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The effect of antipsychotic medications on acoustic startle latency in schizophrenia

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ABSTRACT

Prepulse inhibition of the acoustic startle reflex (PPI) is extensively studied as a biomarker of schizophrenia (SCZ); however, antipsychotic medication can confound the measure. Latency, the time between the startling stimulus and the reflexive eye blink, provides an index of neural processing speed and is 90% heritable. SCZ subjects have slower latency than controls (CON). This study examined the effects of antipsychotic medication on startle latency. 108 CON and 132 SCZ subjects in three medication subgroups (94 on second-generation antipsychotics (SGA), 25 on first-generation antipsychotics (FGA), 13 unmedicated (NoMed)) were tested on a standard acoustic startle paradigm designed to measure startle magnitude, PPI, and latency. Latency was slower in SCZ compared to CON subjects ($p = 0.005$). Latency did not differ between the three SCZ medication groups. When CON were added to that model, both the NoMed subjects ($p = 0.04$) and the SGA subjects ($p = 0.003$) were slower than CON subjects. For PPI, CON did not differ from SCZ analyzed as a single group. When SCZ subjects were divided into medication groups, PPI was lower in NoMed subjects than the CON group ($p = 0.03$), the SGA group ($p = 0.02$) and the FGA group ($p = 0.05$). SCZ subjects on any medication did not differ from CON. Thus, latency was partially normalized by antipsychotic medication, but this did not obscure the slower latency in SCZ compared to CON. Therefore latency is both trait and state related, whereas medication normalized PPI and obscured any difference between SCZ and CON.

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1. Introduction

An endophenotype is a measureable trait that is detected by a biological test (Gottesman and Gould, 2003). An endophenotype approach to the discovery of genes conferring vulnerability to schizophrenia is thought to have an advantage over simply studying genes in the disease phenotype. This is in part because patients defined by an endophenotype are thought to be more genetically homogeneous than those people simply defined as having schizophrenia, thus leading to an easier discovery of vulnerability genes (Braff et al., 2007; Gottesman and Gould, 2003). Furthermore, an endophenotype approach is thought to reveal a discrete neurobiology that underlies disease pathophysiology in a subset of individuals with the disease in question, thus potentially paving the way to discovery of more specific treatments of biological subsets of individuals.

The acoustic startle response (ASR) is a reflexive contraction of the skeletal muscle found in all mammals that occurs in response to a sudden, intense auditory stimulus (Landis and Hunt, 1939). Typically, the pre-attentive acoustic startle response prepares for a quick reaction to threatening stimuli by facilitating a whole-body startle and an eye blink. This phenomenon is mediated by a pontine-based, three-synapse subcortical circuit (Koch, 1999) that has been extensively studied in schizophrenia and in various animal models of psychiatric disease. The ASR is known to demonstrate varied forms of behavioral plasticity, including the extensively studied phenomenon called prepulse inhibition (PPI). This is a reduction of the ASR by a non-startling stimulus presented shortly before the more intense startling stimulus, that is used as an operational measure of sensorimotor gating (Hoffman and Searle, 1968; Graham, 1975). A substantial literature indicates that subjects with schizophrenia have impaired PPI (Braff et al., 2001b), however current treatment with antipsychotic medication has been reported to normalize PPI, at least to some extent (for review see Swerdlow et al., 2008; Turetsky et al., 2007). Such partial normalization of PPI can make gene discovery more complicated, since subjects with schizophrenia cannot be easily studied in an untreated state. Nevertheless, the endophenotype approach to gene discovery in schizophrenia is yielding positive findings (Greenwood et al., 2011; Greenwood et al., 2016).

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Latency of the startle response is the time from presentation of the startling stimulus until the response is elicited. This measure is easily extracted from output data obtained in animal and human startle paradigms. Because startle is mediated by a simple 3-synapse subcortical circuit and is pre-attentive, latency has been proposed as an index of neural processing speed (Hasenkamp et al., 2010). Latency is longer, i.e. slower in schizophrenia subjects than in healthy controls in most studies that report latency (Braff et al., 1978; Braff et al., 1999; Geyer and Braff, 1982; Hasenkamp et al., 2010; Ludewig et al., 2002; Swerdlow et al., 2006; Weike et al., 2000), although there are also reports of no significant difference (Braff et al., 1992; Mackeprang et al., 2002; Parwani et al., 2000). Latency is very highly heritable, up to 90%, in schizophrenia probands and their families and also in healthy control families (Hasenkamp et al., 2010), which finding indicates a large genetic component to the determination of latency. This heritability exceeds that of PPI, reported to be in the 38–58% range (Anokhin et al., 2003; Greenwood et al., 2007; Hasenkamp et al., 2010).

Because the endophenotype approach to discovery of neurobiology and genetics of schizophrenia rests upon the stability of a putative endophenotype across clinical states, it is important to know whether startle latency is normalized in subjects who are treated with antipsychotic medication or remains stable across medication conditions. Startle latency has not been as extensively investigated as PPI, so the question of stability across medication conditions has not been as thoroughly researched. In two prior published papers from our group latency was not affected by medication status (Duncan et al., 2003a; Duncan et al., 2003b), nor was a significant effect reported by Swerdlow et al. (2006), although in the latter study the unmedicated group was quite small. Therefore, the purpose of this study was to examine the effects of antipsychotic medication status on startle latency and, by way of comparison, PPI.

2. Experimental materials and methods

2.1. Subjects

The study and consent form were approved by the Emory University Institutional Review Board and the Research and Development Committee of the Atlanta Veterans Affairs Medical Center. Informed consent for participation in the study was obtained from 192 male and female subjects with schizophrenia (SCZ), and 153 healthy, non-psychiatric controls (CON). Due to effects that menstrual cycle phase can exert on PPI (Jovanovic et al., 2004; Swerdlow et al., 1997), female subjects were tested during the follicular phase only. The diagnosis of schizophrenia was determined through chart review and the Structured Clinical Interview for DSM-IV, Axis-1 (SCID-1; First et al., 2001). Prospective control subjects were excluded if they had a past diagnosis of any major mental illness as evidenced by SCID interview, or they had first degree relatives with a history of a psychotic illness. Potential SCZ subjects were excluded if they had any history of head trauma resulting in sustained loss of consciousness (greater than five minutes), major neurological or medical illness, or a current substance abuse disorder. Subjects who regularly used caffeine or smoked cigarettes were included but maintained their usual use pattern on the test day. All subjects had urine tested for toxicology and were excluded if positive for any drug of abuse. The subjects were tested for auditory acuity by means of an audiometer (Model GS1710, Grason-Stadler, Eden Prairie, MN). To be included, subjects had to detect tones in each ear of ≤40 dB[A] at 0.25, 0.5, 1, 2, 4, and 8 kHz. Current symptoms were rated by means of the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987). The subjects for this study had partial subject overlap with those in Hasenkamp et al., 2010. Specifically, 40 SCZ subjects and 45 CON subjects in this study were included in that earlier publication.

2.2. Startle and latency measurement

Subjects participated in an acoustic startle session lasting 20 min where baseline startle magnitude, PPI, and latency were evaluated using methods described in our previous work (Hasenkamp et al., 2010) and modeled on methods developed by Braff et al. (1992) and Blumenthal and colleagues (Blumenthal et al., 2005). The eye blink component of the acoustic startle reflex, was measured via electromyography (EMG) of the right orbicularis oculi muscle. Two 5-mm silver electrodes filled with gel were placed 1 cm directly below the pupil, and 1 cm below the lateral canthus of the right eye, with a ground electrode positioned over the mastoid behind the right ear. All resistances were ensured to be <6 kΩ. EMG activity was recorded at 1-ms intervals for 250 ms following the onset of the startling stimulus for each trial. Subjects were seated in a sound attenuating audiology booth with eyes open and asked to look straight ahead for the duration of the test session.

All acoustic stimuli were delivered binaurally through headphones (Maico model TDH-39-P; Maico Diagnostics, Eden Prairie, MN). The startle paradigm, of standard design (Braff et al., 1992; Swerdlow et al., 2006), began with an acclimation period of 60 s duration that consisted of 70 dB white noise that continued as background for the remainder of the session. The startling stimuli were 116 dB white noise bursts, 40 ms in duration, that served as pulse-alone stimuli. Prepulse stimuli were 85 dB intensity white noise bursts of 20-ms duration. The session contained four trial types: pulse-alone trials (PA), and prepulse+pulse trials with interstimulus intervals of 30, 60, or 120 ms between the prepulse and pulse stimuli. The prepulse+pulse trials will be designated as 30-ms prepulse+pulse trials, 60-ms prepulse+pulse trials, and 120-ms prepulse+pulse respectively. The main part of the session consisted of three blocks of 12 trials each, for a total of 36 startle stimuli. Each block consisted of three separate trials of each of the four trial types presented in pseudorandom fashion. In addition, a habituation block of 6 pulse-alone stimuli was presented at the beginning and the end of the session. Inter-trial intervals (ITI) were 10–25 s long with an average of 15 s. The total session time was 20 min.

EMG data were recorded every ms for 250 ms following the onset of the startling stimuli. Data processing and reduction was carried out according to the methods of our prior work (Hasenkamp et al., 2010). The signal was amplified and digitized using the computerized startle response monitoring system SR-Lab (San Diego Instruments, San Diego, CA). The signal was then full-wave rectified and subjected to a smoothing routine by the SR-Lab software that calculated a rolling average of 10 data points. The system calculated the baseline value as the average of the minimum and maximum EMG values recorded in the first 20 ms immediately following the startling stimulus. The onset of the blink response was defined as an increase of at least 7.33 μV (6 machine units) from the EMG value during the baseline period. Valid blink responses had to have an onset between 21 and 120 ms after the startling stimulus. To count as a valid blink, the peak magnitude of the blink response had to be a minimum of 12.21 μV (10 machine units) and had to occur no >95 ms after the onset of the response, and no >150 ms after the stimulus. The response amplitude was recorded as zero on trials in which the magnitude of the blink response was insufficient for scoring. For these trials, peak latency was coded as a missing value. Trials were discarded if the baseline EMG during the first 20 ms of recording was >36.6 μV (30 machine units). Subjects were excluded if more than half their pulse-alone trials in Blocks 1–3 were excluded for baseline error or the magnitude was zero (i.e. no-blink trials).

2.3. Statistical analysis

Startle magnitude and peak latency for each trial type was computed as the mean for all valid trials in Blocks 1–3. PPI was calculated for each of the three PPI trial types as the percent inhibition of magnitude in

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