HHS Public Access

Author manuscript

Schizophr Res. Author manuscript; available in PMC 2021 February 01.

Published in final edited form as:

Schizophr Res. 2020 February ; 216: 357–366. doi:10.1016/j.schres.2019.11.013.

Relationship of Prolonged Acoustic Startle Latency to Diagnosis and Biotype in the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) Cohort

Nicholas Massa[1,2], **Andrew V. Owens**[3], **Wesley Harmon**[4], **Arpita Bhattacharya**[5], **Elena I. Ivleva**[6], **Sarah Keedy**[7], **John A. Sweeney**[8], **Godfrey D. Pearlson**[9], **Matcheri S. Keshavan**[10], **Carol A. Tamminga**[6], **Brett A. Clementz**[11,*], **Erica Duncan**[1,3,*]

[1]Atlanta Veterans Affairs Medical Center, Decatur, GA 30033

[2]Rollins School of Public Health, Emory University, Atlanta, GA 30322

[3]Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA 30329

[4]Emory University, Atlanta, GA 30322

[5]University of Washington

[6]University of Texas Southwestern Medical Center

[7]University of Chicago

[8]University of Cincinnati, Department of Psychiatry

[9]Yale University and Institute of Living

[10]Harvard Medical School and Beth Israel Deaconess Medical Center

[11]Departments of Psychology and Neuroscience, Bio-Imaging Research Center, University of Georgia

Corresponding author: Erica Duncan, MD, Mental Health/116A, Atlanta Veterans Affairs Medical Center, 1670 Clairmont Road, Decatur, GA 30033, 404-321-6111, ext 207532, erica.duncan@va.gov.

Contributors

E.I.I., J.A.S., G.D.P., M.S.K., C.A.T., and B.A.C. designed the study and obtained funding to conduct the study. Data were collected by E.I.I., S.K., J.A.S., G.D.P., M.S.K., C.A.T., and B.A.C. Secondary analyses of startle data were designed by N.M. and E.D. The data were analyzed and interpreted by N.M., A.V.O., W.H., A.B., E.D., C.A.T., and B.A.C. The manuscript was written by N.M. and E.D. All authors reviewed and approved the final manuscript.

*Equal contributions by these authors

Disclosures and conflict of interest

Infrastructure support was provided by the Research and Development, the Mental Health Service Lines, and the Center of Visual and Neurocognitive Rehabilitation at the Atlanta Veterans Affairs Medical Center, Decatur, GA. Additional infrastructure support was provided by the Department of Psychiatry and Behavioral Sciences of the Emory University School of Medicine, Atlanta, GA. ED has received research support for work unrelated to this project from Auspex Pharmaceuticals, Inc. and Teva Pharmaceuticals, Inc. Other authors have nothing to disclose. ED is a full time attending psychiatrist in the Mental Health Service Line at the Atlanta Veterans Affairs Medical Center, Decatur, GA. The content is solely the responsibility of the authors and does not necessarily represent the official views of the Department of Veterans Affairs.

Abstract

Background—Latency of the acoustic startle reflex is the time from presentation of the startling stimulus until the response and provides an index of neural processing speed. Latency is prolonged in schizophrenia, is 90% heritable, and predicts conversion to schizophrenia in a high-risk population. The Bipolar-Schizophrenia Network for Intermediate Phenotypes (B-SNIP) consortium investigates neurobiological features found in psychotic disorders spanning diagnostic criteria for schizophrenia (SCZ), schizoaffective disorder (SAD), and psychotic bipolar disorder (BP). We investigated whether differences in startle latency and prepulse inhibition (PPI) occur in probands, their first-degree relatives, and neurobiologically defined subgroups of the probands (Biotypes).

Methods—1143 subjects were included from the B-SNIP cohort: 143 with SCZ, 178 SCZ relatives (SCZ-Fam), 123 with SAD, 152 SAD relatives (SAD-Fam), 138 BP, 183 BP relatives (BP-Fam), and 226 controls (CON). A Biopac system recorded the eyeblink component of the startle reflex during startle testing.

Results—Latency differed by diagnosis ($F(3,620)=5.10$, $p=0.002$): SCZ, SAD, and BP probands had slower latency than CON, with relatives intermediate. Biotypes 1 and 2 had slower latency than CON ($p<0.031$) but Biotype 3 did not differ from CON. PPI did not separate CON from other subjects when analyzed by diagnoses nor when analyzed by biotype. Biotype 1 relatives had slower latency ($F(3,663)=3.49$, $p=0.016$) and more impaired PPI than Biotype 2 and 3 relatives ($F(3,663)=2.77$, $p=0.041$).

Conclusion—Startle latency is prolonged in psychotic disorders that cross traditional diagnostic categories. These data suggest a genetic difference between biotypes that span across clinically defined diagnoses.

Keywords

Latency; Acoustic startle; Prepulse inhibition; Schizophrenia; Bipolar; Biotype

1.1 Introduction

Schizophrenia (SCZ), schizoaffective disorder (SAD) and bipolar disorder (BP) are disabling mental illnesses that each have a prevalence of approximately 1% (McGrath et al., 2008; Merikangas et al., 2011) and account for over $150 billion of total healthcare costs to the US healthcare system (Cloutier et al., 2016; Cloutier et al., 2018). These psychiatric disorders have significant overlap in clinical features, brain structure, synaptic dysfunction, pharmacological treatment, and genetic determinants (Narayanan et al., 2015).

The Bipolar-Schizophrenia Network for Intermediate Phenotypes (B-SNIP) Consortium was created to investigate biological differences and overlap in individuals with SCZ, SAD, or psychotic BP and their first-degree relatives to help guide the development of endophenotypes either within or across DSM diagnoses (Tamminga et al., 2014). Recent research conducted by this consortium has identified three experimental psychosis constructs —biotypes—derived from a battery of cognitive and neurophysiologic measures (Clementz et al., 2016; Pearlson et al., 2016). DSM categories do not map onto the neurobiologically

defined biotypes. Biotype 1 was characterized by poor cognition and impaired sensorimotor function; Biotype 2 was characterized by moderately impaired cognition and hyper-responsivity to sensorimotor events; Biotype 3 subjects, while still psychotic, were most similar to healthy controls (CON) (Clementz et al., 2016).

A potential means of further investigating the neurological function of these individuals across biotypes is through the acoustic startle reflex (ASR), which has been extensively investigated in psychiatric disorders and animal models. It is a reflexive response to sudden intense acoustic stimuli seen ubiquitously in mammals that serves as a pre-attentive reaction to ready the organism to respond to potential threats in the environment. The output reflex is mediated by a pontine-based, three-synapse subcortical neural circuit (Koch, 1999).

A very well researched modulation of the ASR is prepulse inhibition (PPI), a reduction of the ASR by a non-startling stimulus presented shortly before the more intense startling stimulus. PPI has been investigated as an operational measure of sensorimotor gating (Graham, 1975; Hoffman and Searle, 1968; Wynn et al., 2004). Multiple publications have reported impaired PPI in subjects with SCZ (Braff et al., 2001), and PPI is generally accepted as an endophenotype for SCZ used for the discovery of genes associated with SCZ (Greenwood et al., 2016; Greenwood et al., 2011). However, PPI has limitations as it is at least partially normalized by treatment with second generation antipsychotics (Fargotstein et al., 2018; Swerdlow et al., 2008; Turetsky et al., 2007), and has somewhat modest heritability (38–58%; Anokhin et al., 2003; Greenwood et al., 2007; Hasenkamp et al., 2010). PPI was not included in the biological and cognitive battery used to discern biotypes by the B-SNIP consortium (Ivleva et al., 2014).

Startle latency is the time in milliseconds (ms) required for the startle reflex to occur after a startling stimulus. Subjects with SCZ have a slower latency compared to healthy controls (CON) (Braff et al., 1978; Braff et al., 1999; Geyer and Braff, 1982; Hasenkamp et al., 2010; Ludewig et al., 2002; Swerdlow et al., 2006; Swerdlow et al., 2018 ; Weike et al., 2000), although a smaller number of studies did not detect prolonged latency in SCZ (Braff et al., 1992; Mackeprang et al., 2002; Parwani et al., 2000). The slowing of latency persists in those SCZ subjects who are treated with antipsychotic medications (Fargotstein et al., 2018). Startle latency is up to 90% heritable in a sample of SCZ and CON subjects and their first-degree relatives (Hasenkamp et al., 2010). Additionally, slower latency predicts conversion to psychosis during a two-year follow-up period in young subjects at high-risk for development of SCZ (Cadenhead et al., 2013). Latency is thus able to provide a putative index of neural processing speed (Hasenkamp et al., 2010) and can serve as an endophenotype of SCZ separate from PPI (Fargotstein et al., 2018).

The principal aims of this study were to determine whether prolonged acoustic startle latency and impaired PPI were associated with membership in the specific DSM diagnoses (either in probands or in their relatives) and B-SNIP psychosis biotypes since startle latency had not been previously assessed in the B-SNIP cohort. Further, we hypothesized that prolonged latency could be associated with cognitive impairment through impaired functioning of neural circuits during cognitive processing. Therefore, a secondary aim was to investigate whether slowing of latency associated with greater cognitive impairments in

these data across diagnoses. These analyses present an opportunity to refine our understanding of the neurobiology underlying psychotic disorders spanning traditional DSM diagnoses and to further characterize biotypes through independent measures.

1.2 Methods

1.2.1 Cohort Description

1143 individuals from the B-SNIP cohort who had completed the acoustic startle session were analyzed. Within this cohort there were 143 with schizophrenia (SCZ), 178 SCZ first-degree relatives (SCZ-Fam), 123 with schizoaffective disorder (SAD), 152 SAD first-degree relatives (SAD-Fam), 138 who had bipolar disorder (BP), 183 who were relatives of those with BP (BP-Fam), and 226 controls (CON). All proband subjects were clinically stable, medicated outpatients. Relatives of probands with a psychosis diagnosis remained in their respective relative cohorts. CON subjects had no personal history of psychiatric diagnosis, and no family history of SCZ/BP spectrum disorders in either first or second-degree relatives. Axis I diagnoses were based on the Structured Clinical Interview for DSM-IV-TR (First et al., 2001) and Axis II diagnoses in relatives were captured using the Structured Interview for DSM-IV Personality disorders (Pfohl et al., 1997). Subjects were excluded for: a history of seizures or head injury with a loss of consciousness >30min, a diagnosis of substance abuse in the preceding 30 days or substance dependence in the previous 3 months, or a history of systemic medical or neurological disorder known to affect brain function. Subjects were also required to have a negative urine drug screen for drugs of abuse on the day of testing and an age-corrected Wide Range Achievement Test-IV (WRAT) Reading subtest standard score (SS) ≥ 65 (Hochberger et al., 2018; Wilkinson and Robertson, 2006). All probands underwent symptom ratings for psychosis and affective symptom domains as well as assessments for cognition (Brief Assessment of Cognition in Schizophrenia (BACS)) (Keefe et al., 2004).

1.2.2 Biotype Determination

The subjects in the biotype analyses were SCZ, SAD, and BP probands grouped by previously constructed biotypes in prior work from the B-SNIP consortium. Biotype classification was based upon cognitive and neurobiological differences in those with psychosis such that only probands were included in its creation. These biotypes were created with composite biomarker variables of cognitive control (BACS composite score, stop signal task, and antisaccade errors) and sensorimotor reactivity (EEG intrinsic activity, N100 ERP, paired S2 ERP, and P300 ERP) through k-means clustering of the gap statistic and the preclustering step of the TwoStep cluster analysis to statistically differentiate biotypes from one another (Clementz et al., 2016). Acoustic startle data were not utilized in the creation of biotypes due to a prior analysis that found no significant difference in PPI amongst diagnostic groups (Ivleva et al., 2014) and, additionally that too fewer subjects had startle data than data for the other measure used for the cluster analysis (Clementz et al., 2016). In the present cohort, 53 probands and 64 of the relatives were missing sufficient biomarker data to generate a biotype classification. Of the remaining subjects, there were 66 in Biotype 1, 140 in Biotype 2, and 147 in Biotype 3. Other analyses included members of each biotype as well as their relatives. There were 83 family members associated with Biotype 1 (Biotype

1-Fam), 170 family members associated with Biotype 2 (Biotype 2-Fam), and 195 family members associated with Biotype 3 (Biotype 3-Fam).

1.2.3 Acoustic Startle Acquisition

Electromyographic activity (EMG) was captured from the right orbicularis oculi for quantification of acoustic startle magnitude, latency and PPI, using methods described in Ivleva et al. (2014). A session began with a 3-minute acclimation period with 70 dB white noise. Startle pulse alone trials contained 116 dB white noise lasting 40ms. The first 3 startle responses were discarded. The prepulse+pulse trials contained a 20ms, 80 dB white noise prepulse followed by the same 116dB startling pulse. Following the first 3 trials, the paradigm included 18 pulse alone trials; 12 prepulse+pulse trials with a 120ms interstimulus interval (ISI) between prepulse and startling pulse for PPI. Intertrial intervals varied from 12s to 20s. Twelve prepulse+pulse trials with a 4500ms ISI were included to assess prepulse facilitation. Results of those trials will be reported elsewhere. These trials were evenly divided into 2 blocks and were randomized within each block. The acquired EMG signal was filtered with low and high-frequency cutoffs at 28 and 500 Hz, respectively, and then rectified and smoothed using MindWare software (MindWare Technologies, Inc., Gahanna, OH). Startle non-responders were excluded from both the latency and PPI analyses if they had a measurable startle response to less than 50% of the first pulse alone trials as per a prior report on this cohort (Ivleva et al., 2014). Startle magnitude was assessed as the peak magnitude of the EMG contraction, and the latency was assessed as the time of the peak magnitude following the acoustic stimulus (Massa et al., 2017). PPI was calculated as the percent inhibition of magnitude in prepulse+pulse trials compared to the magnitude of pulse alone trials in the 120ms trial types following the formula:

$$\text{PPI} = 100 * \frac{(\text{pulse alone magnitude}) - (120\text{ms prepulse} + \text{pulse magnitude})}{(\text{pulse alone magnitude})}$$

1.2.4 Statistical Methods

Statistical differences in age, race, sex, handedness, medication status, or cognitive function of the cohort was determined by use of one-way Chi square (for categorical variables) or analysis of variance (ANOVA, for continuous variables) using either DSM diagnosis or biotype as the between subject variable. Positive and Negative Syndrome Scale (PANSS) ratings were assessed by use of a one-way ANOVA.

Startle magnitude was not normally distributed, and as such was log transformed to achieve acceptable skewness and kurtosis for use in parametric testing. PPI was calculated using the log-transformed values. To eliminate the effect of the block of the session, the average startle latency and PPI of the two blocks were used in this analysis. Furthermore, in all models assessing latency, the log transformed startle magnitude to pulse alone trials was included as a covariate.

Repeated measures analyses of variance with covariates (ANCOVAs) were used to compare startle outcome measures separately for DSM diagnoses and biotypes. For models that included probands and relatives of these probands, the error terms and corresponding

significance values were adjusted by subtracting the number of relatives from the error term and calculating the corresponding significance using F tables to account for the non-independence of related subjects. Linear regression was used to quantify the association of acoustic startle latency, acoustic startle magnitude, and prepulse inhibition with cognitive variables. Chlorpromazine equivalents for antipsychotic medication were not significant in preliminary models and so were not included in the final models. The covariates included in each ANCOVA model for latency were age, race, sex, diagnosis or biotype, and log transformed startle magnitude to pulse alone trials since the latter significantly affected latency. Magnitude and PPI ANCOVAs included the covariates age, race, sex, diagnosis or biotype, and also site (due to some significant effects on magnitude and PPI). Linear regressions were used to examine the relation of cognition to startle variables in probands. The BACS variable utilized a calculated Z-score adjusted for age and sex so for regressions on BACS the only additional terms in these regressions were race and diagnosis (and log of startle magnitude for regressions examining latency). Terms in the regressions on the WRAT were similar except that age and sex were added since the WRAT was not an adjusted Z-score. All statistics were completed using either SPSS version 23 (Armonk, NY) or SAS 9.4 software (Cary, North Carolina).

1.3 Results

1.3.1 Diagnosis Results

Demographics and descriptive statistics of the cohort (N=1143) based upon diagnosis group (CON, BP, BP-Fam, SCZ, SCZ-Fam, SAD, and SAD-Fam) can be seen in Table 1. As expected, there were several significant differences across subject groups, especially regarding sex, race, age, medications, and PANSS domain and total scores ($p<0.0001$). Table 2 contains the descriptive statistics of the cognition and startle variables used in this publication. Throughout all the cognition variables there was a significant difference in scores across group, with SCZ performing significantly worse as reported previously in the B-SNIP sample (Hill et al., 2013). When assessing latency in this cohort all repeated measures ANCOVAs included age, race, sex, and log transformed startle magnitude to pulse alone trials. All repeated measures ANCOVAs for magnitude and PPI included age, race, sex, and site.

In a repeated measures ANCOVA comparing latency in CON, SCZ and SCZ-Fam subjects, SCZ subjects were slower than CON, with the SCZ-Fam group intermediate between SCZ and CON ($F(2,371)=4.86$, $p=0.008$, $\eta^2=0.018$; Figure 1). Post hoc tests indicated that SCZ subjects were significantly slower than CON in pulse alone trials ($p=0.004$, Hedges $g=-0.29$; Figure 1a) and in 120ms prepulse trials ($p=0.009$, Hedges $g=-0.24$; Figure 1b). SCZ subjects also had slower latency than SCZ-Fam in the 120ms prepulse trials ($p=0.04$, Hedges $g=0.16$; Figure 1b). In a model comparing pulse alone startle magnitude, both SCZ ($p<0.001$, Hedges $g=0.43$) and SCZ-Fam ($p=0.013$, Hedges $g=0.24$) had higher pulse alone magnitudes compared to CON ($F(2,372)=7.354$, $p=0.001$, $\eta^2=0.027$).

In a similar model comparing latency in CON, SAD, and SAD-Fam, SAD subjects were slower than CON with the SAD-Fam group intermediate between SAD and CON ($F(2,342)=3.78$, $p=0.024$, $\eta^2=0.015$; Figure 1). Post hoc tests indicated that SAD subjects

had significantly longer latency than CON in both pulse alone (p=0.008, Hedges g= −0.31; Figure 1a) and 120ms trials (p=0.03, Hedges g= −0.24; Figure 1b). In a one-way ANOVA comparing pulse alone startle magnitude between SAD, SAD-Fam, and CON there were no significant differences between subject groups (F(2,343)=1.82, p=0.16, η^2=0.007).

A repeated measures ANCOVA comparing latency in BP, BP-Fam and CON found significant differences based upon group, with BP the slowest and BP-Fam intermediate (F(2,364)=4.05, p=0.018, η^2=0.015; Figure 1). In post-hoc tests, BP and BP-Fam had significantly longer latency than CON in pulse alone trials (p=0.004, Hedges g= −0.35; p=0.05, Hedges g= −0.29; Figure 1a). In the 120ms trials, BP were also significantly longer than CON (p=0.039, Hedges g= −0.16; Figure 1b). In an ANOVA model comparing pulse alone startle magnitude, both BP (p=0.001, Hedges g=0.51) and BP-Fam (p=0.016, Hedges g=0.39) had higher pulse alone magnitudes compared to CON (F(2,365)=5.90, p=0.003, η^2=0.021).

A model comparing latency in BP, SAD, SCZ, and CON was significant for diagnosis (F(3,620)=5.10, p=0.002, η^2=0.024; Figure 1). In a series of post hoc tests all probands (BP, SAD, and SCZ) were slower than CON in pulse alone trials (p=0.003, Hedges g=−0.35; p=0.012, Hedges g=−0.31; p=0.003, Hedges g=−0.29). Similarly, all probands (BP, SAD, and SCZ) were significantly slower than CON at 120ms trials (p=0.043, Hedges g= −0.15; p=0.036, Hedges g= −0.24; p=0.004, Hedges g= −0.24). A model comparing pulse alone magnitude in BP, SAD, SCZ and CON was significant for diagnosis, with both BP and SCZ having significantly larger magnitudes compared to CON (F(3,620)=6.295, p<0.001, η^2=0.03; p=0.002, Hedges g=0.51; p<0.001, Hedges g=0.43). The SCZ group had a significantly larger pulse alone magnitude when compared to SAD (p=0.016, Hedges g= −0.32).

We constructed ANCOVAs to assess PPI in 120ms trials in each diagnostic subset (SCZ, SCZ-fam or SAD, SAD-Fam or BP, and BP-Fam) compared to CON and in all the probands (SCZ, SAD, BP) compared to CON. PPI was not significant in any of these models (all p-values were >0.4).

1.3.2 Biotype Results

Demographics and descriptive statistics of the cohort (n=801) separated into biotypes and their respective family members can be seen in Table 3. There were many significant differences across subject groups, especially regarding race, atypical antipsychotic medication, and PANSS subscale and total scores (p<0.05). Table 4 contains the descriptive statistics of the cognitive and startle variables used throughout this publication for subjects divided by biotype. Given that the biotype determination factored in cognition, there was a significant difference in cognitive scores across group with Biotype 1 performing significantly worse (see Table 4).

ANCOVA models were used to assess differences in startle latency, magnitude, and PPI between biotype probands and controls or between family members and controls. In the ANCOVA that included only probands and controls, there was a strong trend level association between startle latency and biotype membership (F(3,567)=2.32, p=0.075,

η^2=0.012; Figure 2). Because we hypothesized individual differences in the biotypes, we examined post hocs that indicated that Biotypes 1 and 2 had significantly slower startle latency when compared to CON in pulse alone trials (p=0.03, Hedges g=−0.28; p=0.001, Hedges g=−0.24; Figure 2a), whereas Biotype 3 did not differ from CON. For the 120ms trials, none of the biotypes were significantly slower than CON (p>0.1 Figure 2b).

In a model assessing startle magnitude in biotype probands versus controls, all biotypes had significantly larger pulse alone magnitude compared to CON (F(3,567)=4.327, p=0.005, η^2=0.022). In similar ANOVAs assessing PPI, probands analyzed by biotype did not differ from CON in PPI.

We hypothesized that the underlying genetics of the three biotypes might differ and manifest in startle differences between family members and CON when a family member was classified according to the biotype of their proband relatives. An ANCOVA on biotype that compared latency in family members to CON was significant (F(3,663)=3.49, p=0.016, η^2=0.016). In post hoc tests only Biotype 1-Fam was significantly slower than CON in the pulse alone trials (p=0.011, Hedges g=−0.41; Figure 2a). Additionally, Biotype 1-Fam was slower than Biotype 3-Fam (p=0.039, Hedges g=−0.21). In 120ms trials, Biotype 1-Fam had significantly slower latency than Biotype 2-Fam and Biotype 3-Fam (p=0.027, Hedges g=0.37; p=0.002, Hedges g=0.32; p=0.004, Hedges g=0.42; Figure 2b).

A model comparing startle magnitude between biotype family members and CON indicated significant differences in startle magnitude (F(3,663)=4.51, p=0.004, η^2=0.02). In post hoc tests both Biotype 2-Fam (p=0.002, Hedges g=0.33) and Biotype 3-Fam (p=0.014, Hedges g=0.34) had startle magnitudes significantly larger than CON. Biotype 2-Fam also had a greater startle magnitude when compared to Biotype 1-Fam (p=0.015, Hedges g= −0.23).

In a similar ANOVA comparing PPI in relatives of biotype probands to CON, there was a significant difference in PPI (F(3,663)=2.77, p=0.041, η^2=0.012; Figure 3). Post hoc tests found that PPI in Biotype 1-Fam was significantly reduced compared to both Biotype 2-Fam and Biotype 3-Fam (p=0.006, Hedges g=−0.35; p=0.044, Hedges g=−0.25; Figure 3).

1.3.3 Cognition and Startle Variables

We used multivariate linear regressions to analyze the association between cognition and acoustic startle variables. Models assessing the association between cognition and latency found that slower latency in pulse alone and 120ms trial types was associated with worse composite BACS scores (β=−0.18, p=0.038; β=−0.098, p=0.018). A subsequent series of models examined the association between startle magnitude and cognition. We found that pulse alone magnitude was positively associated with higher WRAT scores (β=0.095, p=0.027). In models examining the association between PPI and cognition, 120ms PPI was positively associated with a higher WRAT score (β=0.092, p=0.015). Other associations between PPI and cognition were not significant.

1.4 Discussion

The main objective of this study was to determine whether startle variables, chiefly latency and PPI, differed from CON in DSM psychotic disorders, and whether a transdiagnostic categorization of subjects based on biotype would reveal differences in startle measures between the biotypes.

This study provides further evidence that startle latency is slower (i.e. longer) in SCZ and SAD subjects when compared to CON subjects. This finding supports previous literature that reported a significant slowing of latency in SCZ compared to CON (Braff et al., 1978; Braff et al., 1999; Fargotstein et al., 2018; Geyer and Braff, 1982; Hasenkamp et al., 2010; Swerdlow et al., 2006). However, it should be acknowledged that several studies that did not detect a difference in startle latency based upon diagnostic group (Braff et al., 1992; Cadenhead et al., 2000; Geyer and Braff, 1982; Parwani et al., 2000). The current study also provides evidence that startle latency is slower in those with BP than CON, and that there is no significant difference in PPI between BP and CON. This is in accord with a prior study by Carroll et al. (Carroll et al., 2007) that reported a significantly longer startle latency in those with mixed-type bipolar disorder when compared to psychiatric controls. Similarly, the study conducted by Sánchez-Morla et al. (2016) reported increased startle latency in those with euthymic BP as compared to CON.

The current study did not find a significant difference in PPI attributed to diagnosis when comparing SCZ, SAD, or BP to CON, recapitulating a similar finding in a smaller set of B-SNIP subjects previously published (Ivleva et al., 2014). This could be attributed to antipsychotic medication status as highlighted and discussed in Fargotstein et al. (2018), given the high proportion of probands subjects with SCZ, SAD, and BP who were on second-generation antipsychotics in the B-SNIP cohort. It should be noted that preliminary regression models did not find a significant effect of medication status (antipsychotic treatment vs. no antipsychotic treatment), but the number of probands not on antipsychotic medication was quite small (BP: 24%, SAD: 13%, SCZ: 12%). Levels of PPI in 120 ms trials are typically higher in both SCZ and CON groups than what we report herein (see review in Hamm et al., 2001). In particular, the low levels of PPI in our CON group may also contribute to the lack of significant differences between our CON and patient groups in addition to the medicated status of our patient groups. Furthermore, baseline startle magnitude was lower in CON than in other subjects groups in this study, for reasons that are unclear. Typically, when pulse alone startle magnitude is low, there is greater PPI given that PPI is calculated as a percent decrease in magnitude to prepulse trials compared to pulse alone trials. Thus, the lower magnitude in CON subjects renders the low PPI in this group noteworthy.

The above points notwithstanding, our negative results for diagnostic group are consistent with the study by Carroll et al. (2007) that reported no significant difference in PPI between those with mixed-type BP compared to controls. However, our results contrast with the study conducted by Sánchez-Morla et al. (2016) that found impaired PPI in euthymic BP when compared to CON. While these studies (Carroll et al., 2007; Sanchez-Morla et al., 2016) both implicate slowing of startle latency in BP spectrum disorder, the association between

BP and PPI is likely confounded by the different disease states of BP studied as well as the presence of psychosis. The overarching purpose of the work being conducted by the B-SNIP consortium is to utilize an intermediate phenotype, or endophenotype approach to the identification of both biomarkers and genes associated with psychosis that span across traditional DSM diagnostic categories. Through this endophenotype approach the B-SNIP consortium has defined three different biotypes that were based upon unique neurobiological characteristics (Clementz et al., 2016). In the current analyses, as shown in Figure 2, the Biotype 1 and Biotype 2 probands were slower in latency than CON whereas Biotype 3 was not. Furthermore, latency was significantly slower in relatives of Biotype 1 probands than in relatives of Biotypes 2 and 3, supporting the possibility of genetic differences between biotypes.

The PPI analysis by biotype found no significant difference between biotype probands and CON, nor amongst the three biotype probands. However, the analysis of relatives of biotype probands indicated that PPI was significantly impaired in Biotype 1 relatives compared to Biotypes 2 and 3 relatives.

In comparison to the other biotypes, Biotype 1 is associated with impaired cognitive function and sensorimotor reactivity, more severe negative symptoms, greater reduction in gray matter density, greater psychosocial impairment, having the highest proportion of affected relatives, higher polygenic risk scores, and lowest cannabis use (Clementz et al., 2016; Hochberger et al., 2018; Ivleva et al., 2017; Reilly et al., 2017; Tamminga et al., 2017). Biotype 3 in prior work was the least impaired in other measures (Clementz et al., 2016). In the current study Biotype 1 relatives have longer latency than Biotype 2 and 3 relatives. In consonance with our new data, decreased gray matter density associates with impaired PPI (Kumari et al., 2005), and SCZ risk genes have been found to associate with slowing of latency and impaired PPI (Greenwood et al., 2011; Hong et al., 2008; Quednow et al., 2009; Roussos et al., 2008a; Roussos et al., 2008b; Roussos et al., 2016; Smith et al., 2017).

A secondary objective of this study was to investigate the relationship between cognition and slowing of startle latency in the current cohort spanning DSM diagnoses. This objective is based on an underlying hypothesis that slowing of neural circuits subserving cognition (as indexed by slowing of startle latency) could in part underlie cognitive impairment. Indeed, we found that slower startle latency associated with worse cognition in our cohort of probands (BP, SCZ, and SAD) and CON. However, the latency versus BACS results herein are in contrast to a study by Hasenkamp et al. (2011) in a cohort of CON and SCZ that did not detect a significant association between decreased cognitive scores and slower acoustic startle latency or increased magnitude. While the results of the paper indicate a potential additional association between startle latency and the Conner’s Continuous Performance Test, it was not significant after Bonferroni correction. There was also a weak correlation between lower startle magnitude and an increase in preservative errors on the Wisconsin Card Sorting Task, however this too did not survive correction for multiple tests. In light of the current results, further study of the interaction of latency and cognition may be warranted.

The findings herein regarding diagnostic and biotype differences in baseline startle magnitude, although not a main focus of this study, are worthy of note. In particular, baseline magnitude was notably lower in our CON group, for unclear reasons. Generally larger startle magnitudes in schizophrenia spectrum subjects has not been reported (Braff et al., 1978; Braff et al., 1992; Swerdlow et al., 2006) and has not been nearly as intensively studied as PPI and, more recently, latency. To put our magnitude findings in context, magnitude is highly heritable in human subjects (Anokhin et al., 2003; Hasenkamp et al., 2010). Decreased magnitude has been reported in bipolar subjects in one study (Carroll et al., 2007) although no difference in magnitude was detected in others (Perry et al., 2001; Barrett et al., 2005). Of note, startle magnitude is modulated by dopaminergic signaling (Davis, 1980), which in turn is highly relevant to the pathophysiology of schizophrenia (Davis et al., 1991).

This study has several limitations. The study consists largely of chronically ill and medicated proband with psychosis. As a result, there are many potential illness and medication confounds that need to be considered such as lifetime disease burden, past substance use disorders, and the chronic effects of medication (Tamminga et al., 2013). Furthermore, the cross-sectional design of the study limits the scope of the association between biotype and acoustic startle response as we are unable to discern the longitudinal effects of biotype membership on this physiological measure. Another limitation is that the startle paradigm used herein did not include prepulse+pulse trials with 30ms or 60ms between prepulse and pulse as has been commonly used in the field. These additional trial types could have conferred additional detail on the between group differences in latency and PPI.

In summary, startle latency is prolonged in psychotic disorders across traditional diagnostic categories. Biotype 1 and 2 probands had slower latency than CON, but Biotype 3 probands did not. These data suggest a genetic difference between biotypes that span across clinically defined psychotic diagnoses. PPI findings were less robust since PPI did not distinguish DSM diagnostic groups from CON nor did PPI differ between biotype probands. However, PPI in relatives of Biotype 1 probands had impaired PPI compared to Biotypes 2 and 3 relatives, suggesting a genetic difference in PPI relevant-genes amongst the biotypes. We hypothesize that acoustic startle latency is a putative index of neuronal processing speed, with the potential to serve as an endophenotype of SCZ and more broadly, psychosis. As a future direction we plan to investigate the genetics underlying the biotypes to determine how their genetics and underlying molecular signature confers risk of psychosis (Lencer et al., 2017). This approach may lead to the discovery of individualized treatments for psychotic patients based on their specific underlying genetics and neurobiology.

Acknowledgments

Funding body agreements and policies

Supported by the National Institute of Mental Health (MH-077851, MH-078113, MH-077945, MH-077852, MH-077862), a NARSAD/Brain & Behavior Research Foundation John Kennedy Harrison Young Investigator Award (17801), and a Veterans Affairs Merit Review grant (I01CX000974). The content is solely the responsibility of the authors and does not represent the official views of the National Institute of Mental Health or the Department of Veterans Affairs.

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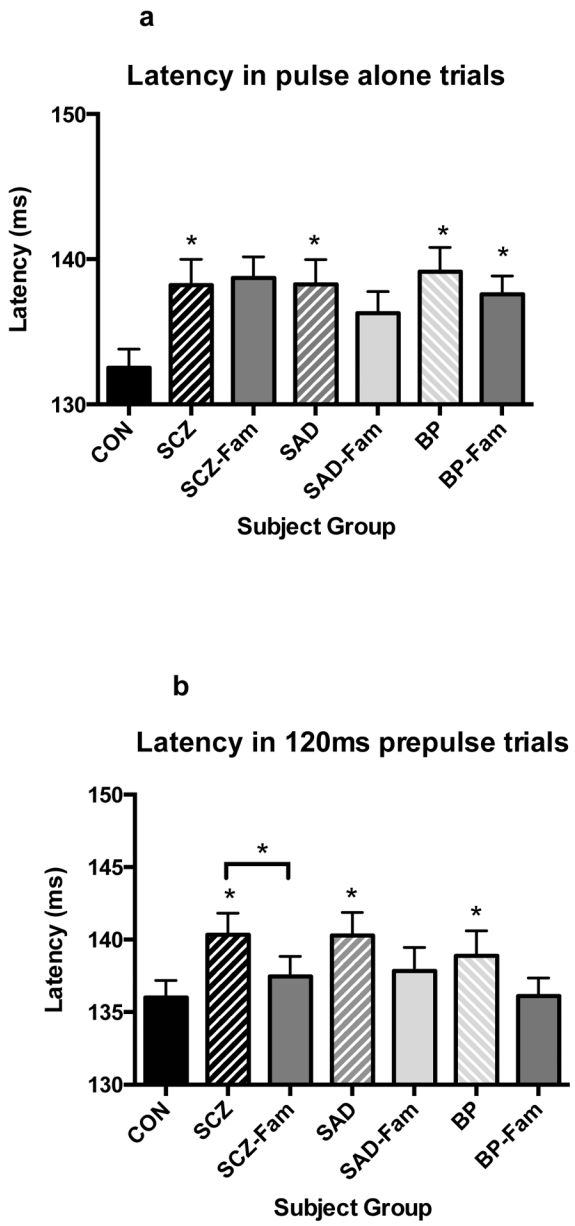

Figure 1.

Difference in startle latency between controls and probands or families of probands by diagnostic group. * indicates difference was significant at $p < 0.05$ compared to controls. Brackets with * indicates significant differences between bracketed groups in post hoc tests ($p < 0.05$). (a) Pulse alone trials. (b) 120 ms prepulse+pulse trials. SCZ = schizophrenia probands; SCZ-Fam = family members of schizophrenia probands; SAD = schizoaffective probands; SAD-Fam = family members of schizoaffective probands; BP = bipolar probands; BP-Fam = family members of bipolar probands;

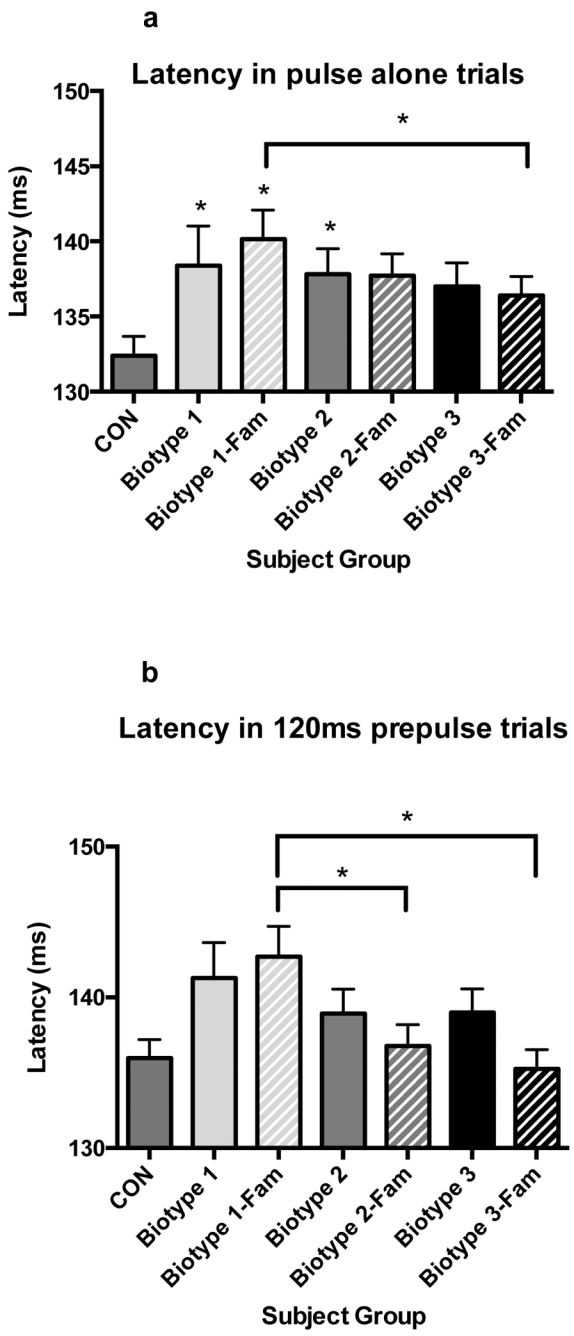

Figure 2.

Difference in startle latency between controls and probands or families of probands by biotype group. * indicates difference was significant at $p < 0.05$ compared to controls. Brackets with * indicates significant differences between bracketed groups in post hoc tests ($p < 0.05$). (a) Pulse alone trials. (b) 120 ms prepulse+pulse trials. Biotype 1-Fam = family members of Biotype 1 probands; Biotype 2-Fam = family members of Biotype 2 probands; Biotype 3-Fam = family members of Biotype 3 probands.

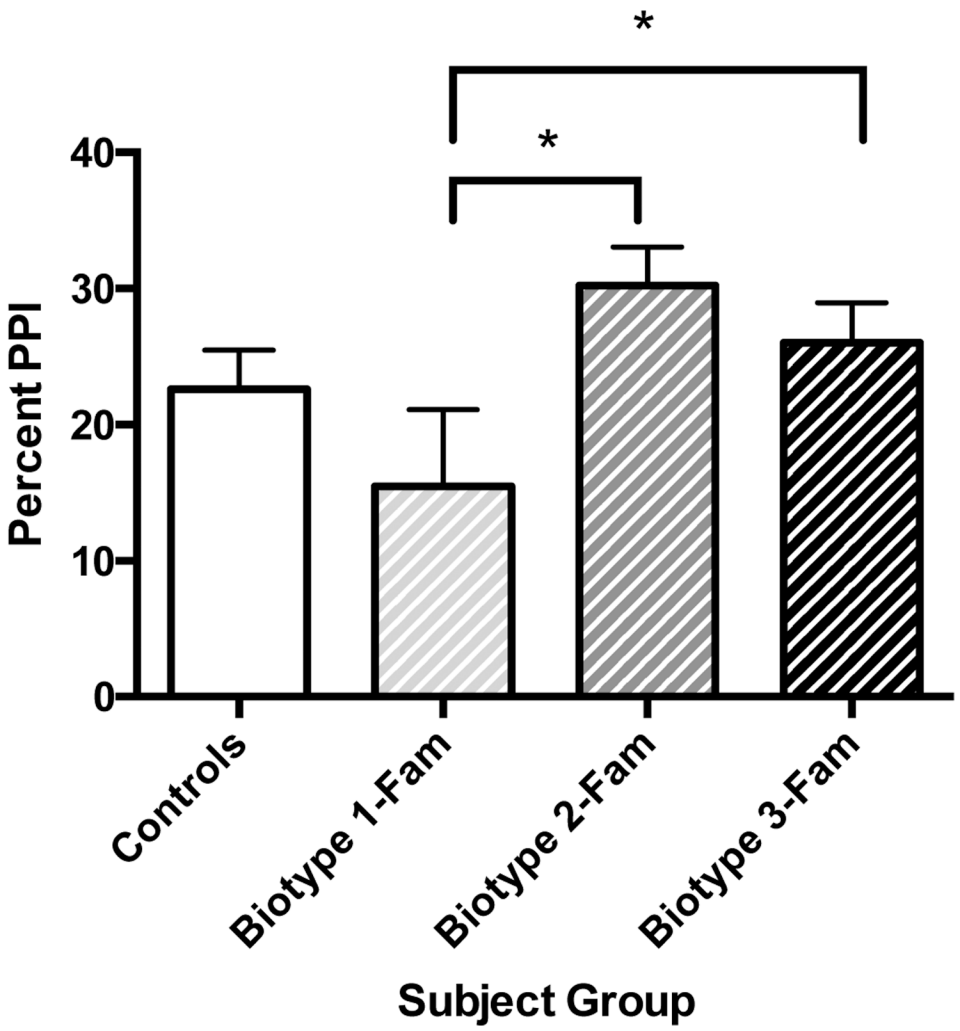

Figure 3.

Percent prepulse inhibition in control subjects and family members of biotype probands. Brackets with * indicate significant differences between bracketed groups in post hoc tests ($p < 0.05$). Biotype 1-Fam = family members of Biotype 1 probands; Biotype 2-Fam = family members of Biotype 2 probands; Biotype 3-Fam = family members of Biotype 3 probands.

Table 1:

Demographic and clinical information by diagnostic group

	Controls	Bipolar	Bipolar Familes	Schizophrenia	Schizophrenia Families	Schizoaffective	Schizoaffective Families	Chi Sq/ F Value	*p* Value
Demographics, n	226	138	183	143	178	123	152		
Sex, n(%)[b]									
Male	106(47.11)	49(35.51)	69(37.70)	94(65.73)	54(30.34)	46(37.40)	46(30.26)	57.85	<.0001
Female	119(52.89)	89(64.49)	114(62.30)	49(34.27)	124(69.66)	77(62.60)	105(69.08)		
Missing	1(0.44)	-	-	-	-	-	1(0.66)		
Race, n(%)[c]									
White	148(65.49)	108(78.26)	154(84.15)	74(51.75)	114(64.04)	68(55.28)	93(61.18)	57.09	<.0001
Black	58(25.66)	20(14.49)	23(12.57)	53(37.06)	50(28.09)	49(39.84)	49(32.24)	50.69	<.0001
Other	20(8.85)	10(7.25)	6(3.28)	16(11.19)	14(7.87)	6(4.88)	10(6.58)		
Ethnicity, n(%)									
Hispanic	26(11.50)	15(10.87)	16(8.74)	18(12.59)	19(10.67)	17(13.82)	19(12.5)	2.46	0.873
Handedness, n(%)[d]									
Right	201(88.94)	110(79.71)	155(84.70)	119(83.22)	152(85.39)	107(86.99)	129(84.87)	16.54	0.168
Left	17(7.52)	20(14.49)	24(13.11)	13(9.09)	16(8.99)	10(8.13)	15(9.87)		
Ambidextrous or Missing	8(3.54)	8(5.80)	4(2.18)	11(7.69)	10(5.62)	6(4.87)	8(5.26)		
Medication, n(%)									
Typical Antipsychotic	0(0.0)	7(5.26)	0(0.00)	12(8.39)	2(1.12)	14(11.38)	1(0.66)	60.25	<.0001
Atypical Antipsychotic	0(0.0)	93(69.92)	11(6.25)	103(72.03)	18(10.11)	92(74.80)	13(8.55)	566.44	<.0001
Mood Stabilizer	0(0.0)	101(75.94)	22(12.50)	30(20.98)	9(5.06)	67(54.47)	14(9.21)	411.7	<.0001
Missing	4	5	7	11(7.69)	9(5.06)	1(0.81)	8(5.26)		
Age, Years, Mean(SD)[a]	37.87(12.77)	35.49(13.48)	40.17(15.89)	34.13(11.93)	43.47(15.87)	38.28(12.17)	39.43(16.28)	7.5	<.0001[e,f,g,h]
Chlorpromazine Equivalents, n	-	82	6	79	12	84	11		
Mean (SD)	-	342.62(359.05)	226.85(191.20)	606.98(502.95)	460.28(585.18)	503.55(418.30)	423.03(528.08)	3.42	0.0052[i]
No Antipsychotic Medication, n	-	33	164	17	149	16	130		
PANSS, n		128	17	128	17	122	19		
PANSS, Mean(SD)									

	Controls	Bipolar	Bipolar Familes	Schizophrenia	Schizophrenia Families	Schizoaffective	Schizoaffective Families	Chi Sq/ F Value	*p* Value
Positive Symptoms	-	13.33(4.25)	13.76(4.92)	17.69(5.6)	17.82(5.93)	18.88(4.86)	15.37(4.55)	19	<.0001[i,j,k]
Negative Symptoms	-	12.66(4.27)	11.71(4.44)	17.31(6.52)	13.94(4.56)	16.27(4.79)	12.11(3.18)	14.6	<.0001[i,j,k]
General Symptoms	-	30.20(7.54)	29.76(9.31)	34.55(8.17)	33.12(9.99)	36.96(8.05)	30.05(7.79)	10.65	<.0001[i,j,k]
Total		56.19(13.29)	55.24(17.24)	69.55(17.38)	64.88(17.58)	72.11(14.91)	57.53(13.41)	18.1	<.0001[i,j,k]

[a]Significant difference between Controls and Bipolar (p<0.05)

[b]Significant difference between Controls and Bipolar Family (p<0.05)

[c]Significant difference between Controls and Schizophrenia (p<0.05)

[d]Significant difference between Controls and Schizoaffective (p<0.05)

[e]Significant difference between Controls and Schizophrenia Family (p<0.05)

[f]Significant difference between Controls and Schizoaffective Family (p<0.05)

[g]Significant difference between Bipolar and Bipolar Family (p<0.05)

[h]Significant difference between Schizophrenia and Schizophrenia Family (p<0.05)

[i]Significant difference between Schizoaffective and Schizoaffective Family (p<0.05)

[j]Significant difference between Bipolar and Schizophrenia (p<0.05)

[k]Significant difference between Bipolar and Schizoaffective (p<0.05)

[l]Significant difference between Schizophrenia and Schizoaffective (p<0.05)

Table 2.

Cognitive scores and startle variables by diagnostic group

	Controls	Bipolar	Bipolar Familes	Schizophrenia	Schizophrenia Families	Schizoaffective	Schizoaffective Families	F Value	*p* Value
Cognitive Testing, n	222	135	172	136	166	118	145		
WRATSB, Mean(SD)	101.81(14.09)	100.85(13.87)	103.36(15.91)	93.97(17.36)	96.27(16.56)	95.18(13.62)	97.72(16.24)	8.55	<.0001 *c,d,e,j*
BACS, Z Scores, Mean(SD)									
Composite	−0.03(1.15)	−0.89(1.33)	−0.05(1.16)	−1.75(1.32)	−0.47(1.21)	−1.51(1.29)	−0.51(1.35)	42.77	<.0001 *a,c,d,e,f,g,h,i,j,k*
Verbal Memory	−0.03(1.14)	−0.41(1.31)	−0.12(1.11)	−0.94(1.34)	−0.3(1.33)	−0.93(1.46)	−0.46(1.27)	11.99	<.0001 *c,d,f,h,j,k*
Digit sequencing	−0.14(1.16)	−0.56(1.09)	−0.02(0.98)	−1.22(1.19)	−0.3(1.13)	−0.95(1.11)	−0.43(1.33)	20.33	<.0001 *a,c,d,g,h,i*
Token Motor	0.01(1.08)	−0.93(1.26)	−0.30(1.09)	−1.38(1.17)	−0.47(1.07)	−1.49(1.08)	−0.36(0.99)	40.23	<.0001 *a,c,d,e,f,g,h,i,j,k*
Verbal Fluency	0.13(1.07)	−0.25(1.20)	0.13(1.18)	−0.78(1.18)	−0.02(1.11)	−0.5(1.14)	0.01(1.16)	12.72	<.0001 *c,d,g,h,i,j*
Symbol Coding	−0.04(1.01)	−0.88(1.09)	−0.10(1.07)	−1.41(1)	−0.51(1.1)	−1.36(1.1)	−0.43(1.18)	39.55	<.0001 *a,c,d,e,f,g,h,i,j,k*
Tower of London	−0.06(1.08)	−0.29(1.26)	0.19(0.96)	−0.88(1.54)	−0.24(1.1)	−0.55(1.19)	−0.23(1.13)	12.32	<.0001 *c,d,j*
Startle testing, n	225	138	182	143	178	123	152		
Latency, ms, Mean(SD)									
Pulse Alone	132.39(19.25)	139.13(19.48)	137.70(17.12)	138.21(21.31)	138.71(19.47)	138.26(18.98)	136.28(18.28)	2.96	0.0071 *a,e*
120ms Prepulse+Pulse	135.98(18.15)	138.94(20.05)	136.24(16.90)	140.35(17.59)	137.46(18.55)	140.29(17.79)	137.84(19.94)	1.51	0.170
Magnitude, μV, Mean(SD)									
Pulse Alone	11.96(0.99)	12.47(1.03)	12.34(0.93)	12.39(1.01)	12.20(1.03)	12.06(0.97)	12.17(1.02)	5.57	<.0001 *a,b,c,k*
120ms Prepulse+Pulse	11.52(0.89)	11.94(0.86)	11.79(0.93)	11.89(0.88)	11.72(0.90)	11.60(0.86)	11.69(0.92)	4.86	<.0001 *a,b,c,k*
Percent PPI, Mean(SD)									
120ms	22.57(43.66)	25.94(44.31)	29.42(41.65)	25.21(44.86)	26.91(37.01)	23.18(40.80)	23.74(42.87)	0.58	0.746

a Significant difference between Controls and Bipolar (p<0.05)

b Significant difference between Controls and Bipolar Family (p<0.05)

c Significant difference between Controls and Schizophrenia (p<0.05)

d Significant difference between Controls and Schizoaffective (p<0.05)

[e] Significant difference between Controls and Schizophrenia Family (p<0.05)

[f] Significant difference between Controls and Schizoaffective Family (p<0.05)

[g] Significant difference between Bipolar and Bipolar Family (p<0.05)

[h] Significant difference between Schizophrenia and Schizophrenia Family (p<0.05)

[i] Significant difference between Schizoaffective and Schizoaffective Family (p<0.05)

[j] Significant difference between Bipolar and Schizophrenia (p<0.05)

[k] Significant difference between Bipolar and Schizoaffective (p<0.05)

[l] Significant difference between Schizophrenia and Schizoaffective (p<0.05)

Table 3:

Demographic and clinical information by Biotype

	Biotype 1	Biotype 1 Families	Biotype 2	Biotype 2 Families	Biotype 3	Biotype 3 Families	Chi-Sq/ F Value*	*p* Value
Demographics, n	66	83	140	170	147	195		
Sex, n(%)[b]								
Male	32(48.48)	30(36.14)	60(42.86)	54(31.76)	73(49.66)	69(35.38)	19.09	0.004
Female	34(51.52)	53(63.86)	80(57.14)	116(68.24)	74(50.34)	126(64.62)		
Race, n(%)								
White	30(45.45)	40(48.19)	95(67.86)	127(74.71)	98(66.67)	150(76.92)	39.68	<0.0001
Black	28(42.42)	35(42.17)	35(25.00)	37(21.76)	37(25.17)	31(15.90)	31.95	<0.0001
Other	8(12.12)	8(9.64)	10(7.14)	6(3.53)	12(8.16)	14(7.18)		
Ethnicity, n(%)								
Hispanic	14(21.21)	15(18.07)	18(12.86)	20(11.76)	14(9.52)	14(7.18)	13.84	0.032
Handedness, n(%)								
Right	56(86.15)	66(79.52)	123(87.86)	147(86.47)	124(84.93)	175(89.74)	14.83	0.251
Left	6(9.23)	14(16.87)	16(11.43)	17(10)	19(13.01)	16(8.21)		
Ambidextrous or Missing	4(4.62)	3(3.61)	1(0.71)	6(3.53)	4(2.05)	4(2.05)		
Medication, n(%)								
Typical Antipsychotic	8(12.31)	1(1.20)	9(6.43)	2(1.18)	12(8.28)	0	51.68	<0.0001
Atypical Antipsychotic	54(83.08)	14(16.87)	112(80.00)	15(8.82)	100(68.97)	10(5.13)	543.53	<0.0001
Mood Stabilizer	33(50.77)	13(15.66)	70(50.00)	16(9.41)	77(53.10)	11(5.64)	288.2	<0.0001
Missing	1	3(3.61)	0	2(1.18)	2	7(3.59)		
Age, Years, Mean(SD)	36.65(13.34)	40.94(14.84)	35.04(11.89)	40.26(16.37)	35.16(12.79)	41.81(16.38)	5.61	<0.0001[b,c]
Chlorpromazine Equivalents, n	46	8	92	13	86	7		
Mean(SD)	519.50(404.83)	325.70(609.86)	557.57(528.88)	594.38(522.16)	403.32(361.45)	150.11(99.62)	2.23	0.052
No Antipsychotic Medication, n	3	65	19	151	33	178		
PANSS, n	64	13	134	19	146	16		
PANSS, Mean(SD)								
Positive Symptoms	17.13(5.68)	15.69(5.09)	17.06(5.63)	17.00(5.28)	15.34(5.12)	13.81(5.68)	2.52	0.029
Negative Symptoms	17.28(6.95)	11.85(5.10)	15.46(4.97)	13.16(3.98)	14.39(5.65)	12.50(3.90)	4.89	0.0002[a,e]

	Biotype 1	Biotype 1 Families	Biotype 2	Biotype 2 Families	Biotype 3	Biotype 3 Families	Chi-Sq/ F Value*	*p* Value
General Symptoms	33.95(8.98)	30.77(8.20)	34.77(8.48)	32.74(9.00)	32.11(7.94)	28.94(9.59)	2.58	0.026
Total	68.36(18.88)	58.31(15.57)	66.30(16.39)	62.89(16.30)	61.84(16.06)	55.25(17.36)	3.61	0.003

*All tests of association include the controls where appropriate

[a]Significant association between Biotype 1 and Biotype 1 Families ($p<0.05$)

[b]Significant association between Biotype 2 and Biotype 2 Families ($p<0.05$)

[c]Significant association between Biotype 3 and Biotype 3 Families ($p<0.05$)

[d]Significant association between Biotype 1 and Biotype 2 ($p<0.05$)

[e]Significant association between Biotype 1 and Biotype 3 ($p<0.05$)

[f]Significant association between Biotype 2 and Biotype 3 ($p<0.05$)

Table 4.

Cognitive scores and startle variables by Biotype

	Biotype 1	Biotype 1 Families	Biotype 2	Biotype 2 Families	Biotype 3	Biotype 3 Families	F Value*	*p* Value
Cognitive Testing, n	64	81	136	161	145	190		
WRATSB, Mean(SD)	88.59(15.15)	91.33(16.34)	94.49(13.37)	98.51(17.01)	103.61(14.45)	103.33(15.17)	16.75	<0.0001[e,f]
BACS, Z Scores, Mean(SD)								
Composite	−2.74(0.88)	−1.20(1.18)	−1.93(0.94)	−0.47(1.25)	−0.22(0.83)	0.15(1.08)	108.99	<0.0001[a,b,c,d,e,f]
Verbal Memory	−1.82(1.2)	−0.90(1.34)	−1.14(1.23)	−0.29(1.27)	0.09(1.05)	0.00(1.10)	38.12	<0.0001[a,b,d,e,f]
Digit sequencing	−1.75(1.05)	−0.81(1.09)	−1.25(0.93)	−0.31(1.23)	−0.15(0.91)	0.10(1.05)	42.70	<0.0001[a,b,d,e,f]
Token Motor	−1.88(0.94)	−0.88(1.06)	−1.54(1.02)	−0.52(1.07)	−0.74(1.2)	−0.04(0.99)	54.96	<0.0001[a,b,c,e,f]
Verbal Fluency	−1.45(1.01)	−0.51(1.10)	−0.88(0.93)	−0.07(1.12)	0.27(1.07)	0.36(1.12)	40.59	<0.0001[a,b,d,e,f]
Symbol Coding	−2.1(0.9)	−0.84(1.09)	−1.5(0.89)	−0.38(1.15)	−0.51(0.91)	−0.11(1.08)	60.83	<0.0001[a,b,c,d,e,f]
Tower of London	−1.53(1.38)	−0.58(1.12)	−0.95(1.26)	−0.22(1.07)	0.22(0.92)	0.21(0.98)	35.22	<0.0001[a,b,d,e,f]
Startle testing, n	65	83	139	170	147	195		
Latency, ms, Mean(SD)								
Pulse Alone	138.39(21.29)	140.16(17.55)	137.82(19.84)	137.73(18.87)	136.99(19.32)	136.41(17.65)	2.62	0.016
120ms Prepulse +Pulse	141.29(19)	142.71(18.19)	138.92(19.22)	136.77(18.59)	139(18.89)	135.26(17.82)	2.61	0.016
Magnitude, μV, Mean(SD)								
Pulse Alone	12.39(1.03)	12.06(0.99)	12.34(1.06)	12.29(1.03)	12.43(0.96)	12.28(0.95)	4.76	<0.0001
120ms Prepulse +Pulse	11.9(0.9)	11.70(0.92)	11.82(0.91)	11.74(0.93)	11.83(0.87)	11.79(0.90)	3.23	0.004
Percent PPI, Mean(SD)								
120ms	24.33(46.69)	15.49(51.11)	25.94(41.57)	30.22(36.78)	32.47(34.12)	26.02(41.12)	2.06	0.056

*All F Values and p Values utilize One-way ANOVAs including the controls

[a]Significant association between Biotype 1 and Biotype 1 Families (p<0.05)

[b]Significant association between Biotype 2 and Biotype 2 Families (p<0.05)

[c]Significant association between Biotype 3 and Biotype 3 Families (p<0.05)

[d] Significant association between Biotype 1 and Biotype 2 (p<0.05)

[e] Significant association between Biotype 1 and Biotype 3 (p<0.05)

[f] Significant association between Biotype 2 and Biotype 3 (p<0.05)