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Sensorimotor gating, cannabis use and the risk of psychosis

T. Winton-Brown [a,*], V. Kumari [b], F. Windler [c], A. Moscoso [d], J. Stone [a], S. Kapur [a], P. McGuire [a]

[a] Department of Psychosis Studies, Institute of Psychiatry, Kings College London, United Kingdom
[b] Department of Psychology, Institute of Psychiatry, Kings College London, United Kingdom
[c] Center of Advanced European Studies and Research, Bonn, Germany
[d] Department of Child and Adolescent Psychiatry, Hospital de D. Estefânia Lisboa, Portugal

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ABSTRACT

Sensorimotor gating, measured as the modification of eye blink startle reflexes to loud acoustic stimuli by quieter preceding stimuli, is altered in those with psychosis, their relatives and those at high clinical risk for psychosis. Alterations have also been shown in cannabis users, albeit to a lesser extent, and cannabis is a known risk factor for the onset of psychosis in clinically and genetically susceptible individuals.

We examined the interaction between clinical risk for psychosis and cannabis use on sensorimotor gating, both Prepulse Inhibition (PPI) and Prepulse Facilitation (PPF). We tested PPI and PPF in participants with an At Risk Mental State (ARMS) for psychosis and a matched control group. Both groups included a proportion of subjects who had recently used cannabis, as confirmed by urinary drug screening (UDS) on the day of testing. We found that ARMS participants showed reduced PPF and PPI relative to controls, the latter driven by a group by cannabis use interaction, with recent use reducing PPI in ARMS participants but not in controls. When the analysis was limited to UDS-negative participants there was significantly reduced PPF in ARMS subjects relative to controls, but no differences in PPI. Within the ARMS group reduced sensorimotor gating, measured by both PPI and PPF, related to reduced overall level of function.

Cannabis use in clinical high risk individuals may increase the risk of psychosis in part through worsening PPI, while PPF is altered in ARMS individuals irrespective of cannabis use. This develops our understanding of cognitive mechanisms leading to the experience of aberrant perceptual phenomena and the subsequent development of psychotic symptoms.

1. Introduction

Sensorimotor gating is thought to play a role in how organisms allocate limited cognitive resources within a sensorially rich environment. Measuring the eyeblink startle reflex to a strong sensory stimulus, or 'pulse', can be used to study aspects of sensorimotor gating by examining the effect of a relatively weak preceding 'prepulse' (PP). This PP modifies the extent of the startle that follows according to the delay between stimuli, the inter-stimulus interval (ISI). When the ISI is short, between 30 and 480 ms, the startle reflex to the pulse that follows is attenuated, a phenomenon known as prepulse inhibition (PPI); with a longer ISI, between 500 and 2000 ms, the startle reflex to the following pulse is augmented, known as prepulse facilitation (PPF). PPI and PPF may reflect distinct processes: PPI at short ISI is thought to represent primarily an automatic pre-attentive gating mechanism (Braff et al., 1992), while attentional modulation of PPI occurs with ISI greater than 100 ms (Braff et al., 2001). PPF may represent later stages of sensory processing such as generalized alerting, orientation and passive attention (Graham, 1975).

In patients with psychotic disorders, deficits in sensorimotor gating may lead to cognitive fragmentation disorganization and psychotic symptoms, but the stage at which processing is altered is unknown (Kapur, 2003). Deficits in PPI in subjects with schizophrenia are well established (reviewed in Braff et al., 2001), and have been related to cognitive impairments and positive psychotic symptoms (Kumari et al., 2008c), and have been correlated with reductions in dorsolateral prefrontal, middle frontal and orbital/medial prefrontal volume (Kumari et al., 2008b). PPI deficits have also been reported in people with schizotypal (Cadenhead et al., 2000; Cadenhead, 2011) and psychosis-prone personality traits (Swerdlow et al., 1995a; Kumari et al., 2008a), and in the relatives of people with schizophrenia (Cadenhead et al., 2000; Kumari et al., 2005). These data suggest that PPI deficits may be a marker of vulnerability for psychosis.

There have been several previous studies of PPI in people at clinical high risk for psychosis. Quednow et al. (2008) found diminished PPI in this group, whereas Cadenhead (2011) found no differences between high risk subjects and controls, but *increased* PPI in high risk subjects who later developed psychosis relative to that in subjects who did not. More recently both Ziermans et al. (2011) and De Koning et al. (2014)

* Corresponding author at: PO 67 Institute of Psychiatry, De Crespigny Park, London, United Kingdom. Tel.: +44 61481262243.
E-mail address: Toby.winton-brown@kcl.ac.uk (T. Winton-Brown).

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found diminished PPI in clinical high risk groups, the latter screening out drug using participants using urinary testing. Biomarkers of clinical outcomes in this group are of particular interest, as they may facilitate the stratification of high risk samples according to the likelihood that an individual will subsequently develop psychosis or recover (Fusar-poli et al., 2012). Studies of PPI in this group also have the advantage of being free of the potentially confounding effects of antipsychotic medication on PPI (Kumari et al., 2007), as clinical high risk subjects are often medication naive.

Although there have been several studies of PPI in relation to psychosis, there have been relatively few studies of PPF (reviewed in Kumari et al., 2004, Schiz Res, Appendix 1/2). Wynn et al. (2004) found reduced PPF in subjects with schizophrenia and their first degree relatives compared to controls. There have not been any studies of PPF in subjects at clinical high risk.

A large proportion of patients with psychotic disorders and subjects at high risk of psychosis use psychoactive substances, particularly cannabis. Cannabis use can induce acute psychotic symptoms and is associated with an increased risk of developing a psychotic disorder (Arseneault et al., 2004; Moore et al., 2007). Little is known of the effects of substance use on PPI or PPF in either clinical or healthy samples, and the importance of UDS screening is well known (Swerdlow et al., 1995b). One study found PPI deficits in cannabis-using healthy controls only in actively attended to trials (Kedzior and Martin-Iverson, 2006)—in these attentional modulation paradigms participants are instructed to actively attend to prepulse and pulse sounds, compared to passive attention designs where no such direction is given. Similar findings emerged from a later study that compared cannabis using and non-using subjects with schizophrenia alongside healthy controls (Scholes-Balog and Martin-Iverson, 2011). Administering cannabinoids during adolescence to mice reproduced PPI deficits and several other markers of schizophrenia, (Gleason et al., 2012) and these were reversed by antipsychotic treatment (Nagai et al., 2006).

In the present study we set out to examine both PPI and PPF of the acoustic startle reflex in medication-free subjects with an At Risk Mental State for psychosis (Yung et al., 2005). They were compared with demographically- and geographically-matched healthy controls, and urinary drug screening was used to test for cannabis and other psychoactive substances. Our main hypothesis was that ARMS subjects would show PPI and PPF deficits relative to controls. A secondary hypothesis was that the findings would be modulated by cannabis use.

2. Methods

2.1. Recruitment

27 ARMS participants were recruited from Outreach And Support in South London (Fusar-Poli et al., 2013), a clinical service for the treatment of people at high risk of psychosis. At intake they were assessed by a psychiatrist using the Comprehensive Assessment of At Risk Mental States (Yung et al., 2005), and ARMS status was confirmed by consensus at multidisciplinary team meeting. All patients were antipsychotic naïve.

27 healthy control (HC) participants were recruited from the same geographical area, from the friends of the ARMS participants and via local advertisements. Control participants were excluded if they had a personal or family history of neurological or psychiatric disorder.

Written informed consent was obtained, and the local Research Ethics Committee approved the study protocol. Participants received compensation for their time and travel.

Prior to testing, all participants were assessed by a psychiatrist (TWB) and clinical scales were administered as follows: Hamilton Anxiety and Depression rating scales (Hamilton, 1960, 1959), Comprehensive Assessment of At Risk Mental States (CAARMS (Yung et al., 2005), and Peters Delusion Inventory (PDI Peters et al., 2004). Predicted IQ was estimated using the National Adult Reading Test (NART Nelson, 1991). Around half of the participants also participated in a separate session as part of another study where the history of substance use and their overall level of use for each substance was quantified on a scale of 0–4 (0 = never; 1 = experimental use, has tried occasionally, 2 = occasional use, has tried small quantitates from time to time; 3 = moderate use, has used small quantities regularly or large quantities occasionally; 4 = severe use, has frequently used large quantities, Table 2).

2.2. Protocol

A commercially available human startle response monitoring system (Mark II, SR-Lab, San Diego, California) was used to generate and deliver the acoustic stimuli, and to record and score the electromyographic (EMG) activity for 250 ms starting from the onset of the acoustic startle stimulus. Acoustic stimuli were presented to participants binaurally through well-sealed headphones (Telephonics TDH-39P). The pulse-alone stimulus was a 40-ms presentation of 114-dB (A) white noise and the prepulse stimulus a 20-ms presentation of 85-dB (A) white noise, both over 70-dB (A) continuous back-ground noise. The noise levels were calibrated using the continuous noise, and checked and re-calibrated on a monthly basis.

The session began with a 5 min acclimatization period consisting of 70 dB(A) continuous white noise. During the experiment, participants received four blocks of 21 trials each, after an initial pulse-alone trial; each block consisted of 3 pulse alone (PA) trials, 3 prepulse alone (PP) trials, 3 prepulse trials with a 30-ms prepulse-to-pulse (onset-to-onset) interval (PPI30), 3 prepulse trials with a 60-ms prepulse-to-pulse interval (PPI60), 3 prepulse trials with a 120-ms prepulse-to-pulse interval (PPI120), 3 prepulse trials with a 1000 ms prepulse-to-pulse interval (1000) and 3 prepulse trials with a 2000 ms prepulse-to-pulse interval (PPF2000). Trials were presented to participants in a pseudorandom order with a mean inter-trial interval of 15 s (range 9–23 s). The experiment lasted for 25 min, including the acclimation period.

The experimental procedures for recording and scoring the startle reflexes have been described in detail previously (e.g. Kumari et al., 2012). The eye blink component of the startle was indexed by recording EMG activity of the orbicularis oculi muscle directly beneath the right eye, using two miniature silver/silver chloride electrodes. Recorded EMG activity was band-pass filtered at 50-Hz, as recommended by the SR-Lab. The EMG data were first inspected on a trial-to-trial basis offline, then scored using the analytic program of this system for response amplitude (in arbitrary analogue-to-digital units; one unit = 2.62 μV) and latencies to response onset and peak. Responses were rejected if the onset and peak latencies differed by more than 95 ms, or when the baseline values shifted by more than 50 units (6.59% of trials). Noisy recordings, indicated by a high number of rejected trials (>30%), were rejected outright; this led to 3 ARMS subjects and 4 HC subjects being excluded from analysis, leaving 23 HC and 24 HC subjects included in the final analysis.

PPI and PPF were computed for each participant separately for each trial type and block. PPI was calculated as $(a - b / a) \times 100$, where "a" = pulse-alone amplitude and "b" = amplitude over prepulse trials. PPF was the inverse calculation: $(b - a / a) \times 100$. Percent of PPI/PPF, rather than absolute amount (i.e. arithmetic difference between pulse-alone and prepulse trials), was used since this procedure reduces the influence of individual differences in startle responsiveness (Csomor et al., 2008). Psychophysiological data were scored blind to diagnosis and group membership.

Participants were told that the purpose of the experiment was to measure their reaction to a number of noise-bursts; no instruction was given on whether to attend or ignore them. They were asked to keep their eyes open during the experiment. Participants who smoked tobacco were not excluded, but they were not admitted to the testing suite until at least 30 minutes after their last cigarette, to minimize the