Mismatch negativity (MMN) and sensory auditory processing in children aged 9–12 years presenting with putative antecedents of schizophrenia

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ABSTRACT

Identification of markers of abnormal brain function in children at-risk of schizophrenia may inform early intervention and prevention programs. Individuals with schizophrenia are characterised by attenuation of MMN amplitude, which indexes automatic auditory sensory processing. The current aim was to examine whether children who may be at increased risk of schizophrenia due to their presenting multiple putative antecedents of schizophrenia (ASz) are similarly characterised by MMN amplitude reductions, relative to typically developing (TD) children. EEG was recorded from 22 ASz and 24 TD children aged 9 to 12 years (matched on age, sex, and IQ) during a passive auditory oddball task (15% duration deviant). ASz children were those presenting: (1) speech and/or motor development lags/problems; (2) social, emotional, or behavioural problems in the clinical range; and (3) psychotic-like experiences. TD children presented no antecedents, and had no family history of a schizophrenia spectrum disorder. MMN amplitude, but not latency, was significantly *greater* at frontal sites in the ASz group than in the TD group. Although the MMN exhibited by the children at risk of schizophrenia was unlike that of their typically developing peers, it also differed from the reduced MMN amplitude observed in adults with schizophrenia. This may reflect developmental and disease effects in a pre-prodromal phase of psychosis onset. Longitudinal follow-up is necessary to establish the developmental trajectory of MMN in at-risk children.

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1. Introduction

Schizophrenia is a neurodevelopmental disorder with onset occurring typically during late adolescence or early adulthood (Murray and Lewis, 1987; Weinberger, 1987). Premorbidly, children who later develop the illness exhibit a developmental trajectory that is subtly distinct from their healthy counterparts (Welham et al., 2009b). These putative developmental antecedents of schizophrenia, which are present already by age 12 years, include motor dysfunctions, lower IQ and poorer academic achievement, disturbances in social, emotional, and behavioural functioning, and subclinical psychotic-like experiences (Kaymaz et al., 2012; Matheson et al., 2011; Welham et al., 2009a). Such antecedents might reflect early passive expression of the disorder or may actively modify risk within the aetiological pathway (Matheson et al., 2011). The identification of salient biological and developmental indices of

schizophrenia risk in children and adolescents may facilitate early detection and inform early intervention and prevention programs (Laurens et al., 2007; Matheson et al., 2011). We previously developed a questionnaire-based community screening method for identifying children aged 9–12 years who may be at elevated risk for the development of schizophrenia by virtue of presenting multiple putative antecedents of the disorder, namely: (i) speech and/or motor developmental delays or abnormalities, (ii) social, emotional, and/or behavioural problems, and (iii) psychotic-like experiences (Laurens et al., 2007, 2008, 2011). Only longitudinal follow-up of these children can determine the specificity and sensitivity with which this triad of antecedents predicts later schizophrenia relative to other psychiatric disorders, or to no disorder. Nevertheless, preliminary evidence gathered from children presenting the antecedent triad indicates that, relative to their typically developing (TD) peers, these children are characterised by abnormalities that are present among adults with schizophrenia, including functional brain abnormality following commission of behavioural errors (Laurens et al., 2010), involuntary dyskinetic movement abnormalities (MacManus et al., 2012), and structural brain abnormalities in the temporal lobes (Cullen et al., in press). Compared to TD children, children presenting antecedents of schizophrenia (ASz) also show poorer intellectual and cognitive functioning (Cullen et al., 2010), elevated social

withdrawal (Matheson et al., in press), and impairments in facial emotion recognition (Dickson et al., in press).

A reduction in the amplitude of the mismatch negativity (MMN), an event related potential (ERP) component that indexes the brain response to auditory change detection (i.e., an automatic process that detects a difference between an incoming stimulus and the sensory memory trace of preceding stimuli), may represent another candidate biomarker (or endophenotype) indexing an increased risk for the development of schizophrenia (Moghaddam and Javitt, 2012). The identification of potential endophenotypes of schizophrenia is important because valid endophenotypes offer objective and cost-effective methods of laboratory screening and subtyping (Light et al., 2012; Luck et al., 2011). They can be employed in the development of novel targeted schizophrenia treatments and in the measurement of treatment outcomes. In research, they can provide insights into disease chronicity and inform our understanding of the relationship between genetic variability and the clinical expression of the disease (Light et al., 2012; Luck et al., 2011). In healthy adults, the MMN is typically observed as a fronto-central negativity of ~0.5–5 μV in amplitude, elicited in the latency range ~100–250 ms, with temporal and frontal generators (Duncan et al., 2009; Giard et al., 1990). In adults with schizophrenia, MMN amplitude correlates with disease severity (e.g., cognitive decline, negative symptoms), functional outcome, and fronto-temporal grey matter volume loss (Green et al., 2009; Light and Braff, 2005; Naatanen et al., 2011; Umbricht and Krljes, 2005). Relative to healthy controls, adults with chronic schizophrenia are characterised by attenuation of MMN amplitude at frontal and temporal scalp regions, but no significant latency differences (Michie, 2001; Michie et al., 2008; Naatanen and Kahkonen, 2009; Turetsky et al., 2007). This is a robust effect with a large mean effect size (0.99) and good test–retest reliability (Turetsky et al., 2007; Umbricht and Krljes, 2005). It is observed in medicated and medication-naive patients alike, and it can persist in spite of changes to medication (Todd et al., 2012).

The MMN also appears sensitive to disease state. For example, Shinozaki et al. (2002) measured the MMN at acute- and post-acute phases in patients with a retest interval of 1 to 13 months. They found an MMN reduction in 13 schizophrenia patients compared to 13 healthy controls, and this reduction was greater at the mastoidal MMN for patients during the acute phase than the post-acute phase. However, no significant schizophrenia phase-related differences were obtained at the Fz electrode.

In regard to the early stages of schizophrenia, there is some indication of a reduced MMN in first-episode schizophrenia patients compared to chronic patients and/or healthy controls (e.g., Hermens et al., 2010; Kaur et al., 2011). However, there are also incompatible findings; that is, of significant differences in MMN amplitude between groups of first-episode patients and healthy controls (e.g., Magno et al., 2008; Salisbury et al., 2002). Apparent inconsistencies in the MMN literature concerning the early stages of schizophrenia and at-risk groups may be in part due differences in the type of auditory deviants employed (e.g., duration, frequency, intensity, pitch). Although the elicited MMNs are ostensibly similar in morphology, they may have distinct neuronal origins in the frontal and temporal cortices (Belger et al., 2012). The duration deviant elicits the most robust MMN amplitude reduction in studies of schizophrenia (Belger et al., 2012; Umbricht and Krljes, 2005).

A number of studies have examined the MMN in groups purportedly *at risk* for developing schizophrenia using a variety of measures. For example, Shin et al. (2009) selected a sample of 16 *ultra-high-risk* (UHR) adults on the basis of reported *attenuated psychotic symptoms*, *brief limited intermittent psychotic symptoms*, and *trait and state risk factors* for a magnetoencephalographic (MEG) study. They found a reduced MMN dipole moment compared to the healthy age-matched controls. Their follow-up MEG study revealed a similar MMN dipole moment reduction in UHR adults and schizophrenia patients, relative to the healthy controls (Shin et al., 2012). Comparable findings of an MMN reduction in UHR groups in electroencephalographic (EEG) data have been reported (Atkinson et al., 2012; Schreiber et al., 1992; Stone et al., 2010). There is also evidence of the MMN reduction among prodromal individuals (Bodatsch et al., 2011; Brockhaus-Dumke et al., 2005), which arguably provides the strongest support for the use of the MMN as biomarker of schizophrenia risk.

In light of these findings, the current aim was to evaluate the MMN as a potential biomarker of risk for schizophrenia in putatively at-risk children who presented multiple putative antecedents of schizophrenia. We hypothesised that ASz children would be similarly characterised by the MMN reduction observed in adults with chronic schizophrenia, relative to TD low-risk control children.

2. Methods

The present MMN data were acquired during the initial phase of a larger prospective longitudinal study of children. Only the methodology relevant to the investigation of MMN is described here. Ethical permission for the study was granted by the Joint South London and Maudsley and the Institute of Psychiatry Research Ethics Committee. Caregivers and children provided written informed consent and assent, respectively, for participation.

2.1. Participants

Participants for this study were identified from the community using a school-based questionnaire screening procedure, which has been described in detail previously (Laurens et al., 2007, 2008, 2012). A community sample of 618 children (aged 9 to 12 years) and their respective primary caregivers completed questionnaires. The child questionnaire comprised the 25-item *Strengths and Difficulties Questionnaire (SDQ)* (Goodman, 2001), and nine items assessing psychotic-like experiences (PLEs) (Laurens et al., 2012). Caregiver questionnaires included quantitative and qualitative measures of developmental delays or abnormalities in speech and motor function (9 items), the parent-report SDQ, parent-report PLE items, and socio-demographic information and family history of health problems (Laurens et al., 2007).

ASz children were defined as those presenting a triad of replicated antecedents of schizophrenia, comprising: 1) a caregiver-reported delay or abnormality in speech and/or motor development; 2) an "abnormal" rating (i.e., approximately top tenth percentile of UK population norms) on at least one SDQ psychopathology scale (i.e., child-reported emotional symptoms, or caregiver-reported conduct problems, hyperactivity-inattention, or peer relationship problems); and 3) child-reported "certain experience" of at least one PLE (Laurens et al., 2007, 2008). TD children were those who presented none of the antecedents on questionnaire, and whose caregivers reported no family history of schizophrenia spectrum illness in any first-, second-, and third-degree relatives (confirmed subsequently via caregiver-report on the Family Interview for Genetic Studies (Maxwell, 1992)). None of the children had ever taken psychotropic medication. Exclusion criteria for both groups were a previous psychotic episode, neurological disorder (e.g., epilepsy), autism or Asperger's disorder, learning difficulties (IQ < 70), and insufficient ability in English language to complete interviews or questionnaires. The percentage of children meeting ASz and TD criteria in the community sample was 9% and 23% respectively. For this study, we invited 48 ASz and 47 TD children to complete a battery of assessments including ERP recordings, among whom 26 ASz (54%) and 24 TD (51%) subsequently provided MMN data for analysis.

2.2. Stimuli and procedure

The MMN recording session was completed as part of a larger battery of assessments that also measured intelligence (*Wechsler*

Abbreviated Scale of Intelligence (Wechsler, 1999)), pubertal development status (*Pubertal Development Scale* (Carskadon and Acebo, 1993)), handedness (*Annett Hand Preference Questionnaire* (Annett, 1970)), and socio-economic status (UK National Statistics Socioeconomic Classification (Office of Population Censuses and Surveys, 1980)). Diagnostic interviews were completed by clinicians with the child's parent using the Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime version (Kaufman et al., 2000).

Stimuli for the MMN task were 1600 tones at 1000 Hz, including 1360 (85%) standards of 25 ms duration and 240 (15%) deviants of 50 ms duration, all with a rise and fall time of 5 ms. These were presented binaurally at 80 dB via Sennheiser HD-215 earphones in four blocks of 400 tones (comprising 340 standards and 60 deviants each), in a pseudorandom order so that the deviants were separated by at least one standard. The stimulus onset asynchrony was 325 ms for each standard and 350 ms for each deviant, which yielded an isochronous interstimulus interval of 300 ms. The four blocks were separated by a rest period, the duration of which was determined by the participant. Participants were instructed to fixate on a cross that was presented in the centre of a PC display screen throughout the task.

2.3. Electrophysiological recording

Electrocortical data were recorded from 30 Ag/AgCl sintered electrodes, arranged according to the international 10–10 system, and referenced to the nose tip. Only data from fronto-central electrodes (i.e., F3, Fz, F4, FC3, FCz, FC4, C3, Cz, C4) are reported here, as the MMN has a characteristic fronto-central predominance. Horizontal and vertical electro-oculograms were recorded from tin electrodes positioned adjacent to the outer canthus of each eye, and above and below the left eye, respectively. The electrical impedance of each electrode was maintained at less than 10 kilo-ohms. These data were acquired continuously via NeuroScan SynAmps hardware with Scan 4.3 software (Compumedics, Charlotte, North Carolina). The sampling rate was 500 Hz, with a gain of 500, and band-pass filtering at .05 to 100 Hz.

2.4. ERP data processing

The EEG data were processed offline using Brain Vision Analyzer software (Brain Products, Gilching, Germany). The investigators were blind to group status during EEG data processing and extraction of MMN component peak amplitude and latency data, with the data subsequently un-blinded for group analyses of these indices. EEG filtering entailed a 0.5 Hz high-pass and 25 Hz low-pass zero-phase Butterworth filters with a 24 dB/octave slope, as well as a 50 Hz

notch filter. The resultant EEG was corrected for ocular artefact using the method of Gratton et al. (1983), and then segmented into 1360 standard, and 240 deviant, stimulus-locked epochs of 600 ms duration (100 ms pre-stimulus to 500 ms post-stimulus). All epochs were baseline-corrected to the 100 ms pre-stimulus epoch. Single trials contaminated by muscular activity or amplifier blocking were excluded. Single trials with voltages exceeding ± 50 μV at any electrode were excluded. Accepted epochs were averaged to produce individual participant waveforms for standards and deviants, and MMN difference waveforms (subtracting standard from deviant waves) were then computed. Choice of latency window for peak MMN component detection in the grand mean difference waveforms was informed by previous studies of adults with schizophrenia that employed a similar MMN administration protocol (Bramon et al., 2004; Hall et al., 2006), and by visual inspection of waveforms (blind to group status). The MMN was defined as the largest negative peak occurring in the range of 75 to 200 ms post-stimulus, which accommodated the individual variability in MMN peak latency that is typical of children relative to adults (Cheour et al., 2000).

2.5. Statistical analysis

Univariate ANOVAs were used to analyse group differences in continuous demographic variables, including *age*, *pubertal development status*, *IQ*, and *time-lapsed* between assessment of antecedents and MMN recording. Chi-square and Fisher's Exact tests were employed in the case of categorical demographic variables, including *sex*, *handedness*, *ethnicity*, and *social class*.

Amplitude and latency data were analysed separately in regard to the standard, deviant, and MMN difference waveforms using repeated-measures ANOVAs, with a between-subjects factor of *group* (ASz, TD), and within-subjects factors of *anterior–posterior* (Frontal, Fronto-Central, Central) and *lateral* (Midline, Left, Right) topography. Greenhouse–Geisser correction was employed with the repeated-measures ANOVAs, and Bonferroni correction for multiple comparisons was applied in post-hoc tests of simple main effects.

3. Results

3.1. Demographic and IQ data

As indicated in Table 1, there were no significant differences between the ASz and TD groups on demographic variables, pubertal development status, or estimated IQ.

Table 1
Demographic characteristics of the children presenting putative antecedents of schizophrenia (ASz) and the typically developing (TD) children.

Demographic variable	ASz (n = 26)			TD (n = 24)			Statistical test
	n	Mean	(SD)	n	Mean	(SD)	
Age (on day of ERP recording)		11 y	(12 m)		11 y	(10 m)	$F(1,48) = .1, p = .9$
Pubertal development scale score[a]		2.4	(1.3)		1.9	(0.9)	$F(1,48) = 3.2, p = .1$
IQ (full-scale estimate)[b]		105	(12)		111	(15)	$F(1,48) = 2.8, p = .1$
Time-lapse between assessment of antecedents and ERP recording		8 m	(6 m)		9 m	(6 m)	$F(1,48) = .5, p = .5$
Sex (male/female)	18/8			14/10			$\chi^2 = .6, df = 1, p = .4$
Handedness (right-dominant/mixed or left-dominant)	19/7			20/4			$\chi^2 = .8, df = 1, p = .4$
Ethnicity[c] (white British/white other/black African or African-Caribbean or mixed white-black African or African-Caribbean/other)	6/5/7/8			11/6/5/2			$p = .2$, Fisher's Exact Test
Socio-economic status based on occupation[d] (professional/managerial and technical/skilled-non-manual/skilled-manual)	3/11/6/5			2/16/3/2			$p = .4$, Fisher's Exact Test

Notes: ERP = event-related potential; y = years, m = months.

[a] Pubertal development scale total score is created as the average of scores obtained on 5 indices of pubertal status (range 1–5); higher scores indicate more advanced pubertal development (a score of 2 indicates an "Early Pubertal" stage; (Carskadon and Acebo, 1993)).

[b] Full-scale IQ estimate derived from the four subtests (two verbal, two performance) and the U.S. normative data comprising the *Wechsler Abbreviated Scale of Intelligence* (Wechsler, 1999).

[c] "Other" included white European (n = 5), Latin American (n = 2), Bangladeshi (n = 1), and mixed (n = 3) ethnicity.

[d] Socio-economic status was coded according to four classes: (i) professional occupations, (ii) managerial and technical occupations, (iii) skilled non-manual occupations, and (vi) skilled-manual occupations.

Among the ASz group, by definition, all 26 children reported at least one 'certainly true' *PLE* response (16 reported two or more experiences), experienced *delays or abnormalities in speech and/or motor development* (23 had speech and 7 had motor delays/abnormalities; including 4 children who presented both), and a *social, emotional, or behavioural problem* on the SDQ (6 had *emotional symptoms* at abnormal level, 13 had *conduct problems*, 11 had *hyperactivity-inattention*, and 13 had *peer relationship problems*). Two ASz children also had a family history of schizophrenia. Diagnostic interviews by clinicians (Kaufman et al., 2000) indicated that three ASz children met diagnostic criteria for attention-deficit hyperactivity disorder (ADHD) and four ASz children met criteria for oppositional defiant/conduct disorders (including two with comorbid ADHD and oppositional/conduct disorders). No child met diagnostic thresholds for anxiety or depressive disorders.

3.2. Electrophysiological data

No child in the study had fewer than 89 epochs (37%) contributing to the mean deviant waveforms. On average, the number of included epochs was not significantly different between the ASz (167.83 ± 37.27; mean $\pm$ SD) and TD (186.75 ± 31.27; mean $\pm$ SD) groups.

Fig. 1 illustrates the grand mean MMN waveforms for each group at the nine scalp electrodes. No significant group differences (main effects or interactions) in MMN peak latency were found. In terms of MMN peak amplitude, a significant *anterior–posterior*-by-*group* interaction was observed ($F(1.6, 75.2) = 4.31, p = .025$). There were no significant main effects or interactions involving *laterality*.
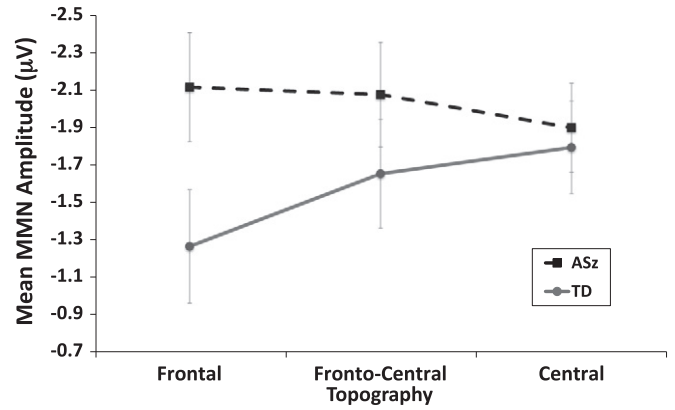
Fig. 2. Significant group difference in MMN peak amplitude at frontal sites in children presenting antecedents of schizophrenia (ASz) and typically developing children (TD). Error bars denote standard error.

Follow-up analysis indicated significantly *greater* overall frontal MMN peak amplitude for the ASz group than the TD group ($F(1,48) = 5.67, p = .021$), as shown in Fig. 2. A summary of the group means for MMN peak amplitudes and their standard errors is available in Supplementary Table 1, and a corresponding summary for latency is available in Supplementary Table 2.

Additional analyses were performed separately on the standard and deviant waveforms (see Supplementary Figs. 1 and 2) in order to
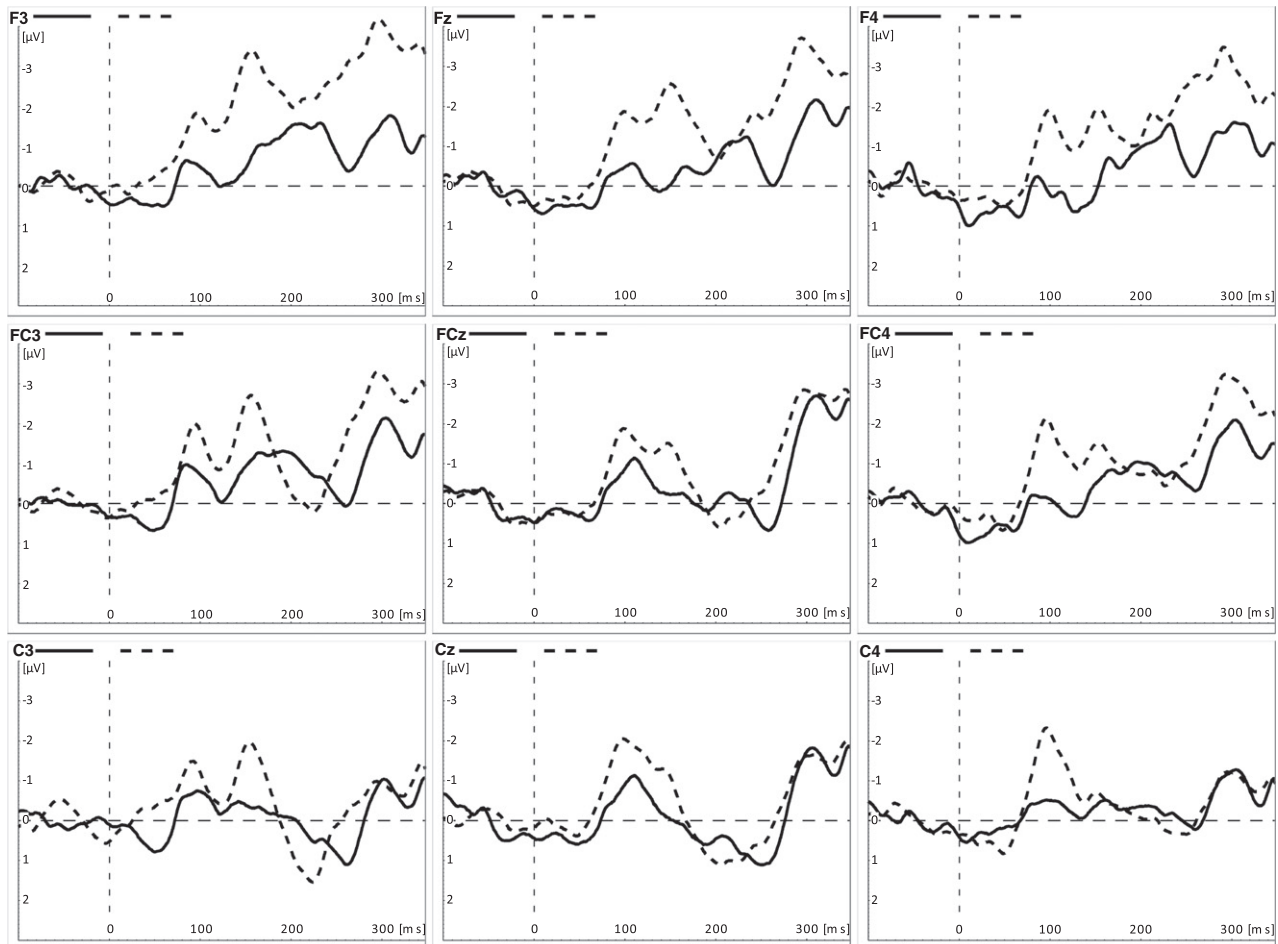
Fig. 1. Grand mean waveforms for the nine frontal, fronto-central, and central sites in children presenting antecedents of schizophrenia (hashed line) and typically developing children (solid line).
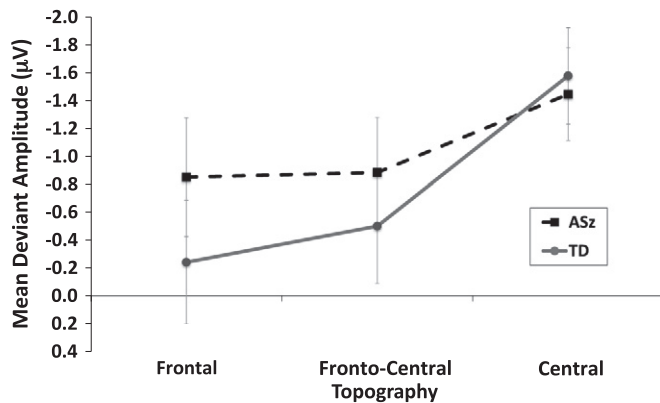
Fig. 3. Significant group difference in mean deviant amplitude at frontal sites in children presenting antecedents of schizophrenia (ASz) and typically developing children (TD). Error bars denote standard error.

elucidate the basis of the peak amplitude group effect in the MMN difference wave. There were no significant group differences in the latency of either the standard or deviant waveforms, or in the amplitude of the standard waveforms. However, a significant *anterior–posterior-by-group* interaction was evident in deviant waveforms ($F(1.2,57.5) = 3.84, p = .048$). The overall frontal amplitude of the deviant waveform was greater for the ASz compared to the TD group ($F(1,48) = 4.25, p = .045$); see Fig. 3.

4. Discussion

We observed an MMN *increase* in children purportedly at risk of schizophrenia (i.e., greater frontal MMN amplitude in the ASz children than the TD children). This MMN amplitude difference primarily reflected the response to the deviant stimuli, which elicited a larger frontal MNN for ASz than TD children. It was anticipated that the MMN effect observed in the ASz children would resemble that commonly found in adults with chronic schizophrenia. However, it is markedly different because it consists of an MMN amplitude increase, rather than a decrease (see reviews; Michie, 2001; Michie et al., 2008; Naatanen and Kahkonen, 2009; Turetsky et al., 2007). This effect is also incompatible with findings from other studies of *at risk* groups (including prodromal patients), which generally also show a reduction in MMN amplitude, albeit of smaller magnitude than in chronic schizophrenia (Atkinson et al., 2012; Bodatsch et al., 2011; Brockhaus-Dumke et al., 2005; Schreiber et al., 1992; Stone et al., 2010). Further, the observed MMN topography has a *frontal* maximum instead of the characteristic *fronto-central* maximum (Duncan et al., 2009).

The existing MMN schizophrenia literature offers no obvious explanation for the relatively increased frontal MMN observed in the ASz children. However, brain volume data that we obtained in an overlapping, though not identical, sample of children may help interpret the MMN effect (Cullen et al., in press). In that study, voxel-based morphometry analysis was used to compare grey matter (GM) and white matter (WM) volumes between groups of 20 ASz and 20 TD children. The ASz children were characterised by significantly *reduced* GM in the right temporal lobe, as well as significantly *increased* GM and WM in the left temporal lobe, relative to the TD children. Temporal GM volume loss is a common finding in chronic schizophrenia, and correlates with MMN amplitude reduction (Rasser et al., 2011). Although speculative, it is conceivable that the relative increase in left temporal GM and WM volume may contribute to the relative MMN amplitude increment observed in the ASz group. The amplitude of the MMN reflects the contributions of its generators, which are located in the auditory and frontal cortices (Naatanen and Kahkonen, 2009). Hence, the observed MMN increment may reflect the underlying structural

abnormalities evident in the temporal lobes of ASz children, specifically increased left temporal GM and WM volumes. Further research is required to test this hypothesis.

It is possible that these MMN and structural peculiarities in the ASz children are the product of maturational and disease processes. Most of the children in the sample were in an early pubertal stage of development at the time of MMN recording. Maturational changes are reflected in MMN amplitude, latency, and scalp topography. Although inter-individual variability in the MMN is high during maturation (Cheour et al., 2000), there is evidence that healthy young children generally exhibit larger MMN amplitudes and longer latencies compared to adults (Cheour et al., 2000; Dunn et al., 2008; Gomot et al., 2000). These differences decline with maturation, and the MMN typically becomes comparable to that of adults in late childhood (Cheour et al., 2000). The topography of the MMN also changes considerably during development—it is generally central in young children, whereas it is more fronto-central in adults (Cheour et al., 2000; Dunn et al., 2008; Martin et al., 2003), possibly reflecting underlying maturational processes in the frontal lobes. Frontal lobe changes occurring during puberty have a major impact on the development of cognition and attention. The frontal MMN component, which has generators in the dorsolateral prefrontal cortex, is believed to index involuntary attention switching (Naatanen et al., 2011; Segalowitz et al., 2010). Considered in light of the developmental MMN literature, and the brain structure abnormalities found in this cohort (Cullen et al., in press), the current finding of greater frontal MMN amplitude in the ASz children raises the possibility that the ASz children may be undergoing a different developmental trajectory than their TD peers, and that this trajectory may be pathological. Perhaps the enhanced frontal MMN is indicative of a delayed trajectory since the MMN tends to be larger in young children.

Maturational changes to the excitatory/inhibitory balance of neurotransmitter systems and underlying brain structure associated with the onset of puberty have been linked to the genesis of a number of psychiatric disorders, including schizophrenia (Lenroot and Giedd, 2010). Puberty entails large-scale destabilisation and restructuring of the brain, including myelination, synaptic pruning, and dopaminergic innervation of the frontal lobes (Lenroot and Giedd, 2010; Segalowitz et al., 2010). These changes significantly alter communication between the fronto-parietal and fronto-temporal networks (Segalowitz et al., 2010). Sex steroid receptors predominate in the frontal lobes and pubertal hormones alter neurotransmitter activity (Lenroot and Giedd, 2010). For example, oestrogen acts upon the cholinergic, noradrenergic, serotonergic, and hypothalamic dopaminergic systems, while oestradiol induces formation of new excitatory synapses, which entails the activation of *N*-methyl-D-aspartate (NMDA) receptors (McEwen, 2002). This has particular relevance to current models of schizophrenia that postulate NMDA receptor hypofunction as a core feature of the disease (Todd et al., 2012). The MMN appears to be an effective index of NMDA system integrity, as evidenced by pharmacological data from studies of humans and animals (Javitt et al., 1996; Todd et al., 2012). It has been proposed that the MMN reduction found in chronic schizophrenia may denote central auditory dysfunction, possibly reflecting deficient memory trace formation due to NMDA receptor hypofunction (Naatanen and Kahkonen, 2009; Naatanen et al., 2011).

In regard to the current findings, the ASz children are purportedly at risk of schizophrenia, yet the frontal MMN increment in the ASz group is ostensibly inconsistent with the well-established findings from adults with chronic schizophrenia. However, some insights are available from pharmacological studies that attempt to model cognitive deficits and neurotransmitter system dysfunction in schizophrenia by perturbing the excitatory (glutamatergic) and inhibitory (GABAergic) neurotransmitter systems in healthy adults. For example, Korostenskaja et al. (2007) administered memantine, an NMDA receptor antagonist, to 13 healthy adults in order to model involuntary attention deficits in schizophrenia believed to be associated with NMDA receptor dysfunction.

MMN amplitude of frontal origin, recorded during a passive auditory oddball task, was enhanced by memantine. This result is unusual because other NMDA receptor antagonists (e.g., ketamine) typically produce an MMN reduction (see review by Kenemans and Kahkonen, 2011). The authors suggested that their unexpected finding may reflect the unique pharmacological properties of memantine (Korostenskaja et al., 2007). Another study examined selective and involuntary attention in 12 healthy adults after administration of haloperidol, a dopamine D2 receptor antagonist, using a dichotic listening task. The results showed that haloperidol enhanced frontal MMN amplitude and involuntary attention, while impairing selective attention (Kahkonen et al., 2001). Findings such as these demonstrate that perturbing the excitatory and inhibitory balance can produce a frontal MMN increment reminiscent of that seen in the ASz children, which may be indicative of pathology occurring during puberty. Further research is necessary to determine the integrity of key neurotransmitter systems in the ASz group, but at this stage, it is reasonable to speculate that the observed MMN effect is unlike that seen in the prodrome or in chronic schizophrenia because it reflects the complex interplay of developmental and disease effects in a pre-prodromal phase of psychosis onset in children at risk of developing schizophrenia.

Other, unmeasured factors, might explain the relative MMN increase obtained in the ASz children relative to their typically developing peers. For example, Chobert et al. (in press) have demonstrated MMN amplitude increases in children following musical training. Failure to assess such potential modifiers of the MMN in our sample is likely to have contributed to the inter-individual variability observed in our study.

Interpretation of the current data in terms of future developmental trajectories and pathology remains highly speculative without the support of follow-up evidence of eventual progression to psychosis, accompanied by the characteristic MMN decrement of chronic schizophrenia. Accordingly, longitudinal follow-up is essential in order to establish the developmental trajectory of MMN in at-risk children. This will be addressed in ongoing follow-up assessments being completed in the children.

In sum, we found a relative increase in MMN amplitude in children purportedly at risk of schizophrenia, which differed from the MMN amplitude reduction typically found in adults with chronic schizophrenia. This outcome may reflect developmental and disease effects in a pre-prodromal phase of psychosis onset in children at risk of developing schizophrenia. Hence, the MMN may have utility as a biomarker for identifying children at risk of schizophrenia. Longitudinal follow-up is necessary to delineate the nature of the developmental trajectory of the MMN in at-risk children.

Acknowledgements

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijpsycho.2013.05.008.

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