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The right hemisphere fails to respond to temporal novelty in autism: Evidence from an ERP study

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ABSTRACT

Objective: This study aimed to investigate electrophysiological correlates of initial attention orienting to temporally novel sound in children with autism (CWA).
Methods: Twenty-one CWA (4–8 years) and 21 age-matched typically developing children (TDC) were presented with pairs of clicks separated by a 0.5 s intra-pair interval, with longer (7–9 s) intervals between pairs. Children watched a silent movie during click presentation. We assessed EEG perturbations and event-related potentials (ERP) in response to sounds of different temporal novelty – first (S1) and second (S2) clicks in the pair.
Results: In TDC, the early attention-modulated midtemporal N1c wave evoked by S1 and corresponding EEG phase locking and power increase were right-lateralized and were bilaterally higher than those evoked by S2. CWA demonstrated abnormal S1 responses, characterized by reduced N1c amplitude and EEG phase locking in the right midtemporal region, reversed leftward lateralization of the phase locking, and diminished later frontal N2 wave. Their brain responses to S2 were essentially normal.
Conclusions: The impaired right hemispheric processing of temporary and contextually novel information and suboptimal lateralization of normally right-lateralized attention networks may be important features of autistic disorder.
Significance: Results of this study contribute to the understanding of autism neurobiology.

1. Introduction

It is common for children with autism to have abnormal reactions to sensory stimuli, especially noticeable in the auditory modality (Dahlgren and Gillberg, 1989; O'Neill and Jones, 1997; Wing, 1969). This can be manifested in hypersensitivity to sound, under-responsiveness to sound or a combination of these sensory disturbances (Ben-Sasson et al., 2008; Grandin and Scariano, 1986; Liss et al., 2006). The presence of sensory abnormalities during the first years of life is strongly associated with a later diagnosis (Dahlgren and Gillberg, 1989; Wing, 1969).

One of the possible causes of atypical reactions to sound in autism can be aberrant attention. When attending to the stimuli, individuals with autism may demonstrate superior sensory-perceptual abilities in auditory and visual domains (Bertone et al., 2005; Bonnel et al., 2003). However, the focus of their attention is narrow and they are unable to broaden their attention quickly (Leekam et al., 2006; Mann and Walker, 2003). Many authors have reported presence of severe difficulties with disengaging and shifting attention, both within one sensory modality and between modalities (Akshoomoff and Courchesne, 1992; Casey et al., 1993; Courchesne et al., 1994; Haist et al., 2005; Townsend et al., 1996; Wainwright-Sharp and Bryson, 1993; Wainwright and Bryson, 1996). Such attention abnormalities resemble those observed in patients with parietal damage (Townsend and Courchesne, 1994). The decreased capability to automatically reorient attention to novel stimuli appearing outside a currently attended focus may be one of the possible causes of behavioral under-responsiveness to sound in autism. Studies of the autonomic nervous system give some support for this hypothesis. Specifically, the affected children often lack electrodermal orienting responses to the first auditory stimulus in a series (Van Engeland, 1984).

The failure to allocate attention automatically may have a negative impact on the child's ability to interact with other people, especially since social interaction is filled with dynamically changing

Abbreviations: CWA, children with autism; TDC, typically developing children; ERP, event-related potential; ERSP, event-related spectral perturbations; ITC, inter-trial coherence; ISI, inter-stimulus interval.

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sources of relevant information. Such impairment, if present early in life, may influence a variety of psychological functions and contribute to development of an autistic phenotype. Up to now there have been no neurophysiological investigations of automatic attention orienting to stimuli presented outside the focus of attention in children with autism. Meanwhile, such investigations could importantly contribute to understanding of the mechanisms of sensory abnormalities in this disorder. In this study we approached this issue using event-related potentials (ERPs) and time–frequency analysis of EEG.

The amplitude of the first negative-going cortical component of auditory ERP (N1; negative wave with a latency of approximately 100 ms after stimulus onset) is strongly sensitive to attention variation. It has been suggested that N1 reflects automatic 'catching attention to auditory stimulus' (Näätänen, 1986). Previous studies have consistently reported abnormalities in the late attention-related components of auditory ERP (P3, Nc) in autism (Courchesne, 1987), yet have produced ambiguous findings on the earlier N1 component. The N1 amplitude was found to be normal, decreased or even increased in individuals with autism compared to controls (for review see Bomba and Pang, 2004). The inconsistency of results may be, at least partly, explained by inadequate control for the subject's attention and diversity of experimental paradigms (Courchesne, 1987).

Indeed, the design of a particular experiment may strongly affect N1 parameters. There are two major subject-related aspects of the auditory stimulation modulating N1 amplitude: the subject's prior preparation for performing a task (prior attention) and his/her prior uncertainty about stimulus timing (time uncertainty) (Näätänen and Picton, 1987). The relative contribution of these two factors may be experimentally manipulated by changing attention towards the stimuli and by varying inter-stimulus intervals (ISI).

Näätänen and Picton (1987) noted that the direction of a subject's attention toward/away from the stimulation is the main subjective factor influencing the N1 amplitude when stimuli are presented with short (up to 3 s) ISIs. In this case, the contribution of time uncertainty is negligible and N1 amplitude is higher when stimuli are presented within an attended, compared to an unattended, channel. When stimuli are unattended and presented with relatively long (more than 3 s) ISIs the time uncertainty becomes an important factor infusing N1 amplitude. The longer the ISI, the greater is the subjective time uncertainty of the stimulus and the higher is N1 amplitude.

The amplitude of the N1 wave, elicited by auditory stimuli appearing outside the channel of attention (e.g. when a subject reads a book), increases in parallel with increasing ISI from 0.5 s up to tenths of seconds (Davis et al., 1966). As a consequence, when auditory stimuli are presented in blocks of two or more in a row, the N1 wave is large at the beginning of the sequence and displays abrupt amplitude reduction due to stimulus repetition (stimulus repetition effect). The short-term decrease of N1 is caused by 'refractoriness-like' processes (Näätänen and Picton, 1987; Sable et al., 2004), while N1 increment after a long interval of silence can be explained by low predictability of the auditory stimulus (Näätänen and Picton, 1987). The N1 wave in the later case reflects automatic allocation of recourses for processing a temporally novel event or, in other words, the initial orienting response (Atienza et al., 2001). This mechanism of orienting towards temporally or contextually novel sound is fundamentally different from that of mismatch negativity (MMN) – another change detection process that is triggered by alterations in the physical quality of repetitive sound (Näätänen et al., 2007; Näätänen and Picton, 1987).

The reduction of N1 amplitude has been repeatedly reported in schizophrenia patients, especially when sounds were presented after relatively longer silent intervals (Blumenfeld and Clementz, 2001; Clementz and Blumenfeld, 2001; Jansen et al., 2004; Shelley et al., 1999). These findings suggest that schizophrenia patients may have difficulties with reorienting their attention to temporally novel events. Together with N1 evidence, autonomic (Hultman and Ohman, 1998) and fMRI (Laurens et al., 2005) studies also support the presence of attention orienting abnormalities in schizophrenia. Within this framework, if a reduced N1 amplitude after a long silent period is characteristic of children with autism, this will suggest deficiency of the simplest form of attention orienting – automatic reorientation toward auditory stimuli in a non-attended channel. However, the majority of previous auditory ERP studies in autism were carried out using 'oddball' paradigm or 'passive hearing' conditions with short ISIs (usually less than 3 s), where effect of 'temporal novelty – initial orienting' on N1 amplitude was likely to be cancelled out. No data on the N1 in response to unattended auditory stimuli presented with long ISI have been reported in autism thus far.

In the present study we addressed this topic using the double click paradigm. The clicks were presented in pairs with short (500 ms) intervals in a pair and longer (7–9 s) intervals between pairs. We expected that if the putative N1 abnormality (amplitude reduction) was related to the deficit in automatic orienting to a temporally novel sound, then this abnormality should be detected in the N1 wave elicited by the first click (S1), while response to the second click (S2) should be normal or less disturbed. We also analyzed a child's behavior and heart inter-beat intervals during the session. This was done in order to test for the presence of possible between-group differences in prior attention to auditory stimuli and/or level of autonomic arousal.

In adults, the N1 wave has maximal amplitude at vertex (Cz). Unlike adults, children aged 4–8 years normally show maximal amplitude of the N1 wave over midtemporal regions where it was previously named N1c (Bruneau et al., 1997). Similarly to vertex N1 wave of adults, this temporal N1c component strongly decreases in amplitude with stimulus repetition with short interval (Karhu et al., 1997). Moreover, similarly to vertex N1 component in adults, child temporal N1c is modulated by stimulus intensity. Vertex N1 in children, on the other hand, does not demonstrate such modulation (Bruneau et al., 1997). In the present study we analyzed the N1c at T7 and T8 locations taking into account the prominence of the temporal N1c wave in children and similarity of its properties to those of vertex N1 in adults.

The comparison of the N1 findings with those of the later ERP negativity (N2) was also of interest. In children, ERP to a sequence of simple auditory stimuli was shown to evoke N2 wave at frontal and central sites (Karhu et al., 1997). Unlike N1, the vertex N2 wave increased in amplitude with stimulus repetition at short ISIs (e.g. 1 s) and it was suggested to reflect automatic build-up of neuronal representations in developing networks. Both the N1 and the N2 ERP components are sensitive to attention abnormalities in children (Kilpelainen et al., 1999). In autism, reduction of negativity in the N2 time range was reported in an oddball paradigm (Ciesielski et al., 1990). We expected that in children with autism this component might be suppressed during paired click presentation as well, reflecting a deficit at this relatively later stage of information processing.

Many of ERPs features may be viewed as time/frequency perturbations of underlying field potential (Delorme and Makeig, 2004). This approach assumes that there are two distinct processes contributing to an averaged ERP waveform: (1) phase resetting of ongoing EEG upon stimulus presentation; and (2) stimulus-induced changes of EEG amplitude. The spectral power increase and partial phase resetting contribute differentially to the ERPs evoked by the first and the following auditory stimuli in a train (Fuentemilla et al., 2006). The analysis of both of these EEG characteristics may, therefore, give complementary information regarding putative autism-control differences. Blumenfeld and Clementz (2001) have noted that frequency domain analysis yields