Published in final edited form as:

Psychiatry Res. 2011 July 30; 188(2): 208–216. doi:10.1016/j.psychres.2011.04.011.

Startle Reactivity and Prepulse Inhibition in Prodromal and Early Psychosis: Effects of Age, Antipsychotics, Tobacco and Cannabis in a Vulnerable Population

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Abstract

The use of biomarkers in the study of the prodrome and first episode of psychosis provides a means of not only identifying individuals at greatest risk for psychosis but also understanding neurodevelopmental abnormalities early in the course of illness. Prepulse inhibition (PPI), a marker that is deficient in schizophrenia and after developmental manipulations in animal models, was assessed in 75 early psychosis (EP), 89 at risk (AR) for psychosis and 85 comparison subjects (CS) at baseline and 6 months. Consistent with findings in chronic schizophrenia, PPI was stable with repeated assessment and EP subjects had reduced PPI but this was most evident in tobacco smokers. A significant positive PPI and age association in AR and EP samples, but not CS, demonstrated potential neurodevelopmental differences in early psychosis. Unexpected findings included the fact that medication naive EP subjects, as well as AR subjects who later developed psychosis, had *greater* PPI, introducing the possibility of early compensatory changes that diverge from findings in chronic patients. In addition, subjects with a history of cannabis use had greater startle reactivity while EP and AR subjects who used cannabis and were also taking an antipsychotic had *greater* PPI, again highlighting the potentially important cannabis/psychosis association.

Keywords

Prodrome; Schizophrenia; Neurodevelopment; First Episode; Age

1. Introduction:

The use of biomarkers in the study of the prodrome and first episode of psychosis provides a means of not only identifying individuals at greatest risk for psychosis but also understanding neurodevelopmental abnormalities early in the course of illness. Schizophrenia typically emerges during a period of active brain development in late adolescence or early adulthood. A greater understanding of the emerging neuropathological changes can lead to better informed treatment and perhaps prevention of the devastating

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Financial Disclosures:

None

effects of psychotic illness. The startle reactivity and prepulse inhibition (PPI) paradigm is an important behavioral marker in psychopathological research and may provide insight into the mechanism by which psychosis evolves.

PPI is an index of sensorimotor gating and is used to understand brain disorders that are characterized by gating deficits. In the PPI paradigm, weak lead stimuli are thought to activate inhibitory neural processes that blunt the motor response to intense, abrupt startling stimuli (acoustic, visual, tactile). PPI is typically reduced in individuals with schizophrenia, their first degree relatives and schizotypal personality disorder (Braff et al., 1992; Braff et al., 1978; Cadenhead et al., 1993; Cadenhead et al., 2000b; Cadenhead et al., 2000c; Hamm et al., 2001). PPI is stable with repeated testing (Abel et al., 1998; Cadenhead et al., 1999; Ludewig et al., 2002) and heritable (Greenwood et al., 2007), suggesting its utility as an endophenotype and as a vulnerability marker for psychosis risk (Braff and Freedman, 2002; Cadenhead, 2002; Gottesman and Gould, 2003). Genetic studies have identified single nucleotide polymorphisms associated with neuregulin-1, catechol-O-methyltransferase, serotonin-2A receptor and dopamine-D3 receptor that are strongly linked with PPI and schizophrenia (Hong et al., 2008b; Quednow et al., 2008b; Roussos et al., 2008a; Roussos et al., 2008b; Brauer et al., 2009; Quednow et al., 2009). Animal studies have identified an extended forebrain/pontine circuit that modulates PPI (limbic cortex, ventral striatum, ventral pallidum, pontine tegmentum) (Swerdlow, 1992; Swerdlow et al., 1999). The neurotransmitters (dopamine, serotonin, glutamate) active at several levels of this circuitry cause disruptions in PPI by stimulation of D₂ dopamine receptors (amphetamine or apomorphine); activation of serotonergic systems; of blockade of N-methyl-D-aspartate (NMDA) receptors (phencyclidine (PCP) or ketamine) (Geyer et al., 2001). Translational studies demonstrate the emergence of PPI deficits after developmental manipulations such as isolation rearing of rat pups (Powell and Geyer, 2002), suggesting that it may be a useful marker in understanding a neurodevelopmental disorder such as schizophrenia.

Relatively few studies have reported PPI in early psychosis (Aggernaes et al.; Mackeprang et al., 2002; Ludewig et al., 2003; Meincke et al., 2004; Kumari et al., 2007; Quednow et al., 2008a). While the majority found PPI deficits in the first episode, they were not always robust (eg, only in males, specific PPI condition, antipsychotic specific) and it was those patients who were antipsychotic naïve who showed the greatest deficits. Quednow et al (Quednow et al., 2008a) were the first to report that individuals putatively prodromal (or “at risk”) for psychosis (N=52) had reduced PPI similar to unmedicated patients with first-episode schizophrenia (N=18), whereas schizophrenia patients treated with atypical antipsychotics had almost normal PPI. The finding that atypical antipsychotics may “normalize” PPI has been reported in patients with schizophrenia as well as clinically normal subjects (Swerdlow et al., 2006b; Vollenweider et al., 2006; Wynn et al., 2007; Swerdlow et al., 2008). Quednow et al (Quednow et al., 2008a) did not finding any sex or cigarette smoking effects in their early psychosis sample in contrast to other studies that typically report males have greater PPI than females and smokers have greater PPI than non-smokers (Swerdlow et al., 2006a; Woznica et al., 2009). Another recent manuscript {Zieman et al, In press} replicated the German study and also found stable PPI deficits in subjects at risk for psychosis (N=44) who were tested at baseline and 2 year follow-up.

The aim of the current study was to assess startle reactivity and PPI in a large sample of subjects at risk (AR) for or in the early stages of psychosis (EP) at initial evaluation and after repeated assessment. It was predicted that groups would not differ in startle reactivity but that AR and EP subjects would have deficits in right sided PPI, consistent with our previous reports (Cadenhead et al., 2000a) in schizophrenia spectrum subjects. It was also predicted that PPI deficits would be greatest in those AR subjects who later develop a psychotic episode (~25-40% in 2 years) (Cannon et al., 2008). Finally, it was predicted that

PPI would be stable in early psychosis despite changing clinical state, demonstrating the utility of PPI as a vulnerability marker or endophenotype for psychosis (Braff and Freedman, 2002; Cadenhead, 2002; Gottesman and Gould, 2003).

An exploratory aim was to assess the effects of cannabis use in addition to other demographic factors known to influence PPI (e.g., age, sex, gender, tobacco, antipsychotics), on startle measures. The epidemiological literature demonstrates an association between the early use of cannabis and later risk for psychotic illness (Andreasson et al., 1987; Arseneault et al., 2002; Weiser and Noy, 2005; Moore et al., 2007) which has lead to translational studies that investigate the role of cannabinoid receptors and endocannabinoids in dopamine regulation and the pathophysiology of schizophrenia (Vinod and Hungund, 2006; D'Souza, 2007; Muller-Vahl and Emrich, 2008; Fernandez-Espejo et al., 2009; Galve-Roperh et al., 2009; Koethe et al., 2009b). In an animal model of PPI, developmental manipulations using chronic pubertal cannabinoid administration in rats have been shown to disrupt PPI in adult animals (Schneider and Koch, 2003) suggesting that early cannabis use may lead to PPI deficits in vulnerable individuals. Of the few PPI/cannabis studies in humans, one reported no difference in PPI or startle reactivity in chronic cannabis abusers (Quednow et al., 2004) while another (Kedzior and Martin-Iverson, 2006) showed deficits in a paradigm that included an attentional PPI component, introducing the possibility that the deficits observed in cannabis abusers were related to attentional deficits rather than preattentive processing since no PPI deficits were seen in the "ignore" condition. The effects of cannabis on PPI have not been published in a psychotic or AR population.

2. Methods:

2.1 Participants

Startle reactivity and PPI were assessed in 75 EP patients, 89 individuals AR for psychosis and 85 non-psychiatric comparison subjects (CS) between the ages of 12 and 35. All subjects provided written informed consent after the procedures were fully explained (UCSD IRB# 030829).

2.2 Recruitment and Assessment:

An educational, community outreach program was developed in the San Diego community to inform health professionals, public school officials and family members of mentally ill individuals about the Cognitive Assessment and Risk Evaluation (CARE) program at University of California San Diego (Seeber and Cadenhead, 2005).

All subjects were assessed with the Structured Interview for DSM-IV Axis I (>16 years) or the Schedule for Affective Disorders and Schizophrenia for School-Age Children (Kaufman et al., 1996) to identify or rule out Axis I disorders. The Schedules for the Assessment of Negative and Positive Symptoms (SAPS/SANS) (Andreasen, 1984a; Andreasen, 1984b) and the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) were used for symptom assessment. The Global Assessment of Functioning (GAF) (Hall and Parks, 1995) scale and the Social Adjustment Scale (SAS) were used to assess global, role and social functioning.

EP subjects had developed psychosis per the SCID/KSADS within the last 2 years. AR subjects were assessed with the Structured Interview for Prodromal Syndromes (SIPS) (Miller et al., 2003; Cadenhead et al., 2005; Seeber and Cadenhead, 2005) that characterizes the prodromal syndrome as a recent onset of subsyndromal psychotic symptoms and/or a recent decline in functioning in individuals with a 1st degree relative with psychosis. CS did not meet criteria for DSM-IV Axis I or II disorders (First et al., 1996a; First et al., 1996b), prodromal symptoms or have a family history of psychosis. Individuals with a history of

neurological disorders, serious head injury, hearing impairment, or current substance misuse were excluded based on history and urine toxicology screening.

2.4 Acoustic Startle Paradigm:

Subjects were screened for hearing impairment (<45 dB 1000 Hz). Smokers were allowed to smoke up to 30 minutes prior to startle testing to avoid nicotine withdrawal or intoxication. Electrodes (Ag/AgCl) were placed below and at the outer canthus of each eye and on the mastoids with resistances less than 10 kohms (Cadenhead et al., 2000c). The startle stimuli were presented binaurally through headphones (Model TDH-39-P, Maico, Minneapolis, MN). A standard Gould amplifier and computerized startle response monitoring system (SR-Lab, San Diego Instruments Inc) was used to administer stimuli and record data. A 70 dB [A] broadband background noise was used with a pulse (115 dB [A], 40 ms noise burst) presented either alone or following a prepulse (86 dB [A], 20 ms noise burst that precedes the pulse by 30, 60 or 120 ms). The paradigm began with a 5 minute acclimation period then 5 pulse alone stimuli followed by 60 trials consisting of 2 blocks of 6 trials each of the three prepulse conditions and 12 pulse alone stimuli presented in a fixed, pseudorandom order. The paradigm ended with 5 more pulse alone stimuli for a total of 70 trials.

EMG activity was band-pass filtered (1-1000 Hz) and a 60-Hz notch filter eliminated interference. The system recorded 250 1-ms readings starting at the onset of the startle stimulus. Startle response onset was defined as a shift of six digital units from the value 18 to 100 ms after the stimulus. Eyeblinks were defined as spontaneous and excluded when the onset and peak latencies differed by more than 95 ms (Braff et al., 1992). If the value shifted by more than 10 units, this response was excluded.

Initially, all trials were screened for errors (Braff et al., 1992). Startle data was analyzed using wave-form averaging (EMG analyst software Model V3.09, Paradigm Development Company 1992) (Cadenhead et al., 1999). After applying a 10-point smooth, the magnitude was assessed using the average of all points between 5 and 20 ms from stimulus onset. The magnitude of the peak startle response (highest point relative to baseline between 30 and 100 ms) was determined for the four different trial types within each block.

Subjects who demonstrated a relative lack of startle stimulus elicited eye blink (<4.7 microvolts) were excluded (5 CS, 1 AR and 3 FE subjects) for the PPI analyses. This number was determined by examining the distribution of mean startle magnitude (Braff et al., 1992).

The following startle measures were examined (Cadenhead et al., 1999): 1) reactivity, or the magnitude of response, 2) habituation or the decrement in reactivity with repeated stimulus administration, 3) prepulse inhibition (PPI) or the percentage of change in startle magnitude to prepulse+pulse versus pulse-alone trials ($((\text{pulse} - \text{prepulse+pulse})/\text{pulse}) * 100$) (Braff et al., 1992), 4) stability of the startle measures between test sessions was also assessed.

2.5 Statistics:

Statistical analyses were performed using SPSS 17.0. All data were checked for normality and, when indicated, were transformed to obtain a normal distribution prior to using parametric statistics. Non-normal PPI data was converted to positive values then log10 transformed yielding normal distributions for all PPI conditions.

The analyses of reactivity (across 4 blocks) and PPI (across 3 interstimulus intervals - ISIs) were initially conducted assessing group and laterality effects (right and left eye) as well as demographic factors (e.g., age and sex) known to influence startle variables with repeated measures ANOVAs per a priori hypotheses. Greenhouse-Geisser epsilon corrections were

used to adjust degrees of freedom if assumption of sphericity was violated and did not alter results. Follow-up exploratory analyses of both reactivity and PPI assessed effects of tobacco and cannabis on startle measures. Antipsychotic treatment effects were analyzed in separate analyses within the AR and EP groups and followed up with the addition of tobacco and cannabis to the analyses. All significant interactions effects (eg, smoking, cannabis, group, sex, ISI, eye, antipsychotic) were deconstructed using ANOVA to better understand significant effects on startle reactivity or PPI. Exploratory analyses to examine prediction of future psychosis in the AR sample were then performed comparing AR subjects who later developed a psychotic episode to those who did not. The stability of PPI was assessed with repeated measures ANOVA with time as an additional variable and Intraclass Correlation Coefficients (ICC) (Shrout and Fleiss, 1979).

3. Results:

3.1 Clinical Assessment:

3.1.1 Baseline: There were significant group differences in age, sex, tobacco, cannabis and antipsychotic history at baseline assessment (Table 1) so these variables were included in analyses of experimental variables.

3.1.2 Follow-up: Follow-up clinical assessment and PPI were performed on 27 EP, 52 AR and 31 HS between 6 months and 1 year (mean 6.5 months). There were no demographic differences between the group who received follow-up and those who did not. At follow-up, six (11.5%) of the 52 AR subjects had become psychotic and developed schizophrenia (N=4) or affective psychosis (N=2).

Table 2 shows the comparison of clinical symptom ratings at baseline and follow-up. The study included a naturalistic treatment design, so no specific intervention was introduced. All subjects were referred to treatment if indicated. The AR subjects showed a significant reduction in prodromal symptoms while the EP subjects showed a non-significant reduction in symptom ratings. There was a significant improvement in GAF score and BPRS in both AR and EP groups. There were no changes in the SAS in either group.

Of the original 89 AR subjects who received PPI, we were able to contact many by telephone or face to face interview to assess whether they had transitioned to psychosis. The rate of psychosis at follow up was as follows: 4/75 (5.3%) at 6 months, 7/67 (10.5%) at 1 year, 8/55 (14.6%) at 18 months, 8/45 (17.8%) at 2 years and 9/31 (29.0%) at 3 years.

3.2 Startle Magnitude:

Reactivity was assessed using a repeated measures ANOVA design with eye (2 levels – right and left) and block (4 levels) as within subject factors, sex (2 levels – male and female) and group (3 levels – CS, AR, EP) as between subjects factors and age as a covariate. There were no significant main effects for group, sex or age. As predicted, there were no significant group effects but there were significant block ($F[3,723]=32.05$, $p<.001$), block X eye ($F[3,723]=3.35$, $p<0.05$) and block X sex ($F[3,723]=3.67$, $p<0.05$) interaction effects due to habituation, or decrement in startle magnitude, across the session that was greater in females and in the right eye. There was no evidence of habituation differences between groups.

3.2.1 Tobacco and Cannabis Effects on Startle Magnitude: When tobacco and cannabis use were added as between subjects factors, there was no main or interaction effect for tobacco, but there was an unanticipated cannabis ($F[1,223]=4.16$, $p<0.05$) effect because

the cannabis users (N=125) had greater startle magnitude compared to non-users (N=124) (See Figure 1).

3.2.2 Antipsychotic effects on Startle Magnitude: To assess the effect of antipsychotics on startle reactivity, EP subjects on (N=56) and off (N=19) antipsychotics were compared. There was a significant antipsychotic effect ($F[1,73]=4.44$, $p<0.05$), with EP subjects on antipsychotics having greater reactivity across the session. Similar analyses were also performed within the AR sample on (N=23) versus off (N=65) antipsychotics at the time of the testing. There were no significant effects of antipsychotics on startle reactivity within the AR group but there was a trend interaction effect between eye and antipsychotic ($F[1,258]=3.78$, $p=0.055$) since AR subjects who were on an antipsychotic had greater startle magnitude bilaterally (estimated marginal mean[SEM]: Right 67.6[8.8], Left 64.8[9.2]) compared to those AR subjects not taking an antipsychotic who had reduced startle reactivity on the right side (55.1 [5.2]) compared to the left (62.8[5.5]).

3.2.3 Prediction of Psychotic Risk and Startle Magnitude: To explore potential risk factors for later psychosis in the AR group, the startle reactivity of 7 AR subjects who later developed a psychotic illness was compared to that of 37 AR subjects who had not developed psychosis at 2 year follow-up. There were no evident differences between groups.

3.2.4 Startle Magnitude Summary: There were no group differences in startle reactivity or habituation but cannabis users from all groups had greater startle magnitude as did EP and AR subjects who were taking an antipsychotic medication.

3.3 Prepulse Inhibition:

Initially an omnibus ANOVA was performed with eye (2 levels - right and left) and ISI (3 levels: 30, 60, 120 ms) as within subjects factors; group (3 levels – CS, AR, EP) and sex (2 levels – male and female) as between subjects factors and age as a covariate. There was no significant group or eye effects but there were significant ISI ($F[2,466]=23.65$, $p<0.001$, increased PPI with larger ISI), sex ($F[1,233]=5.47$, $p<0.05$; males greater PPI than females) and age ($F[1,233]=11.06$, $p<0.001$; greater PPI with increasing age) effects.

To further explore the significant age effects on PPI, Pearson Correlations were performed between age and each of the 3 PPI conditions. As seen in Table 3, there were significant correlations with age across all groups in the 30 and 60 ms ISI PPI conditions. Separate correlations by group revealed that the significant correlations were driven by the AR and EP groups but not the CS. Figure 2 illustrates the correlations across groups in the 60 ms ISI condition.

In summary, although there were no significant PPI group effects, the expected ISI and sex effects were observed as well as an unanticipated age effect that was driven by greater PPI with increased age in the AR and EP samples.

3.3.1 Tobacco and Cannabis Effects on Prepulse Inhibition: To explore the effects of tobacco and cannabis on PPI, the ANOVA was repeated with tobacco smoking and cannabis use as between subjects factors. The significant sex effect was no longer present suggesting that substance use may in part account for the observed sex differences in PPI in this sample. There was a near significant group X tobacco interaction ($F[2,215]=2.85$, $p=0.06$) and significant interaction effects with eye and group (eye X group: $F[2,215]=5.85$, $p<0.005$; eye x group X tobacco: $F[2,215]=3.36$, $p<0.05$) that were deconstructed by examining each eye separately below.

3.3.1.1 Right Eye: There were significant age, group ($F[2,216]=3.86$, $p<0.05$), group X tobacco ($F[2,216]=4.40$, $p<0.05$) and ISI X sex X tobacco ($F[2,432]=4.05$, $p<0.05$) effects. The group effects were accounted for by reduced PPI in the EP group relative to both the CS and AR groups (both $p<0.05$ with LCD post-hoc). Deconstruction of the group X tobacco interaction (see Figure 3) revealed that the group effects were driven by the group who used tobacco. The CS and AR subjects who smoked cigarettes had larger PPI relative to those who did not smoke while the opposite was true in the EP group (reduced PPI in smokers compared to non-smokers). In addition, male smokers ($N=38$) had larger PPI in the 60 and 120 ms ISI conditions while female non-smokers ($N=85$) had reduced PPI in the 30 ms condition accounting for the ISI X sex X tobacco interaction.

3.3.1.2 Left Eye: There were no significant group effects or interaction effects for group on the left. Therefore the remaining PPI analyses were performed with right eye data.

3.3.1.3 Summary of Cannabis and Tobacco Effects on Prepulse Inhibition: When tobacco and cannabis were added to the analysis, there was no longer a sex effect present and the EP group showed reduced PPI that was most evident in the sample who smoked tobacco. All PPI group findings were present on the right side, consistent with our previous report of right, but not left, sided PPI deficits in schizophrenia spectrum subjects (Cadenhead et al., 2000d).

3.3.2 Antipsychotic Effects on Prepulse Inhibition: ANOVAs (using ISI as a within subjects factor and antipsychotic as a between subjects factor) were performed separately within the EP and AR groups to specifically analyze the effects of antipsychotics on PPI and further sort out interaction effects with tobacco and cannabis.

3.3.2.1 Early Psychosis: There was a significant main effect of antipsychotic treatment ($F[1,70]=6.44$, $p<0.05$) because EP patients on an antipsychotic ($N=54$) had *less* PPI than unmedicated patients ($N=18$) (see Figure 4). There was also a significant ISI X antipsychotic effect ($F[2,69]=4.20$, $p<0.05$) since the group differences were in the 30 and 60 ms ISI conditions. The unmedicated EP group was newly diagnosed, had not yet begun treatment and had a greater level of acuity as evidenced by more positive symptoms compared to the sample on antipsychotics (Mean Global SAPS [Standard Deviation]: Unmedicated = $9.44[4.6]$, Medicated = $5.88[4.2]$; $t[68]=3.05$, $p<0.005$).

When cannabis and tobacco were added to the analysis of antipsychotic effects for exploratory purposes, there was a significant antipsychotic X cannabis X tobacco ($F[1,58]=7.0$, $p<0.01$) interaction effect that was accounted for by opposite trend effects of cannabis ($F[1,45]=2.93$, $p=0.09$; PPI in $N=36$ cannabis smokers > than PPI in $N=20$ who never smoked cannabis) and tobacco ($F[1,45]=3.40$, $p=0.07$; PPI in $N=18$ tobacco smokers < than PPI in $N=38$ non-smokers) on PPI within the sample on antipsychotics (see Figure 5).

3.3.2.2 At Risk: Within the AR sample there was no main or interaction effects for antipsychotic treatment. When cannabis and tobacco were added in the exploratory analysis, there was a significant cannabis X ISI X antipsychotic effect ($F[2,146]=3.08$, $p<0.05$) due to increased PPI at the 60 ms ISI among cannabis smokers on an antipsychotic (see Figure 5).

3.3.2.3 Summary of Antipsychotic Effects on Prepulse Inhibition: Medication naïve, acutely ill EP subjects had greater PPI than those who were on an antipsychotic, in contrast to previous literature (Swerdlow et al., 2006b; Vollenweider et al., 2006; Wynn et al., 2007; Quednow et al., 2008a; Swerdlow et al., 2008). In addition, antipsychotic treated EP and AR subjects who also used cannabis had greater PPI while PPI was reduced in antipsychotic treated EP subjects who smoked tobacco.

3.3.3 Risk of Future Psychosis and Prepulse Inhibition: To determine whether those AR individuals who later developed a psychotic illness differed from those who did not, the baseline PPI data for 8 subjects who had transitioned to psychosis at 2 year follow-up was compared to that of 37 who had not developed psychosis. Although the sample size was small, there was a significant difference between those AR subjects who later developed psychosis and those who did not ($F[1,43]=5.94$, $p<0.05$, Partial Eta Square 0.12, Cohen d of 60 msec ISI = 0.89) because the AR subjects who later developed psychosis had *greater* PPI at baseline assessment (see Figure 5).

Given the significant cannabis and antipsychotic effects on startle reactivity, these analyses were repeated with startle reactivity (pulse alone) as a covariate and the significant results did not change.

3.3.4 Stability of Prepulse Inhibition: The repeated measures ANOVA (ISI as a within subjects factor, group as between subjects factor) was performed with time (baseline and follow-up) as an additional within subjects variable in the analysis. There were no significant main effects of time ($F[1,100]=0.03$, ns) or group X time interaction effects ($F[2,100]=1.32$, ns), suggesting that PPI for all groups was stable over time.

Intraclass correlation coefficients (ICC) (see table 4) between baseline and follow-up revealed significant ICC's across all groups at all ISIs but the most stability was noted at the larger ISI's (60 and 120 ms). When separate ICCs were performed within each group, the same general pattern was evident.

4. Discussion:

Detailed analyses suggest a complex interaction between startle measures, age, sex, antipsychotic effects and exposure to environmental risk factors in early psychosis.

4.1 Startle Reactivity:

As predicted, there were no significant differences between groups in startle reactivity, but there was evidence of increased startle magnitude in individuals who had a history of ever using cannabis across all three groups. It is not possible to determine whether startle reactivity was enhanced by cannabis use, or if individuals prone to use cannabis are more reactive, given the cross sectional design of this study. There were no significant effects of nicotine use on startle reactivity consistent with previous human and animals studies that have shown mixed results of nicotine (Acri et al., 1991; Acri et al., 1995; Della Casa et al., 1998; Mueller et al., 1998; Faraday et al., 1999; Duncan et al., 2001a; Grillon et al., 2007; Robinson et al., 2007; Perkins et al., 2008).

In contrast to the extensive human and animal literature that shows no differences or a reduction in startle magnitude with antipsychotic treatment (Yee et al., 2004; Csomor et al., 2009), the early psychosis subjects on an antipsychotic in this study had greater startle reactivity compared to unmedicated subjects. Consistent with the PPI findings (see below) in this sample of early psychosis patients, it is possible that the early phase of psychosis is physiologically different from the chronic form of the illness.

4.2 Prepulse Inhibition:

Confirming the initial hypothesis, EP subjects demonstrated right sided deficits in PPI although this difference appeared to be driven by the group who smoked tobacco (Figure 3). Additionally, PPI was larger in both CS and AR subjects who smoked cigarettes relative to those who did not while the opposite was true in the EP group. Within the EP group who

was on an antipsychotic medication, the effect of cigarette smoking was most evident (reduced PPI in smokers relative to non-smokers).

A number of studies have demonstrated the acute PPI-enhancing effects of nicotine and in humans and animals (Hong et al., 2008a; Mizoguchi et al., 2009). In the present study, the cigarette smokers did not smoke for 30 minutes prior to testing so they did not have maximal nicotine levels and were not in nicotine withdrawal. Nevertheless, as a group, smokers did have greater PPI than non-smokers but this effect was primarily present in those individuals who were male and in the CS or AR samples. This finding of reduced PPI in the EP sample who smoked and was also on an antipsychotic is surprising but may in part be related to the fact that this was an early psychosis sample and many were newly medicated (N=56, mean weeks on antipsychotic = 21.44 [range 1-92]). It is known that cigarette smoking induces hepatic microsomal enzymes that increase the rate of metabolism of many psychotropic drugs including antipsychotics (Zevin and Benowitz, 1999), so it is therefore possible that the cigarette smokers had lower antipsychotic levels (Wu et al., 2008) accounting for the reduced PPI. On the other hand, Li et al (Li et al., 2009) report that adolescent, but not adult, exposure to nicotine produces a robust disruption of PPI in adult rats suggesting that nicotine exposure during adolescence may have long-term detrimental effects on sensorimotor gating ability. Given the epidemiological literature that shows an association between early cigarette smoking and later psychosis (Weiser et al., 2004), it is also possible that the observed PPI reductions in early psychosis patients who smoke represents an interaction between early nicotine exposure and risk for psychosis.

In contrast to previous studies that have demonstrated enhanced PPI in schizophrenia patients on atypical antipsychotics, the EP subjects on an antipsychotic had *reduced* PPI relative to EP subjects who were not on an antipsychotic. Further examination of the data (Figure 4), however, shows that the EP subjects on an antipsychotic actually had PPI similar to the CS group but it was the medication naïve EP subjects who had *greater* PPI accounting for the group differences.

The AR sample in this study did not differ from the CS in PPI which is in contrast to the results of the Quednow et al (Quednow et al., 2008a) study who showed deficits in the AR sample as well as unmedicated EP subjects. The PPI paradigm used in the Quednow study is nearly identical to the present study in terms of equipment, stimuli, background noise, dB level, and analysis but only one ISI (120 ms) rather than three (30, 60, 120 ms in the present study) was used, perhaps accounting for the difference in results. In contrast to our sample of healthy subjects of whom only 14.1% smoked cigarettes, the Quednow et al study included 35.5% smokers in their control group who were allowed to smoke ad lib (whereas in the current study they did not smoke for 30 minutes before PPI testing). Although Quednow et al did not find a significant effect of smoking in their study, is possible that the differences in the rate of smoking in German control subjects as well as higher levels of nicotine in those who did smoke contributed to greater PPI in the German controls and the difference in results of the group analysis between the two studies

An unexpected finding in the current study, however, was that the small number of AR individuals who went on to develop a psychotic episode at 2 years had *greater* PPI than those AR individuals who had not developed psychosis at 2 years. This is especially intriguing given that the medication naïve (and more acute) EP group also had greater PPI suggesting that compensatory mechanisms may be evident early in the course of illness consistent with hyperactivation findings seen with functional magnetic resonance imaging in high risk subjects (Seidman et al., 2007; Fusar-Poli et al., 2009). It is possible that this finding of increased PPI early in the course of illness represents the initial change in the neural circuitry modulating PPI prior to the appearance of sensorimotor gating deficits in

more chronic forms of the illness. Although preclinical studies show reduction in PPI in response to dopamine agonists and NMDA antagonists (Geyer et al., 2001), recent studies in normal subjects have revealed evidence of increased PPI under certain conditions (high novelty seeking, low baseline PPI, specific doses) in response to dopamine agonists (amphetamine, pramipexole) (Swerdlow et al., 2009a; Talledo et al., 2009), and NMDA antagonists (ketamine, memantine) (Duncan et al., 2001b; Abel et al., 2003; Swerdlow et al., 2009b). The mechanism by which PPI might be increased in the early stages of psychosis, and where in the modulatory frontal, limbic or mesolimbic circuitry (Swerdlow et al., 2008), this occurs, is unknown but has implications for pre-emptive treatment development. Longitudinal follow-up along with the use of multimodal techniques will allow us to explore the neural mechanism underlying this interesting result. If it were possible to identify an early process that is different from chronic forms of the illness both physiologically and neurochemically, for example, it would provide an important target for early intervention.

This is the first published study to the author's knowledge to assess the effect of cannabis history on PPI in individuals with psychosis. Separate analyses within the EP and AR samples revealed consistent findings of greater PPI in individuals who had a history of cannabis use along with antipsychotic treatment. Given that the baseline analyses were cross-sectional, it is not possible to determine whether the history of cannabis use somehow enhanced the known effects of antipsychotics on PPI. Although individuals in this study were assessed over time, there were an insufficient number of subjects who started antipsychotics or began smoking cannabis during the course of the study to assess changes over time due to these factors.

The PPI paradigm has been used to test the therapeutic effect of exogenous cannabinoids including cannabidiol (CBD). Mice administered CBD show increased PPI (Nagai et al., 2006; Long et al., 2009). In addition, PCP exposed rats (Ballmaier et al., 2007) have reduced PPI that improves after self administration of cannabinoids. CBD is the second most abundant component of Cannabis Sativa and has weak partial antagonistic properties at the CB1 receptor. CBD inhibits the reuptake and hydrolysis of anandamide, an endogenous CB1 receptor agonist that has been shown to be elevated in antipsychotic and cannabis naïve patients with schizophrenia (Giuffrida et al., 2004; Leweke et al., 2007) and in the prodromal phase of illness (Koethe et al., 2009a). Because CBD can reverse many of the biochemical, physiological and behavioral effects of CB1 receptor agonists, recent studies have explored the possible role of cannabinoids including CBD in the treatment of psychosis (Koethe et al., 2009a). It is therefore possible, that cannabis use potentiated antipsychotic effects or altered endocannabinoid action in the early psychosis subjects and these effects are demonstrated with PPI. Given that the subjects in this study had not smoked cannabis on the day of testing and the dosing or composition (THC to CBD ratio) of cannabis used was not controlled or assessed, it is not possible to generalize from animal studies that assess acute administration of THC or CBD. Additionally, given the current findings that suggest altered physiologic response in early stages of psychosis and clinical studies that differ from preclinical findings, it is premature to speculate about the mechanism by which cannabis might affect PPI in early psychosis. Future translational work and replication of the current findings are essential to confirm whether the association of cannabis history, antipsychotic treatment and PPI is meaningful and has implications for early intervention.

Significant age effects were a consistent finding in the analysis of PPI. The age effects were most prominent in the AR sample. Age effects have been reported in studies of PPI but they are generally noted in older subject groups and to show an inverse relationship with age (Ellwanger et al., 2003; Kumari et al., 2008). Although PPI is thought to be at a mature level by puberty (Ornitz, 1999), the current findings suggest that the development of PPI may be delayed or abnormal in adolescents who are vulnerable to psychotic illness, consistent with

the notion of abnormal neurodevelopment in individuals who later develop psychosis. Specific assessment of pubertal status in future studies may help to better control for physical age in studies of adolescents with neurodevelopmental abnormalities.

Despite the many factors that affect PPI, and the fact that all AR and EP subjects improved clinically over time, it was possible to replicate stability findings in normal subjects (Cadenhead et al., 1999) and now demonstrate stability of PPI over repeated assessment in early psychosis subjects. Reliable, stable measurement of behavioral effects is essential if a measure is to be used as an endophenotype, a vulnerability marker for psychosis or a measure of treatment effects.

4.3 Caveats and Conclusions:

Unexpected findings emerged in the current study that provide evidence for an altered physiological response in the early course of psychotic illness that is very different from chronic forms of the illness. Possible compensatory changes, including increased startle reactivity and PPI, suggest that the evolving neurobiological changes in the early course of illness are dynamic and perhaps alterable by substances such as nicotine and cannabis as well as antipsychotic medication. Larger longitudinal samples, such as that being collected in the North American Prodromal Longitudinal Studies (NAPLS) consortium (Addington et al., 2007), will allow us to directly look at the effect of multiple demographic and environmental factors on startle measures. In addition, well controlled studies that directly investigate subjects on and off antipsychotics along with use of tobacco and cannabis may help to further elucidate this complex picture and lead to important insights that will inform translational studies and treatment development.

Acknowledgments

This work was supported by the National Institute of Mental Health MH60720, Cognitive Assessment and Risk Evaluation (CARE). The author would like to thank the CARE Program staff including Nasra Haroun, MD, Tracy Alderman, PhD, Anju Hurria, MD, Isabel Domingues, MD, and Karin Kristensen, PsyD for their help in diagnostic and clinical assessment and Kathleen Shafer, BS, Jason Nunag, BS, Stephen Reding, MA, Angela Eastvold, PhD, Jessica Keith, BA, Iliana Marks, BS, Katherine Seeber, MD, and Daniel Roman, BA for their administrative and technical assistance.

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Figure 1. Startle reactivity across the test session demonstrating habituation in startle magnitude as well as the significant effect of cannabis use history on startle reactivity.

Figure 2. Scatter plot showing the significant correlations between age and prepulse inhibition (PPI) at the 60 ms interstimulus interval (ISI) in at risk and early psychosis groups but not the comparison subjects.

Figure 3.

The significant PPI group effect was primarily driven by the group who smoked tobacco. The significant group X tobacco interaction that shows opposite effects of smoking in the comparison and at risk groups versus the early psychosis sample is demonstrated with PPI collapsed across all interstimulus intervals.

Figure 4.

Demonstrates that at risk (AR) subjects who later developed a psychotic episode at 2 year follow-up (AR+P) had greater prepulse inhibition (PPI) than those AR subjects who had not developed psychosis in the same time period (AR – P). The more acute early psychosis subjects who were antipsychotic naïve (EP - AP) at the time of assessment had greater PPI compared to EP subjects receiving an antipsychotic (EP+AP). PPI for the comparison subjects (CS) is included for comparison.

Figure 5. Illustrates increased PPI in antipsychotic treated early psychosis and at risk subjects who had a history of cannabis use versus those who did not.

Table 1

Description of the Baseline Population

	Comparison (<i>n</i> =85)	At Risk (<i>n</i> =89)	Early Psychosis (<i>n</i> =75)	Contrasts ^a
Mean (Range)				
Age	20.5 (12-30)	19.0 (12-30)	21.5 (13-34)	C
%				
Sex				B
Male	45.9	60.7	76.0	
Female	54.1	39.3	24.0	
Family History of Psychosis		48.9	33.3	C
Current Antipsychotic Use		27.0	74.7 ^b	C
History of Cannabis Use				B, C
Yes	34.1	48.3	70.7	
No	65.9	51.7	29.3	
Current Tobacco Use				B
Yes	14.1	18.0	32.0	
No	85.9	82.0	68.0	
Mean (SD)				
SIPS Positive	0.13 (0.60)	9.89 (4.77)		A
SIPS Negative	0.28 (0.85)	10.92 (6.70)		A
SIPS Disorganized	0.15 (0.50)	5.83 (3.80)		A
SIPS General	0.16 (0.58)	6.60 (4.26)		A
GAF	86.45 (3.45)	50.38 (10.73)	43.49 (9.07)	A, B, C
SAPS		5.25 (3.02)	6.68 (4.48)	C
SANS		6.51 (4.51)	9.54 (5.23)	C
SAS	1.59 (0.28)	2.39 (0.43)	2.34 (0.51)	A, B

^aSignificant contrasts (Chi Square, t-test: $p < 0.05$): A=comparison subjects vs at risk group; B=comparison subjects vs early psychosis group; C=at risk group vs early psychosis group.

^bN=1 on a typical antipsychotic, the remainder were on an atypical antipsychotic. SIPS=Structured Interview for Prodromal Syndromes; GAF=Global Assessment of Functioning; SAPS/SANS=Schedule for the Assessment of Positive/Negative Symptoms; SAS=Social Adjustment Scale.

Table 2

Comparison of Baseline and Follow-up Clinical Measures

	Mean (SD)			
	Baseline		Follow-Up	
	At Risk (n=52)	Early Psychosis (n=29)	At Risk (n=52)	Early Psychosis (n=29)
SIPS Positive	10.3 (4.9)		3.9 (3.5) ^a	
SIPS Negative	10.1 (6.7)		5.7 (5.4) ^a	
SIPS	5.8 (4.0)		3.2 (3.4) ^a	
Disorganized				
SIPS General	5.9 (4.4)		2.3 (2.7) ^a	
SAPS	5.4 (3.0)	7.9 (4.3)	2.8 (2.6) ^a	6.0 (3.9)
SANS	6.1 (4.3)	9.6 (4.8)	4.8 (4.5) ^a	8.4 (5.4)
BPRS	15.5 (6.3)	18.8 (7.4)	9.7 (5.6) ^a	11.7 (5.4) ^a
GAF	52.1 (9.5)	42.2 (9.1)	59.2 (13.3) ^a	48.6 (8.7) ^a
SAS	2.4 (0.5)	2.3 (0.4)	2.2 (0.5)	2.2 (0.4)

SIPS=Structured Interview for Prodromal Syndromes; GAF=Global Assessment of Functioning; SAPS/SANS=Schedule for the Assessment of Positive/Negative Symptoms Total; SAS=Social Adjustment Scale; BPRS=Brief Psychiatric Rating Scale Total

^aSignificant paired sample t-tests (p<0.01)

Table 3

Association between Prepulse Inhibition (PPI) and Age

PPI ISI (ms)/ Eye	All (N=241)	Comparison (N=81)	At Risk (N=88)	Early Psychosis (N=72)
30/R	0.24 ^c	0.13	0.39 ^c	0.22
60/R	0.24 ^c	0.15	0.28 ^c	0.28 ^a
120/R	0.08	0.12	0.10	0.02
30/L	0.21 ^c	0.13	0.31 ^b	0.12
60/L	0.21 ^c	0.18	0.23 ^a	0.18
120/L	0.09	0.06	0.09 ^a	0.07

^a
p<0.05^b
p<0.005^c
p<0.0001

Table 4

Stability of Prepulse Inhibition (Intraclass Correlation Coefficients)

PPI ISI (ms)/ Eye	All (N=110)	Comparison (N=30)	At Risk (N=52)	Early Psychosis (N=28)
30/R	0.60 ^a	0.66 ^b	0.57 ^b	0.64 ^a
60/R	0.83 ^c	0.79 ^b	0.82 ^c	0.87 ^b
120/R	0.82 ^c	0.85 ^c	0.81 ^c	0.81 ^c
30/L	0.51 ^c	0.57 ^a	0.50 ^b	0.32
60/L	0.78 ^c	0.81 ^c	0.78 ^c	0.73 ^c
120/L	0.86 ^c	0.89 ^c	0.86 ^c	0.81 ^c

^a
p<0.05^b
p<0.005^c
p<0.0001