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Special Contribution

Mismatch Negativity as a Psychophysiological Index of Cognitive Function in Schizophrenia

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It is now widely accepted that cognitive deficits, beyond other psychiatric symptoms (e.g., delusion, hallucination, emotional flattening, social withdrawal and apathy), is far most relevant to social functional outcome in schizophrenia. Accordingly, the treatment target has been shifted to the area, developing new drugs that facilitate cognitive function and building up new psychosocial rehabilitation programs that directly approach the cognitive deficits. Despite the desirability to target these deficits, no standard neuropsychological test batteries exist for assessing the level of cognitive function. Mismatch negativity (MMN), an auditory event-related potential component, is a measure of preattentive information processing and its amplitude has repeatedly been demonstrated to be reduced in schizophrenia. MMN deficits are a robust feature in chronic schizophrenia and indicate abnormalities in automatic context-dependent auditory information processing and auditory sensory memory in schizophrenia. Moreover, the deficits have been related to poor social functioning level and social skills acquisition, hypofunction of NMDA system, and illness duration, which indicate the validity of accepting MMN as a biomarker of the disease. In this article, we present a summary of the discussions about the plausibility of MMN to be used as a neurobiological index for assessing the cognitive function and also its predictability of social functional outcome in schizophrenia.

Key words: cognitive function; functional outcome; mismatch negativity; *N*-methyl-D-aspartate; schizophrenia

Cognitive impairment as a core feature of schizophrenia

Schizophrenia is a major mental disorder, which is clinically diagnosed based on a set of characterized "positive" (e.g., hallucinations, delusions and psychomotor excitement), "negative" (e.g., emotional flattening, social withdrawal and apathy) and "cognitive" (disturbances in memory, attention and problem solving) symptoms. Among these symptoms, cognitive impairment has been noticed as the core feature of schizophrenia since Bleuler described "schizophrenias" almost one hundred years ago. Attention has been increasingly focused on cognition since Green (1996) clearly demonstrated that the cognitive impairment was the strongest factor that should affect the social and functional outcome. Green (1996) divided the functional outcome into three sections according to type of outcome measure. The first section represents community (social and occupational) functioning and the second, assessment of social problem solving and the third, ability to ac-

Abbreviations: CPT, continuous performance test; ERP, event-related potential; MATRICS, Measurement and Treatment Research to Improve Cognition in Schizophrenia; MMN, mismatch negativity; NMDA, *N*-methyl-D-aspartate; PCP, phencyclidine; SCD, scalp current density analysis

Table 1. Major features of cognitive impairment of schizophrenia

a) All domains of cognition, including attention, executive function, secondary (storage) memory, working memory, and semantic memory, may be affected.
b) The pattern of deficits may vary widely among individuals with schizophrenia.
c) The mean deficit in these domains may be 1–3 standard deviations below normal, although about 15% of patients with schizophrenia test within the normal range in all domains.
d) For most patients, impairment is only slowly progressive after the first episode of psychosis.
e) Some components of the deficit are present during childhood and early adolescence but usually in mild form.
f) Deficits in specific types of cognition are of key importance for work and social function in schizophrenia, more so even than positive or negative symptoms.

quire psychosocial skills from their psychosocial rehabilitation programs. Among various cognitive domains, verbal memory was associated with all types of functional outcome, vigilance was related to social problem solving and executive functioning was related to community functioning. The major features of the cognitive impairment of schizophrenia are summarized in Table 1 (Meltzer et al., 1999).

The conventional antipsychotic drugs such as chlorpromazine and haloperidol, referred to as dopamine antagonists, were certainly effective against "positive" symptoms but generally ineffective against "negative" and "cognitive" symptoms. Meanwhile, many researchers demonstrated that the new drugs, referred to as serotonin dopamine antagonist and multi-acting receptor-targeted antipsychotics, or atypical antipsychotic drugs, showed a favorable effect on cognition using neuropsychological test batteries, however, whether the new drugs could affect the social functional outcome was not at all clear. One of the reasons for the negative results could be that the effect size of the drugs (0.5–1.5 SD) on cognitive function was not ample enough to reach the normal level (the difference between patients with schizophrenia and normal controls being 1.0–3.0 SD) and thus, was unable to affect the social functional outcome. There has been a national project sponsored by National Institute of Mental Health named MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) in the United States, which aims to develop novel drugs for the treatment of cognitive impairments in schizophrenia. Also, in the field of psychosocial treatment, "cognitive remediation therapy", which refers to the procedures used to directly improve cognitive function, has attracted growing interest of individuals engaged in psychiatric services.

The assessment of cognitive impairment in schizophrenia

The assessment of cognitive impairment in schizophrenia has owed much to neuropsychological test batteries. As noted above, the findings are in agreement in that the new drugs are effective on cognitive function in general, however, the specificity of the effect of each drug has not been clarified. Although the pharmacological profiles of these drugs were clearly different between each other, the cognitive profiles that were affected by these drugs were not as clearly distinct as expected.

The inconsistent and nonspecific findings are, at least in part, caused by the relatively weak validity of neuropsychological tests. First, as prompt response is required in many tests, the performance level is affected not only by the stimulus processing speed but also by the motor speed, which makes the interpretation of the results difficult. Moreover, as the assessment using neuropsychological tests depend solely on behavioral indices, they are subject to motivational

influences, which should also be contaminated in the assessment of cognitive function. Finally, the construct validity of neuropsychological tests has not been well established. For instance, "continuous performance test (CPT)" is usually intended to measure vigilance as well as sustained attention over time (Cornblatt et al., 1989). During the task, subjects are presented with single letters or numbers in a short duration that appear at a rapid fixed rate. The subjects are required to respond with a button press each time a predesigned target stimulus appears. It can be assumed that other psychometric properties such as automatic stimulus perceptual capacity, independent from either vigilance or attention, may contribute to the CPT performance. Also, in our previous study, we investigated the relationship between the scores in Tower of Hanoi test and Wisconsin Card Sorting Test, which are both well known as measures of executive functioning, however, we found no relationship between them in schizophrenia patients (Katoh et al., 2003).

In the MATRICS project, researchers are now focusing on several neuroimaging and electrophysiology biomarkers to gain reliable and sensitive indices associated with the brain activity underlying more specific cognitive domains. As is well known, electrophysiological methods are superior in terms of time sensitivity but limited in spatial resolution as compared with neuroimaging methods. Magnetoencephalogram measurements hold high quality of spatial information as well as time sensitivity, whereas they still have limitation in that they can only detect the current in the tangential direction to the scalp. Scalp current density analysis (SCD) is another method used for improving spatial resolution, which was calculated by taking the Laplacian of the scalp potential surface generated by spherical spline interpolation (Nunez, 1981; Perrin et al., 1989). As SCD computation is equivalent to applying a high-pass spatial filter to the potential fields, the maxima and minima of their distribution are clearer than those of the potential fields. Moreover, since the sensitivity of the SCD mappings decreases with the depth of the generator in the brain, they may allow the splitting of the overlapped components arising from the cortex that show distinct sink/source patterns. Formally, it is based on simplifications of Poisson's equation relating the field potential at any point in the conductive medium to their underlying current generators, so that a local generator of an extracellular negativity (current sink) corresponds to local neuronal depolarization, while a local generator of a positivity (current source) corresponds to hyperpolarization. Although the anatomical and physiological organization of putative generator regions must be carefully evaluated before attributing physiological correlates to SCD components, it can be reasonably assumed that SCD is useful in elucidating the cortical activities associated with the component specified.

Concerning the advantage of electrophysiological methods such as event-related potentials (ERP) in temporal resolution, they allow the early stages of sensory and perceptual information processing, as well as later cognitive and premotor processes to be distinguished precisely in time. Moreover, overall processing speed can be assessed without contamination by motor dysfunction. Disadvantages include the fact that ERP components have not been identified across the full array of candidate cognitive domains under consideration and are relatively limited in measuring sustained processing.

Up to date candidate components for the assessment of cognitive impairment in schizophrenia may come from sensory and early cognitive processing. For instance, mismatch negativity (MMN, see Fig. 1), an early auditory ERP elicited by deviant stimuli even though the subjects ignored the series of stimuli, has some attractive features such as good test-retest reliability (Kathmann et al., 1999; Kujala et al., 2001) and has been shown to correlate with functional outcome (Light and Braff, 2005). MMN is an ERP component that is generated when a stimulus violates the invariance or regularity of the previous series of standard stimuli. MMN has been considered to be independent of subjects' attention, however, some studies have reported that under exceptional

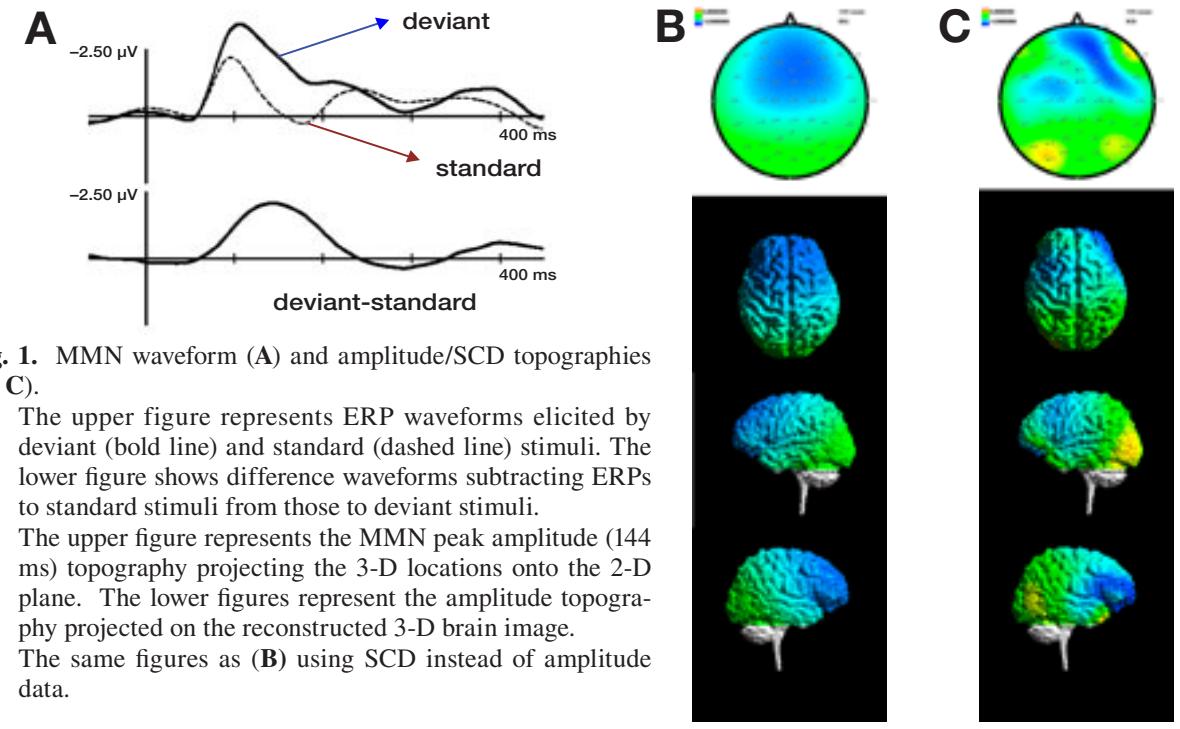

Fig. 1. MMN waveform (**A**) and amplitude/SCD topographies (**B**, **C**).
A: The upper figure represents ERP waveforms elicited by deviant (bold line) and standard (dashed line) stimuli. The lower figure shows difference waveforms subtracting ERPs to standard stimuli from those to deviant stimuli.
B: The upper figure represents the MMN peak amplitude (144 ms) topography projecting the 3-D locations onto the 2-D plane. The lower figures represent the amplitude topography projected on the reconstructed 3-D brain image.
C: The same figures as (**B**) using SCD instead of amplitude data.

circumstances attention can indirectly modulate MMN (Trejo et al., 1995; Sussman et al., 1998). MMN is best observed in the difference waveform subtracting the ERP responses to standard stimuli from those to deviant stimuli and usually peaks within 100 and 240 ms after the deviant stimulus is presented. It's maximum negativity is seen over fronto-central region and it reverses its polarity near the mastoid in a nose-referenced montage. Larger differences between the standards and deviants and lower probability of the deviants are associated with larger MMN amplitude. In the most simple paradigm an infrequent stimulus that differs in any physical characteristic such as frequency, duration, intensity or location is presented among repeatedly presented standard stimuli, however, violations of more abstract regularities not directly related to physical characteristics of the stimuli (e.g., repetition of a tone in series of alternating tones) also generate MMN. Thus, MMN generation depends on the context in which a specific stimulus is presented. MMN is therefore considered an index of preattentive auditory processing, reflecting automatic context-dependent information processing and auditory sensory memory. This early component has the possible advantage of being relatively automatic and less prone to "noise" from top-down cognitive influences or practice effects, thereby potentially being more direct probes of the functional integrity of underlying neural structures. MMN can be contrasted with later components such as the P300, the error-related negativity, or slow waves such as the contingent negative variation, which are thought to reflect some of the critical cognitive disturbances in schizophrenia but are subject to top-down influences such as task instructions or strategy differences. Furthermore, numerous studies have identified the neural substrates generating MMN in primary and secondary auditory cortices (Hari et al., 1984; Scherg et al., 1989; Javitt et al., 1994; Alho, 1995; Levänen et al., 1996; Celsis et al., 1999; Opitz et al., 1999, 2002; Downar et al., 2001; Jemel et al., 2002; Müller et al., 2002; Liebenthal et al., 2003; Sabri et al., 2004) and in frontal cortex (Giard et al., 1990; Levänen et al., 1996; Rinne et al., 2000; Yago et al., 2001; Downar et al., 2001, 2002; Jemel et al., 2002; Müller et al., 2002; Opitz et al., 2002; Liebenthal et al., 2003; Sabri et al., 2004); however, those generating later

components have not been so clearly identified.

Näätänen and Michie (1979) suggested a functional dissociation between the two generators, with the temporal generator associated with establishment of memory traces and comparison with incoming stimulus attributes and the frontal generator related to involuntary triggering of attention invoked by the detected change. Although a few studies have provided some support for this view (Müller et al., 2002; Sabri et al., 2004, 2006; Shalgi et al., 2007), direct evidence for the suggested division of function between the superior temporal and frontal cortices is still lacking.

MMN in schizophrenia

MMN deficits, mostly amplitude reduction, are a robust feature in chronic schizophrenia and indicate abnormality in preattentive context-dependent auditory information processing and sensory memory in these patients. Overall, the mean effect size on MMN amplitude reduction was 0.99 (95% confidence intervals: 0.79–1.2) (Umbricht and Krljes, 2005).

Since the first report of abnormal MMN in schizophrenia by Shelley et al. (1991), there have been numerous studies on MMN in schizophrenia using various stimulus conditions (e.g., type of deviants, probability/degree of deviants) and subjects' populations (e.g., sex, age, duration of illness). Generally, in terms of the probability and degree of deviant stimulus, the lower the probability and the stronger the deviance, the larger the amplitude of MMN becomes. Most frequently used types of deviance were those differing in tone frequency and tone duration. MMN elicited by the deviant stimuli differing in duration appeared more impaired in schizophrenia than those differing in tone frequency (Michie et al., 2000; Javitt et al., 2000b; Umbricht et al., 2003), however, the meta-analysis reported by Umbricht and Krljes (2005) demonstrated that the difference between types failed to reach significance level. Moreover, they suggested that the frequency MMN deficits associated with illness duration and thus, may index ongoing neuropathological changes in the auditory cortex in schizophrenia. In line with the view, Yamasue et al. (2004) demonstrated that the magnetic global field power of mismatch response to change in phonemes in the left hemisphere was significantly correlated with left planum temporale gray matter volume in patients with schizophrenia. The finding suggests that structural abnormalities of the planum temporale may underlie the abnormalities of MMN generation in schizophrenia.

MMN deficits associated with suppressed NMDA action in schizophrenia

The evidence from genetic, brain imaging, clinical and pharmacologic studies suggests that schizophrenia is a heterogeneous group of disorders (Kirkpatrick et al., 2001; Harrison and Weinberger, 2004). All current antipsychotics exert their effects primarily by blocking the D2 dopamine receptors. However, with the exception of clozapine in a subgroup of patients, the conventional and even new drugs leave most patients substantially disabled due to negative symptoms and cognitive impairments. There is now strong reason to suspect abnormalities in *N*-methyl-D-aspartate (NMDA) receptor function may contribute to these symptoms that are resistant to antipsychotic medications.

Since their introduction nearly 50 years ago, the dissociative anaesthetics such as ketamine and phencyclidine (PCP) were known to cause a psychotic syndrome that was difficult to distinguish from schizophrenia (Itil et al., 1967). Based upon emerging pharmacology of the NMDA receptors, Javitt and Zukin (1991) proposed that the psychomimetic effects of PCP were due to blockade of the NMDA receptors. Since then, numerous studies demonstrated that negative and cognitive symptoms as well as neurophysiological signs of schizophrenia were sensitive to the psychomimetic effects of ketamine even in low dose level

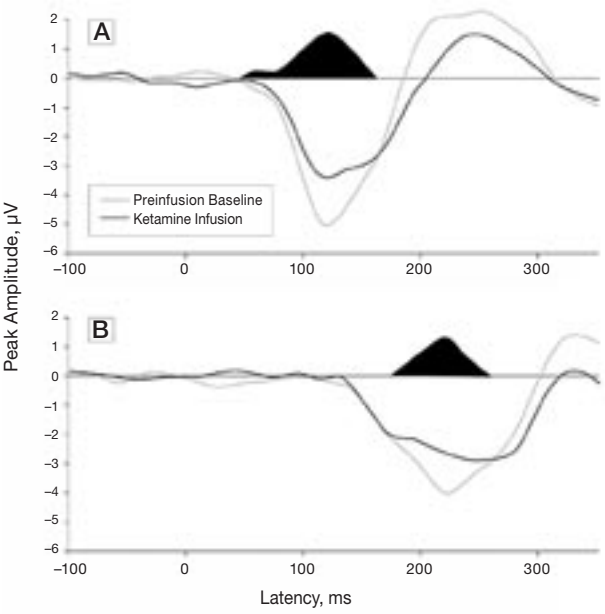

Fig. 2. Effects of ketamine administration on MMN in the pitch (**A**) and duration (**B**) deviance condition (n = 20).

The gray lines represent the MMN wave during the baseline recording before ketamine administration; the black line, during infusion of ketamine; and the dark area, the difference between the two curves (i.e., the reduction of MMN during ketamine administration) (Reprinted with permission from *Ketamine-induced deficits in auditory and visual context-dependent processing in healthy volunerrs: Implicatioans for models of cognitive deficits in schizophrenia*, by Umbricht et al., Archives of General Psychiatry, volume 57, pages 1139–1147. Copyright© 2000 by the American Medical Association. All rights reserved).

(Krystal et al., 1994; Radant et al., 1998; Adler et al., 1999; Newcomer et al., 1999; Umbricht et al., 2000; Lahti et al., 2001).

Javitt et al. (1996) used a combination of intracortical recording and pharmacological micromanipulations in monkeys and demonstrated that both competitive and noncompetitive NMDA antagonists blocked the generation of MMN. These findings suggest that, on a neurophysiological level, MMN represents selective current flow through open, unblocked NMDA channels. Also in humans, Umbricht et al. (2000) reported 27% and 21% reduction of MMN amplitude caused by ketamine administration in pitch and duration deviance conditions, respectively (Fig. 2). Moreover, the authors demonstrated that ketamine induced performace deficits in the AX-CPT (CPT in which subjects were required to press a button whenever the letter "A" was followed by the letter "X" while all other sequences were to be ignored) characterized by specific increases of BX errors (erroneous response to "X" not preceded by "A"), reflecting a failure to form and use transient memory traces of task relevant information. Thus, NMDA receptor dysfunction was thought to underly deficits in transient memory at both automatic and controlled levels of information processing in schizophrenia.

MMN deficits and cognitive impairments in schizophrenia

It cannot be emphasized too strongly that the main goal of psychiatric treatment is not only to relieve the symptom levels or even improve cognitive impairments per se, but also to ameliorate the patients' sufferings presumably by reinforcing their social skills and facilitating their levels of QOL. Therefore, whether MMN represents the domain of cognitive function closely related to social functional outcome is obviously an essential point from clinical point of view.

MMN deficits in schizophrenia do not seem to be related consistently to symptom domains, although a few studies found significant correlations with negative symptom levels (Catts et al., 1995; Hirayasu et al., 1998; Javitt et al., 2000a; Kasai et al., 2002). Given the strong evidence from studies by Näätänen and their colleagues (Näätänen et al., 1992) that MMN indexes auditory sensory memory and automatic context-dependent information processing, it is surprising that not much attention has been given to possible relationships of deficits in MMN to deficits in higher cognitive functions. There are only few studies reporting such relationships, suggesting that MMN deficits are particularly pronounced in patients with memory impairment (Baldeweg et al., 2004; Umbricht et al., 2004; Kawakubo et al., 2006). Baldeweg et al. (2004) used a new stimulation protocol with continuously changing ("roving") standard stimuli in order to measure the effect of standard

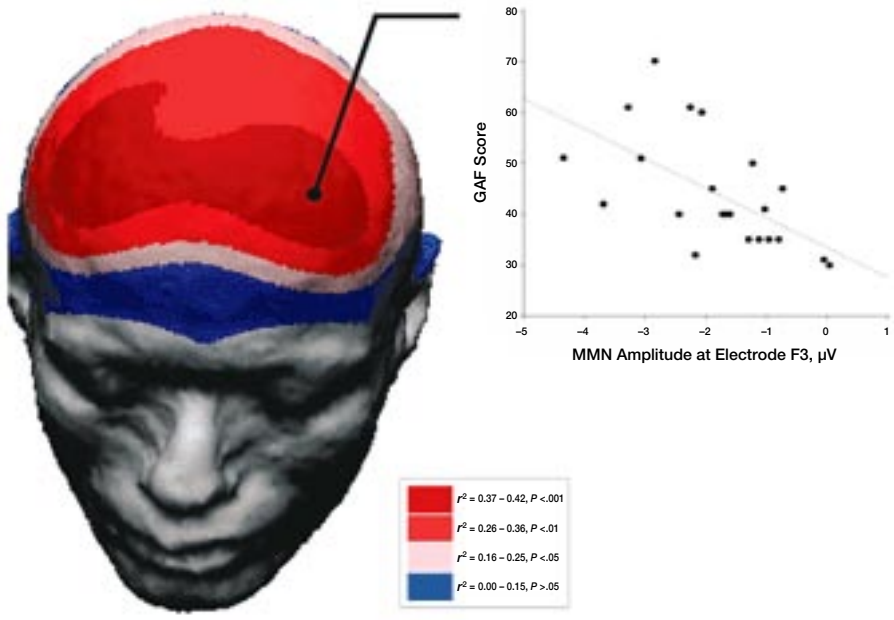

Fig. 3. MMN is significantly associated with clinician-rated global assessments of functioning in schizophrenia patients at frontocentral electrodes ($\alpha = 0.01$). The different shades represent the degree of association between GAF Scale scores and MMN across individual electrode site using Spearman 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 ($r = –0.65$, $P < 0.001$) (Reprinted with permission from *Mismatch negativity deficits are associated with poor functioning in schizophrenia patients*, by Light and Braff, Archives of General Psychiatry, volume 62, pages 127–136. Copyright© 2005 by the American Medical Association. All rights reserved).

repetitions on MMN (memory trace effect), which was robustly correlated with the degree of neuropsychological memory impairment in general rather than static measures of ERP magnitude. Kawakubo et al. (2006) measured MMN elicited by change in tone duration and phoneme duration in 23 schizophrenia patients in addition to evaluation for auditory verbal memory and executive function. They found that MMN under the phoneme duration condition was significantly associated with scores for verbal memory but not with executive function whereas tone duration MMN was not correlated with indices of either verbal memory or executive function. Considering that verbal memory is thought to be one of the main targets in treatment, due to the large effect size of it's impairment in schizophrenia patients as compared with the performance in healthy individuals and also it's strong relationship with various types of functional outcome (Green et al., 1996), the findings suggest that further assessment of MMN in response to speech sound may be of greater importance than MMN in response to simple tones.

MMN deficits related to functional outcome?

Let us now focus on our main concern, that is, the relationship between MMN deficits and social functional outcome. Can measurement of MMN be of use in assessing the community functioning level and/or ability of social problem solving and/or ability to acquire psychosocial skills from their psychosocial rehabilitation programs? Do MMN deficits predict poor social functional outcome longitudinally? Not enough answers have been obtained yet.

Light and Braff (2005) first reported that MMN deficits were associated with poor social functional status. In their study greater MMN deficits were associated with lower Global As-

sessment of Functioning (GAF) Scale ratings and also with lower level of independence in community living situation (Fig. 3). Kawakubo et al. (in press) investigated the relationship between MMN and the degree of social skills acquisition following 3 months training in schizophrenia patients to see whether MMN can predict social skills acquisition longitudinally. They found that larger SCD values for right frontal/temporal MMN elicited by across phoneme change (deviant stimulus; /o/, standard stimulus; /a/) at baseline were significantly associated with the degree of improvement in total social skills scores assessed by a structured role play test. It should be noted that SCD computation improves spatial resolution level and Giard et al. (1990) successfully differentiated the current activities arising from the temporal generator and those from the frontal generator involving mainly the right hemisphere by using SCD. The findings that the social skills acquisition was associated with the right frontal/temporal SCD component but not with the bilateral temporal SCD components may indicate that the social skills acquisition was more strongly related to involuntary triggering process of attention rather than auditory sensory memory function. Moreover, tone duration MMN along with phoneme duration MMN showed no relationship with social skills acquisition. As in the study mentioned above done by the same research group, the impairment in early automatic processing of speech sound may be relevant to schizophrenia patients' social functional outcome.

Conclusions and future directions

Deficits in MMN generation are a robust feature in schizophrenia. The neural substrates and neurotransmitter functions subserving MMN is becoming clear. MMN deficits are present in clinically unaffected family members (Jessen et al., 2001; Michie et al., 2002), which suggest it may be a potentially useful endophenotype to allow the investigation of potential abnormalities in genes coding for the various subunits of the NMDA receptor in a subgroup of patients defined by MMN deficits. Moreover, as a preattentional cognitive index, MMN may accurately characterize the integrity of sensory network dysfunction free of attentional or motivational artifacts, which is an additional advantage of this component to be used as a biomarker.

It remains controversial, however, in terms of which domain of higher cognitive functions MMN deficits are associated with. Moreover, we have only limited information about the relationship between MMN and social functional outcome in schizophrenia. Taking into consideration the MMN in response to speech sound was associated with verbal memory and also with social skills acquisition, further studies using more sophisticated paradigms, such as those assessing language functions might be promising.

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