Delayed preattentional functioning in early psychosis patients with cannabis use

Nicole Pesa · Daniel F. Hermens · Robert A. Battisti · Manreena Kaur · Ian B. Hickie · Nadia Solowij

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Abstract
Rationale Cannabis use is prevalent among the early psychosis (EP) population. The event-related potentials, mismatch negativity (MMN) and P3a are reduced in EP. Cannabinoids have been shown to modulate N-methyl-D-aspartate receptors which are involved in MMN generation. Objectives This study is the first to investigate the effects of cannabis use on MMN/P3a in EP. Methods EP was defined as a history of psychosis or psychotic symptoms with no progression to date to chronic schizophrenia. Twenty-two EP patients with cannabis use (EP+CANN), 22 non-cannabis-using EP patients (EP-CANN) and 21 healthy controls participated in this study. MMN/P3a was elicited using a two-tone, auditory paradigm with 8% duration deviants. Results As expected, EP-CANN showed marked reductions in MMN/P3a amplitudes compared to controls. However, EP+CANN showed evidence of a different pattern of neurophysiological expression of MMN/P3a compared to non-using patients, most notably in terms of delayed frontal MMN/P3a latencies.

Conclusions This study provides further evidence that MMN/P3a deficits are present during early psychosis and suggests that this biomarker may have utility in differentiating substance- from non-substance-related psychoses.

Keywords Cannabis · Marijuana · Mismatch negativity · P3a · Psychosis · MMN

Introduction
Cannabis use is prevalent among the first episode psychosis (FEP) population (Green et al. 2004) and worsens both symptoms and outcome (McConchie et al. 2006; Di Forti et al. 2007; Petersen et al. 2007). Heavy and prolonged cannabis use increases the risk of developing psychotic symptoms, and cannabis has been indicated as a component cause of schizophrenia (Arseneault et al., 2005; Moore et al. 2007).

Evidence has accumulated for impairment in a variety of cognitive domains, including attention, memory, inhibition and executive functioning, following both the acute administration (Solowij and Pesa 2010) and prolonged use (Solowij et al. 2002; Solowij and Pesa 2010) of cannabis among otherwise healthy users in the general population. These impairments appear similar in nature to deficits found in patients with schizophrenia (Solowij and Michie 2007). Neuroimaging studies have reported dose-related hippocampal volume reduction in long-term heavy cannabis users of a magnitude similar to that observed in schizophrenia and associated also with the development of subclinical psychotic symptoms (Yücel et al. 2008). Together, this evidence suggests overlapping neurobiological underpinnings of the effects of cannabis and schizophrenia.

The nature of cognitive functioning in the cannabis-using psychosis population is less clear, with some studies finding...
that cannabis further worsens cognitive performance (Liraud and Verdoux 2002; Pencer and Addington 2003; D’Souza et al. 2005), while others, on the other hand, have found improved cognitive performance (Kumra et al. 2005; Stirling et al. 2005; Jockers-Scherübl et al. 2007; de la Serna et al. 2010; Yücel et al. 2012). A recent meta-analysis (Yücel et al. 2012) suggested that this latter finding may have been confounded by studies that focused on a general history of cannabis use, rather than current cannabis use among patients per se. In addition, the meta-analysis revealed that patients with early onset of cannabis use may display less cognitive impairment than those who initiate cannabis use at a later age. The authors concluded that cannabis-using psychosis patients may have better cognitive functioning compared to their non-using counterparts because of a subgroup of individuals who, premorbidly, were cognitively intact, and their early exposure to cannabis precipitated the onset of psychosis (Yücel et al. 2012). This suggests a less vulnerable group who might, otherwise, not have developed psychosis. Further research into vulnerability biomarkers may elucidate the complex role of cannabis use in the development of psychosis and the underlying neurobiology. One such biomarker is the mismatch negativity brain event-related potential (ERP).

The auditory mismatch negativity (MMN) is an ERP component elicited to any violation of a repetitive pattern in stimulation, for example, a rare deviant tone embedded within a series of more frequent standard tones (Shelley et al. 1991), thus creating a neural ‘mismatch’ in sensory memory (Näätänen 1990; Umbricht and Krljes 2005). The glutamatergic system (Javitt et al. 1996; Umbricht et al. 2000; Harrison and Weinberger 2005) and, in particular, N-methyl-D-aspartate receptors (NMDAR) are critically involved in the generation of MMN (Javitt et al. 1996; Umbricht et al. 2000). MMN amplitude reduction commonly observed in schizophrenia (Umbricht and Krljes 2005) has been attributed to deficient NMDAR-dependent neurotransmission (Umbricht et al. 2000; Javitt et al. 2008). The generation of MMN appears to index the functional state of NMDAR-mediated transmission, as evidenced by studies showing that the administration of the NMDAR antagonist, ketamine, reduces MMN (as well as inducing psychotic symptoms) in healthy volunteers (Umbricht et al. 2000; Umbricht et al. 2003). Of particular relevance, the primary constituent of cannabis, Δ9-tetrahydrocannabinol (THC) (Fan et al. 2010) and other cannabinoids have been found to directly attenuate NMDAR activity (Hampson et al. 1998; Pertwee 2008; Kano et al. 2009; Liu et al. 2009; Puighermanal et al. 2009).

Reduced MMN amplitude is a robust finding in schizophrenia (Umbricht and Krljes 2005; Javitt et al. 2008; Shelley et al. 1991; Michie 2001; Michie et al. 2002), and there is speculation that MMN elicited to duration deviant sounds may be the most susceptible to dysfunction in schizophrenia (Michie 2001; Umbricht and Krljes 2005; Näätänen and Kahkonen 2009). Compared to the chronic schizophrenia literature, few studies have examined MMN in first episode or recent onset psychosis. Consistent with established schizophrenia patients, significantly reduced MMN amplitude has been reported in prodromal (Brockhaus-Dunke et al. 2005; Bodatsch et al. 2011), ultra-high risk (UHR; Atkinson et al. 2012), first episode (Salisbury et al. 2007; Jahshan et al. 2009; Hermens et al. 2010) and recent-onset (e.g. Javitt et al. 2000; Todd et al. 2008; Jahshan et al. 2012) psychosis samples. Notably, similar deficits have been found in a broad range of FEP patients, that is, those with either affective- or schizophrenia-spectrum primary diagnoses (Hermens et al. 2010; Kaur et al. 2011), suggesting that MMN impairments may not be as specific (to chronic schizophrenia) as previously thought (Javitt et al. 2008). Due to its strong association with illness duration, MMN has been suggested to be an index of progressive neurophysiological changes in the auditory and frontal cortex spanning prodromal stages through to chronic stages of psychotic illness (Umbricht and Krljes 2005; Salisbury et al. 2007; Todd et al. 2008).

Given the prevalence of cannabis use in FEP, the potential for cannabinoids to modulate NMDARs and the proposed endophenotypic status of the MMN (Solowij and Michie 2007; Umbricht and Krljes 2005), studies have begun to examine the effect of cannabis use on MMN. The first such study examined the acute administration of THC (10 mg) and cannabis extract (containing 10-mg THC and 5.4-mg cannabidiol (CBD)) in healthy volunteers (Juckel et al. 2007). While THC did not affect frequency MMN per se, the administration of cannabis extract resulted in larger MMN amplitude at central sites. This finding was interpreted as being due to CBD and its antipsychotic-like properties. A second study investigated the effects of chronic cannabis use on duration and frequency MMN (Roser et al. 2010). While initial differences between users and non-users were not sustained after controlling for duration of nicotine use, frontal MMN to frequency deviants remained significantly reduced in a chronic/heavy cannabis user subgroup compared to a short-term/light user subgroup. The duration of cannabis use correlated with smaller amplitude frequency MMN at frontal sites (marginally significant after correcting for duration of nicotine use). Most recently, this research group reported that acute administration of subanaesthetic doses of ketamine to healthy volunteers did not affect frequency or duration MMN amplitudes, but coadministration of the cannabinoid receptor antagonist rimonabant resulted in frontally reduced duration MMN (Roser et al. 2011). Finally, reduced frontal frequency MMN was reported in long-term cannabis users relative to controls (Rentzsch et al. 2011). This study also included schizophrenia patients with and without cannabis use and found increased frontal MMN in the former relative to the latter, and MMN amplitude in the cannabis-using patients did not differ significantly from controls. These studies suggest that various parameters of...
cannabis use might modulate MMN and that the effects of cannabis use on MMN may differ in patients with psychosis compared to otherwise healthy users, perhaps in a similar fashion to what has been reported regarding the effects of cannabis on cognitive function.

The positive ERP component ‘P3a’ co-occurs with the MMN (Light et al. 2007) and is thought to index automatic reorienting processes, occurring most prominently at fronto-central sites (Halgren et al. 1998; Polich 2007; Javitt et al. 2008). MMN and P3a latencies increase sequentially when measured concurrently, suggesting that they are related (Javitt et al. 2008), leading some researchers to term the combination of these components as the ‘MMN/P3a complex’ (Hermens et al. 2010; Kaur et al. 2011; Mager et al. 2005). Several studies have shown reductions in the P3a component to be present in schizophrenia (Turetsky et al. 1998; Mathalon et al. 2000; Turetsky et al. 2009) and in FEP (Hirayasu et al. 1998; Salisbury et al. 1998; Hermens et al. 2010; Kaur et al. 2011). Both MMN and P3a amplitudes show a strong relationship with higher order cognitive processes in healthy subjects and with functional status in patients (Braff and Light 2007; Hermens et al. 2010). While no studies have specifically investigated the P3a in cannabis users with or without other psychopathology, studies examining the canonical P3 (or ‘P300’) have shown delayed latencies in both of these populations (Solowij 1998; Linszen and Nieman 2004).

This is the first study to investigate the MMN/P3a complex in an early psychosis sample with comorbid cannabis use. It is important to determine the effects of cannabis use on a vulnerability marker for schizophrenia, given (1) that cannabis use is a risk factor for developing psychosis, (2) the high prevalence of use in this population and (3) the similarities in cognitive deficits and associated neurobiology between schizophrenia and chronic cannabis users. It was predicted that the non-using psychosis group would show reduced MMN compared to healthy controls, but that cannabis users with early psychosis would show increased MMN compared to their non-using peers. On the basis of previous literature (e.g. Hirayasu et al. 1998; Salisbury et al. 1998; Hermens et al. 2010), it was predicted that the non-using psychosis group would also show a reduction in P3a amplitude. In line with findings from Linszen and Nieman (2004), it was predicted that the cannabis-using early psychosis group would show delayed P3a latencies and, potentially therefore, also delayed MMN latencies.

Methods

Participants

Twenty-two early psychosis (EP) patients with cannabis use (EP+CANN), 22 non-cannabis-using early psychosis patients (EP-CANN) and 21 healthy controls (CON) matched for age and gender participated in this study. Demographic characteristics are shown in Table 1. Patients were recruited from a specialised tertiary referral service for the assessment and early intervention of youth mental health problems (Scott et al. 2009). Healthy control participants were recruited, via advertisements, from the same community. The diagnostic status of each patient was determined by a psychiatrist according to DSM-IV-TR criteria (American Psychiatric 2000). Primary diagnoses for the EP+CANN group were first episode schizophrenia (n=5), schizoaffective disorder (n=2), schizophreniform disorder (n=2), brief psychotic disorder (n=2), substance induced psychosis (n=2), bipolar with psychotic features (n=6) and major depression with psychotic features (n=2). Primary diagnoses for the EP-CANN group were first episode schizophrenia (n=9), schizoaffective disorder (n=2), schizophreniform disorder (n=5), atypical psychosis (n=1), bipolar with psychotic features (n=2) and major depression with psychotic features (n=4). All but three patients were medicated at time of testing. Of those medicated, all were treated with second-generation antipsychotic medications, 11 were prescribed an additional antidepressant, and 4 an additional mood stabiliser. One participant wore binaural hearing aids. All other participants had

Table 1 Demographic characteristics of the sample: mean (SD)

<table>
<thead>
<tr>
<th></th>
<th>EP+CANN (n=22)</th>
<th>EP-CANN (n=22)</th>
<th>CON (n=21)</th>
<th>Between group, p value</th>
<th>Pairwise comparison, p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>22.7 (3.7)</td>
<td>21.6 (3.7)</td>
<td>23.2 (3.6)</td>
<td>.356</td>
<td>–</td>
</tr>
<tr>
<td>Gender (% female)</td>
<td>38.1</td>
<td>30.4</td>
<td>60.0</td>
<td>.136</td>
<td>–</td>
</tr>
<tr>
<td>Years of education</td>
<td>11.8 (2.7)</td>
<td>12.2 (2.5)</td>
<td>15.5 (3.1)</td>
<td>&lt;.001</td>
<td>.848</td>
</tr>
<tr>
<td>WTAR FSIQ</td>
<td>98.6 (9.5)</td>
<td>98.3 (8.4)</td>
<td>106.3 (7.3)</td>
<td>.005</td>
<td>.991</td>
</tr>
<tr>
<td>AUDIT</td>
<td>10.6 (9.2)</td>
<td>5.0 (5.4)</td>
<td>5.7 (5.0)</td>
<td>.018</td>
<td>.023</td>
</tr>
</tbody>
</table>

EP+CANN early psychosis patients with cannabis use, EP-CANN early psychosis patients without cannabis use, CON healthy controls, WTAR FSIQ Wechsler Test of Adult Reading Full Scale IQ, AUDIT Alcohol Use Disorders Identification Test
normal hearing. Controls had no history of any psychiatric disorder.

Exclusion criteria for all groups were a history of major neurological disorder, major medical illness, intellectual disability, developmental disability, head injury and poor English fluency. The primary inclusion criterion for both psychosis groups was a history of psychosis or psychotic symptoms with no progression to date to chronic schizophrenia. The specific inclusion criterion for the EP+CANN group was a history of past or current cannabis use (defined as at least monthly use for at least 1 year), while any history of regular cannabis use was an exclusion criterion for both other groups. A history of cannabis and other drug use was obtained by semi-structured interview and self-report (WHO-ASSIST; Humeniuk et al. 2008). Cannabis use parameters assessed in the EP+CANN group were age of onset of cannabis use (mean 14.5 years; SD 2.2), duration since first use (mean 7.5 years; SD 3.8), frequency of cannabis use in the last month (median 30.0 days; range 1–30), quantity of cannabis in the last month (median 270.0 cones; range 4–1200) and duration of abstinence from cannabis (median 21.0 days; range 0–2,190). Of the 22 patients in the EP+CANN group, 10 were past users, and 12 were current users. Current versus past user status was based on use (or not) within the 6 months prior to testing. Alcohol use was assessed using the Alcohol Use Disorders Identification Test (AUDIT) (Babor et al. 1992). In the EP+CANN group, six had a history of polysubstance use that included amphetamines, cocaine and MDMA.

Cannabis users were required to abstain from cannabis use for at least 12 h prior to assessment, with the same period required of all participants for alcohol abstinence. All assessments were conducted on the same day. A saliva sample (Oratect-II) was taken on the day of testing to confirm the presence of cannabinoids in the current cannabis users and to corroborate self-reported abstinence from other drugs in all groups. This study was approved by the University of Sydney Human Research Ethics Committee. Participants gave written informed consent prior to participation.

Clinical and cognitive assessment

Symptom severity and current functional status were assessed using the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1962), the Hamilton Depression Rating Scale (HAM-D; Hamilton 1967) and the Social and Occupational Functioning Assessment Scale (SOFAS; Goldman et al. 1992). Positive (items 4, 12, 15) and negative symptom (items 3, 13, 16) scores were extracted from the BPRS according to (Nicholson et al. 1995). Premorbid intelligence was estimated using the Wechsler Test of Adult Reading (WTAR; Wechsler 2002).

Neurophysiological testing

Participants were presented with 2,500 pure tones at a regular 500-ms stimulus onset asynchrony (SOA) (rise and fall times 10 ms) in a pseudo-random sequence comprising 92% standard tones (50 ms, 1,000 Hz, 75 dB SPL) and 8% deviant tones varying in duration (100 ms). Tones were presented binaurally via headphones while participants watched a silent film. They were instructed to ignore the tones and relay the film’s storyline upon its conclusion. Electroencephalogram (EEG) data were acquired using a NuAmps system and Scan software (SynAmps2, SCAN 4.3.1 software) from 64 sites (including mastoids) according to the standard 10-10 International system. Data were referenced to a nose electrode, and vertical and horizontal electro-oculogram (EOG) was monitored. All impedances were kept below 5 kΩ. EEG and EOG data were continuously sampled at 500 Hz, amplified with a gain of 20,000 and digitally filtered using a 0.01- to 100-Hz bandpass filter.

EEG data were low-pass filtered at 20 Hz, epoched from 100 ms pre- to 450 ms post-stimulus onset and baseline corrected. Eyeblink artefact was corrected (Semlitsch et al. 1986), and segments containing artefacts exceeding ± 100 μV were rejected. MMN difference waveforms were obtained by subtracting ERP waveforms elicited by standard stimuli from those elicited by deviant stimuli. MMN and P3a peak amplitudes were, respectively, determined as the largest negative deflection occurring 100–250-ms post-deviant stimulus onset (Nääätänen 1992; Duncan et al. 2009) and the largest positive deflection occurring 220–400-ms post-stimulus onset (Frodl-Bauch et al. 1999; Turetsky et al. 2009). MMN measures were obtained across midline fronto-central sites (Fz and Cz) and temporal sites (M1 and M2). P3a was obtained at midline fronto-central sites only.

Statistical analyses

Differences in demographic, clinical, cognitive and neurophysiological measures were tested using one-way analysis of variance (ANOVA) with p-values<.05 considered significant. In instances where Levene's test was not met, the corrected degrees of freedom and p-values according to Brown–Forsythe's test were reported. Follow-up Tukey tests were used to determine pairwise comparisons. Pearson's correlations (or Spearman's if variables were not normally distributed) were used to determine associations between cannabis use parameters and clinical variables with MMN and P3a components. Correlations were restricted to cannabis use parameters and symptomatology. Analysis of covariance (ANCOVA) was used to adjust for the potential influence of alcohol and IQ on MMN and P3a measures, given that groups significantly differed on these variables.
Results

Demographic

Matching for gender ratio and age was achieved (see Table 1). The control group had a higher level of education and higher estimated premorbid IQ compared to both EP groups (education: \( p < .001 \); IQ: \( p < .05 \)), while psychosis groups did not differ from each other (both \( p > .05 \)). Of note, EP+CANN engaged in significantly more risky drinking behaviour than EP-CANN (\( p < .05 \)) and marginally more than controls (\( p = .06 \)), while the latter groups did not differ in AUDIT scores (\( p > .05 \)). Of note, EP+CANN and EP-CANN did not differ in age at onset of first psychotic symptoms (\( p > .05 \)), indicating that with similar current ages, they also did not differ in the duration of illness.

Clinical and cognitive findings

Clinical and cognitive measures are shown in Table 2. As expected, both EP groups showed significantly poorer ratings for all clinical and cognitive measures compared to controls (all \( p < .01 \)), but did not differ from each other. Of note, there was a trend towards more positive symptoms in the EP+CANN group compared to their non-using peers (\( p = .051 \)).

Neurophysiological findings

MMN analysis

Mean and peak amplitudes as well as peak latencies are provided in Table 3. There were significant main effects of group for MMN peak amplitude at fronto-central \( [Fz: F(2, 63) = 6.0, p < .01; Cz: F(2, 63) = 4.8, p < .05] \), but not mastoid sites (\( p > .05 \)). These main effects appear due to significantly reduced MMN peak amplitudes in EP-CANN compared to controls (Cz: \( p < .01 \); Fz: \( p < .05 \)), with no significant difference being found for the EP+CANN group compared to controls (all \( p < .05 \)). Despite the same overall pattern of results, there were no significant group differences in mean MMN amplitude.

Significant group main effects were found for MMN peak latency at Fz and the right mastoid \( [Fz: F(2, 63) = 6.1, p < .01; M2: F(2, 63) = 4.9, p = .01] \). EP+CANN showed significantly delayed latencies compared to controls (Fz: \( p < .01 \); M2: \( p < .05 \)) and EP-CANN (Fz: \( p < .05 \)). Additionally, the EP-CANN group showed delayed latencies at M2 (\( p < .01 \)) compared to controls.

P3a analysis

Significant group main effects in both mean \( [Cz: F(2, 63) = 12.3, p < .001] \) and peak \( [Fz: F(2, 63) = 4.2, p < .05; Cz: F(2, 63) = 12.2, p < .001] \) P3a amplitudes were found (see Fig. 1). Reductions were found for both psychosis groups compared to controls at Cz (mean both \( p < .001 \); peak both \( p < .001 \)), while the psychosis groups did not differ from each other (\( p > .05 \)). At Fz, however, only the EP-CANN group showed a significantly reduced peak amplitude compared to controls (\( p < .05 \)).

Significant group main effects in latency were found at Fz \( [F(2, 63) = 3.42, p < .05] \) but not Cz (\( p > .05 \)), with the EP+CANN group peaking significantly later than the EP-CANN group (\( p < .05 \)).

IQ differences, comorbid substance use and current versus abstinent cannabis users

No significant interactions with neurophysiological variables were observed when IQ and AUDIT scores were included as covariates (\( p > .05 \)), and results remained unchanged. To determine whether group differences were associated with cannabis

| Table 2 | Clinical and cognitive measures. Mean (SD) for each group |
|---|---|---|---|---|---|
| | EP+CANN \((n=22)\) | EP-CANN \((n=22)\) | CON \((n=20)\) | Between group, \( p \) value | Pairwise comparison, \( p \) value |
| Age of onset of psychotic symptoms \( ^b \) | 19.3 (5.0) | 20.3 (4.3) | – | .471 | – | – | – |
| HAM-D | 12.1 (7.0) | 8.7 (9.9) | 1.8 (2.0) | \(< .001 \) | .302 | \(< .001 \) | .008 |
| BPRS \(^c \) | 42.8 (13.9) | 38.57 (15.8) | 26.0 (2.1) | \(< .001 \) | .509 | \(< .001 \) | .004 |
| Positive symptoms | 6.7 (3.9) | 4.7 (2.7) | 3.3 (.0) | \(< .001 \) | .051 | \(< .001 \) | .126 |
| Negative symptoms | 5.0 (2.5) | 6.5 (3.9) | 3.2 (.4) | \(< .001 \) | .173 | .106 | .001 |
| SOFAS | 52.5 (10.0) | 58.3 (15.9) | 92.7 (2.8) | \(< .001 \) | .225 | \(< .001 \) | \(< .001 \) |

\(^a\) Denotes three group comparison

\(^b\) Denotes independent samples \( t \) test analysis

\(^c\) Denotes total score: general psychiatric symptoms

HAM-D Hamilton depression rating scale, BPRS brief psychiatric rating scale, SOFAS social and occupational functioning assessment scale

and not polydrug use, the six polydrug users were removed, and the analyses were repeated. Results remained unchanged except for MMN latency at Cz \( F(2,57) = 3.66, p < .05 \), where significant group differences emerged between EP+CANN (who were delayed) compared to both EP-CANN and controls (both \( p < .05 \)), while the latter groups did not differ (\( p > .05 \)).

Current versus past cannabis users within the EP+CANN group did not differ on any measure except for peak MMN latency at the left mastoid \( t(20) = -3.30, p < .01 \), which was delayed in the current users. By removing past users and repeating the analyses, the only significant group main effect revealed was for MMN latency at the left mastoid \( F(2,51) = 4.83, p < .05 \). Current users peaked significantly later than controls (\( p < .01 \)), while no other group differences were observed (\( p > .05 \)).

Associations between cannabis use parameters or clinical variables and neurophysiological findings

**Correlations with MMN**

There were five significant correlations between cannabis use parameters and MMN. Quantity and frequency of use in the last month were positively correlated with both mean (quantity: rho = .53, \( p < .05 \); frequency: rho = .55, \( p < .05 \)) and peak amplitude (quantity: rho = .63, \( p < .05 \); frequency: rho = .60, \( p < .05 \)) at the right mastoid. Duration of abstinence was negatively correlated with peak latency at the left mastoid (rho = -.66, \( p < .01 \)). When current (\( n = 12 \)) and abstinent (\( n = 10 \)) users were separated, associations between quantity and frequency remained only for current users (see Table 4).

Thus, the higher the quantity and frequency of current cannabis use are, the larger is the MMN at the right mastoid. Duration of use was also positively associated with MMN latency at Fz (\( r = -.70, p < .05 \)) for current users only, indicating the longer the duration of current use, the longer the latency at this site.

While there were no significant correlations between positive symptoms and MMN, there were nine associations for negative symptoms in the combined EP groups. Negative symptoms were positively associated with both mean and peak MMN amplitude at midline fronto-central sites (\( p < .05 \)) and negatively correlated with peak latency at Cz (\( p < .05 \)). For each association, worsening negative symptoms corresponded to a reduction in MMN amplitude and shorter latencies.

**Table 3** Mean and peak amplitudes (μV) and peak latencies (ms) for MMN and P3a components: mean (SD) for each group

<table>
<thead>
<tr>
<th></th>
<th>EP+CANN (n=22)</th>
<th>EP-CANN (n=22)</th>
<th>CON (n=20)</th>
<th>ANOVA F</th>
<th>Pairwise comparison, p value</th>
</tr>
</thead>
<tbody>
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<td><strong>MMN</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fz</td>
<td>Peak amp.</td>
<td>-4.7 (1.6)</td>
<td>-4.0 (1.8)</td>
<td>-6.0 (2.2)</td>
<td>6.0**</td>
</tr>
<tr>
<td></td>
<td>Peak lat.</td>
<td>203.1 (27.4)</td>
<td>184.3 (17.0)</td>
<td>181.6 (19.9)</td>
<td>6.1**</td>
</tr>
<tr>
<td></td>
<td>Mean amp.</td>
<td>-2.2 (1.2)</td>
<td>-1.9 (1.6)</td>
<td>-3.0 (1.9)</td>
<td>2.4</td>
</tr>
<tr>
<td>Cz</td>
<td>Peak amp.</td>
<td>-4.2 (2.2)</td>
<td>-3.8 (2.0)</td>
<td>-5.8 (2.6)</td>
<td>4.8*</td>
</tr>
<tr>
<td></td>
<td>Peak lat.</td>
<td>195.1 (32.1)</td>
<td>182.3 (18.9)</td>
<td>182.4 (20.3)</td>
<td>1.9</td>
</tr>
<tr>
<td></td>
<td>Mean amp.</td>
<td>-1.9 (1.3)</td>
<td>-1.6 (1.8)</td>
<td>-2.5 (2.0)</td>
<td>0.2</td>
</tr>
<tr>
<td>M1</td>
<td>Peak amp.</td>
<td>2.3 (1.7)</td>
<td>2.2 (1.2)</td>
<td>2.9 (1.1)</td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td>Peak lat.</td>
<td>169.8 (22.5)</td>
<td>174.5 (16.1)</td>
<td>166.1 (11.1)</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>Mean amp.</td>
<td>0.9 (1.3)</td>
<td>0.6 (0.9)</td>
<td>0.9 (0.9)</td>
<td>1.3</td>
</tr>
<tr>
<td>M2</td>
<td>Peak amp.</td>
<td>2.2 (1.3)</td>
<td>2.1 (1.1)</td>
<td>2.8 (1.3)</td>
<td>2.1</td>
</tr>
<tr>
<td></td>
<td>Peak lat.</td>
<td>177.0 (21.8)</td>
<td>179.8 (16.0)</td>
<td>163.2 (16.5)</td>
<td>4.9**</td>
</tr>
<tr>
<td></td>
<td>Mean amp.</td>
<td>0.9 (0.8)</td>
<td>0.9 (0.9)</td>
<td>1.1 (1.0)</td>
<td>0.5</td>
</tr>
<tr>
<td>P3a</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fz</td>
<td>Peak amp.</td>
<td>3.2 (3.0)</td>
<td>2.9 (1.8)</td>
<td>4.9 (2.3)</td>
<td>4.2*</td>
</tr>
<tr>
<td></td>
<td>Peak lat.</td>
<td>313.8 (48.9)</td>
<td>283.1 (33.9)</td>
<td>293.1 (33.9)</td>
<td>3.4*</td>
</tr>
<tr>
<td></td>
<td>Mean amp.</td>
<td>0.6 (1.2)</td>
<td>0.6 (1.0)</td>
<td>1.3 (1.1)</td>
<td>3.0</td>
</tr>
<tr>
<td>Cz</td>
<td>Peak amp.</td>
<td>3.6 (2.5)</td>
<td>3.7 (2.1)</td>
<td>6.6 (2.2)</td>
<td>12.2**</td>
</tr>
<tr>
<td></td>
<td>Peak lat.</td>
<td>295.7 (42.2)</td>
<td>282.6 (35.7)</td>
<td>283.0 (21.8)</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Mean amp.</td>
<td>0.8 (0.9)</td>
<td>0.9 (1.0)</td>
<td>2.1 (1.0)</td>
<td>12.3**</td>
</tr>
</tbody>
</table>

\( ** \) Denotes \( p < .01 \); \( * \) denotes \( p < .05 \)

amp amplitude (μV), lat latency (ms)
Correlations with P3a

There were no correlations between positive or negative symptoms in the combined EP groups with any P3a measures ($p > .05$) or between cannabis use variables and P3a measures in the EP+CANN group as a whole ($p < .05$). However, when current and abstinent cannabis users were separated, there was a significant positive relationship between duration of cannabis use and P3a latency in current users at Cz ($r = .73$, $p < .05$).

Discussion

This study is the first to investigate the additive effect of regular cannabis use in a group of early psychosis patients on a vulnerability marker for psychosis. Consistent with previous findings, the non-using early psychosis group showed a marked reduction in both MMN (Javitt et al. 2000; Brockhaus-Dumke et al. 2005; Salisbury et al. 2006; Todd et al. 2008; Jahshan et al. 2009; Hermens et al. 2010; Bodatsch et al. 2011; Atkinson et al. 2012) and P3a (Hirayasu et al. 1998; Salisbury et al. 1998; Hermens et al. 2010; Kaur et al. 2011) amplitudes compared to controls. Notably, EP patients who used cannabis showed a different pattern of neurophysiological expression for both MMN and P3a components compared to non-using patients, with the seemingly additive impairment of significantly delayed MMN latencies. Cannabis use parameters were more strongly associated with MMN measures than P3a.

General evidence for a different pattern of neurophysiological expression in the MMN component was found for psychosis patients who used cannabis compared to those that did not. Cannabis use did not significantly increase MMN amplitude; however, similar to Rentzsch et al. (2011), a relatively consistent pattern emerged across groups for MMN peak amplitude, with patients who used cannabis appearing to lie intermediate between controls (who showed the highest MMN amplitude) and patients who did not use cannabis (who showed the lowest MMN amplitude). These findings parallel neuropsychological findings in the literature, where cannabis-using patients show ‘superior’ neuro-psychological functioning compared to non-using patients (Stirling et al. 2005; Jockers-Scherübl et al. 2007; de la Serna et al. 2010; Yücel et al. 2012). The current sample of users may represent a subgroup who shows lower individual vulnerability for psychosis (as indexed by larger MMN) which may be better resolved by comprehensive
analyses of family history and genetic investigation. The findings also suggest that MMN may have utility in differentiating substance-related from non-substance-related psychosis (Hermens et al. 2009).

Some have also suggested that cannabis may possess neuroprotective qualities when use is initiated prior to the onset of psychosis (Stirling et al. 2005; Jockers-Scherübl et al. 2007). Indeed, the current sample initiated their cannabis use prior to the onset of their first expression of psychotic symptoms. Neuroprotective mechanisms could potentially be driven by cannabidiol (CBD), a constituent of cannabis plant matter that has been shown to possess anxiolytic or even antipsychotic properties (Zuardi et al. 2006) and to ameliorate some of the adverse effects of THC (Morgan et al. 2010), as well as potentially increasing MMN amplitude in the presence of THC (Juckel et al. 2007). An alternative explanation may be that non-using patients avoided cannabis use because of their symptomatology, whereas their using counterparts were less symptomatic prior to cannabis use, with the net result being that both patient groups were similarly unwell at the time of testing. Only longitudinal studies can adequately address these issues.

In our sample, current quantity and frequency of use were strongly associated with MMN amplitude at the right mastoid, with greater use correlating with larger amplitudes. It is possible that cannabis use (and particularly exposure to CBD) mediates an existing deficit. These findings are distinct from those found in cannabis users without psychopathology (Roser et al. 2010), indicating that cannabis has a differential effect on MMN in the presence of psychosis, and in line with the recent findings in cannabis-using patients with established schizophrenia (Rentzsch et al. 2011). However, Rentzsch et al. (2011) did not find any associations between MMN amplitudes and cannabis use measures, and hypothesised that differences in the effects of cannabis on MMN between healthy and psychotic patients may stem from differences in endocannabinoid system functionality. This seems likely given that cannabis use has been found to differentially affect levels of endogenous cannabinoids such as anandamide in healthy volunteers compared to patients with psychosis (Leweke et al. 2007). Prolonged exposure to cannabis may differentially affect endocannabinoid system functioning with resultant effects on other neurotransmitter systems in individuals with and without psychosis.

The cannabis-using group showed significantly delayed MMN latency compared to both other groups. Duration of use was positively associated with MMN latency, indicating that the longer that cannabis is used, the slower is the latency. In ERP studies of long-term cannabis users without psychopathology, altered neurophysiological responses (e.g. Battisti et al. 2010a; Battisti et al. 2010b) have been suggested as being indicative of poorer neural efficiency. It has been suggested that users may recruit additional brain regions or compensatory processes that require increased neural effort to satisfactorily complete tasks (Ramaekers et al. 2009; Battisti et al. 2010a; Battisti et al. 2010b). These processes may take longer to accomplish, which, in turn, may result in slowed processing. Such processes may be

| Table 4 | Correlations between cannabis use parameters and MMN measures in current users |
|------------------|------------------|------------------|------------------|------------------|------------------|
|               | Age of onset of cannabis use* | Duration since first cannabis use (years)* | Frequency of cannabis use in the last month (days/month)* | Quantity of cannabis use in the last month (cones per month)* | Duration of abstinence from cannabis (days)* |
|               | Fz Peak amp. | −0.48 | −0.18 | 0.38 | −0.17 |
|               | Peak lat. | 0.70* | −0.47 | −0.45 | −0.53 |
|               | Mean amp. | −0.32 | −0.61 | −0.36 | −0.52 |
|               | Cz Peak amp. | −0.52 | −0.3 | 0.25 | −0.41 |
|               | Peak lat. | 0.55 | 0.18 | −0.31 | 0.06 |
|               | Mean amp. | −0.32 | −0.3 | 0.13 | −0.41 |
|               | M1 Peak amp. | −0.02 | 0.43 | 0.23 | −0.17 |
|               | Peak lat. | 0.25 | −0.32 | 0.28 | −0.24 |
|               | Mean amp. | −0.17 | 0.61 | 0.38 | 0.06 |
|               | M2 Peak amp. | 0.05 | 0.91** | 0.76* | 0.06 |
|               | Peak lat. | 0.06 | −0.43 | −0.07 | −0.06 |
|               | Mean amp. | −0.31 | 0.86** | 0.29 |

amp amplitude, lat latency

*Correlation is significant at the .05 level (two-tailed)

**Correlation is significant at the .01 level (two-tailed)

*Pearson’s correlations (r)

*Spearman’s correlations (rho)
reflected by prolonged MMN latency in the current study. Alternatively, there may be a delay in the activation of the structures that subserve MMN. Finally, given that reduced MMN may indicate impaired processing of salient stimuli (Todd et al. 2011), the current findings suggest that cannabis-using psychosis patients may attribute greater salience to insignificant stimuli resulting in a delayed response or prolonged MMN latency. These effects are not dissimilar to those recently observed during acute intoxication (Bhattacheriya et al. 2012). While the cannabis-using patient group was characterised by somewhat higher positive symptom scores, positive symptoms were not related to any MMN variables, indicating that these findings are driven by cannabis use.

Similarly, with regard to P3a findings in the literature, both non-using (Hirayasu et al. 1998; Salisbury et al. 1998; Linszen and Nieman 2004; Hermens et al. 2010) and cannabis-using (Linszen and Nieman 2004) psychosis patients have shown a marked reduction in peak P3a amplitude compared to controls, with users also exhibiting prolonged latencies (Linszen and Nieman 2004). These findings suggest that psychosis groups show similar impairment in the ability to allocate attentional resources (Polich 2007), but that this ability in users is slowed.

Shorter P3a latencies are thought to reflect better cognitive performance (Beauchamp and Stelmack 2006; Polich 2007). Although users did not differ from non-using patients on IQ, when current users were separated from past users, duration of current use was associated with latency at the central site, indicating that the longer the duration of cannabis use is, the slower is the P3a latency. Similar to MMN, it may be that users do not utilise neural resources efficiently (Ramaekers et al. 2009; Battisti et al. 2010a; Battisti et al. 2010b), and this is reflected by a delayed P3a latency. Alternatively, given that the latencies and peak amplitudes of MMN and P3a components increase sequentially when they are measured concurrently (Valkonen-Korhonen et al. 2003; Javitt et al. 2008), prolonged P3a latencies may be a consequence of an already delayed MMN latency.

There are some limitations to the current study. Our findings may have been affected by clinical heterogeneity; however, we have recent evidence to suggest that the patient subgroups represented in this study are similarly impaired in MMN/P3a (Kaur et al. 2011; Kaur et al. in press). Similarly, there may be potential effects of medication; while antipsychotics have not been shown to affect the neurophysiological components investigated in this study (see Michie 2001), less is known about the effects of mood stabilisers and antidepressants. Given that mean amplitude is calculated by dividing the overall amplitude over the latency window by the length of the window (Münz et al. 2000), the general lack of mean amplitude findings is likely due to the length of the latency windows selected. However, upon visual inspection of the data, it was necessary to select longer latency windows in order to examine latency delays in the cannabis-using group. It is acknowledged that a different pattern of MMN and P3a results may have ensued had we adjusted the latency window to one which was smaller (e.g. Braff and Light 2007). However, current results would have been limited by using shorter latencies with patients falling outside these ranges. The latency ranges used were within normal limits for both MMN (Näätänen 1992; Duncan et al. 2009) and P3a (e.g. Frodl et al. 1999; Turetsky et al. 2009). A second limitation may be the use of overlapping windows for MMN and P3a components particularly during peak selection. However, latencies and peak amplitudes of MMN and P3 components increase sequentially when they are measured concurrently (Valkonen-Korhonen et al. 2003; Javitt et al. 2008), safeguarding against incorrect peak selection (Valkonen-Korhonen et al. 2003).

Substance use other than cannabis, including alcohol, polydrug use and nicotine, may have impacted upon neurophysiological findings. The cannabis-using group consumed significantly more alcohol as indexed by higher AUDIT scores than both other groups and contained six polydrug users. Although early psychosis patients who engage in risky drinking behaviour (but not cannabis use) have been shown to have decreased MMN at temporal sites (Chitty et al. 2011), controlling for alcohol use in the current study did not alter results. Similarly, results remained unchanged when polydrug users were removed and analyses repeated, except for an additional significant difference between psychosis groups emerging for MMN latency. While users often mix tobacco with cannabis, nicotine does not appear to affect MMN in the psychosis population (Inami et al. 2007), and as such, we did not assess tobacco use in our participants. Given recent evidence that nicotine may potentially interact with cannabis use in modulating MMN (Roser et al. 2010), this could be considered a limitation of our study.

Finally, the present study included both current and abstinent cannabis users in the cannabis-using psychosis group. While separating current versus abstinent users revealed no significant differences in MMN measures except for latency at the left mastoid, current use appeared to have the greatest effect on MMN, with highly significant associations between some cannabis use parameters and MMN/P3a measures evident only in current users, despite the reduced power resulting from inclusion of only half the initial sample size. A different pattern of results may have emerged using a larger sample of current users only. Despite these limitations, this study provides important new evidence that there may be additive effects of cannabis (related to current use as well as abstinence) on a biomarker for schizophrenia and shows that such biomarkers may have utility in differentiating between drug- and non-drug-affected psychoses (Hermens et al. 2009).
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Conflict of interest None.

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References

Battisti RA, Roodenrys S, Johnstone SJ, Pesa N, Hermens DF, Solowij N (2010a) Chronic cannabis users show altered neurophysiological functioning on stroop task conflict resolution. Psychopharmacol (Berl) 212:613–624