ORIGINAL ARTICLE

Mismatch Negativity Deficits Are Associated With Poor Functioning in Schizophrenia Patients

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Background: Schizophrenia patients exhibit widespread deficits in many domains, ranging from abnormalities in preattentional sensory processing to gross impairments in everyday functioning. Mismatch negativity (MMN) is an event-related potential measure that occurs in the absence of directed attention. While many studies have reported MMN deficits in schizophrenia patients, little is known about the functional significance of MMN deficits in schizophrenia patients.

Objective: To determine if a schizophrenia-linked deficit in MMN, an "automatic" preattentional measure, is associated with impairments in everyday functional status, level of independence in living situation, and the ability to perform tasks routinely encountered in everyday situations.

Setting and Participants: Twenty-five patients with a *DSM-IV* diagnosis of schizophrenia recruited from inpatient and outpatient community facilities affiliated with the University of California, San Diego, and 25 healthy, nonpsychiatric, comparison subjects.

Main Outcome Measures: Mismatch negativity, clinical symptoms, performance on a multidimensional laboratory-based functional skills assessment battery, clinician ratings on the Global Assessment of Functioning Scale, and level of independence in community living situation.

Results: Schizophrenia patients had significantly reduced MMN ($P<.001$). Greater levels of MMN impairment were associated with lower Global Assessment of Functioning Scale ratings. Consistent with clinical ratings, patients with greater MMN impairments were more likely to live in highly structured vs independent settings. A regional analysis of MMN revealed that the largest correlations of MMN to everyday functioning were present at frontocentral recording sites (eg, $r_s=-0.65$). In contrast, MMN deficits were not associated with symptom severity or performance on laboratory-based tasks measuring skills that are often considered necessary for independent living.

Conclusions: This pattern of results suggests that MMN deficits represent a core neurophysiological dysfunction that is linked to global impairments in everyday functioning in schizophrenia patients. These deficits in automatic preattentive information processing account for up to 42% of the variance in global functional status in schizophrenia patients. Thus, basic preattentional cognitive deficits may be excellent measures for predicting functional outcome. Longitudinal studies are needed to better understand the relationships between deficits in automatic sensory information processing, associated neural substrate dysfunctions, and deficits in everyday functioning across the course of the illness.

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PATIENTS WITH SCHIZOPHRENIA exhibit widespread deficits in many domains that range from abnormalities in basic sensory registration and processing[1-4] to impairments in higher cognitive operations, such as sustained attention, processing speed, working memory, verbal memory, and executive functioning.[5] Traditional neuropsychological tests are moderately robust predictors of everyday functioning in schizophrenia patients.[6,7] Performance on these tests is optimal when patients are maintaining persistent intellectual focus, energy, or effort over time to effectively and productively complete the tasks.[8,9] Although neuropsychological test performance is stable over time in schizophrenia patients,[5] individual performance may be significantly affected by the extent to which the cognitive tests seem to require these conative (ie, effortful) features.[10]

In contrast to neuropsychological tests, some neurophysiological measures probe the earliest stages of cognition (eg, basic sensory registration, discrimination, habituation, and inhibition), are automatically elicited, and require little or no effort, attention, engagement, or even awareness on the part of the subject.[8,11] Deficits in such elementary sensory processes could underlie clinical symptoms and putative downstream deficits in more

complex cognitive operations and real-life functioning[8,12-15] or may directly relate to real-life functioning independent of symptoms and higher-order, effortful, cognitive processes.

Event-related potential (ERP) measures allow investigators to quantify the neuronal processing associated with sensory and cognitive events with excellent temporal (ie, millisecond range) resolution. Cortical ERPs (latency, 50-150 milliseconds) reflect stimulus-dependent processing within sensory-specific cortical regions.[16] Mismatch negativity (MMN) is an auditory ERP component that is elicited when a sequence of repetitive standard sounds is interrupted infrequently by deviant "oddball" stimuli (eg, infrequent stimuli that differ in duration or pitch from the more frequently presented stimuli). The MMN occurs rapidly: following deviant stimuli, the response onset can be as early as 50 milliseconds and peaks after an additional 100 to 150 milliseconds. Physiologically, MMN is the first measurable brain response component that differentiates between frequent and deviant auditory stimuli and reflects the properties of an automatic, memory-based, comparison process.[17]

In the auditory domain, maximal mismatch responses are evident at frontocentral scalp recording sites, with phase reversal at posterior scalp electrodes (eg, mastoids).[11] Magnetoencephalography, high-density electroencephalography, functional imaging, and studies of patients with discrete brain lesions indicate that the auditory MMN is generated within the primary and secondary auditory cortices with probable contributions from bilateral, dorsolateral prefrontal cortices.[18-28] In addition, MMN is often used to probe frontotemporal brain systems across a range of developmental and neuropsychiatric disorders.[29-35]

Mismatch negativity has many advantages for psychiatric and cognitive neuroscience studies, including the exploration of the neural substrates of schizophrenia and its treatment.[34,36,37] First, MMN can be rapidly assessed and has test-retest reliability coefficients (range, 0.60-0.80; particularly using oddball stimuli that differ in duration)[38-40] that are comparable to many widely used behavioral neurocognitive measures.[41,42] Second, the mismatch response seems to reflect a predominantly automatic process: it is not under subject control, requires no overt behavioral response from subjects, and can be elicited while subjects perform other mental activities in parallel without apparent interaction or interference.[11] In this context, well-defined MMN waveforms can be obtained from sleeping infants,[43-45] adults,[46,47] patients with extremely severe brain injuries, and even comatose patients.[32,48,49] Since MMN occurs even in the absence of conscious and effortful attention, it seems to index a form of preattentive sensory (echoic) memory.[11] While later ERP components occurring 300 to 500 milliseconds after stimulus presentation (eg, P3b) are also sensitive to changes in stimulus characteristics and sequencing, they are only elicited in response to attended stimuli and are, therefore, associated with attention-dependent and active cognitive processes. Attention-dependent cognitive functions assessed by traditional neuropsychological tests or long-latency ERP methods (eg, P3b) can be markedly influenced by motivational factors, level of task engagement, performance incentives, self-monitoring, and emotional factors.[9,10,50-53] In contrast, preattentional cognitive measures such as MMN offer promise for accurately characterizing the integrity of sensory network dysfunction free of attentional or motivational artifacts in studies of neuropsychiatric patient populations.[8,34]

Third, deficits in MMN represent a remarkably robust finding in schizophrenia research. Shelley et al[3] identified MMN deficits in schizophrenia patients using deviant stimuli that differed in duration (ie, duration MMN) from standard stimuli. Since then, there have been several published reports of reduced MMN in schizophrenia patients using various stimulation parameters (pitch, duration, and intensity stimulus manipulations) and conditions (active-attend vs passive-ignore deviant stimuli).[36] Duration-deviant MMN deficits are also relatively specific to the disorder of schizophrenia as opposed to bipolar disorder, major depression,[54,55] and obsessive-compulsive disorder.[56-58] In schizophrenia patients, MMN deficits do not seem to be ameliorated by first-generation antipsychotic medications,[59] risperidone,[60] or clozapine.[23,59] Similarly, clinical changes from acute to post-acute illness do not correspond to a normalization of MMN deficits in patients with chronic disease.[61] In contrast to studies of patients with chronic schizophrenia, normal-range MMNs have been reported in first-episode patients,[62] with preliminary data indicating that MMN deficits emerge in concert with progressive temporal lobe volume loss that occurs early in the course of the illness (Dean Salisbury, PhD, oral communication, 2004).

Fourth, previous studies have demonstrated that *N*-methyl-D-aspartate (NMDA) dysfunction may play a crucial role in schizophrenia-related deficits in MMN. *N*-methyl-D-aspartate receptor antagonists selectively diminish MMN generation in awake monkeys,[63] and subanesthetic doses of ketamine hydrochloride, an NMDA antagonist, selectively decrease MMN in healthy human volunteers without affecting other ERP activity.[64] Umbricht et al[65] also found that lower baseline MMN was significantly associated with psychotic behavioral effects and experiences induced by subsequent ketamine administration. Thus, MMN may serve as a neurophysiological assay of NMDA receptor functioning in models of schizophrenia.

Finally, clinically unaffected family members of schizophrenia patients[66,67] and children at risk for developing schizophrenia[68] have reduced MMN amplitudes. Thus, MMN seems to represent a specific trait-related endophenotype[67] for studying the complex genetics of schizophrenia.[69] From a broad clinical perspective, MMN may be useful for assessing the everyday functional correlates of deficits in automatic frontotemporal information processing in schizophrenia.[8]

While several studies have examined MMN deficits in schizophrenia patients, little is known about the functional correlates and consequences of this (and other) early sensory information processing deficits (eg, gamma band entrainment, prepulse inhibition, and P50 ERP suppression). In contrast, other measures of cognition using neuropsychological tests, which may be dependent on effort or conation, have been extensively studied regarding their correlations with functional outcome.[70,71] This study

was conducted to determine if a deficit in the processing of deviant vs frequent auditory stimuli is associated with indexes of functioning and symptom severity in a heterogeneous sample of schizophrenia patients. Specifically, we sought to determine if MMN deficits are associated with (1) clinician ratings of functioning, (2) level of independence in living situation, and (3) performance on a multidimensional functional skills assessment battery designed for use in severely mentally ill adult populations.[72] We hypothesized that greater MMN impairment would be associated with relatively lower levels of functional status and reduced performance on laboratory-based measures of functional capacity in schizophrenia patients.

METHODS

SUBJECTS

Subjects consisted of 25 schizophrenia patients and 25 healthy comparison subjects. All participants were assessed on their capacity to provide informed consent, and after subjects were given a detailed description of their participation in the study, written consent was obtained via the following methods approved by the University of California, San Diego (UCSD), institutional review board (No. 030510 and 020394). All subjects underwent a urine toxicology screen to rule out recent drug use. In addition, schizophrenia patients were assessed using the Structured Clinical Interview for *DSM-IV*,[73] and were carefully screened to ensure that they did not have an Axis I diagnosis other than schizophrenia and had not experienced a neurologic insult, such as significant head trauma and/or loss of consciousness.

Healthy comparison subjects were recruited through newspaper advertisements and flyers posted at the UCSD medical center. All subjects underwent screening interviews[74] to rule out past or present Axis I or II diagnoses or drug abuse. Audiometer testing (model SCR2; Saico, Assens, Denmark) was used to ensure that all participants had normal hearing in both ears and could detect 45-dB sound pressure level tones at 500, 1000, and 6000 Hz. There were no statistically significant differences in hearing thresholds between the schizophrenia patients and nonpsychiatric comparison subject groups or significant correlations between hearing thresholds and dependent measures.

The schizophrenia patients were recruited from community residential facilities and via physician referral. All patients were clinically stable, with most prescribed psychotropic and nonpsychotropic medications. Most patients were prescribed second-generation antipsychotic medications (n=21); 3 patients reported not taking antipsychotic medications in at least the 7 days before testing. Eleven patients were living in board-and-care facilities; 14 patients were living independently or with their family at the time of testing. Patients were diagnosed as having the following subtypes: paranoid (n=8), undifferentiated (n=8), disorganized (n=6), and residual (n=3). **Table 1** contains demographic and clinical information. While the schizophrenia patients were significantly older (Table 1), age was not significantly associated with MMN in the schizophrenia patients (r_s = 0.23, P = .26). The patients also had significantly fewer years of education (Table 1), a common observation in schizophrenia research. There were no statistically significant (*P*=.77) differences in the proportion of men and women in each group.

In the schizophrenia patients, clinical symptoms were assessed with the Scale for the Assessment of Negative Symptoms[75] and the Scale for the Assessment of Positive Symptoms.[76] A disorganized symptom summary score was calculated by averaging the Scale for the Assessment of Negative Symptoms/Scale for the Assessment of Positive Symptoms inappropriate affect, positive formal thought disorder, and bizarre behavior items for each subject following previously established methods.[77] The Global Assessment of Functioning (GAF)[78] Scale and the UCSD Performance-Based Skills Assessment (UPSA)[73] were used to assess functional status and functional capacity (described later).

Table 1. Demographic and Clinical Characteristics of the 2 Groups

Characteristic	Value, Mean (SD)
Nonpsychiatric subjects (14 men and 11 women)	
Age, y	32.4 (8.4)
Education, y	15.4 (2.4)
Schizophrenia patients (16 men and 9 women)	
Age, y*	39.4 (9.6)
Education, y†	12.4 (1.7)
Duration of illness, y	17.7 (10.2)
No. of hospitalizations	6.4 (7.6)
GAF Scale score	44.6 (10.8)
UPSA score	81.18 (15.45)
SAPS score	6.05 (5.31)
SANS score	12.45 (5.33)

Abbreviations: GAF, Global Assessment of Functioning; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; UPSA, University of California, San Diego, Performance-Based Skills Assessment.

*Schizophrenia patients were older than nonpsychiatric subjects (t_{48} = –2.76, $P < .01$).

†Schizophrenia patients completed fewer years of education than nonpsychiatric subjects (t_{48} = 5.13, $P < .001$).

GAF SCALE

The GAF Scale was used for assessing patients' overall level of functional status across psychological, social, and occupational domains via a single anchored measure.[78] The GAF Scale is divided into 10 ranges of functioning. Each 10-point range contains a description with 2 components: (1) symptom severity and (2) functioning. The GAF Scale rating was selected within a particular decile if either the symptom severity or the level of functioning fell within the range during the 1-week period before MMN testing. Following *DSM-IV* procedures,[78] in situations in which individual's symptom severity and level of functioning were discordant, the final GAF Scale rating reflected the worse of the 2. The patients who participated in this study received GAF Scale ratings that ranged from 30 to 70 (mean, 44.6; SD, 10.8).

UCSD PERFORMANCE-BASED SKILLS ASSESSMENT

In contrast to the GAF Scale and many other measures of functioning, the UPSA directly measures performance on tasks that are commonly encountered in everyday situations and considered necessary for independent functioning in the community. The UPSA was designed for use in patients with serious and persistent mental illnesses in a laboratory setting and is, thus, classified as a surrogate measure of functional capacity.[7,72] Participants role play skills that are considered essential to functioning in the community, and performance is scored

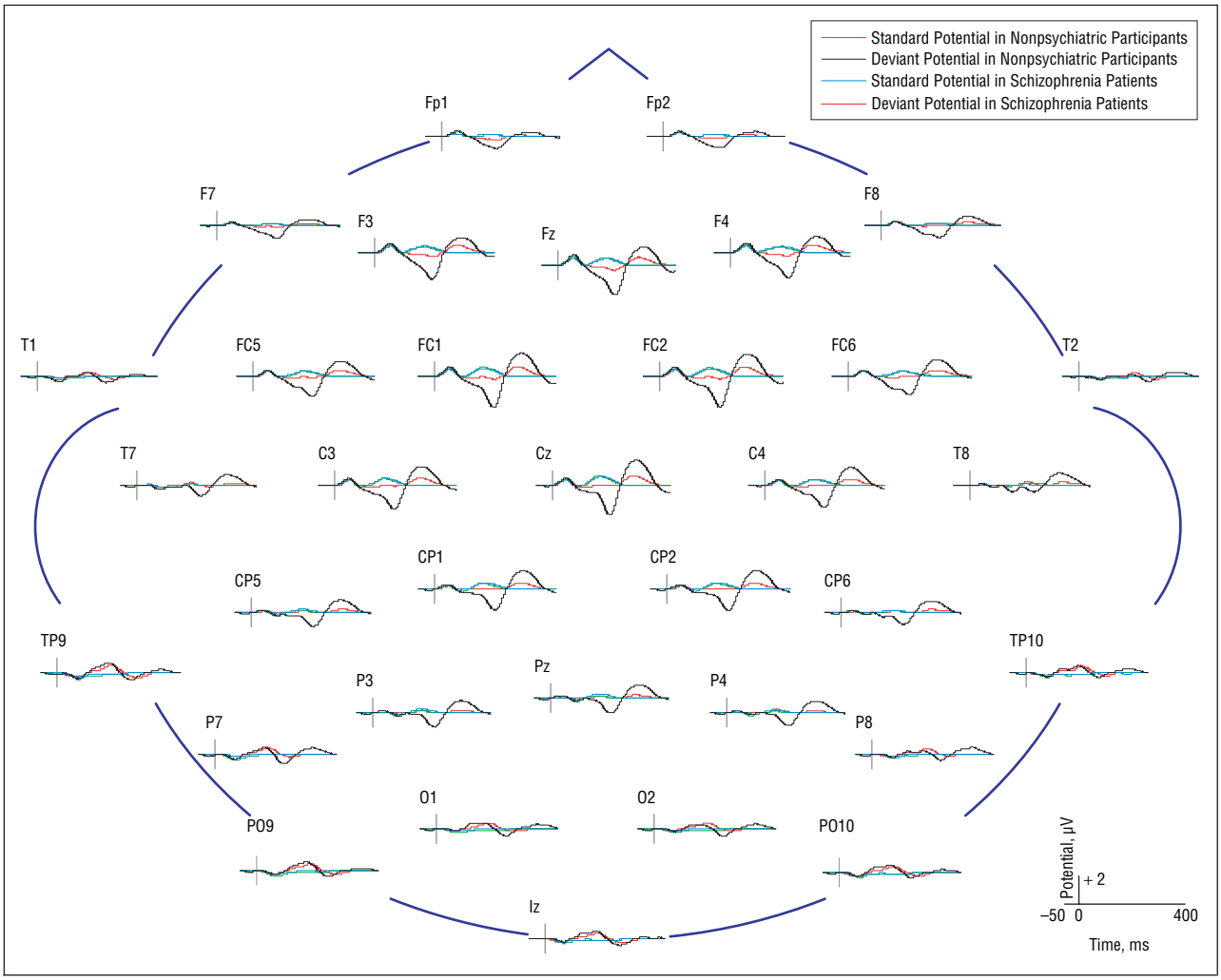

Figure 1. Grand average standard and deviant event-related potentials in nonpsychiatric participants and schizophrenia patients. Schizophrenia patients and nonpsychiatric comparison subjects had nearly identical grand average responses to standard ($P = .90$), but not deviant ($P = .10$), tones. Schizophrenia patients had significantly ($P<.001$) smaller event-related potential responses to deviant tones at frontocentral electrodes in the 100- to 200-millisecond range. This abnormality in processing the deviant tones accounts for their reductions in mismatch negativity amplitude.

across 5 domains: (1) general organization and planning (eg, preparing for an outing to the beach or zoo), (2) finance (eg, counting change and paying a bill by personal check), (3) communication (eg, emergency and nonemergency telephone use), (4) transportation (eg, planning the use of a public bus system), and (5) household chores (eg, preparing a shopping list for items in a mock grocery store). Subscale scores range from 0 to 20 points; total scores range from 0 to 100 points.[72]

LEVEL OF INDEPENDENCE IN THE COMMUNITY LIVING SITUATION

Patients were rated according to their level of independence in their community living situation as a measure of functional status on a scale of 1 to 4 following established methods.[6,7,79] The anchors were as follows: 1, patient lives in a setting with 24-hour supervision, such as a locked intensive inpatient ward; 2, patient lives in a setting with close monitoring, such as a long-term treatment facility, or lives only with family members or a private custodian; 3, patient lives in a semi-independent board-and-care or transitional living facility or lives independently but requires regular external help from family, friends, or social services; and 4, patient is successful in living independently and autonomously in an apartment or home.

MISMATCH NEGATIVITY

Subjects were presented with binaural tones (1-kHz 85-dB sound pressure level, with 1-millisecond increase/decrease) with a fixed stimulus onset-to-onset asynchrony of 500 milliseconds using a stimulus unit (SR-HLAB; San Diego Instruments, Inc, San Diego, Calif). Standard ($P=.90$, 50-millisecond duration) and deviant ($P=.10$, 100-millisecond duration) tones were presented to subjects in pseudorandom order[67] using foam insert earphones (model 3A; Aearo Company Auditory Systems, Indianapolis, Ind). During the 20- to 25-minute electroencephalographic recording session, subjects watched a silent, benign, cartoon videotape to divert attention from the tones, minimize boredom, and reduce eye movements.[67] Subjects were continuously monitored through a 1-way mirror, and short breaks were offered to ensure alertness and comfort during the recording session.

Electroencephalographic recordings were acquired with a Neuroscan NuAmp system (Neuroscan Laboratories, El Paso, Tex). The electroencephalogram was recorded from the scalp through 34 sintered silver/silver chloride electrodes using an electrode cap (EasyCap; Falk Minow Services, Herrsching-Breitbrunn, Germany). The following 34 equidistant electrode positions were used: Fp1, Fp2, Fz, F3, F4, F7, F8, FC1,

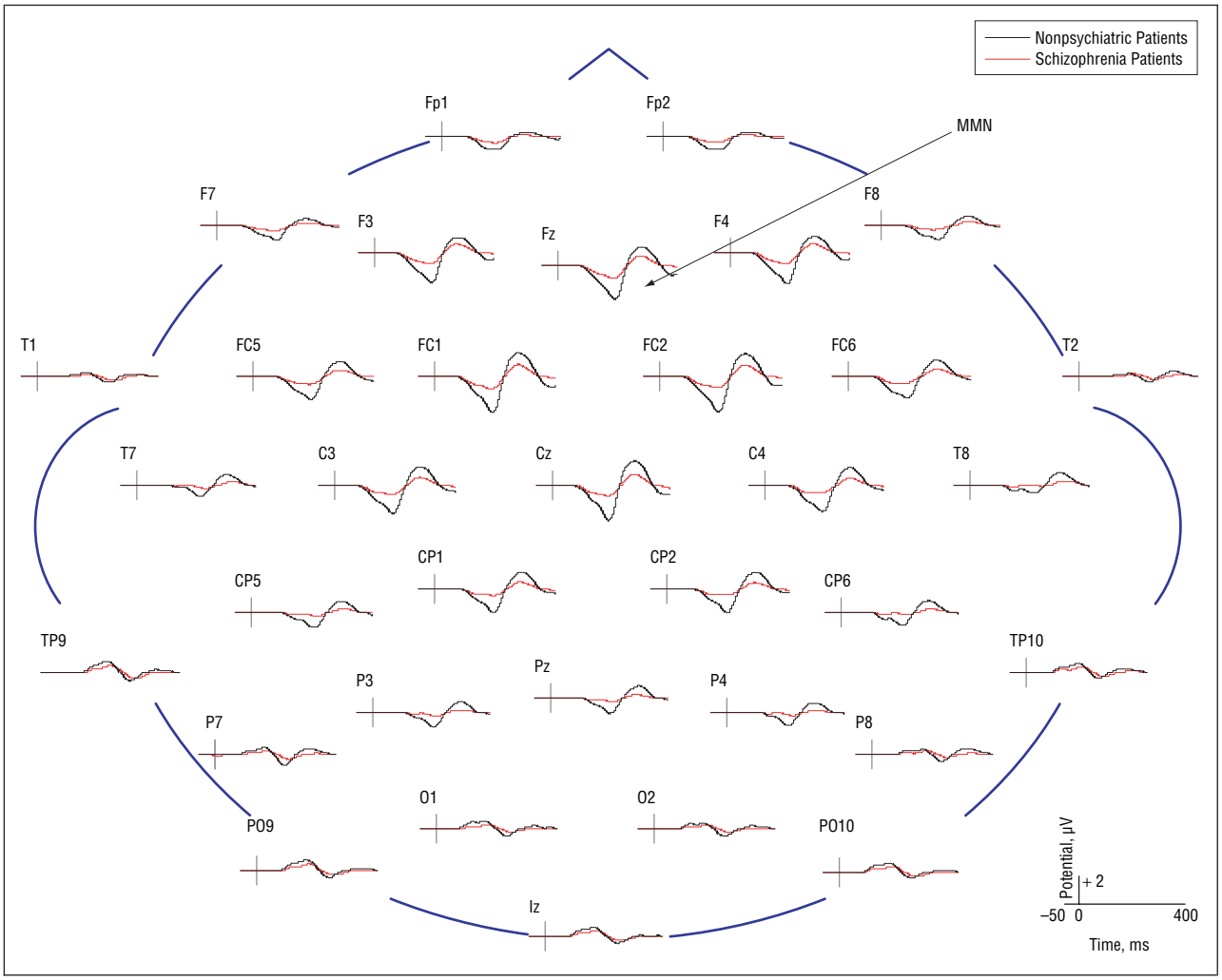

Figure 2. Grand average mismatch response waveforms in nonpsychiatric participants and schizophrenia patients. Patients with schizophrenia had significantly ($P<.001$) reduced grand average mismatch responses most evident at frontocentral electrodes over the 100- to 200-millisecond range, with phase reversal at posterior electrodes (eg, TP9 and TP10). MMN indicates mismatch negativity.

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 (**Figure 1**). Electrodes placed at the tip of the nose and at Fpz served as the reference and ground, respectively. Four additional electrodes placed above and below the left eye and at the outer canthi of both eyes were used for monitoring blinks and eye movements. All impedances were kept below 4 kΩ. Signals were digitized at a rate of 1 kHz, with system acquisition filter settings at 0.5 to 100 Hz. Electroencephalography and stimulus markers were recorded continuously. During testing, online 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 milliseconds following stimuli). Electroencephalographic acquisition was terminated when a minimum of 225 artifact-free deviant trials were collected. No subject required presentation of more than 300 deviant tones to obtain 225 artifact-free epochs during acquisition. Data processing was performed off-line and blind to group membership using automated procedures. First, continuous recordings were mathematically corrected for eye movement artifact using established methods.[80] Continuous data were divided into epochs relative to the onset of stimuli (–100 to 500 milliseconds), and centered at the mean of the prestimulus baseline. Following blink correction, epochs containing greater than ±50 µV in frontal recording sites (F7, F8, Fp1, Fp2, F3, F4, and Fz) were automatically rejected.[62] Event-related potential waveforms were generated for the responses to standard and deviant tones (Figure 1). On average, schizophrenia patients and healthy comparison subjects had 247 and 255 artifact-free deviant trials, respectively, following off-line processing. Mismatch negativity waveforms were generated by subtracting ERP waveforms in response to standard tones from the ERPs generated in response to the deviant tones (**Figure 2**). The resultant MMN subtraction waveforms were low-pass filtered at 20 Hz (0-phase shift and 24-dB/octave roll-off) to remove any residual high-frequency artifact.[62] The MMN amplitude was measured as the mean voltage from 135 to 205 milliseconds.[67]

STATISTICAL ANALYSES

A repeated-measures analysis of variance with the 34 scalp electrodes as a within-subject factor, group as a between-subject factor, and age as a covariate was performed to assess differences in mismatch responses between the schizophrenia patients and nonpsychiatric subjects. Independent *t* tests were used to follow up significant group × electrode interactions, with $\alpha = .01$ to reduce type I errors. To assess the relationship of mismatch responses (mean amplitudes across 135-205 millisec-

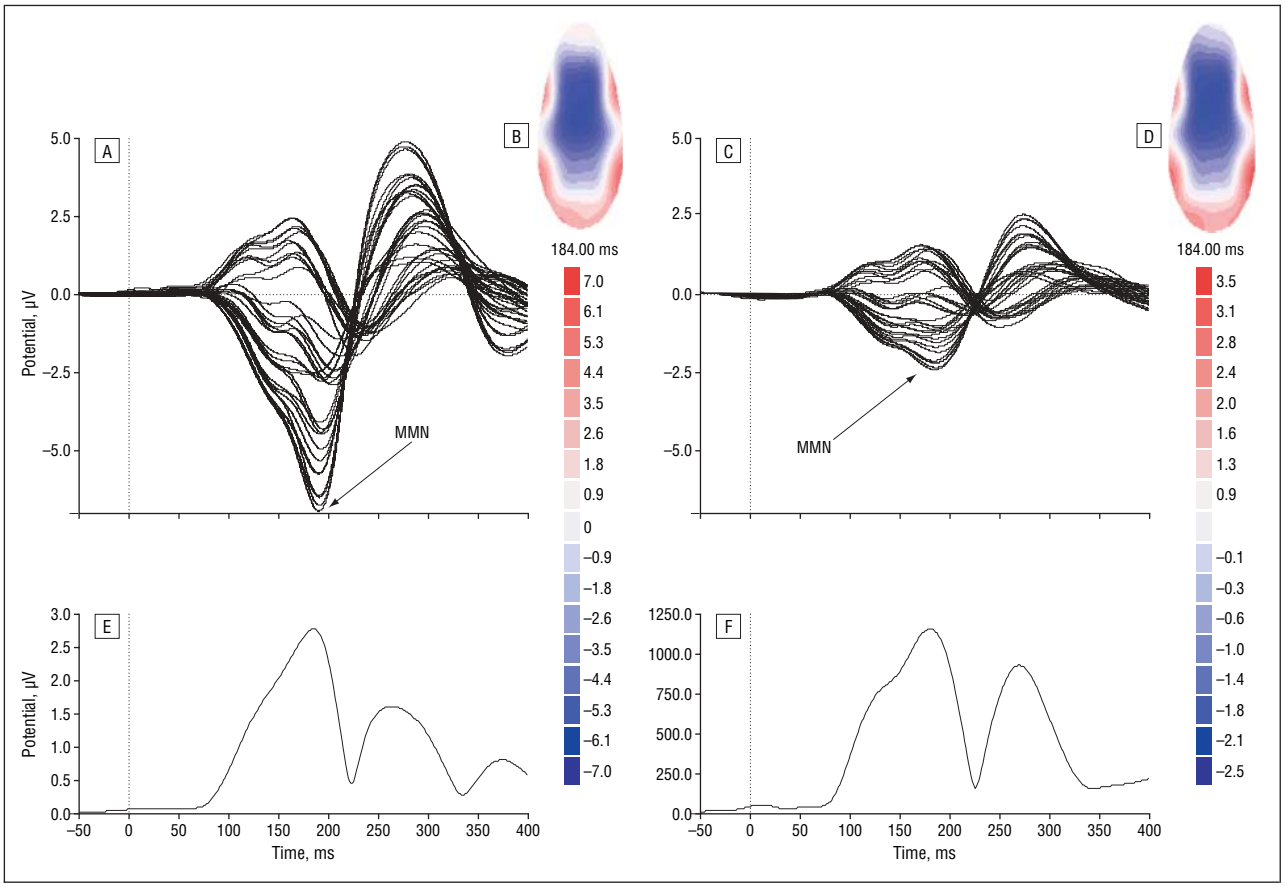

Figure 3. Butterfly plots and 2-dimensional scalp topography of grand average mismatch responses in nonpsychiatric subjects (A and E, respectively) and schizophrenia patients (C and F, respectively) and amplitude-normalized 2-dimensional scalp topographies of mismatch responses in nonpsychiatric subjects and schizophrenia patients (B and D, respectively). Butterfly plots (A and C) overlay grand average responses from all electrodes to evaluate the mean global field power of the mismatch responses (E and F) (different amplitude scaling is used). The mismatch response peaks in the 190- to 200-millisecond range. Patients with schizophrenia had significantly ($P<.001$) smaller mismatch response amplitudes, but comparable topographic distributions, when amplitude differences were corrected. MMN indicates mismatch negativity.

onds) with clinical symptoms and functional measures, Spearman rank correlation coefficients were generated and plotted across scalp recording sites.

RESULTS

Significant MMNs were present in all subjects, verified by visual inspection of butterfly plots and mean global field power peaks (**Figure 3**) in the MMN range that were at least 2 times the amplitude of any activity present in the 100 milliseconds before stimulus onset. A repeated-measures analysis of variance revealed a statistically significant electrode × group interaction ($F_{2.71,127.29}=17.75$, $\varepsilon=0.08$, $P<.001$). Since age was not a significant covariate (main effect $F=1.91$, $P>.15$; electrode × age interaction $F=1.73$, $P>.15$), it was excluded from further analyses. Consistent with previous studies,[18,54] follow-up t test comparisons indicated that schizophrenia patients had significantly smaller mismatch responses at frontocentral recording sites (Fp1, Fp2, Fz, F3, F4, F7, F8, FC1, FC2, FC5, FC6, Cz, C3, C4, CP1, CP2, CP5, CP6, Pz, P3, P4, T7, and T8; $t>4.0$ for all, $P<.01$ for all), with phase reversal at posterior electrodes that was not significantly different from that of the nonpsychiatric subjects (P7, P8, PO9, PO10, O1, O2, T1, T2, TP9, TP10, and Iz; $t<1.5$ for all, $P>.10$ for all). Grand average mismatch responses are presented in Figure 2, with descriptive statistics for MMN amplitudes presented in **Table 2**. Grand average butterfly plots and mean global field power for schizophrenia patients and nonpsychiatric comparison subjects are presented in Figure 3. To assess lateralized differences between schizophrenia patients and the healthy comparison subjects, a repeated-measures analysis of variance was performed on frontocentral sites at which significant group differences were detected. No statistically significant main effects of hemisphere ($F=1.89$, $P>.10$) or group × hemisphere interactions ($F=1.11$, $P>.10$) were observed, consistent with the findings of Umbricht et al.[54] After correcting for amplitude differences between the nonpsychiatric subjects and schizophrenia patients, there were no group differences in the topography of mismatch responses (Figure 3), also consistent with the findings of Umbricht et al.[54]

Using Spearman rank correlation analyses, mismatch responses were not significantly associated with severity of positive or negative symptoms, hearing thresholds, duration of illness, or number of hospitalizations ($r_s<0.4$ for all, P for all). In contrast, mismatch responses were significantly associated with GAF Scale rat-

ings (r_s=–0.40 to –0.65; F3, F4, F7, F8, FC1, FC2, FC5, FC6, Fz, C3, C4, CP1, CP2, and Cz) and level of independence in community living situation (r_s=–0.40 to –0.60; F3, F7, FC1, FC2, FC5, FC6, Fz, and T7). Three-dimensional plots of significant correlations between MMN and GAF Scale ratings across electrode sites are presented in **Figure 4**.

In contrast to our expectations, MMN was not significantly correlated with performance on UPSA subscales or total score (r_s<0.4 for all, P>.10 for all). The UPSA total scores were, however, significantly associated with negative symptoms (r_s=–0.60, P<.001), delusions (r_s=–0.58, P<.001), and inattention (r_s=–0.78, P<.001) ratings on the Scale for the Assessment of Negative Symptoms and the Scale for the Assessment of Positive Symptoms. The UPSA total scores were also significantly correlated with GAF Scale score and degree of independence in community living situation (for both, r_s=0.44, P<.05). The degree of association between UPSA scores and independence in living situation is comparable to that presented by Twamley et al[7] (r=0.43-0.48).

COMMENT

The results of the present study demonstrate that MMN deficits are highly associated with reduced functional status (ie, GAF Scale ratings and level of independence in community living situation) in schizophrenia patients. In this study, MMN deficits accounted for up to 42% of the variance (r_s=–0.65, P<.001) in functional status in this cohort of patients. To our knowledge, this is the first report of a significant relationship of a preattentional cognitive deficit with impaired functional status in schizophrenia patients, ie, an association across the distinct domains of neurophysiological and everyday functioning. In fact, the MMN deficits in this study correlate with impaired functioning at levels that are much higher than the correlation between neurocognitive measures and functional status and outcome.[6,70,71]

One explanation for the observed MMN–everyday function relationship is that the subject sample was recruited from various settings and included patients whose clinical status ranged from long-term hospitalization to independent living. Some of the schizophrenia patients who participated in this study were clinically stable, independently living, and employed and drove themselves to the laboratory for testing, whereas others required hospitalization in a long-term, locked care facility. Thus, this sample provided substantial range in everyday functioning that facilitated identifying correlations with physiological measures. By not limiting this sample to the most extremely impaired (or best functioning) population of schizophrenia patients, the study design may have provided greater sensitivity to detect brain-behavior relationships that are relevant to the functional correlates of schizophrenia. However, even the highest functioning schizophrenia patients in this study still had MMN amplitudes that were smaller than the mean of the nonpsychiatric participants (Figure 3 and Table 2).

There is a growing recognition of the importance of understanding the concept of functioning in schizophrenia.

Table 2. Descriptive Statistics of Mismatch Responses and Measures of Functioning in Nonpsychiatric Subjects and Schizophrenia Patients

Electrode	Nonpsychiatric Subjects*	Schizophrenia Patients*†	Effect Size‡
C3	–4.68 (1.67)	–1.67 (1.38)	–1.97
C4	–4.35 (1.56)	–1.49 (1.24)	–2.04
CP1	–3.61 (1.62)	–1.18 (1.25)	–1.69
CP2	–3.53 (1.51)	–1.11 (1.21)	–1.78
CP5	–2.05 (1.41)	–0.36 (1.11)	–1.34
CP6	–1.80 (1.41)	–0.23 (0.98)	–1.32
Cz	–5.21 (1.87)	–1.76 (1.36)	–2.14
F3	–5.02 (1.85)	–1.99 (1.11)	–2.05
F4	–5.06 (1.77)	–1.91 (1.08)	–2.22
F7	–2.60 (1.24)	–0.78 (0.69)	–1.88
F8	–2.60 (1.26)	–0.75 (0.76)	–1.84
FC1	–5.77 (1.91)	–2.10 (1.34)	–2.26
FC2	–5.60 (1.84)	–2.03 (1.30)	–2.27
FC5	–4.09 (1.63)	–1.41 (1.12)	–1.95
FC6	–3.94 (1.52)	–1.32 (1.05)	–2.04
Fp1	–2.68 (1.12)	–1.06 (0.58)	–1.91
Fp2	–2.72 (1.15)	–1.10 (0.63)	–1.82
Fz	–5.52 (1.93)	–2.14 (1.17)	–2.18
Iz	1.81 (1.45)	1.36 (0.87)	0.39
O1	1.07 (1.32)	1.00 (0.89)	0.06
O2	0.85 (1.50)	1.03 (0.90)	–0.15
P3	–1.70 (1.45)	–0.29 (1.08)	–1.11
P4	–1.50 (1.43)	–0.14 (1.04)	–1.10
P7	0.99 (1.32)	1.06 (0.90)	–0.06
P8	0.73 (1.53)	0.99 (0.92)	–0.22
PO10	1.72 (1.46)	1.41 (0.85)	0.26
PO9	2.05 (1.42)	1.51 (0.87)	0.47
Pz	–2.01 (1.60)	–0.49 (1.13)	–1.11
T1	0.63 (0.98)	0.89 (0.73)	–0.31
T2	0.47 (0.99)	0.74 (0.77)	–0.30
T7	–1.05 (1.27)	0.19 (0.82)	–1.19
T8	–1.26 (1.54)	0.09 (0.93)	–1.09
TP9	1.99 (1.26)	1.60 (0.86)	0.37
TP10	1.52 (1.30)	1.35 (0.87)	0.16

*Data are given as mean (SD) mismatch response.
†Schizophrenia patients have significantly reduced mismatch responses over frontocentral electrodes.
‡Calculated as the standardized mean difference: (mean of nonpsychiatric subjects–mean of schizophrenia patients)/pooled SD. In some electrodes, effect size differences exceeded 2 SDs.

In contrast to the strong relationship of MMN with everyday functional status, MMN was not significantly associated with performance on face-valid tasks of operations that are putatively necessary for independent living (eg, making change on the UPSA battery). Thus, another crucial result of the present study is the dissociation of functional capacity (ie, ability to perform tasks necessary for independent living) and functional status (ie, level of independence in the community). While traditional neurocognitive deficits modestly relate to impairments in functional status in schizophrenia patients,[6,71] surprisingly few studies have directly assessed the relationship of symptoms, cognition, and neurophysiological processes to surrogate functional capacity tasks, such as the UPSA, or to in vivo assessments of everyday functioning.[7,72] Indeed, most studies of functional status in schizophrenia research use measures that rely on self-report, proxy report, or clinician ratings that may not fully reflect pa-

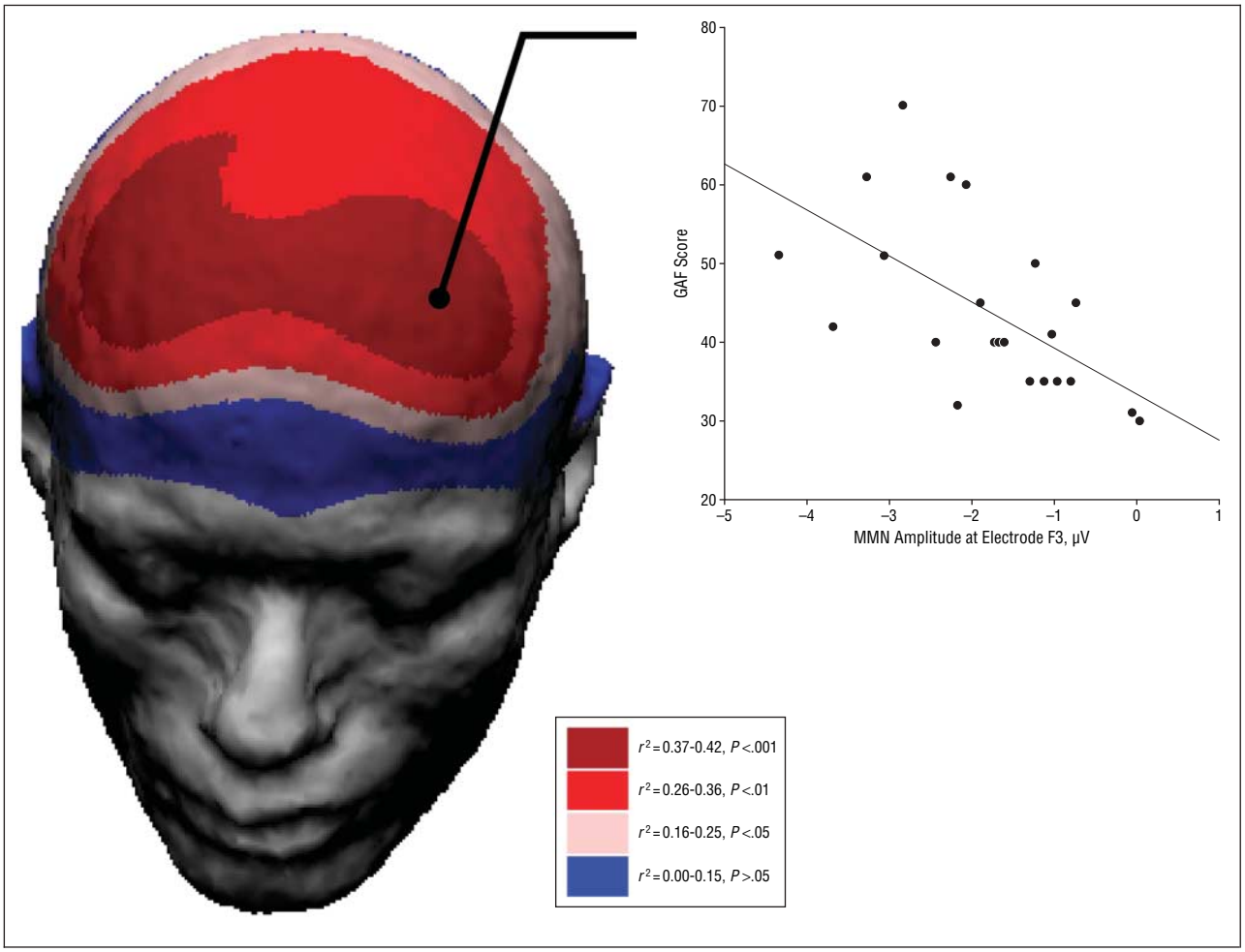

Figure 4. Mismatch negativity (MMN) is significantly associated with clinician-rated global assessments of functioning in schizophrenia patients at frontocentral electrodes (α=.01). The different shades represent the degree of association between Global Assessment of Functioning (GAF) Scale scores and MMN across individual electrode sites using Spearman nonparametric rank correlations. Significant associations were present at the following electrodes: F3, F4, F7, F8, FC1, FC2, FC5, FC6, Fz, C3, C4, CP1, CP2, and Cz. The panel on the right shows the position of electrode F3 and the correlation of MMN to GAF Scale score (r_s=−0.65, P<.001).

tients' functioning across multiple domains (eg, finances, communication, and use of transportation). In the present study, we found that performance on a surrogate functional capacity battery (ie, UPSA) was correlated with functional status to a degree that is comparable to previous reports (r_s=0.44 vs r_s=0.45, which was previously reported[7]). In contrast, UPSA performance is highly correlated with neuropsychological test performance (r=0.60 to r=−0.78).[7] Hence, our data are consistent with the notion that performance on surrogate laboratory-based tasks such as the UPSA reflects the construct of functional capacity rather than actual functional status.

Deficits in MMN are relatively specific to schizophrenia patients compared with patients with other major psychiatric disorders,[54-58] and are present in clinically unaffected family members of schizophrenia patients.[66-68] Thus, MMN deficits may be a potentially useful endophenotype in genetic studies.[8,69] The fact that MMN is reduced in some clinically unaffected family members of schizophrenia patients[66-68] demonstrates that MMN is not always associated with functional impairment, as is true of many other genetically mediated endophenotypes.[69] This pattern of results is consistent with a 2-hit model in which a genetically mediated neurophysiological deficit leads to vulnerability that may be expressed as schizophrenia if a second nongenetic insult occurs to the central nervous system.[69]

In the present study, the schizophrenia patients were significantly older than the nonpsychiatric comparison subjects. While previous studies have observed age-related changes in MMN,[81,82] schizophrenia patients have large-effect size deficits vs healthy comparison subjects in duration-deviant MMN studies even when age is carefully matched between groups.[55] Most important, the age difference between groups does not explain the correlation between MMN and measures of functional status within the group of schizophrenia patients.

In conclusion, these data demonstrate that MMN deficits are highly associated with poor functional status in schizophrenia patients. Based on the literature reviewed, MMN also indexes vulnerability for schizophrenia, the state of NMDA receptor functioning, and the integrity of frontotemporal brain systems. Longitudinal studies are needed to determine if MMN deficits, which may progress after the first episode of the illness,[62] predict long-term functional outcome. These studies are also

needed to identify relevant variables that mediate the relationship of MMN and other preattentional processing deficits[8] to everyday functioning. These mediating variables may include temporal lobe volumes, NMDA neurotransmission, neurocognition, and genetic factors. In addition, understanding the interactions between basic neurophysiological cognitive operations and clearly defined and measured everyday functioning is an important future direction in schizophrenia research. The results of the present study support the importance of MMN and perhaps other neurophysiological cognitive measures for use as targets in treatment studies aimed at assessing and improving cognition and everyday functioning in schizophrenia.[8]

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