Central auditory dysfunction in schizophrenia as revealed by the mismatch negativity (MMN) and its magnetic equivalent MMNm: a review

Risto Naätänen¹,²,³ and Seppo Kähkönen¹⁴,⁵

¹ Cognitive Brain Research Unit, Department of Psychology, University of Helsinki, Helsinki, Finland
² Department of Psychology, University of Tartu, Tartu, Estonia
³ Centre of Integrative Neuroscience (CFIN), University of Aarhus, Aarhus, Denmark
⁴ BioMag Laboratory, Helsinki University Central Hospital, Helsinki, Finland
⁵ Pain Clinic, Department of Anaesthesiology and Intensive Care, Helsinki University Central Hospital, Helsinki, Finland

Abstract
Since the early 1990s, the auditory change-detection response, mismatch negativity (MMN) and its magnetoencephalographic (MEG) equivalent MMNm have been applied in a large number of studies on schizophrenia. These studies have enhanced our understanding of the central auditory dysfunction underlying schizophrenia. The attenuation of the MMN amplitude is a systematic and robust neurophysiological finding in these patients. The gradual attenuation of the MMN amplitude resulting from frequency change reflects the progress of the disease, particularly the impairment occurring as a function of illness duration, whereas the MMN deficiency for duration change may be more closely linked to the genetic aspect of the illness. Electroencephalographic (EEG) and magnetoencephalographic (MEG) studies, together, suggest that both the temporal and frontal cortices contributing to MMN generation are affected in schizophrenia patients. Furthermore, abnormalities in auditory perception and discrimination revealed by a deficient temporal MMN generator process might be associated with patients’ positive symptoms, whereas the ramped frontal attention-switching function, suggested by the attenuated responses of the frontal MMN generator, might contribute to the negative symptoms such as social withdrawal. In addition, gradual MMN amplitude reduction, in particular that for frequency change, reflects cognitive and functional impairment occurring as a function of illness duration. Finally, as MMN can be detected even in animals such as the mouse, it might provide a useful biomarker for assessing the effects of the drugs developed to fight the cognitive and functional impairments in schizophrenia patients.

Received 15 January 2008; Reviewed 20 March 2008; Revised 23 July 2008; Accepted 29 July 2008; First published online 4 September 2008

Key words: Auditory discrimination, magnetoencephalographic equivalent of MMN (MMNm), mismatch negativity (MMN), schizophrenia.

Introduction
Schizophrenia is a debilitating illness which is associated with three main types of perceptual, cognitive, and behavioural changes: (1) positive symptoms (e.g. auditory hallucinations); (2) negative symptoms (e.g. flattening of affects, social withdrawal); (3) gradual cognitive and functional decline (present in some but not in all patients). The brain abnormalities and changes underlying these symptoms are, however, still deficiently understood. Since the early 1990s, the auditory change-detection response, mismatch negativity (MMN) and its magnetoencephalographic (MEG) equivalent MMNm, have been widely used methods in the study of the mechanisms of schizophrenia. The results of these studies have yielded valuable knowledge of the different types of brain abnormalities underlying schizophrenia. The present paper is a review of these studies.

MMN as an index of central auditory function
The neuronal basis of human cognition has been extensively studied non-invasively by recording
event-related potentials (ERPs), which are averaged electroencephalographic (EEG) responses time-locked to external stimuli or internal events. The EEG, offering a method with high temporal resolution on a millisecond scale, has been used to record MMN, a potential that is elicited by any discernible change in auditory stimulation even in the absence of attention or behavioural tasks. MMN reflects pre-attentive detection of auditory changes that occurs in the human auditory and frontal cortices and triggers involuntary attention shifting towards deviant or novel stimuli (Giard et al., 1990; Näätänen et al., 1978; Näätänen and Michie, 1979). Further, MMN generation is possible only if a memory trace representing the regularity or invariance of the stimulation has been established before the occurrence of a deviant stimulus (Baldeweg et al., 2004; Näätänen and Winkler, 1999; Näätänen et al., 2007; Winkler et al., 1996). MMN is therefore an index of auditory discrimination and also of sensory or ‘echoic’ memory (representing the preceding stimuli) involved in this discrimination. Importantly, as previously mentioned, motivational factors do not contaminate the measurement, as MMN can be elicited even in the absence of attention (even though its amplitude can under some circumstances be affected by the withdrawal of attention; Woldorff et al., 1991, 1998; for a review, see Näätänen et al., 2007). Therefore, MMN is ideal for studies of the neural bases of auditory discrimination and involuntary attention in schizophrenia.

**MMN amplitude reduction in schizophrenia**

In an earlier study, Shelley et al. (1991) found that the MMN amplitude for an occasional duration increment in a repetitive tone was considerably smaller in schizophrenia patients than in controls, suggesting that their duration discrimination is compromised. Javitt (1993), in turn, was the first to show frequency-MMN deficiency in schizophrenia patients. The duration-MMN result was subsequently corroborated by Catts et al. (1995) and Michie et al. (2000). The latter authors also found that the MMN abnormalities in response to duration changes, particularly in those to duration increments, were even more robust than those to frequency changes (see also Davalos et al., 2003; Michie, 2001). Importantly, Catts et al. (1995) found that in bipolar patients, duration-MMN was not affected, supporting the specificity of duration-MMN deficiency in schizophrenia (for corroborating of frequency- and duration-MMN results, see Umbricht et al., 2003a). Recently, Fisher et al. (2008), using the ‘optimal paradigm’ (Näätänen et al., 2004) for recording five different MMNs in parallel (see also Thönnessen et al., 2008), found that MMN attenuation for duration decrements occurred only in schizophrenia patients with auditory hallucinations. Moreover, in these patients, MMN to intensity changes was also attenuated in amplitude (but only in relation to the MMN of healthy controls, not to that of non-hallucinating patients; see also Oades et al., 1996).

Furthermore, schizophrenia patients have a reduced MMN not only to changes in simple sound features but also to changes in speech sounds (Kasai et al., 2002a; for corroborating MEG results, see Kasai et al., 2002b; Yamasue et al., 2004). Yamasue et al. (2004) also found that the phoneme-change MMNm strength in the left hemisphere correlated with the left planum temporale grey-matter volume in schizophrenia patients. This suggests that left-hemisphere structural planum-temporale abnormalities may underlie the functional abnormalities of fundamental language-related processing in schizophrenia patients. In addition, Kawakubo et al. (2006) found that a MMN deficit with respect to the duration decrement of a speech sound (but not of a sinusoidal tone) was associated with poor auditory verbal memory in schizophrenia patients.

As previously mentioned, medication did not abolish MMN abnormality in schizophrenia patients (Catts et al., 1995; Kasai et al., 2002c; Kawakubo et al., 2006; Korostenskaja et al., 2005; Umbricht et al., 1998, 1999). Furthermore, this abnormality was present irrespective of the inter-stimulus interval (ISI), the deviant-stimulus probability, and the magnitude of stimulus change (Javitt et al., 1998). The fact that this MMN deficiency was observed both with short and long ISIs indicates that the problem is in memory-trace formation (and thus in perception; see Näätänen and Winkler, 1999) rather than in a shortened memory-trace duration. Hence, this data pattern is orthogonal to that obtained in patients with Alzheimer’s disease, at least to that obtained with respect to the frequency-change MMN (Pekkonen et al., 1994). With short ISIs, these patients have a normal MMN, suggesting normal memory-trace formation and perception, whereas it is abnormally small or totally absent when the ISI is prolonged, indicating that their auditory sensory-memory traces are abnormally short. Moreover, MMN changes in ageing resemble those occurring in Alzheimer patients but are considerably milder; this was demonstrated by Pekkonen et al. (1996) using frequency and duration MMNs.

According to a recent meta-analysis, applying strict inclusion criteria (Umbricht and Krljes, 2005), 32 MMN studies had been carried out on schizophrenia...
up to the end of 2003. These studies showed, with a few exceptions, a considerably reduced MMN amplitude for a frequency or duration change. The estimate of the magnitude of the overall effect size was 0.99, which is considered large by the accepted standards.

Auditory- vs. frontal-cortex MMN attenuation

MMN has two main generators: (1) one in the bilateral auditory cortex (Giard et al., 1990), underlying pre-perceptual sound-change detection in the auditory cortex, which probably triggers (2) the frontal-cortex MMN generator, associated with the initiation of attention switch (call for attention; Öhman, 1979) to sound change (Giard et al., 1990; Rinne et al. 2000; see also Jemel et al., 2002; Oades et al., 2006; Schall et al., 2003; see, however, Deouell, 2007). In scalp ERP recordings, it is difficult to disentangle these two MMN subcomponents from each other, whereas nose-referenced mastoid and MEG recordings enable the estimation of the main part of the auditory cortex-induced MMN process with no overlap with MMN process occurring in the frontal cortex.

Consequently, some recent studies (Baldeweg et al., 2002; Sato et al., 2003) have reported that schizophrenia primarily attenuates MMN for duration or frequency change recorded with the frontal electrodes receiving input from both frontal and auditory cortices, whereas the polarity-reversed MMN recorded from the mastoids (receiving no frontal cortex contribution) was not affected (for corroborating results with MMN to change in a complex-tone pattern, see Alain et al., 1998). This pattern of results, interpreted by Baldeweg et al. (2002) as reflecting a dampened frontal attention-switching function, correlated with negative symptoms in Baldeweg et al.’s (2004) study. For corroborating results, see Sato et al. (2002); see also Oades et al. (1996). This dampening might contribute to the negative symptoms (such as social withdrawal) by diminishing involuntary attention switches to socially relevant auditory cues such as loudness or stress changes in speaker voice or the change from one speaker to another (see also Javitt et al., 1998; Oades et al., 1996; Sato et al., 2002).

Nevertheless, MEG studies (Ahveninen et al., 2006; Kreitschmann-Andermahr et al., 1999; Pekkonen et al., 2002; Thönnesen et al., 2008) have also demonstrated MMNm (the magnetic equivalent of MMN) attenuation in schizophrenia patients, indicating the involvement of the auditory cortex, left auditory cortex in particular (Hirayasu et al., 1998), in MMN abnormality in these patients. For corroborating MMN results obtained in a high-density EEG study applying

MMN as an index of cognitive and functional decline in schizophrenia

Umbricht and Kršjes’ (2005) meta-analysis also showed a systematic increase in effect size as a function of illness duration both for frequency and duration changes (although not quite significant for duration), indicating that this MMN amplitude attenuation, at least for frequency change, reflects disease progression. It is possible that the MMN amplitude deficit specifically indexes the gradual cognitive and functional deterioration in schizophrenia patients: Light and Braff (2005a), in a very important study, recently found a strong correlation between the global-assessment-of-functioning (GAF) score and the MMN amplitude for tone-duration prolongation in schizophrenia patients. Moreover, this MMN amplitude was highly predictive of patients’ level of independence in their domestic situations. The authors concluded that the pattern of their results suggests that ‘MMN deficits represent a core neurophysiological dysfunction that is linked to global impairments in everyday functioning in schizophrenia patients‘ (Light and Braff 2005a, p. 127). [In a similar vein, Jung et al. (2006) recently found that MMN amplitude attenuation in patients with multiple sclerosis (MS) indexes a cognitive decline occurring in a portion of these patients.]

Downloaded from http://ijnp.oxfordjournals.org/ by guest on November 4, 2016
Furthermore, the correlation between the MMN amplitude deficit for duration increment and GAF scores (Light and Braff, 2005a) was replicated in longitudinal studies 1–2 yr later, indicating a stable relationship (Light and Braff, 2005b). Consistent with this, Baldeuw et al. (2004) had previously found a correlation between patients’ deficit in the ‘MMN memory trace effect’ as recorded with the frontal electrodes for duration increment and impairments in cognitive (memory) functions. (The memory-trace effect refers to MMN enhancement as a function of the number of the preceding standards in the ‘roving-standard’ paradigm in which the standard-stimulus frequency is changed after each duration deviance.)

Light and Braff (2005a), however, found no association between MMN deficits and performance in laboratory-based tasks measuring skills that are often considered necessary for independent living, suggesting that the performance in surrogate laboratory-based tasks reflects functional capacity rather than the actual functional status (see also Toyomaki et al., 2008).

Furthermore, the relationship between duration-increment MMN and the functional status of patients was also found by Kawakubo et al. (2007). Interestingly, this relationship is also present in normal subjects (Light et al., 2007; for an analogous result for frequency-MMN, see Bazana and Stelmack, 2002), and is of the same magnitude and topographic distribution as that in schizophrenia patients. In a similar vein, larger MMNs for syllable change were recorded in children with higher levels than in children with lower levels of general intellectual functioning (Liu et al., 2007). In addition, Toyomaki et al. (2008) found that MMN deficits for duration prolongation are related to impairments in executive functioning in schizophrenia patients. Similarly, Kiang et al. (2007) observed that MMN deficiency is associated with proverb-interpretation abnormalities in schizophrenia. Furthermore, Kawakubo et al. (2007) found that MMN was predictive of the acquisition of social skills during a 3-month social-skills training programme in schizophrenia patients. This result involved the right-frontotemporal scalp current density for the across-phoneme MMN (but not that for MMNs to change in the duration of a vowel or pure tone). Together, these findings indicate that pre-attentive processes assessed with MMN account for substantial proportions of variance in key cognitive domains and real-world daily functioning both in schizophrenia patients and in healthy subjects.

However, it is unlikely that the structural or functional central auditory system changes occurring in schizophrenia patients directly cause this cognitive and functional decline, at least the changes are not responsible for all the decline. Nevertheless, it is possible that they indirectly contribute to the gradual cognitive and functional loss via intellectual deprivation (cf. the effects of sensory deprivation). This deprivation would be caused by the blurring of auditory input, most importantly that of speech input, and by the dampening of the automatic attention-switching function supporting the adequate reception and analysis of speech-related and other auditory stimulation and thus the continuous contact with the environment (see also Hirayasu et al., 1998; Shenton et al., 1997; Toyomaki et al., 2008). Consistent with this, Matthews et al. (2007) recently obtained MMN and behavioural evidence of a selective impairment in the encoding of inter-aural time cues in schizophrenia patients. This impairment could, according to the authors, have a detrimental effect on the ability to locate sounds in natural settings, and thus it could contribute to the social communication problems of these patients. In particular, as differences in the spatial location of sounds are a key cue used by listeners when selectively attending to relevant sounds in the presence of multiple competing sounds, any decline in the capacity to use spatial cues will interfere with the ability to control the focus of attention effectively and further impair the patients’ communication skills and other modes of functioning.

**MMN in separating first-episode and chronic patients**

Consistent with the results showing that the cognitive and functional decline develops gradually during the disease progression (for a review, see Umbricht and Krijes, 2005), several studies suggest that MMN enables the separation of first-episode and chronic schizophrenia patients from each another. In one of these studies, Salisbury et al.’s (2002) first-episode patients did not differ from controls with respect to the MMN amplitude for frequency change of a simple tone, whereas their chronic patients showed a distinct MMN attenuation (see also Salisbury et al., 2007). This data pattern was recently corroborated by Devrim-Üçok et al. (2008) who also used MMN to tone-frequency change. In addition, they obtained similar results even when only neuroleptic-naive patients were included. Furthermore, Umbricht et al. (2006) recorded a relatively smaller attenuation of the frequency MMN amplitude in their first-episode patients than chronic patients, whereas the duration-MMN amplitude behaved more as a trait index, being
equally attenuated in the two patient groups. Moreover, across all patients, frequency- and duration-MMNs were greater in amplitude in patients who had at least attended some college compared to those who had not. Post-hoc analyses demonstrated that the effect of education for both frequency- and duration-MMN amplitudes was only significant in the first-episode, not in the recent-onset or chronic groups. MMN deficiency at illness onset may index a more pervasive brain pathology and be observed only in a subgroup of patients, possibly in those with more precursors of schizophrenia or with an elevated risk of developing chronic schizophrenia (Umbricht et al., 2006).

In addition, very recently, Todd et al. (2008) found that at an early phase of their illness, patients had MMN deficits for duration and intensity changes, but not for frequency changes. After a prolonged illness the MMN amplitudes for duration and frequency changes were clearly smaller than after an illness of short duration, but these effects appeared to be due to ageing rather than to the duration of illness. For intensity change, in contrast, the MMN amplitudes for short and long illness duration were very similar, although in matched controls the age-related fall in MMN amplitude was considerable (see also Oades et al., 2006).

The N-methyl-D-aspartate (NMDA) receptor functional deficiency hypothesis

Javitt et al. (1996) proposed that the compromised sensory-memory trace formation in schizophrenia patients can be explained by their deficient NMDA-receptor functioning. This would explain, according to the authors, both the MMN abnormalities and the deteriorated auditory discrimination in these patients. This hypothesis received support from the authors’ monkey experiments in which the (epidurally recorded) MMN elicited by loudness decrement was abolished by MK-801 (an NMDA receptor antagonist) injection which left the afferent responses intact. Moreover, very recently, MK-801 was found to induce MMN amplitude attenuation for frequency change in the rat by Tikhonravov et al. (2008). In addition, Umbrich et al. (2000) observed that ketamine (an anesthetic with NMDA-receptor antagonizing properties) attenuated the MMN amplitude of normal subjects both for frequency change and duration increment. Furthermore, in a particularly important study, Umbrich et al. (2002) found that normal subjects with a smaller-frequency MMN amplitude (before any drug intake) were more affected (i.e. had a larger number of ‘psychotic’ responses on the Brief Psychiatric Rating Scale; BPRS) by a small dose of ketamine than subjects with a larger MMN amplitude. In addition, an analogous result was obtained for duration-MMN. Further, Kreitschmann-Andermahr et al. (2001), in a test–retest study design, found that ketamine increased MMNm latency and decreased the MMNm dipole moment, whereas it affected neither the N1m latency nor dipole moment. In contrast, however, Oranje et al. (2000) found no significant effect of ketamine on MMN to frequency change, only a clear trend.

Memantine, a compound that also acts via NMDA receptors and improves memory in patients with Alzheimer’s disease, increased the MMN amplitude for frequency change in healthy subjects whereas it did not affect the simultaneously recorded MMNm, suggesting that memantine primarily affects the frontal MMN generators not recordable with MEG (Korostenskaja et al., 2007). However, glycine, which augments the NMDA receptor function by stimulating the glycine modulatory site of the NMDA receptor, attenuated the duration-MMN amplitude in normal subjects (Leung et al., 2008). Further, antipsychotics such as clozapine (Schall et al., 1998; Umbricht et al., 1998), risperidone (Umbricht et al., 1999), and olanzapine (Korostenskaja et al., 2005) did not enhance MMN amplitude in schizophrenia patients. However, very recently, a 6-wk administration of N-acetyl-cysteine, a glutathione precursor that can potentiate the activity of NMDA receptors, increased the MMN amplitude for frequency change in schizophrenia patients (Lavoie et al., 2007). Moreover, there was tentative evidence for the improvement of the clinical condition of these patients.

Other neurotransmission systems than the glutamatergic system also regulate MMN functioning. The important role of the GABA system in modulating MMN was shown by Rosburg et al. (2004) who found that lorazepam increased the MMNm latency for intensity change (but not significantly for frequency and duration change). Furthermore, acute tryptophan depletion, which reduces the serotonin synthesis in the brain, increased MMN amplitudes in the EEG and decreased MMNm latency both for frequency and duration change, indicating that serotonin may be involved in MMN generation (Käähkönen et al., 2005). This is supported by Oranje et al.’s (2007) recent results showing that the highly selective serotonin reuptake inhibitor escitalopram increases the MMN amplitude compared to placebo. The 5-HT1A receptors are not responsible for this modulation, however, as the 5-HT1A agonist psilocybin changed neither the
MMN amplitude nor latency significantly for frequency and duration changes (even though a trend could be seen) (Umbricht et al., 2003b). Furthermore, the cholinergic system might modulate MMN as scopolamine administration was observed to reduce the MMNm amplitude for frequency change (but did not affect that for duration change) (Pekkonen et al., 2001, 2005).

Further, transdermal (Inami et al., 2005) and oral (Baldeweg et al., 2006) administration of nicotine accelerated MMN latency in normal subjects. Moreover, Dunbar et al. (2007) found an increase in the frequency-MMN amplitude and a shortening of its latency after the administration of the selective neuronal nicotinic receptor agonist AZD3480 in normal subjects. Moreover, Inami et al. (2007) reported that nicotine administration shortened the frequency-MMN latency in healthy control subjects, but not in non-smoking schizophrenia patients. The authors concluded that the impaired MMN response to nicotine administration in non-smoking schizophrenia patients may be attributed to low nicotinic receptor function, implicated in the dysregulation of the glutamatergic system. It seems that the main excitatory glutamate system (in particular the NMDA receptors) and the main inhibitory GABA system are involved in MMN generation in humans. However, there are also other neurotransmitter systems that might contribute to the generation of MMN. This possibility should be further investigated.

As MMN can be measured even in animals such as the rat (Astikainen et al., 2006; Tikhonravov et al., 2008) and the mouse (for duration but not frequency change; Umbricht et al., 2005), it should facilitate the selection of potential drugs in the pre-clinical phase before testing them in healthy human subjects and in schizophrenia patients.

**MMN as an index of genetic disposition to schizophrenia**

In healthy subjects, the MMN amplitude is genetically strongly transmitted (with heritability estimates exceeding 60%) (Hall et al., 2006). Consistent with this, a MMN amplitude reduction for duration increment was observed in asymptomatic relatives of schizophrenia patients (Michie et al., 2002; see also Brockhaus-Dumke et al., 2005) but studies in larger samples have either not confirmed these findings (Bramon et al., 2004; for an analogous result with frequency-change MMN; see Ahveninen et al., 2006) or showed a trend only (Price et al., 2005). However, Hall et al. (2007) recently found a significant, though modest, genetic correlation between the amplitude of the duration-increment MMN and schizophrenia, suggesting that it is a potentially valid endophenotype for schizophrenia. Furthermore, Jessen et al. (2001) found that healthy first-order relatives of schizophrenia patients had an attenuated MMN amplitude for frequency change (see also Schreiber et al., 1992), although, as previously mentioned, it is possible that MMN to frequency change better reflects the progression of, rather than the genetic disposition to, illness.

Studies addressing the effects of the catechol-O-methyl transferase (COMT) gene are particularly informative: the carriers of this gene, who can have structural malformations of the heart, palate and face, a mild to moderate learning disability, and communication impairments (Ryan et al., 1997; Scambler, 2000), also have (with a possible exception of the COMT<sup>108/158Val</sup> allele; Glatt et al., 2003) a considerably increased risk (30%) of schizophrenia (Egan et al., 2001; Murphy et al., 1999; Pulver et al., 1994; Shprintzen et al., 1992). It was recently found by Baker et al. (2005) that their MMN amplitude for both simple auditory (duration and frequency) changes and syllabic changes was considerably attenuated. Furthermore, these MMN amplitude attenuations correlated with the magnitude of the deterioration of behavioural sound discrimination for both types of sounds. These behavioural and MMN effects were stronger in the 22q11DS subjects carrying the COMT<sup>108/158Met</sup> allele (a greater risk of schizophrenia) than in those carrying the COMT<sup>108/158Val</sup> allele. The authors concluded that because MMN depends on NMDA receptor function (Javitt et al., 1996), modification of MMN by the COMT Val<sup>108/158Met</sup> polymorphism in 22q11DS points towards abnormal dopamine–glutamate interactions within the neural system generating MMN. For the better understanding of the basis of the cognitive dysfunction in schizophrenia, further molecular genetic studies are clearly needed.

**MMN as an index of structural brain changes**

In schizophrenia patients, a gradual decrease of the left-hemisphere temporal (Heschl’s gyrus) grey-matter volume (Hirayasu et al., 1998, 2000; Kasai et al., 2003a,b) tends to occur. Recently, Salisbury et al. (2007) found that patients first-hospitalized with schizophrenia, bipolar patients, and healthy controls did not differ from each other with respect to the frequency-MMN amplitude, whereas after a 1.5-yr follow-up only schizophrenia patients had a reduced MMN amplitude and attenuated left-hemisphere
Heschl’s gyrus grey-matter volume. [Some of this volume reduction was present in some of the patients at the first hospitalization (see also Hirayasu et al., 2000), and in these patients, in contrast to the other groups, there was a reduction in MMN amplitude which correlated with the decrease in Heschl’s gyrus volume.] Furthermore, these MMN and structural changes occurring during the follow-up period strongly correlate with each other. These findings indicate an interrelated progressive reduction of functional and structural measures, suggesting the presence of progressive pathological processes early in schizophrenia which can be monitored by using MMN. According to a recent review by van der Stelt and Belger (2007), this suggests that MMN could have profound theoretical and clinical implications for understanding and treating schizophrenia.

Conclusions

The reduction of the MMN amplitude for duration and frequency change of a repetitive sound seems to index a central, well-replicated pathophysiological mechanism of auditory dysfunction in schizophrenia. The frequency-MMN attenuation indexes the functional and cognitive decline in these patients whereas the duration-MMN deficit appears to be more closely related to the genetic disposition of the patient. The MMN data reviewed here suggest that three kinds of interrelated (see Javitt et al., 1997) brain changes may underlie schizophrenia: (1) a deficient memory-trace formation in the neurophysiological mechanisms of auditory sensory memory (as indicated by the finding that a normal MMN could not be elicited under any circumstances; Javitt et al., 1998). This is probably due to deficient NMDA receptor functioning in these patients and accounts, at least in part, for their abnormal auditory perception and deficient discrimination, and might also account for some of their auditory hallucinations. Furthermore, (2) a dampened frontal attention-switching function (possibly contributing to social withdrawal) is suggested by the attenuated responses of the frontal MMN generator. In addition, (3) the loss of the left-hemisphere Heschl’s gyrus grey-matter volume, also reflected by MMN, might in part explain the deteriorated speech perception and contribute to speech sound-related hallucinations observed in some schizophrenia patients.

The gradual functional and cognitive deterioration, indexed by the gradually increasing MMN deficit particularly for frequency change (Umbricht and Krljes, 2005) occurring in these patients, might also be explained, at least in part, by long-term effects of the previously mentioned brain changes resulting in intellectual deprivation: besides more direct effects, these brain changes cause blurring of auditory input and deterioration of the patients’ speech-dependent and other communication.

Moreover, MMN can separate the first-episode and chronic patients from each other and index the time-course of the disease, in particular the gradual functional and cognitive decline occurring in these patients. Finally, in the near future, MMN might provide a useful biomarker for assessing the response to medication in trials designed to improve the cognitive and functional impairments in schizophrenia patients (see Lavoie et al., 2007; Light and Braff 2005b).

Acknowledgements

We are grateful to Ms. Piia Lehmus for secretarial help and to Dr Ilkka Linnankoski for correcting the language. The preparation of this manuscript was supported by The Academy of Finland (grant no. 122745).

Statement of Interest

None.

References


from mismatch negativity potentials. *International Journal of Psychophysiology* 59, 49–58.


preattentive processing deficit in schizophrenia. Biological Psychiatry 30, 1059–1062.


