing free of attentional and motivational artifacts that may confound the assessment of some higher cognitive operations in clinical populations such as schizophrenia patients (Braff & Light, 2004).

Many studies have convincingly demonstrated that patients with schizophrenia have robust deficits in MMN (cf. Turetsky et al., 2007; Umbricht & Krljes, 2005; Michie, 2001) and P3a (e.g., Mathalon, Ford, & Pfefferbaum, 2000; Turetsky, Colbath, & Gurr, 1998; Grillon et al., 1990). MMN deficits appear to be specific to schizophrenia relative to many other severe and persistent mental illnesses such as bipolar, major depressive (Umbricht et al., 2003; Catts et al., 1995), and obsessive-compulsive disorders (Oades, Dittmann-Balcar, Zerbin, & Grzella, 1997; Oades, Zerbin, Dittmann-Balcar, & Eggers, 1996; Towey et al., 1994). Remarkably,

MMN deficits in schizophrenia patients are highly associated with patients' impairments in daily functioning, level of independence in their community living situation, and functional outcome (Kiang et al., 2007; Kawakubo & Kasai, 2006; Light & Braff, 2005a, 2005b). Across studies, schizophrenia patients with more severe functional impairments had relatively smaller (i.e., less negative) MMNs than higher functioning patients. Specifically, we recently (Light & Braff, 2005a) reported that tone-duration MMN deficits in schizophrenia patients were highly associated (r = -.65) with clinician ratings of global daily functioning in 25 chronic schizophrenia patients and that the MMN functioning correlation followed the same fronto-central topographic distribution as MMN deficits in schizophrenia patients. In a related study of patients longitudinally assessed during a 15-month interval, we (Light & Braff, 2005b) confirmed that the MMN deficits in schizophrenia were highly associated with ratings of functional status at both the first (r = -.63) and second (r = -.68) test sessions, indicating that the MMN functioning relationship is stable even across relatively long time intervals. This association of MMN and functional deficits in schizophrenia patients has been replicated and extended by an independent research group, where a relationship was observed between functional deficits and MMN in response to a duration change of Japanese speech sounds (r = -.53; Kawakubo & Kasai, 2006). Other studies of schizophrenia patients have found that MMN is associated with verbal memory deficits (Kawakubo et al., 2006; Baldeweg, Klugman, Gruzelier, & Hirsch, 2004), executive functioning (Kiang et al., 2007), and the degree of social skills acquisition following 3-month training program (Kawakubo et al., 2007). To our knowledge, however, the relationships between automatically elicited ERP components and both cognitive and functional measures in nonclinical populations have not been previously reported. Thus, the hypothesis of the present study was that MMN and P3a indices of automatic sensory discrimination would be significantly associated with measures of higher cognitive operations and psychosocial functioning in healthy, nonpsychiatric, normally functioning individuals.

METHODS

Subjects

Subjects included 20 consecutively enrolled nonpsychiatric participants (11 men and 9 women; mean age ± *SD* = 35.9 ± 11.5 years) recruited through newspaper advertisements and fliers posted at the University of California, San Diego (UCSD) medical center after standard procedures of the UCSD Schizophrenia Program from June 2004 to January 2005. All participants were assessed as being capable of providing informed consent. After complete description of the study to the subjects, written informed consent was obtained using methods approved by the UCSD Institutional Review Board (030510 and 040564). Individuals were not pre-selected based on their community functioning, cognitive, or neurophysiological data. All subjects received a urine toxicology screen to rule out recent drug use and were assessed using the *Structured Clinical Interview for DSM-IV* to ensure that they did not have an Axis I (First, Spitzer, Gibbon, & Williams, 1996) or II (First, Spitzer, Gibbon, Williams, & Benjamin, 1996) diagnosis, including substance abuse or dependence within the past 6 months. In addition, subjects were not included if they had a history of neurological insult, such as significant head trauma and/or loss of consciousness in accordance with our established screening methods (Light et al., 2006; Swerdlow et al., 2006; Light & Braff, 2005a, 2005b). Audiometric testing was used to ensure that all participants had normal hearing and were able to detect 40-dB tones at 1000 Hz (mean ± *SD* = 12.8 ± 6.1 dB). All subjects had completed at least 12 years of formal education (mean ± *SD* years completed = 15.7 ± 2.1 years) and had Wide Range Achievement Test 3 (WRAT3) Reading scores within the normal range (mean ± *SD* = 108.7 ± 10.6).

Assessment of Global Functioning

A modified Global Assessment of Functioning (GAF) Scale (Hall, 1995) was used for assessing participants' overall level of functional status across psychological, social, and occupational domains via an anchored measure in accordance with previously published methods (McGlashan et al., 2003, 2006; Miller et al., 2003; Hall, 1995). This modified form of the GAF has a structured scoring system with detailed anchors describing functional behaviors. Because of the enhanced structure, the modified GAF yields higher intraclass correlation coefficients and may also be more resistant to rater bias than the original GAF (Hall, 1995). Indeed, the interrater reliability of the modified GAF conducted in our laboratory was very high (intraclass correlation coefficient = .96, $p < .001$) and significantly correlated with the original GAF ($rs > .73$-$.82$, $p < .05$). All ratings were performed by a PhD-level clinical study recruiter/diagnostician in the context of the *Structured Clinical Interview for DSM-IV Axis I and Axis II* assessments. The rater was blind to the neurophysiological recordings and cognitive data. The nonpsychiatric participants of this study were asymptomatic, high functioning, and performed within the normal range on all cognitive measures (Table 1).

Cognitive Assessments

The WRAT3 reading subtest was used to assess single-word reading ability (Wilkinson, 1993). Verbal memory was assessed via the California Verbal Learning Test II (CVLT-II) using the List A 1-5 total score to assess immediate recall, long-delay free recall to measure the verbal recall of words during a 20-minute interval, and recognition discriminability to index the ability to detect whether a word was previously presented (Delis, Kramer, Kaplan, & Ober, 2000). Perseverative responses and number of categories completed on the Wisconsin Card Sorting Test-64 (WCST-64) were used to assess concept formation and conceptual flexibility (Heaton, 1993). Performance on the Letter-Number Sequencing (LNS) test was used to assess the immediate on-line storage and repetition of auditory information (forward condition) as well as working memory via manipulation and retrieval of stored information (reordering condition; Perry et al., 2001; Gold, Carpenter, Randolph, Goldberg, & Weinberger, 1997; Wechsler, 1997).

Event-related Potentials

Electroencephalograph (EEG) data acquisition, stimulation, and processing was performed in accordance with previously published methods (Light & Braff, 2005a,2005b). Briefly, EEG was recorded with a NuAmps system (Neuroscan Labs, El Paso, TX) using sintered Ag/AgCl electrodes arranged in a cap (EasyCap, Herrsching-Breitbrunn, Germany) at the following 34 equidistant positions: Fp1, Fp2, Fz, F3, F4, F7, F8, FC1, FC2, FC5, FC6, Cz, C3, C4, CP1, CP2, CP5, CP6, Pz, P3, P4, P7, P8, O1, O2, PO9, PO10, Iz, T1, T2, T7, T8, TP9, and TP10. Electrodes placed at the tip of the nose and at Fpz served as the reference and ground, respectively. EEG was digitally re-referenced off-line to linked mastoids (TP9/TP10). Four additional electrodes placed above and below the left eye and at the outer canthi of both eyes were used for identifying blinks and eye movements. All impedances were less than 4 kΩ. Signals were digitized at a rate of 1 kHz with system filter settings at 0.5 to 100 Hz. Subjects were presented with binaural stimulation (1-kHz computer-generated square-wave stimuli, 85 dB sound pressure level [SPL]) with a fixed stimulus onset-to-onset asynchrony of 505 msec. Standard ($p = .90$; 50-msec duration) and deviant ($p = .10$; 100-msec duration) stimuli were presented to subjects in pseudorandom order while subjects watched a silent video. Subjects were instructed to pay careful attention to the video as they may be asked questions about it at the end of testing.

During testing, on-line ERP averages to standard and deviant tones were also acquired to monitor signal quality and track the number of sweeps free of gross artifact (±100 μV across the -100 to 500 msec following stimuli). Recording was terminated when a minimum of 225

artifact-free deviant trials were collected. Data processing was performed off-line using automated procedures by an experienced research technician who was blind to the psychosocial ratings and cognitive performances. First, continuous recordings were mathematically corrected for eye movement artifact (Semlitsch, Anderer, Schuster, & Presslich, 1986). Continuous data were epoched relative to the onset of stimuli (-100 to 500 msec) and centered at the mean of the prestimulus baseline. After blink correction, epochs containing more than ±50 μV in frontal recording sites (F7, F8, F3, F4, and Fz) were automatically rejected (accepted deviant sweeps mean ± *SD* = 271.5 ± 49.8). MMN waveforms were generated by subtracting ERP waveforms in response to standard tones from the ERPs generated in response to the deviant tones. The resultant MMN subtraction waveforms were low-pass filtered at 20 Hz (zero-phase shift, 24-dB/octave roll-off) to remove any residual high-frequency artifact. The peak latencies and mean amplitudes of MMN and P3a were calculated across the 135- to 205-msec and 250- to 300-msec latency ranges.

Statistical Analyses

Well-defined MMNs and P3a responses were present in all subjects and verified by inspection of butterfly plots and mean global field power peaks across the 100- to 300-msec region (Figure 1) that were at least twice the magnitude of any activity in the 100 msec before stimulus onset (Light & Braff, 2005a). For both MMN and P3a, the largest responses were evident at electrode Fz (see Figure 2 for individual waveform averages obtained from electrode Fz). Thus, Pearson's correlation analyses were initially restricted to electrode Fz to reduce the likelihood of identifying spurious relationships from multiple pairwise correlations. If a significant correlation was observed at Fz, topographic correlational plots were performed to examine the distribution and spread of the association. To further minimize the likelihood of Type I errors that could occur from performing multiple statistical tests, correlations were deemed significant only if observed associations accounted for at least 30% of the variance at Fz and multiple adjacent electrodes were also significant.

RESULTS

MMN amplitude was significantly associated with GAF ratings at several fronto-central electrodes with the largest correlation at Fz (r = -.62, p = .004; Figure 3). In contrast to the observed correlation with functional ratings, MMN was not significantly associated with any of the neurocognitive test performances (Table 2). Like the MMN, the P3a was also significantly associated with GAF ratings with the largest correlation at electrode Fz (r = .63, p = .003; Figure 4), where the response is largest. P3a amplitude was significantly associated with performance on tests of verbal memory but not with measures of word reading and pronunciation, immediate attention, working memory, or perseverative thinking (Table 2). As shown in Figure 5, the correlations between P3a and verbal memory measures were not largest at Fz but extended to more central electrodes (e.g., electrode FC1 CVLT-II List A total: r = .72, p < .001; delayed recall: r = .55, p < .05; recognition discriminability: r = .58, p < .01). Whereas the peak latency of MMN was not significantly associated with any cognitive or functional measures, latency of the P3a was significantly associated with both working memory performance (r = -.53, p < .05) and functional ratings (r = -.48, p < .05).

DISCUSSION

The results of the present study demonstrate that neurophysiological measures of automatic auditory change detection are associated with higher order cognitive and psychosocial functioning in normal adults. Although MMN and P3a were both associated with psychosocial functioning, the P3a component was also strongly linked to the successful higher order

encoding, retrieval, and discrimination of previously presented verbal information. In addition, the latency of the P3a was significantly correlated with working memory performance.

Although MMN is presumed to reflect the automatic and preattentive detection of change in a repetitive stream of information, the subsequent P3a component is not as well understood in the context of typical MMN studies. Nonetheless, MMN and P3a as used in the present study were elicited in response to unattended task-irrelevant stimuli. It is remarkable that these elementary components of basic sensory information processing accounted for up to 52% of the variance in verbal memory performance and 40% of the variance in clinician ratings of psychosocial functioning. Associations of this magnitude and topographic distribution across scalp regions (e.g., Figures 3-5) where the neurophysiological components are usually largest are unlikely to be because of chance alone or attributable to Type I error. Indeed, the present findings of an association of MMN and psychosocial functioning in normal subjects also parallel results previously obtained in studies of schizophrenia patients (Light & Braff, 2005a,2005b) in both the strength of association (explaining ~40-50% of variance) and distribution across scalp regions (i.e., fronto-central electrodes). This equivalence of associations across groups and studies is striking, because the present sample of healthy, nonpsychiatric subjects performed within the normal range on all of the functional and cognitive measures. Despite these normal performances, the subjects still exhibited enough range to reveal robust associations among disparate measures (i.e., EEG, cognitive, and functional).

These data indicate that early central nervous system information processing in clinically normal individuals is strongly associated with cognitive and real-world psychosocial functioning. The profound deficits of early information processing and daily functioning in schizophrenia patients might be expected to be linked to some underlying pathology within brain mechanisms linked to memory or other systems that appear to contribute to the overall pattern of results. Thus, MMN and P3a reflect processes that both contribute to interindividual variance in normal populations and are sensitive to neurobiological disturbances linked to schizophrenia (cf. Braff & Light, 2005). Finer parsing of domains of functioning may reveal that measures of early information processing are associated with distinct aspects of normal function in healthy subjects (e.g., work satisfaction) versus more pathological components of functioning in schizophrenia patients (e.g., inability to tolerate interactions with others). This finer parsing of function is currently being investigated to assess the contribution of early information processing abnormalities to the cognitive and functional impairments of patients with schizophrenia.

In conclusion, the results of the present study demonstrate an intriguing relationship of basic sensory processing with higher order measures of learning and memory and psychosocial functioning in healthy individuals. It is conceivable that the neural substrates that regulate automatic monitoring and detection of environmental changes trigger a cascade of higher order processing. The outcome of this cascade might be a determination of whether environmental cues are salient and in need of further processing versus trivial, allowing for suppression and inattention in accordance with classic information processing theories (Johnston & Heinz, 1978; Norman, 1968; Broadbent, 1965; Deutsch & Deutsch, 1963; Treisman, 1960; Broadbent, 1958; Cherry, 1953). Efficiency at such elementary neurophysiological levels can free up attention-dependent, controlled cognitive resources for the successful encoding, retrieval, and discrimination of task-relevant information, which, in turn, facilitates the iterative and responsive processing necessary for adaptive cognitive and social functioning (cf., Bazana & Stelmack, 2002; Näätänen et al., 2001). Additional studies are needed to determine if the relationships observed in the present study extend to other cognitive domains that were not assessed (e.g., visual memory). Future investigations are also needed to delineate the neural

circuitry that underlies the neurophysiological processes that contribute to “downstream” integrative cognitive and functioning.

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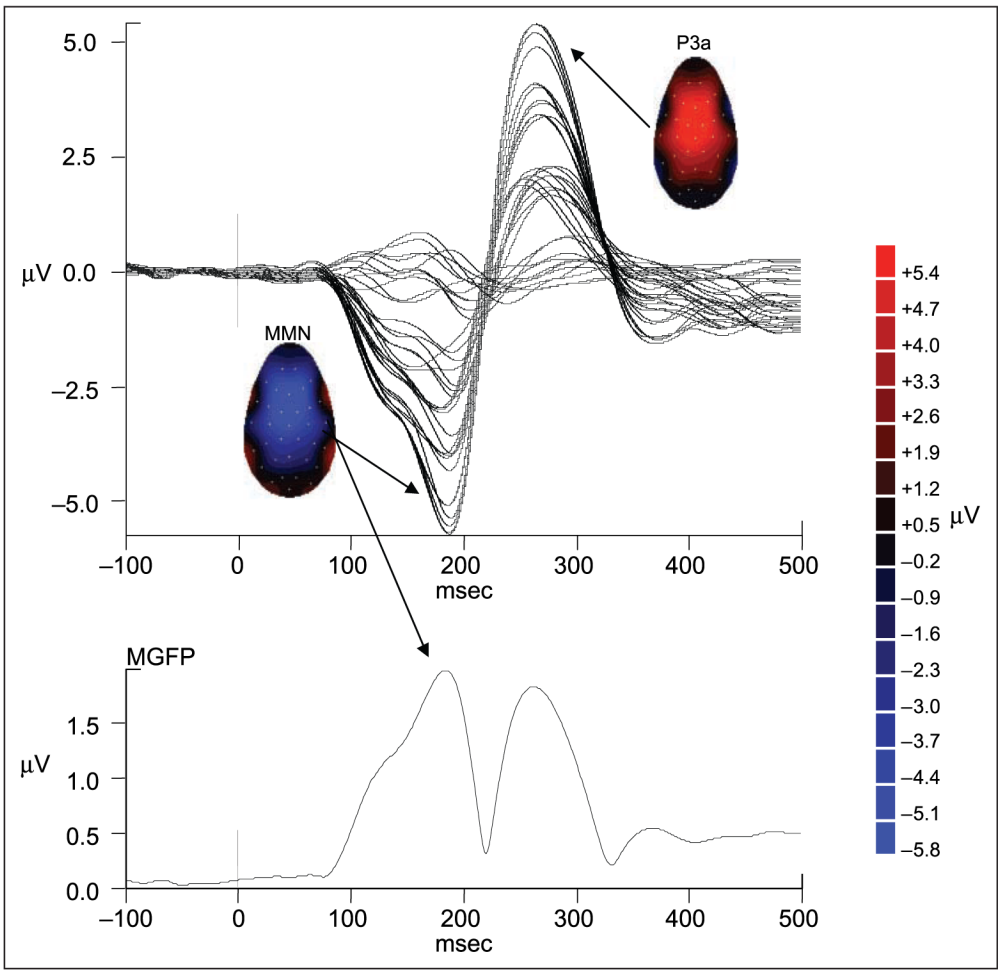

Figure 1.

Butterfly plot and mean global field power (MGFP) of grand average ERPs. The “butterfly” plot overlays the grand average responses from all electrodes to evaluate the mean global field power (MGFP, lower) of the MMN and P3a responses. Both MMN and P3a are large signal-to-noise ratio components with maximal responses occurring at Fz (see Figure 2 for the waveforms obtained from each subject at electrode Fz) as shown in the topography maps.

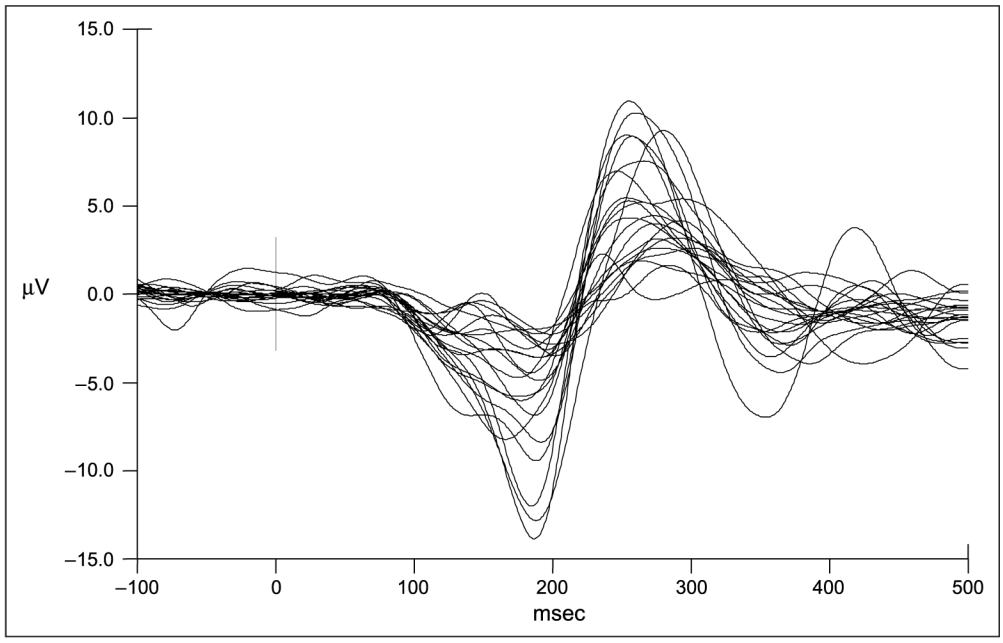

Figure 2.
Averages from each participant. This figure shows the individual waveform averages (electrode Fz) obtained from each of the participants in the study.

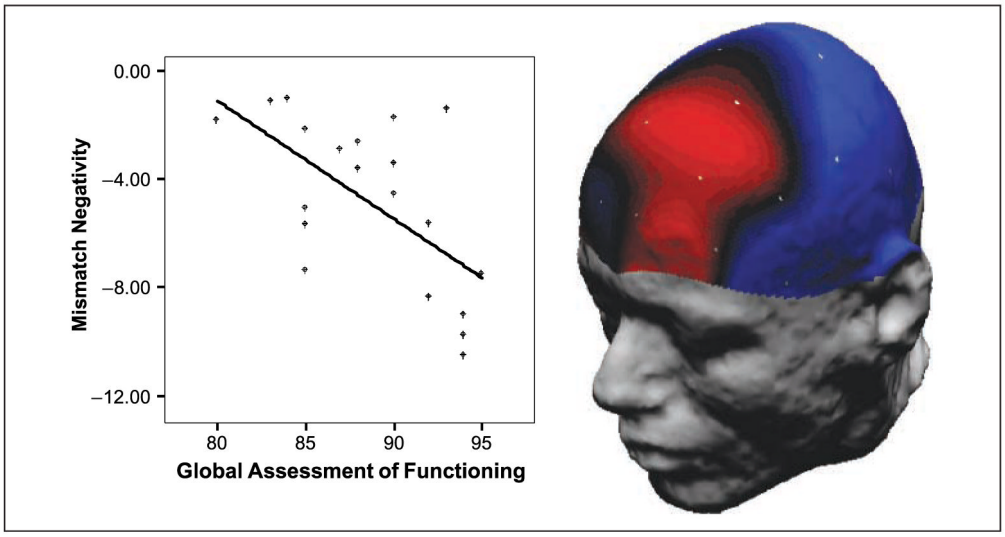

Figure 3.

MMN is associated with ratings of psychosocial functioning. (Left) Scatterplot between MMN and functional ratings at electrode Fz. (Right) Topography of the correlation plotted across electrode sites. Blue regions are considered nonsignificant, accounting for less than 30% of the variance between measures. Red and black indicate significant correlations at fronto-central electrodes.

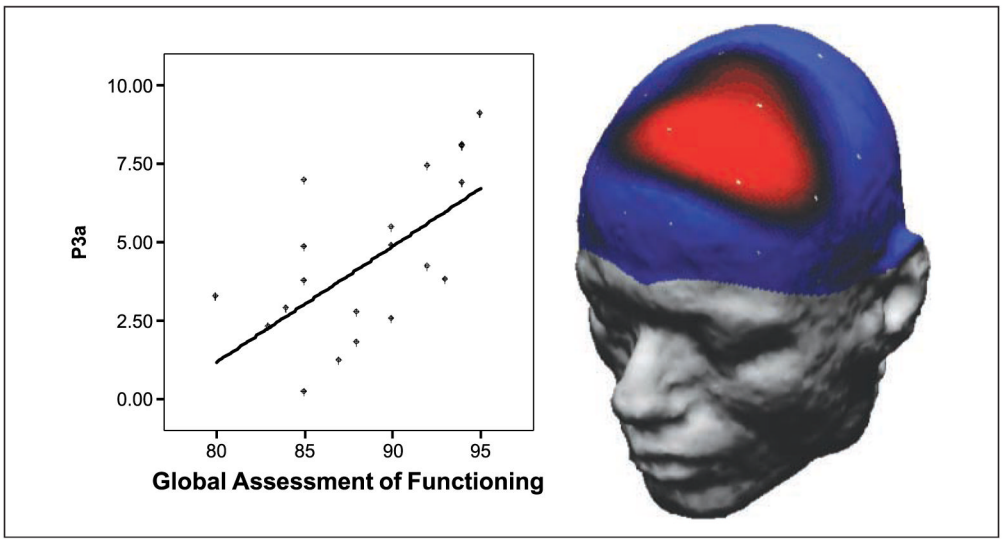

Figure 4.

P3a is associated with ratings of psychosocial functioning. (Left) Scatterplot between P3a and GAF ratings at electrode Fz. (Right) Topography of the correlation plotted across electrode sites. Blue regions are considered nonsignificant, accounting for less than 30% of the variance between measures. Red and black indicate significant correlations at fronto-central electrodes.

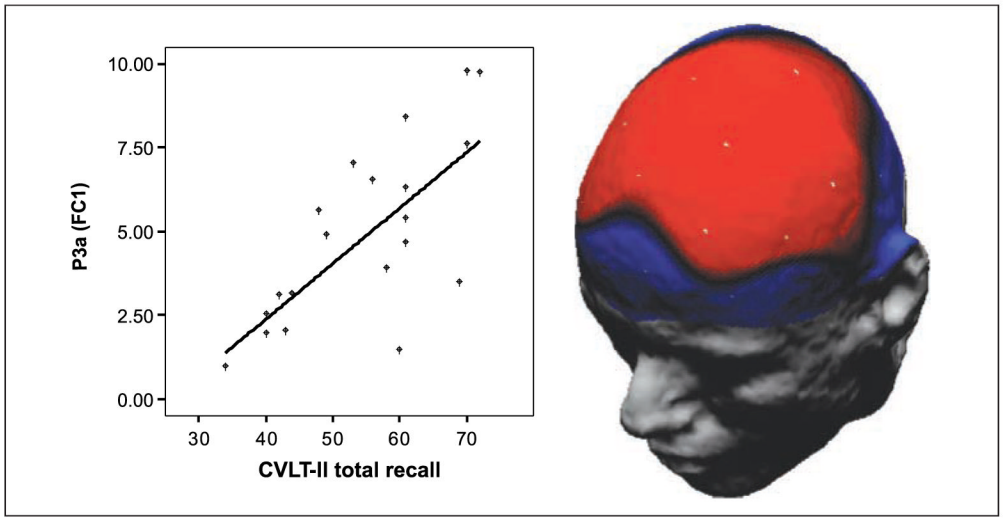

Figure 5.

P3a is associated with verbal memory performance. (Left) Scatterplot of P3a and CVLT-II List A, total recall ratings at electrode FC1 ($r = .72$, $p < .001$). (Right) Topography of the correlation plotted across electrode sites. Blue regions are considered nonsignificant, accounting for less than 30% of the variance between measures. Red and black indicate significant correlations at fronto-central electrodes.

Table 1
EEG Variables and Cognitive Performances

	Mean	***SD***
MMN		
Mean amplitude (135-205 msec)	-4.92	3.07
Peak latency	184.55	13.23
P3a		
Mean amplitude (250-300 msec)	4.39	2.53
Peak latency	267	16.62
WRAT3		
Reading standard score	108.74	10.22
Reading total score	51.89	4.85
LNS		
Forward	15.00	3.48
Reorder	11.80	3.23
Reorder scaled score	11.50	3.52
WCST-64		
Perseverative responses	8.55	4.83
Perseverative responses *T* score	49.21	8.05
Categories completed	3.35	1.50
CVLT-II		
Total recall	54.60	11.53
Total recall *T* score	54.85	10.55
Delayed recall	11.90	2.88
Delayed recall scaled score	0.18	0.75
Recognition discriminability	3.24	0.72
Recognition scaled score	0.13	0.89
Modified GAF scale	88.7	4.32

Table 2

Correlations of MMN and P3a (Electrode Fz) with Cognitive and Functional Variables

	MMN	***P3a***
WRAT3		
Reading total score	0.01	0.20
LNS		
Forward	0.37	0.22
Reorder	-0.12	-0.22
WCST-64		
Perseverative responses	0.07	-0.06
CVLT-II		
Total recall	0.08	0.64**
Delayed recall	-0.11	0.45*
Recognition discriminability	-0.35	0.52*
Modified GAF scale	-0.62**	0.63**

* $p < .05$.

** $p < .01$.