Mismatch negativity in detection of interval duration deviation in schizophrenia

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Temporal processing deficits have been noted in behavioral studies assessing patients with schizophrenia. The current study sought to explore the physiology of temporal perception while controlling the effects of motivation, attention and other cognitive processes that may contribute to behavioral measures of temporal processing. Mismatch negativity (MMN) waveforms were measured in response to variations in the temporal parameters of an ongoing train of pure tones. A standard inter-stimulus interval of 400 ms was interrupted, on average, every 20th tone by an inter-stimulus interval of 340 ms. Amplitude of MMN waveform elicited by the temporal deviance was significantly reduced in the schizophrenia group compared with controls (p = 0.016). Results suggest that behavioral difficulties on time processing tasks in schizophrenia may reflect a physiological deficit in temporal perception in this population rather than simply more general difficulties in attention or motivation. NeuroReport 14:1293–1296 © 2003 Lippincott Williams & Wilkins.

Key words: Interval discrimination; MMN; Schizophrenia; Time perception

INTRODUCTION

Cognitive deficits are regarded as a hallmark feature of schizophrenia [1]. It is believed that selected neurocognitive deficits may contribute significantly to one’s success in daily functioning, predicting ~40–50% of the variance in adaptive and community functioning [2]. Many schizophrenia researchers have focused on deficits pertaining to executive functioning (e.g. attention, working memory, planning). These deficits have historically been associated with the daily living difficulties patients with schizophrenia face [3]. A different type of processing that has been relatively overlooked, but may also contribute to daily-living difficulties for schizophrenics, is the ability to process time.

Researchers have argued that the ability to estimate time may have far-reaching effects in a person’s daily living and quality of life. Volz et al. [4] suggest that time processing may affect behaviors such as sequencing events and planning. Others believe that temporal processing may contribute to understanding warning signals that predict later events [5].

Early research involving temporal processing in schizophrenia provided us with initial indicators that time estimation may be dysfunctional in schizophrenia [6]. More recently, researchers have found that individuals with schizophrenia are impaired on both auditory and visual temporal processing tasks [7]. However, limitations of previous research include very small sample sizes and the lack of consensus in tasks described as temporal processing measures. Often, temporal processing experiments utilize what would be considered estimation tasks and perception tasks together as a measure of temporal processing, rather than separating the tasks to better clarify the processes. A further limitation is the degree of nontemporal information that has been included in the temporal processing tasks utilized. Poynter and Homa [8] point out that temporal perception tasks often require the subject to attend to non-temporal information which probably affects temporal processing performance.

Considering these factors and possible limitations, our initial behavioral study assessed temporal processing by manipulating interval durations only, rather than manipulating the durations of tones [9]. Significant deficits were observed in the schizophrenia group. More specifically, the patient group required the interval durations to be more deviant from the standard to detect a difference in duration. Controls were generally able to differentiate minute differences in duration (e.g. 60 ms), while patients with schizophrenia continued to make errors up to 150 ms. These findings may represent temporal deficits, but they also may reflect more global deficits in attention to time-dependent features, in mediating cognitive processes, or reflecting different response biases between the groups.

Our initial studies, along with previous studies of time processing have focused on behavioral indices of temporal processing. It is arguable that these behavioral studies may be confounded by lack of motivation, deficits in attention or motor activity or other mediating cognitive processes [10]. To address these potential confounds and to explore the possibility of a physiological contribution to these
deficits, a pre-attentive physiological measure of brain activity elicited by temporal variations in auditory stimuli was employed in the present study.

Mismatch negativity (MMN) was utilized to assess temporal processing. MMN is elicited in response to infrequent deviant stimuli in the context of recurring standard stimuli [11]. An advantage of MMN is the fact that it is elicited in the absence of attention or motor response and therefore may better control for mediating cognitive processes [12]. It has been argued that MMN reflects very early processing within the supratemporal auditory regions, suggesting dysfunction at the level of the auditory sensory cortex [11,13].

In schizophrenia, results have been mixed regarding deficits in MMN. Utilizing various deviant stimulus dimensions, several studies have found reduced MMN in this patient population [14], while others do not note a deficit [15]. MMN has traditionally been obtained in response to deviations in pitch, intensity, or duration of tones [16]. However, MMN has recently been utilized to assess the ability to detect changes in interval duration, absent of any other changes in stimuli. These results suggest that MMN reflects accurate discrimination of auditory temporal interval durations [17]. The current study utilized MMN to assess temporal interval discrimination in schizophrenia compared to normal controls.

MATERIALS AND METHODS

Participants: Participants consisted of 10 subjects who met DSM-IV criteria for schizophrenia, confirmed via a structured interview. Eleven normal controls were recruited through advertisements. Previous research suggests that there may be an effect of age on MMN amplitude [19]. Difference in mean age between groups was not statistically significant (t = 0.49, p = 0.625). The mean (±s.d.) age of participants in the schizophrenia group was 40.9 ± 10.5 years (range 20–50 years). Mean age for controls was 38.5 ± 11.6 (range 24–58 years).

Respondents were screened for psychiatric histories. Individuals were excluded for a current diagnosis of major depression, substance abuse, neurological disorders, head trauma, or for any personal or first-degree family member history of psychosis. All subjects gave written consent for participation, as approved by an appropriate Institutional Review Board, and were paid $30 for participation. Given that the use of typical neuroleptics may be associated with adverse effects on timing tasks, only subjects treated with atypical neuroleptics were selected [18]. Nine subjects were treated with either olanzapine or risperidone, one subject was unmedicated.

Mismatch negativity procedure: Gold-plated electrodes were attached to the following 10-20 scalp locations: Fz, Cz, Pz, left mastoid, right mastoid. Brain activity evoked by auditory stimuli was referenced to an electrode attached to the nose, bandpass filtered from 0.05 to 30 Hz, and digitally sampled at 1000 Hz. A ground electrode was attached to the left ear.

Eye movements were monitored with electrodes attached above and directly lateral to the left eye. Insert-earphones were used to binaurally present pure tones (1000 Hz, 50 ms in duration) to the subjects. Brain evoked responses were collected in a passive condition. Participants were administered a total of 4000 tones while watching a silent movie with subtitles. The standard interval between tones was 400 ms, and a deviant interval of 340 ms occurred on average every 20th interval.

Data analysis: Continuously recorded signals were separated into 400ms epochs with a 100 ms prestimulus interval relative to timing pulses. Tone-onset served as time 0. Baseline correction involved subtracting average voltage of the 100 ms prestimulus interval and was applied to each single trial. Trials for which any channel exceeded ±75 μV were removed from further analysis. The number of sweeps remaining after artifact rejection did not differ significantly between control and schizophrenic subjects for either standard or deviant waveforms. Following rejection of artifact, standard and deviant evoked responses were averaged separately off-line for each subject. Standard evoked response averages were subtracted from deviant evoked response averages and the MMN amplitude was defined as the peak negativity between 140 and 210 ms post-stimulus latency range in subtraction waveforms (deviant—standard).

RESULTS

MMN amplitude was significantly different between groups at Cz (t = −2.67; p = 0.016) and Fz (t = −2.06; p = 0.054). The control group exhibited greater MMN amplitude to the deviant interval compared to the patients with schizophrenia (Fig. 1).

MMN latency was not significantly different between groups (t = 1.14; p = 0.27; Table 1). The lack of significant group differences in latency suggests that the differences in MMN noted between groups reflects the ERP activity associated with the deviant stimuli, not the standard stimuli [10].

DISCUSSION

Previous research has focused on behavioral measures of temporal processing in schizophrenia. A variety of measures assessing temporal perception, temporal estimation and time reproduction have detected differences in the ability to process time between patients with schizophrenia and normal controls [9]. One concern that has arisen regarding behavioral measures of cognition in the study of schizophrenia is the possible confounding effect of other cognitive variables such as motivation or attention [20]. In an attempt to control for these possible confounding variables while assessing the physiology of time perception, MMN was analyzed. MMN is considered to be a preattentive index and does not require the participant to respond to stimuli. Controlling for the effects of attention and motivation, the patients’ performances measured by MMN were similar to previous behavioral findings. In general, patients’ physiological responses to deviant temporal information are significantly reduced compared to the normal controls. It should be noted that recently researchers have argued that in some situations, MMN may be modulated by attention [21]. Müller and colleagues [21] suggest that concurrent tasks during MMN recordings that direct attention towards auditory stimuli effect the MMN amplitude. However, this effect does not appear
when subjects are administered a concurrent visual task. As noted previously, subjects in the current study viewed a silent movie with subtitles. A further concern that arises regarding attention and MMN amplitude is the possible affect of sensory gating deficits in the schizophrenia population. Sensory gating is a widely recognized deficit in this population that affects the individual’s ability to filter out irrelevant stimuli [22]. It would seem that if MMN amplitude could be increased with attention to the deviant stimuli, that you may expect to see increased MMN amplitude in the patient population as a product of the inability to ignore the auditory stimuli. However, the results suggest that the MMN amplitude was significantly reduced compared to the control group. While the role of attention and sensory gating deserve greater investigation, our results do not lead us to believe that the MMN amplitudes noted were modulated by attentional processes.

**CONCLUSION**

Based on previous behavioral studies and the current electrophysiological results, schizophrenics appear to possess temporal processing deficits. These findings suggest that individuals with schizophrenia have an impaired internal clock that appears to disrupt temporal processing across a variety of conditions.

Temporal processing has historically been associated with various skills such as planning, sequencing, and anticipating events [23]. Researchers studying other psychiatric populations have suggested that temporal processing abilities may influence performance on a number of higher level cognitive processes and may be partially responsible for behavioral problems that are attributed to other characteristics, such as inattention or impulsivity [24]. Given that temporal processing deficits are noted in schizophrenia across a variety of measures, it appears that the contribution of these deficits to daily living difficulties

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**Table 1.** Two-sided, independent-sample t-test results for MMN latency and amplitude.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean controls</th>
<th>Mean patients</th>
<th>t-value</th>
<th>2-sided p-value</th>
</tr>
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<tr>
<td>MMN latency (ms)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Fz</td>
<td>171</td>
<td>162</td>
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<td>0.22</td>
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<tr>
<td>Cz</td>
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<td>172</td>
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<tr>
<td>Pz</td>
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<td>167</td>
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<td>0.82</td>
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<tr>
<td>MMN amplitude (µV):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fz</td>
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</tr>
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<tr>
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<td>0.95</td>
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<td>-1.32</td>
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</tr>
</tbody>
</table>
and on other measures of higher order cognitive processes warrants further research.

REFERENCES