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Can new paradigms bring new perspectives for mismatch negativity studies in schizophrenia?

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Abstract

Attenuation of mismatch negativity (MMN), event-related potential (ERP) that assess dysfunction in auditory change detection, is a robust finding in schizophrenia. Most studies on MMN in schizophrenia use a two-tone paradigm in which the deviant sound has a different duration or frequency. Because this oddball paradigm has provided consistent results over time and has proven to be a reliable research tool, it dominates this area of research. Over twenty years of investigation into MMN in schizophrenia have shown that change in any of the characteristics of stimulation results in MMN; however there is surprisingly little evidence on MMN in schizophrenia from studies using stimulation other than the typical oddball paradigm. In this paper we focus on studies which have assessed auditory change discrimination in schizophrenia employing paradigms other than a typical oddball. We also briefly discuss research on visual MMN in schizophrenia. The aim was to highlight how research using new paradigms has added to understanding of MMN in schizophrenia. In conclusion we discuss stimulation which could be useful for future research on MMN in schizophrenia.

Keywords: Mismatch negativity, Auditory, Visual, Event-related potential, Schizophrenia, Deviant sound, Oddball, Multi-feature, Roving paradigm

Introduction

The limited computational resources of human and animal neuronal circuitry are challenged every day by receiving large volumes of data from a diverse environment. According to the perceptual load theory (Lavie et al. 2014) automatic processes are used to assign neuronal computational resources to relevant stimuli and ignore irrelevant stimuli. One of the main roles of automatic pre-attentive processes in the brain is to identify relevant environmental stimuli and prevent exceeding the system's analytical capacity by the volume of data transferred from sensory receptors. There is mounting research evidence that the mismatch negativity (MMN) is the event-related potential (ERP) that reflects the detection of novelty. Neural networks recognize novel information by continually comparing incoming stimuli with recent perception (Näätänen et al. 2012). When incoming stimuli do not match the memory trace of previous stimuli the novelty is detected by mechanisms which result in generation of MMN.

The stimulation commonly used to elicit MMN is the auditory oddball paradigm; this consists of a series of standard tones infrequently interrupted by deviant tones

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which differ in some feature (usually duration or frequency) from the standard tones. The MMN waveform is calculated by subtracting the average standard stimuli evoked ERP from the average deviant evoked ERP waveform. The magnitude of MMN is thus dependent on formation of accurate memory traces in response to standard stimuli (Baldeweg and Hirsch 2014) and the ability to discriminate incoming deviant stimuli accurately. MMN-related information processing has been interpreted as detection of discrepancies between prediction model based on information about preceding and factual incoming stimuli (Winkler 2007). In a typical oddball paradigm the peak MMN amplitude occurs 100-250 ms after the presentation of the stimuli (Fig. 1). The largest negative MMN amplitude is recorded at fronto-central electrodes (Duncan et al. 2009).

Generation of MMN is context-dependent, which means that the design of the paradigm determines whether a given stimulus is perceived as standard or deviant. MMN can also be elicited by changing sequence pattern of stimulation rather than any physical feature of the stimuli, for example by repeating a stimulus in a sequence of changing stimuli (Macdonald and Campbell 2013). In summary, MMN reflects the brain's ability to detect auditory changes automatically.

Animal experiments have shown that elicitation of a MMN is directly dependent on the functionality of NMDA receptors. An experiment conducted on monkeys (Javitt et al. 1996) found that epidural MMNs were abolished by administration of an NMDA receptor antagonist. Research using the partial NMDA antagonist ketamine (Javitt et al. 2012) provided support for the hypothesis that glutamate plays an important role in the pathophysiology of auditory perception in psychosis.

Interestingly, as well as confirming the importance of the glutamatergic system to generation of MMN, human research has linked impaired detection of auditory deviants to vulnerability to ketamine-induced psychotic symptoms. A study of healthy volunteers (Umbricht et al. 2000) reported that after administration of ketamine total score on the Brief Psychiatric Rating Scale (BPRS) and psychosis factor scores were

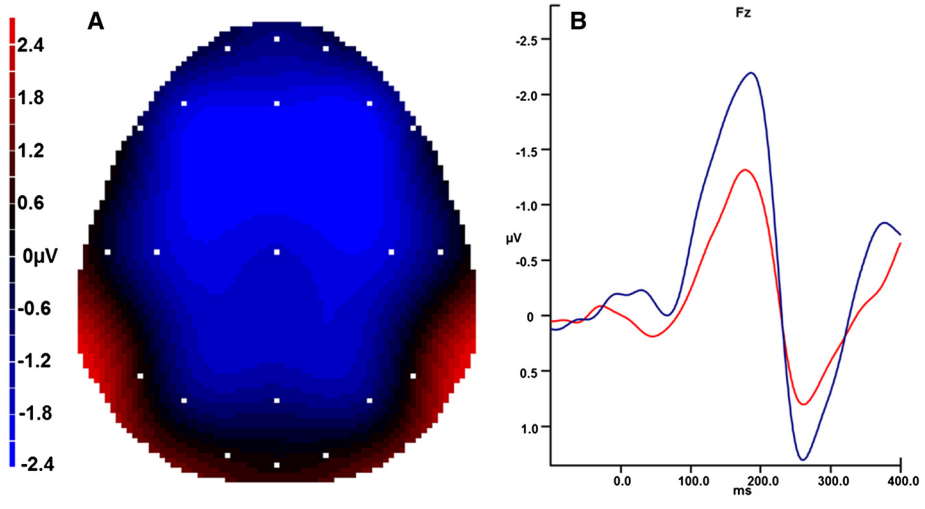

Fig. 1 Characteristics of MMN (mismatch negativity). **a** Distribution of duration MMN mean amplitudes on the scalp at the time of a peak latency in control group is presented. An inversion of the amplitude towards positive values (red color) is observed over mastoid and occipital electrodes. (Authors' data). **b** Grand averaged duration MMN waveforms at Fz electrode (red line – schizophrenia patients, blue line healthy controls) are presented. (Authors' data)

significantly higher, and MMN amplitude was significantly smaller, than after administration of a placebo. Importantly, subsequent analysis of the data from this experiment (Umbricht et al. 2002) revealed a negative correlation between MMN amplitude during the placebo and total BPRS score in the ketamine condition).

The auditory components of MMN generators are located in frontal and bilaterally in temporal lobes in primary and secondary auditory cortices (Alho 1995). Importantly for this discussion, the exact location of generators varies according to the nature of the stimulation used (Alho 1995; Tiitinen et al. 1993).

Since it was first described (Näätänen et al. 1978) the MMN has been applied in numerous areas of research (Näätänen et al. 2012). MMN is elicited automatically; the process does not depend on the attention of the subject, so that it has been used frequently in research with less cooperative subjects. Impairment of MMN in neuropsychiatric clinical populations has been associated with cognitive deficits (Näätänen et al. 2011; Näätänen et al. 2014). In this paper we review research on MMN in schizophrenia, focusing on research using stimulation other than the auditory oddball paradigm.

Review

"State of the art" – MMN in schizophrenia

Attenuation of the MMN elicited by changes in auditory stimulation is a consistent finding in patients diagnosed with schizophrenia (Umbricht and Krljes 2005). Interest in MMN in schizophrenia started with the first study to show reduced MMN amplitude in schizophrenia patients relative to healthy controls using an oddball paradigm with duration deviants (Shelley et al. 1991). This finding has been replicated numerous times and linked to clinical findings, for example for duration deviants in oddball reduced MMN was associated with poor functioning measured by Global Assessment of Functioning Scale (Light and Braff 2005a, 2005b) and deficits in social cognition in schizophrenia (Wynn et al. 2010).

The largest study of MMN in schizophrenia conducted to date (428 schizophrenia patients and 286 non-psychiatric comparison subjects; Rissling et al. 2012) confirmed that schizophrenia patients showed a reduction in MMN amplitude to duration but did not find correlations between diminished MMN and clinical characteristics such as the number of hospitalizations, duration of illness or intensity or frequency of positive or negative symptoms.

MMN is also a promising biomarker for conversion to psychosis in high-risk patients (Bodatsch et al. 2011; Perez et al. 2014; Higuchi et al. 2014; for review see Nagai et al. 2013b; Näätänen et al. 2015). Although dysfunction in auditory deviance prediction has been reported in number of clinical populations (Näätänen et al. 2012), there is also some evidence that MMN reduction is specific to schizophrenia (Baldeweg and Hirsch 2014; Umbricht et al. 2003). A large cohort study of schizophrenia and control subjects (Light et al. 2012) compared the endophenotypic status of MMN with other neurophysiological and neuropsychological indicators. MMN parameters were stable over a one-year period and, along with P3a (part of the P300 event-related potential), was the best candidate for an endophenotype of schizophrenia. A recent review (Light and Näätänen 2013) described MMN as a "breakthrough biomarker" for NMDA receptor dysfunction in schizophrenia.

Further, Rasser et al. (2011) linked MMN deficits to the anatomical and functional brain changes associated with schizophrenia, by showing that loss of cortical tissue in

schizophrenia patients was correlated with a reduction in the MMN to frequency deviance, and that reductions in gray matter volume in the right Heschl's gyrus were correlated with reduction in the MMN to duration.

There has been a lot of research on associations between MMN and demographic variables. It was shown that frequency MMN was smaller in chronic but not first episode schizophrenia patients (Salisbury et al. 2002). A later study (Kiang et al. 2009) of large groups of participants found a significant reduction in duration MMN amplitude with age in both healthy controls and schizophrenia patients aged between 18 and 65 years old. A study which compared frequency and duration deviance MMN found that duration MMN was more stable over the course of schizophrenia (Michie et al. 2000); there is however evidence that the reduction in duration MMN is greater in the early stages of schizophrenia or even in patients in the prodromal stage (Bodatsch et al. 2011; Perez et al. 2014; Higuchi et al. 2014; Hermens et al. 2010; Jahshan et al. 2012; Nagai et al. 2013a); similar findings have been reported for the magnetic counterpart of MMN (Shin et al. 2012).

In summary, MMN has played a significant role in research on schizophrenia, but it is worth asking if it remains a valuable and informative technique for research in this field.

The potential of MMN as a technique for research on cognitive deficits was noted by CNTRICS (Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia) which described MMN as a reliable, 'mature' investigation tool (Green et al. 2009; Luck et al. 2011) and recommended it as a method of evaluating cognition in clinical trials.

A recent review (Todd et al. 2013) recommended the intensive use of MMN in translational studies as means of investigating the pathophysiology of schizophrenia. Nevertheless, it has also been argued that future research on MMN in schizophrenia would benefit from the use of more sophisticated paradigms than the typical oddball paradigm (Umbricht and Krljes 2005).

Beyond duration and frequency deviants

Our brief overview of the use of MMN in research on schizophrenia suggested that differences in the deficits associated with frequency or duration deviance change detection are important. It has been concluded (Umbricht and Krljes 2005; Näätänen and Kähkönen 2009) that schizophrenia is associated with greater impairment in detection of changes in duration than changes in frequency of stimulation and that this difference is especially noticeable early in the course of illness. Moreover, duration of illness seems to have greater impact on frequency MMN (the amplitude of frequency MMN decreases with time after diagnosis) than on duration MMN, which appears to be more stable over the course of schizophrenia. It should be noted, however, that a recent metaanalysis suggested that duration MMN was also affected by normal aging in non-psychiatric populations (Cheng et al. 2013b). It has also been argued that all MMN paradigms rely on a similar neuronal mechanism and that use of different stimulation modes and formats might be an obstacle to comparative analysis (Todd et al. 2013).

There are only a few studies on schizophrenia patients whereby methodology diverge from the traditional oddball with frequency or duration deviants. The summary in Table 1 suggests that using novel deviants in the oddball task or a more complex stimulation design can provide interesting, new information.

Table 1 MMN studies of schizophrenia with stimulation beyond duration and frequency deviants

Study	Subjects	Paradigm	Deviants	Main findings	Comments and conclusions
Baldeweg et al. 2002	14 schizophrenia patients and 14 healthy controls	Roving paradigm (changing number of standards between deviants: 2, 6, 18 or 38)	Frequency (12 frequencies from 700 to 1250 Hz) and duration deviants (50 ms)	Attenuation of MMN amplitude over frontal sites but not over mastoids was found in schizophrenia.	Isolated frontal MMN generator impairment in schizophrenia was suggested.
Baldeweg et al. 2004	28 schizophrenia patients; 20 healthy controls	Roving paradigm (changing number of standards between deviants: 2, 4, 8, 18 or 36)	Frequency (12 different frequencies ranging from 700 to 1250 Hz) and duration deviants (50 ms)	"MMN slope" (mean value of a relative gain of MMN amplitudes observed each time the number of standards was increased) was negatively correlated with cognitive tests ratings.	The dysfunction in memory trace formation seem to contribute to attenuation of MMN. For the first time reduction of MMN was associated with worse cognitive performance in schizophrenia.
Baldeweg and Hirsch 2014	49 schizophrenia, 25 bipolar, 15 dementia patients; 49 healthy controls	Roving paradigm (changing number of standards between deviants: 2, 6 or 36)	Frequency (12 different frequencies ranging from 700 to 1250 Hz) and duration deviants (75 ms)	Only for schizophrenia patients a significant attenuation of MMN, when compared to healthy controls was found.	This study provided evidence for specificity of reduction of MMN in schizophrenia.
Fisher et al. 2008b	24 schizophrenia patients and 12 healthy controls	3 different oddballs (stimulation replicated from Kasai et al. (2002))	Tone duration deviant, phenome duration deviant, across-phoneme deviant	Perceived clarity of AVH (auditory verbal hallucinations) correlated with reduction of MMN elicited by phenome paradigms but not pure tone stimulation.	This study opposes general notion that MMN is not influenced by symptoms experienced by patients.
Fisher et al. 2008a	24 schizophrenia patients and 12 healthy controls	Multi-feature paradigm developed by Näätänen et al. (2004)	Duration, frequency, location, gap and intensity deviants	In the hallucinating patients group duration, frequency and intensity MMN amplitude was significantly reduced, when compared to healthy controls and non-hallucinating patients.	It is another study from the same research group providing evidence that forming MMN might be influenced by the individuals clinical status.
Fisher et al. 2012b	12 schizophrenia patients and 15 healthy controls	Multi-feature paradigm developed by Näätänen et al. (2004)	Duration, frequency, location, gap and intensity deviants	Correlations of AVH features measured with PSYRATS (Psychotic Symptom Rating Scale) scale with attenuated gap and location MMN and negative correlation of chlorpromazine equivalents and location MMN amplitude.	Applying deviants other than frequency and duration was informative for analysing auditory stimuli processing in schizophrenia.

Table 1 MMN studies of schizophrenia with stimulation beyond duration and frequency deviants *(Continued)*

Fisher et al. 2012a	12 schizophrenia patients	Optimized multi-feature paradigm developed by Fisher et al. (2011b	Duration, frequency and intensity deviants	An administration of a nicotine significantly shortened latency of intensity MMN. Changes in intensity MMN were correlated with increased AVH clarity.	Stimulating nicotine action seems to have more significant impact on intensity than on duration or frequency MMN.
Fisher et al. 2011a	12 schizophrenia patients and 12 healthy controls	Optimized multi-feature paradigm developed by Fisher et al. (2011b)	Duration, frequency and intensity deviants	Reduction of duration and intensity MMN amplitude correlated with positive symptom ratings. Attenuation of duration MMN was more significant in patients with more severe AVH.	This study extends research on neurophysiological background of positive symptoms in schizophrenia.
Fisher et al. 2014	10 schizophrenia patients and 13 healthy controls	Oddball	Pure tone frequency deviant and environmental sound deviant (baby cry)	Amplitude and latency of MMN to novel environmental deviant was significantly reduced in schizophrenia. Amplitude of MMN was positively correlated with positive symptoms and AVH ratings.	This study explores applicability of a novel stimulation in eliciting ERP's in schizophrenia.
Friedman et al. 2012	26 schizophrenia patients and 19 healthy controls	Modified oddball; all stimuli were harmonics (500 Hz, 1000 Hz and 1500 Hz for standards)	Intensity, frequency and duration deviants	Poorer premorbid educational status, longer illness duration and worse scoring on the independent living scale correlated with reduced duration and intensity MMN.	Results of the study confirm importance for evaluation of different deviant features in MMN research in schizophrenia.
Gjini et al. 2010	12 schizophrenia patients and 12 healthy controls	Oddball with three deviants and oddball with single abstract deviant	Frequency, duration, white-noise and abstract feature deviants (standards were paired tones of ascending frequency and deviants paired tones of descending frequency)	Negative correlation between P50 gating and abstract MMN amplitude was weaker in schizophrenia patients than in healthy controls. Only white-noise MMN was significantly reduced in the schizophrenia group.	Introducing novel deviants enabled more insight into auditory information processing in schizophrenia. No significant results were found for frequency and duration MMN.

Table 1 MMN studies of schizophrenia with stimulation beyond duration and frequency deviants *(Continued)*

(Kawakubo et al. 2007)	13 schizophrenia patients	3 different oddballs (stimulation replicated from Kasai et al. (2002))	Tone duration deviant, phenome duration deviant, across-phoneme deviant	Significant correlation was found between larger MMN to across-phoneme deviant and better improvement in social scores after 3 month social skills training.	Phoneme oddball was better than tone oddball in predicting improvement in social skills.
Kreitschmann-Andermahr et al. 1999	15 schizophrenia patients and 16 healthy controls	Oddball	Two different frequency deviants (1050 Hz and 5000 Hz) and tone omission deviant	A reduction of MMNm (MMN magnetic counterpart) for all deviants show dysfunction of temporal MMN generators.	The reduction of an omission MMNm suggests that an error prediction impairment contributes to schizophrenia deficits.
Matthews et al. 2007	18 schizophrenia patients and 19 healthy controls	3 oddballs (each with different deviant type)	Three types of deviants with delayed arrival-time or different phase or loudness of a stimuli for the left and right ear	Schizophrenia group showed dysfunction in processing spatial (arrival-time or phase difference) but not loudness deviants when compared to healthy controls.	The results suggest specific impairment in exact discrimination of time cues in schizophrenia.
Rissling et al. 2013	20 schizophrenia patients and 20 healthy controls	Oddball	Duration and white-noise deviant	Attentional demand (both auditory and visual) modulated white-noise MMN and P3a in schizophrenia patients and healthy controls. Attentional modulation of auditory change detection seem to be intact in schizophrenia.	MMN to white-noise deviant seems to be more sensitive to changes in attention load and direction (visual vs auditory) than duration MMN.
Thönnessen et al. 2008	12 schizophrenia patients and 12 healthy controls	Pure-tone oddball and multi-feature paradigm designed by Näätänen et al. (2004)	Duration and intensity deviants in the oddball; duration, frequency, intensity, gap and location deviants in the multi-feature paradigm;	The MMNm was significantly reduced in the schizophrenia group over left auditory cortex for all deviants (only gap and location over right auditory cortex) presented in multi-feature paradigm. No significant difference between groups were found for oddball.	This study suggest that MMNm elicited by multi-feature is more accurate than oddball paradigm in identifying deficits in forming MMN in schizophrenia. For both paradigms, no significant reduction of electrical MMN in schizophrenia was observed.

Table 1 MMN studies of schizophrenia with stimulation beyond duration and frequency deviants *(Continued)*

Todd et al. 2008	43 schizophrenia patients and 42 healthy controls	Oddball	Intensity, frequency and duration	A reduction in duration and intensity MMN in short-illness patients with schizophrenia. In a long-illness group only frequency MMN were significantly reduced.	This study revealed potential for more variable stimulation to create patterns for some groups of patients and healthy controls.
Todd et al. 2014	33 schizophrenia patients and 58 healthy controls	Oddball composed of two stimuli sequences one with a pseudorandom and one with fixed order of stimuli	Duration, frequency, intensity and ascending frequency deviant; in fixed order sequence all frequency deviants were preceded with duration and all ascending frequency preceded intensity ones.	Intensity, duration and ascending frequency but not frequency MMN were smaller in schizophrenia. When the deviants were paired MMN for the second deviant was equally reduced in schizophrenia patients and healthy controls.	Method used for a computation of MMN (traditional vs feature-controlled) significantly influenced results. Introduced oddball design failed to reveal additional impairment in stimuli processing in schizophrenia.

Although there is a substantial and increasing body of evidence that auditory change detection is impaired in schizophrenia, issues such as the influence of antipsychotic medication and symptom severity on MMN generation require further investigation. Use of novel stimulation formats such as multi-feature paradigms (Fisher et al. 2008b, Fisher et al. 2011a, Fisher et al. 2012a, Fisher et al. 2012b) or novel stimuli like phonemes (Fisher et al. 2008a) or real-life sounds such as babies' cries (Fisher et al. 2014) has provided evidence on associations between size of MMN and the clarity or subjective location (outside or inside the head) of auditory hallucination. Studies which used typical oddball tasks were inconclusive with respect to the association between auditory hallucinations in schizophrenia and MMN amplitude (Fisher et al. 2012b).

A study using Japanese phonemes as the deviant stimuli in an oddball reported that schizophrenia patients showed an increase in MMN amplitudes after 3 months of social skills training (Kawakubo et al. 2007). The key point from the perspective of this review is that this study also used a traditional oddball paradigm and that there was no change in the amplitude of MMN to duration deviants after training. It is important to emphasize, however, that this study did not include a control group and the sample was very small (n = 13).

The MMN waveform has several components (Todd et al. 2013), which are difficult to disentangle applying a two-tone oddball paradigm. Research using a roving paradigm in which the standard stimuli were varied provided more insight into dysfunction of MMN mechanism in schizophrenia as it provided evidence for deficits in the formation of memory traces for standards (Baldeweg et al. 2004; Baldeweg and Hirsch 2014). Another oddball study (Matthews et al. 2007) showed that novel deviants could be used to investigate the exact nature of the deficit in discrimination of time cues in schizophrenia.

There are also technical advantages to using a multi-feature paradigm rather than typical oddballs, namely: more information about detection of various stimuli can be collected in shorter recording time (Näätänen et al. 2004) and signal to noise ratio is better (Thönnessen et al. 2008).

Visual MMN in schizophrenia

Although human perception relies more on the visual than the auditory system, it is only recently that research on MMN in schizophrenia has been extended to include tasks involving visual stimuli. The report of deficits in detecting changes in visual stimuli in schizophrenia was published after 17 years of intensive research on auditory change detection in schizophrenia (Urban et al. 2008). In this study the greatest reduction in the amplitude of the visual MMN (vMMN) in schizophrenia was recorded at the frontal midline electrode (there was also a reduction in amplitude at the parietal and occipital electrodes). Interest in vMMN is rising, but the findings of this pioneering study on vMMN in schizophrenia have been replicated in just a few studies.

Attenuation of visual MMN in schizophrenia was subsequently confirmed at posterior scalp regions (Neuhaus et al. 2013). These results should be analyzed carefully as they were obtained using a task which did not divert attention from deviant stimuli, which has been suggested to be an essential condition for observation of a vMMN (Stefanics et al. 2014). The authors of the study argued, however, that they could separate neighboring, probably attention-dependent negativities from vMMN (Neuhaus et al. 2013).

A third study used affective stimuli – fearful or happy faces - to generate vMMN (Csukly et al. 2013). In the schizophrenia group there was no significant vMMN response to deviant stimuli. Group comparisons revealed that the larger vMMN elicited by fearful faces in the control group was localized at the central and temporal electrodes, whereas the vMMN to happy faces was localized to central electrodes. In this study the schizophrenia group also showed worse facial recognition performance. This study was also the first to demonstrate an association between impairments in a putative error prediction mechanism and impairments in recognition of facial expressions.

Previous studies have reported an association between worse global and social functioning in schizophrenia and the amplitude of the MMN to tone increment (Light and Braff 2005a) and emotion recognition (Hooker and Park 2002). It was suggested (Csukly et al. 2013) that reduced vMMNs in schizophrenia patients were a reflection of impairments in emotion recognition, which is undoubtedly one of the crucial, nonverbal determinants of social functioning, and that vMMN might be an indicator of processes linking basic neurophysiological findings to clinical findings in schizophrenia.

Research implementing vMMN paradigms in schizophrenia is evolving. At present, these studies pose more questions about schizophrenia than they have answered. Visual stimulation requires more patient cooperation than auditory stimulation; it is important that subjects comply with instructions not to look away from the monitor. Nevertheless, the studies discussed in this section provide evidence that the deficit in MMN in schizophrenia is not confined to the auditory modality. Further research is needed if visual MMN is to become as important to schizophrenia research as based on MMN derived from processing of auditory stimuli.

Suggestions for future research

The large and increasing number of publications on MMN in various research fields means that there is also a considerable amount of work on refining paradigms and study designs. Clinical research on conditions such as schizophrenia and autism could benefit from this methodological research.

Although making detailed recommendations for research on specific disorders is beyond the scope of our review we suggest that it is important to pay attention to the stimuli used to elicit MMNs as impairments in MMN may be dependent on different stimuli in different clinical conditions and may well be different from the impairment found in schizophrenia (Näätänen et al. 2012). This means that it is important to tailor the task to the population being investigated. Näätänen et al. (2014) concluded, with respect to assessment of the mechanisms underlying MMN impairments associated with disorders of language “the use of more complex stimulation may reveal information not otherwise obtained”.

In our opinion the studies reviewed above indicate that different paradigms are sensitive to different underlying impairments; we suggest that diversifying the tasks used to elicit MMN in schizophrenia research would pay dividends. This perspective is based on information processing theories and basic research on perception and analysis of incoming stimuli.

First of all, we use perception load theory to support our position. Perception load theory posits that even a simple stimulus can impose a high load on the perceptual system if features such as size or lack of contrast mean that it is at the limits of the

sensory system (Lavie et al. 2004). A typical oddball task using a duration deviant does not exceed the sensory discriminatory capacity of schizophrenia patients: the longer auditory stimuli are detected and this is reflected in the presence of a MMN, albeit one which is smaller than that observed in healthy controls. Only when the discrimination becomes more difficult, as in the roving paradigm, can one observe phenomenona associated with high perceptual load. When a roving paradigm was used deviants which were presented after a small number of standards elicited MMN in healthy controls but not in schizophrenia patients (Baldeweg et al. 2004) and similar results were reported with visual stimuli (Csukly et al. 2013). There is, however, some research which conflicts with the hypothesis that reductions in MMN amplitude are a result of discrimination deficits. It was shown that the difference between MMN amplitudes in schizophrenia patients and controls was greater when there was a bigger difference between the frequency of standard and deviant stimuli (Javitt et al. 1998). Use of a wider range of MMN paradigms would help to create neurophysiological profiles for particular perceptual impairments and clinical conditions. It would then be possible to investigate associations between neurophysiological characteristics and neuropsychological or social variables. There has already been a study of the relationship between clozapine dose and MMN amplitude using frequency and duration deviance (Horton et al. 2011).

Second, the evidence suggests that analysis of more complex aspects of auditory stimuli, such as harmonic properties, involves more cortical region. Moreover, it has been suggested that organization of all brain regions forming auditory system is based on a harmonic principle (Wang 2013). Obviously, research which relies on discrimination between two sinusoidal tones cannot provide insight into the physiology of such a complex functional system.

Additionally, the sinusoidal tones used in typical oddball tasks are very different from the kinds of auditory stimuli we encounter in everyday life, including verbal communication, as these are harmonic.

A study using magnetoencephalography reported that the organization of MMN generators was tonotopic (Tiitinen et al. 1993). It was reported that a duration deviant created from harmonics results in a larger MMN than a single tone sinusoidal deviant (Zion-Golumbic et al. 2007). It was argued that every feature of a sound is analyzed separately and that changes are additive; duration of harmonic deviant stimuli elicit large MMN because they represent alterations in the length of all features of a sound. It was on this basis that multi-feature paradigms where designed. The paradigm using stimuli consisting of eight partials (Pakarinen et al. 2010) is of particular interest. Authors (Pakarinen et al. 2010) introduced novel deviants by manipulating the intensity or frequency of one component of a stimulus. They proposed a paradigm in which there was no 'standard' stimulus, based on the assumption that each feature of a stimulus is analyzed separately. In a sequence of complex stimuli only one sound feature changes from one stimulus to the next, while others features are repeated and act as standards.

An issue which is critical to the hypotheses about the mechanism underlying the MMN is whether it is triggered by violation of predictions about the incoming stimuli (Winkler 2007). It has also been suggested that MMN arise because there is adaptation in a group of neurons responding to standards and that subsequent presentation of a deviant stimulus elicits a different group of un-adapted neurons thus generating a negative ERP

waveform (Garrido et al. 2009). A recent study of healthy volunteers provided strong evidence for the hypothesis that MMNs are derived from violation of predictions (Wacongne et al. 2011). A paradigm which provided violations of local and global (across several sequences of sounds) expectations was used to test the validity of the two hypotheses. It is notable that a previous study using a very similar design found important differences in how auditory stimuli were processed by healthy controls and patients with disorders of consciousness (Bekinschtein et al. 2009). Interestingly, studies using a roving paradigm have provided evidence that both adaptation and predictive mechanisms contribute to MMN (Schmidt et al. 2012, Schmidt et al. 2013). An important issue for schizophrenia research is whether impairments in prediction or adaptation mechanisms or both are responsible for deficits in detection of changes in auditory stimulation. A model based on data from roving paradigm studies suggests that deficits in MMN are the result of impairments in neuronal circuits responsible for predictions about stimuli (Baldeweg and Hirsch 2014).

Schizophrenia research will only benefit from introducing novel stimulation paradigms if there is general agreement on the method of eliciting, recording and quantifying MMN (Duncan et al. 2009). Campanella and Colin (2014) pointed out that when studies do not use recommended methods it is more difficult to interpret the results. Applying new paradigms requires additional effort to develop new methodological recommendations for them and this could explain that new stimulation is not widely used in basic, and especially clinical research.

The issue of the specificity of MMN deficits to schizophrenia also arises when considering vMMN as there is evidence of dysfunction in visual processing in bipolar disorder (Maekawa et al. 2013) and major depressive disorder (Chang et al. 2011). The effects of other variables such as aging, duration of illness, psychopathology, antipsychotics *etc.* on vMMN are not known. But even at this stage it is clear that vMMN has potential as a tool for investigating recognition of affective stimuli. A paradigm using schematic faces to depict emotions is a notable recent introduction (Kreegipuu et al. 2013); this followed previous reports on vMMN elicited in emotion recognition paradigm (Susac et al. 2004). A task using changing auditory affective stimuli has also been shown to elicit MMN and has been used in research on autism (Fan and Cheng 2014). Another study has linked affective prosody (visual stimulation) and deficits in auditory discrimination (Jahshan et al. 2013). There is also a growing body of evidence that deficits in visual perception in schizophrenia (Butler et al. 2007; Brenner et al. 2009) are due to an impairment in the mechanisms used to convey visual information to the visual cortex.

The studies we have discussed can be used as a basis for further investigation into relationships between bottom-up and top-down visual processing in schizophrenia. The features of the vMMN, particularly its cortical location and the fact that it does not depend on attention, make it a potentially interesting tool for research on sensory integration processes in schizophrenia.

Conclusions

In spite of the fact that MMN can be elicited by a great variety of stimuli it seems that most data on MMN in schizophrenia is based on research using an auditory oddball paradigm with deviants to duration and frequency. The advantages of this are that it makes it easy to compare studies; however the homogeneity of stimuli may limit the

development of MMN as a valuable biomarker. For example there is evidence of age-related changes in the amplitude of frequency (Cheng et al. 2013a) and duration (Cheng et al. 2013b) MMN; such effects might bias the results of controlled studies of MMN in schizophrenia (Todd et al. 2014).

Research based on use of the other than typical two-tone oddball paradigm has quite often provided new information on auditory impairments in schizophrenia, contributing in particular to understanding of the pathophysiology of MMN deficits and their relationship to use of antipsychotic medication or particular symptoms. Research on detection of changes in visual stimulation has recently emerged as an interesting alternative to research on traditional auditory MMN. Although data on vMMN in schizophrenia are scarce, visual stimuli may be more useful for investigating MMN related to, for example, emotion recognition.

The body of evidence presented in this review supports the notion that use of a wider range of stimulation other stimulation modalities has enabled researchers to broaden investigations into the MMN system and thereby improve our understanding of deficits in pre-attentive change detection in this clinical population.

Competing interests
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author's contributions
MJ wrote the first draft of the manuscript. AW revised the manuscript. Both authors' read and approved the final manuscript.

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