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Evaluation of new MMN parameters in schizophrenia

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Short communication

Abstract. ERPs could be helpful in the objectification of many psychological measures. In the last few decades one of the most commonly used ERPs has been the mismatch negativity (MMN) potential. It may be used to detect cognitive dysfunction in patients suffering from schizophrenia, dementia, depression, and can also be successfully applied in treatment monitoring. Nevertheless, changes of MMN parameters (prolongation of latency or reduction of amplitude) are not sufficiently specific to help to diagnose particular diseases. In this study we looked for more strict and specific MMN characteristics selective for schizophrenia. Fifteen healthy human subjects and twelve suffering from schizophrenia spectrum disorders were studied. Two new parameters were considered: the speed of ascending part of MMN slope (SAS) and the half area of the MMN wave. These two measures could differentiate the early stages of cognitive processing disturbances in schizophrenia spectrum disorders.

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Electrophysiological measurement of auditory cortex sensitivity to stimulus change, namely the mismatch negativity (MMN), revealed that schizophrenia is associated with deficits in pre-attentive auditory processing (Michie et al. 2000).

MMN is an event-related potential (ERP) observed as negative voltage fluctuations on the subject's scalp with latency of about 100-250 ms from stimulus onset (Heinze et al. 1999, Näätänen 1995, Näätänen and Alho 1995, Sinkkonen and Tervaniemi 2000). The MMN is presumably generated by a mismatch process between the sensory input from a deviant stimulus and a neural sensory-memory trace representing the physical features of the standard stimulus. MMN can be elicited by any discriminable occasional change in a sound sequence irrespective of the direction of the subject's attention or task (Rinne et al. 2000), so this process is thought to be automatic, as well as sensory analysis of auditory input and its encoding into memory trace. It probably reflects pre-attentive stages of information processing (Näätänen 1998). Therefore, the MMN opens the unique possibility of an objective measure of the central presentation of a sound. MMN is a very useful tool for neurophysiological and psychophysiological analysis, and can be used in clinical research as well (Heinze et al. 1999). It appears possible to assess discriminative capabilities in individuals whose auditory capabilities are difficult to determine, including those with severe cognitive impairment (Heinze et al.1999). Despite of its rather recent discovery (Näätänen et al. 1978, Näätänen and Michie 1979), the MMN already holds a number of promising applications. Thus, combined with observations of psychiatric conditions, MMN may provide novel insights into the pathophysiology of neuropsychiatric states (Gene-Cos et al. 1999). The special interest in MMN for clinical applications is that it is elicited independently of the direction of attention, thus making it possible to study auditory discrimination, sensory memory, and involuntary attention in subjects unable or unwilling to cooperate (Näätänen 2000). Among the most promising applications of MMN are the assessment of cognitive brain development and dysfunction in newborns (Ceponiene et al. 2002a, Cheour et al. 2002) and infants (Cheour-Lunthanen et al. 1996, Kushnarenko et al. 2002), normal aging (Ceponiene et al. 2002b, Kraus et al. 1992), Alzheimer's disease (Pekkonen 2000, Pekkonen et al. 1996a,b, 2001, 2002), schizophrenia (Alfimova et al. 1999, Javitt et al. 1998, McCarley et al. 1997, Michie et al. 2000), investigation of alcohol-induced and other degenerative brain disorders (Ahveninen et al. 1999) and as an index of auditory dysfunction in dyslexia (Kujala 2002).

In a number of investigations the reduction of MMN amplitude in both medicated and unmedicated patients has been shown. Reduction of MMN by approximately 50% in schizophrenia suggests an impairment of auditory and sensory cortex with a probable anatomic locus in the superior temporal gyrus (McCarley et al. 1997). However, Kathman et al. (1995) did not find any significant differences between MMN amplitude in healthy and patient groups, although the latency in schizophrenia patients was prolonged. This could be a sign of non-specific slowness of automatic information processing in psychiatric disorders. In some chronic schizophrenia patients the reduction of MMN amplitude correlates with reduction of effectiveness of echoic memory (Salisbury et al. 2002).

The MMN is originally defined as a component of the difference wave obtained by subtracting the average response to frequent (standard) sounds from that to infrequent (deviant) sounds. Traditionally, accents has been put on MMN latency and amplitude (Sinkkonen and Tervaniemi 2000). Latency is usually measured as the time from the stimulus onset to the most prominent part of the wave. And the magnitude could be measured as peak to peak voltage.

Clinical signs and behavioral measurements typically are more sensitive and more specific than measurements of ERPs (Pratt 2000) including MMN. In this respect, MMN has proven to be less informative than such evoked potentials as the short latency auditory and somatosensory potentials or the cortical visual evoked potential, all of which have been shown to be sensitive to subtle, and often subclinical, neurological impairments that other methods of evaluation might miss. Furthermore, there is a deep gap in nosological specificity of MMN. For example, MMN amplitude may be reduced both in children with hyperactivity disorder and with lack of attention (Kemner et al. 1996). The MMN amplitude is reduced in chronic alcoholics (Polo et al. 1999). Some authors reported prolonged MMN latency in chronic alcoholic patients (Kathman et al. 1995).

The sensitivity and nosological specificity (by means to the relation of the particular disorder or disease) of ERPs, between them of MMN, may be improved by introduction of new measures alleviating some of the limitations of ERPs (our unpublished data): the effects of

aging and nonspecific aspects of auditory pathway function (Pratt 2000).

In regard to that, we are considering two new measurements of MMN. One of our new suggested measurements is the speed of the ascending slope of the MMN (SAS). It could reflect some specific aspect of pre-attentive processing of presented stimuli. This measurement is commonly used in plethysmographic recordings. The second our new proposed measurement for the MMN is the integrative area of the MMN. The example of use of this kind of measurement for the interpretation of the other ERP-contingent negative variation wave (CNV) we could find in Aristova (1999) and Slezin et al. (2001). We know that the amplitude of the signal depends on the number of the excited neurons. So, it is the quantitative measure of the neurons involved in the processing of certain stimuli. Therefore, the integrative area of MMN involves not just the maximal value of the neuronal resources (what usually is difficult to determine), but the sum of all neurons involved in processing (the integrated value). It must be pointed that the priority to the half MMN area must be given as compared to the whole MMN area due to the difficulties of identifying the end of the MMN wave.

It is possible that this measurement could be helpful in identifying the quantity of neuronal resources involved in signal processing. We suppose that introduction of both these new MMN measurements could be helpful in solving MMN problems and could be useful in clinical recordings.

The aim of this study was to look for differences between traditional MMN parameters such as latency and amplitude and the newly introduced parameters in schizophrenic patients and control subjects.

Twenty five subjects were tested in this study: 12 patients with schizophrenia spectrum disorders (5 females, 7 males), mean age 31.92 years (SD = 11.28, range 18-55 years), and 15 normal controls (7 females, 3 males), mean age 34.73 years (SD = 10.72, range 23-55 years). Diagnoses in all 12 cases according to ICD-10 were made by clinicians using all available information. A diagnosis of schizophrenia was considered in 1 case, 5 cases with schizoaffective disorder of depressive type; 3 patients had schizoaffective disorder, mixed type, 1 psychosis, and 2 delusional disorder. Healthy controls had no known neurological or psychiatric problems.

The recording sessions were always carried out between 9 a.m. and 2 p.m. During the study subjects were sitting in a chair and read self-selected text (Kraus et al. 1992, Näätänen et al. 1978). They were instructed not to attend to the tones. The stimulus intensity was individually adjusted to 60 dB above the hearing threshold. The standard tone was 1,000 Hz and 75 ms plateau duration (including 5 ms rise and 5 ms fall times). Deviant tones had a frequency of 1,000 Hz and a 25 ms duration (including 5 ms rise and 5 ms fall times). Tones were binaurally presented to the subject's left and right ear in random order (90% standards, 10% deviants). During the recording 60 deviant tones were presented. The inter-stimulus interval (ISI) was 1 s. The ERPs were recorded from F3, Fz, F4, C3, Cz, C4, and Pz sites using Ag/AgCl electrodes. Ear electrodes served as a reference for all electrodes and the grounding electrode was attached to the forehead. Usually, 2 recording sessions with 1 min interval using the same recording protocol were performed.

The analysis period was 500 ms. The raw signal was amplified in the frequency band of 0.15-30 Hz and stored on a computer disk.

Processing of data included: (i) the MMN was calculated by subtracting the standard-stimulus ERP from the deviant-stimulus ERP separately for each subject and condition. Main parameters – latency and amplitude – were calculated for each MMN wave. MMN was identified as a negative peak within a range of 100-200 ms from stimulus onset, and its amplitude was measured as peak-to-peak voltage fluctuation. Correlation with age was calculated; (ii) the mean values of the parameters and their correlation with age were compared between schizophrenics and controls; (iii) SAS was calculated in the following way: the ascending slope of the MMN wave from the point of slope rise onset to the maximum of the curve was approximated with line (Fig. 1), and the fluxion ($\Delta x/\Delta y$) of the extrapolation line was calculated; (iv) integral of half the MMN wave area was calculated and compared between schizophrenics and controls.

Statistical evaluation included data analysis with t-test. The degree of freedom (df) in all cases was 25. In cases of the non-normal distribution, non-parametric analysis Mann-Whitney U-test evaluated the significance of possible between groups differences.

The main results are as follows: (i) latency and amplitude of MMN: the mean MMN latency for the control group was 173.0 ms (SD = 10.0). For patient group it was 167.5 ms (SD = 15.6). The mean of MMN amplitude for normal group was -4.03 μV (SD = 2.5) and for schizophrenics it was -2.79 μV(SD = 1.25). The difference between controls and patients was non-significant in both latency (P=0.42) and amplitude (P=0.13); (ii)

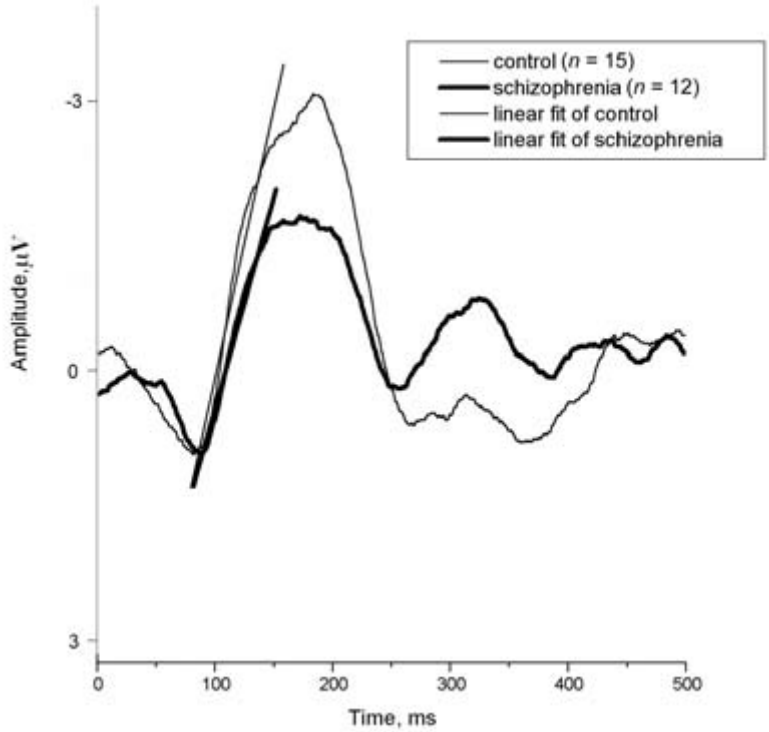

Fig. 1. Mismatch negativity (MMN) recorded from Fz (frontal midline region) of the scalp from a group of control subjects and a group of patients with schizophrenia. The subtraction waveform is generated by subtracting the ERP to standard, high probability tones from the ERP to deviant, low probability tones.

speed of ascending MMN slope: averaged MMN responses of schizophrenics and controls with extrapolation lines are depicted in Figure 1. The mean of SAS value for the schizophrenia group was 0.36 μV/ms (SD = 0.15) and for normal controls 0.55 μV/ms (SD = 0.2) (Fig. 2a). The difference between SAS in schizophrenic and controls was significant (P=0.01); (iii) half area of the MMN: analysis of the half area of the MMN revealed that it is statistically significantly (P=0.03) lower in schizophrenic patients (mean 1,398.0 ms x μV, SD = 569.3) as compared to normal controls (mean 1,950.0 ms x μV, SD = 672.1 (Fig. 2b). The smaller area of the MMN in schizophrenia could be interpreted as less neuronal resourses in pre-atentive processes. This difference is more prominent than in case of the P300 in schizophrenia, where different reasons for reduced neuronal resourses exists; (iv) correlation with age; only two parameters – half area of the MMN in control group (r=0.58, P<0.05) and the amplitude of the MMN in schizophrenia group (r=0.58, P<0.05) demonstrated significant correlation with age. No other parameters had a significant correlation with age; (v) differences between calculated parameters in schizophrenia and control group: significant difference between patient and control groups was found with regard to the newly introduced MMN parameters – SAS and half area of the MMN. The difference between schizophrenia and control groups was insignificant in case of MMN latency and amplitude. Why do the amplitude and latency of the MMN does not show such significant differences? We could suppose that MMN latency is measure relative to the SAS and MMN amplitude is relative to half MMN area. And as MMN amplitude, the half MMN area could reflect the amount of neuronal resourses involved in cognitive processing. But unlike the MMN amplitude, the half area parameter is more representative because it characterizes MMN wave more fully and reflects not only its amplitude but its form as well. In the case of MMN latency, we could speculate about the speed of cognitive processing. But it is a very relative measure as compared to SAS. SAS directly reflects the speed of the rise of the MMN wave, i.e., reflects the speed of neuronal arousal processes during this stage of information processing. Therefore, SAS and half MMN area could be concidered as more valuable in describing cognitive processes reflected in the MMN wave.

As we know, MMN reflects automatic, preattentive stages of cognitive processing. We propose that the

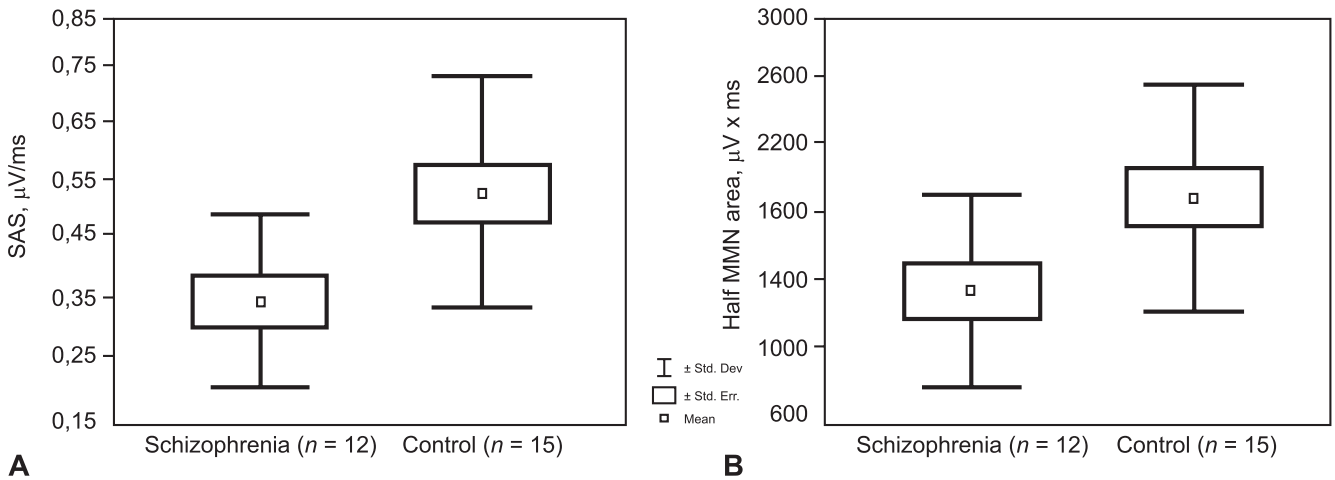

Fig. 2. Plots of mean, standard deviation and standard errors of mean. This figure illustrates: SAS (A) and half MMN area (B) values for schizphrenics and controls.

newly introduced parameters SAS and half MMN area provide us valuable information about the preattentive stages of information processing.

CONCLUSION

The speed of ascending part of mismatch negativity potential slope (SAS) and a new parameter "half MMN area" could be used to differentiate early stages of cognitive processing disturbances in schizophrenia spectrum disorders.

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