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Sensorimotor gating in healthy adults tested over a 15 year period

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ABSTRACT

Background: Prepulse inhibition (PPI) of startle, an operational measure of sensorimotor gating, is used to study normal and pathological brain function. From 2001 to 2016, we screened healthy subjects (HS) to establish their suitability for tests of drug effects on PPI. Because of the size and systematic characterization of this sample across variables of relevance to PPI, we now report these screening results.
Methods: Acoustic startle and PPI were assessed in HS to identify those eligible for studies of drug effects on PPI from 2001 to 2016, yielding 457 "eligible" subjects.
Results: Data confirmed the consistency of PPI across this 15-year period, and supported the role of several variables previously reported to moderate either startle or PPI.
Conclusions: Startle and PPI are robust physiological measures that are predictably moderated by specific physiological variables in healthy adults. As such, these measures serve as robust markers of neurobiological processes in healthy and patient populations.

1. Introduction

Quantitative laboratory measures of brain function provide evidence for "target engagement" that can be used within an experimental medicine strategy for identifying novel psychotherapeutics. Measures of particular interest are ones regulated by identifiable forebrain circuitry relevant to common psychiatric disorders, particularly if those measures are impaired in patient groups. Sensorimotor gating of startle, measured by prepulse inhibition (PPI), is regulated by disorder-relevant forebrain circuitry (cf. Swerdlow, Geyer, & Braff, 2001), and is impaired in several major psychiatric disorders, including schizophrenia (cf. Swerdlow, Weber, Qu, Light, & Braff, 2008; Swerdlow, Braff, & Geyer, 2016).

Among the approximately 2850 Pub Med citations for "prepulse inhibition" and 6350 for "startle reflex", there are many reports that identify physiological factors that moderate these measures, across mammalian species. In humans, these factors include age, sex, sexual orientation, race, resting blink rate, eye color, certain single nucleotide polymorphisms (SNPs), nicotine and caffeine use and specific personality structures, among others (Table 1). In most case, the relatively small sample sizes, the smaller subgroups associated with specific factors, the apparent sensitivity of many variables to stimulus parameters and test session designs, and the post-hoc nature of the analyses, make it challenging to interpret the robustness of the relationships between these factors and the dependent measures. On the other hand, clearly characterizing such moderators enables investigators to understand potential sources of uncontrolled variance in their studies, and to design their sample characteristics accordingly.

One longstanding line of inquiry in our laboratory has been the effects of drugs – particularly dopamine (DA) agonists and NMDA antagonists – on startle and PPI in healthy adults (Swerdlow, Eastvold et al., 2002; Swerdlow et al., 2003; Swerdlow, Talledo, Sutherland, Nagy, & Shoemaker, 2006; Swerdlow, Lelham et al., 2009; Swerdlow, van Bergeijk, Bergsma, Weber, & Talledo, 2009; Swerdlow, Bhakta et al., 2016; Talledo, Sutherland Owens, Schortinghuis, & Swerdlow, 2009). For both clinical and scientific reasons, subjects in these studies are carefully screened to establish the absence of medical and psychiatric illness and substance use, to match experimental groups based on comparable response characteristics (Swerdlow, Eastvold et al., 2001; Swerdlow, Geyer et al., 2001), and to determine the presence of an adequately robust startle reflex to enable reliable measures of PPI. Over the course of 15 years of studies of drug effects on startle and PPI, 487 adult subjects were screened in our laboratory using one particular startle test session, yielding 457 subjects who qualified as both "healthy subjects" and "startle responders". While the same startle session was used for all subjects, different complementary measures were collected from subgroups of these subjects over this 15-year period, so that many putative moderating factors were evaluated in siz-

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Table 1
Demographic and physiological variables as possible moderators of startle and PPI.

Startle Variable	Reported Moderator	Example Reference
Startle magnitude	Age	Ellwanger et al. (2003)
	Race	Swerdlow et al. (2005)
	Caffeine	Andrews et al. (1998)
Reflex Peak Latency	Startle magnitude	Hoffman and Searle (1968)
	GRID2 (*Glutamate Receptor, Ionotropic, Delta 2*)	Gensler et al. (2013)
PPI	Sex	Swerdlow et al. (1993)
	Sexual orientation	Rahman et al. (2003)
	Age	Ellwanger et al. (2003)
	Race	Hasenkamp et al. (2008)
	Rs4680	
	Smoking	Roussos et al. (2008)
	Resting blink rate	Della Casa et al. (1998)
	Personality Scales	Swerdlow et al. (2003) Kumari, Antonova et al. (2008)

able numbers of subjects. Our focus has now progressed to studies almost exclusively in patient populations, and we will no longer be adding substantially to this database of healthy subjects. Thus, we now describe findings of startle and PPI in this sample of 457 healthy adults, spanning 15 years of laboratory testing.

2. Methods

The several studies represented in this report were all approved by the UCSD Human Subject Institutional Review Board. Subjects were recruited via public advertisements and were paid for their study participation. Written informed consent was obtained from all subjects. While a cursory description of portions of these data is found among the published reports of these drug studies, mostly in the form of "matching" or "screening" data, the analyses herein have never been reported previously.

Over a 15-year period, 487 adults completed screening for drug challenge studies in our laboratory. Women were included in these studies only in the most recent 6 years of testing. Studies in the past 5 years also tended to include older subjects, based on the need to age-match these healthy subjects with older patient cohorts (Fig. 1A). Screening included an initial telephone contact and one laboratory visit. After passing a screening phone interview (assessing current and past medical and psychiatric history, medication and recreational drug use, and family history of psychosis), subjects came to the laboratory (for women, within 72 h of menses onset). A schematic diagram of a typical screening day schedule is seen in Fig. 1B.

During the screening visit, subjects were informed of the potential risks and benefits of the study, read and signed a consent for study participation, underwent a screening medical interview, a structured clinical interview (Structured Clinical Interview for DSM-IV-Non-Patient (SCID-NP) (First, Spitzer, Gibbon, & Williams, 1997)), physical examination and electrocardiogram to rule out exclusionary medical conditions, and completed a urine toxicology test with exclusion for any drug; women underwent a urine-based pregnancy test. Audiometry confirmed hearing threshold < or = 40 dB(A) at 1000 Hz.

Startle was measured as previously described (e.g. Swerdlow, Light et al., 2006). Broadband noise (70 dB(A)) preceded active stimuli by 3 min and persisted as a background noise during the test. For much of this 15-year period, blinks during acclimation were counted remotely by trained staff (inter-observer R = 0.97 (Swerdlow, Stephany et al., 2002)). The session consisted of 42 trials, with 6 conditions: a 118 dB(A) 40 ms noise burst (pulse alone) and the same burst preceded 10, 20, 30, 60, 120 ms by a 5 ms discrete prepulse 16 dB above background (i.e. resulting in "gaps" of 5, 15, 25, 55 and 115 ms between prepulse offset and pulse onset); using 16 dB prepulses with this startle system, prepulse-associated EMG activity is <0.5% of startle stimulus-induced levels (Swerdlow, Light et al., 2006) and does not correlate with key startle measures (Swerdlow, Wasserman et al., 2002). Stimulus rise time was near-instantaneous. The variable inter-trial interval averaged 15 s (range 10–20 s). Total test time was 15 min. A total of 457 subjects (Table 1) who demonstrated the established minimum startle response magnitude (≥10 startle units; 1.31 μV/unit) and passed other screening criteria advanced to one of a series of double-blind, within-subject cross-over design studies; results of these drug challenges have been reported separately, as cited throughout this report.

The software parameters by which voluntary and spontaneous eye blinks were recognized and excluded were applied consistently across the 15 years of data collection, and were derived as previously reported from published criteria (Braff, Grillon, & Geyer, 1992; Graham 1975). Onset latency was defined by a shift of 6 digital units from baseline during the 18–100 ms after the stimulus (Graham 1975). Peak latency was defined as the point of maximal amplitude within 150 ms from the startling stimulus. Responses were defined as spontaneous and therefore excluded when the onset and peak latencies differed by >95 ms. Responses were also excluded when the baseline values shifted by more than 90 units. Very few trials (<0.1%) were excluded using these parameters. "Nostim" trials (EMG measurement without stimulus delivery) were interspersed mid-way between trials throughout the session, but did not impact inter-trial intervals and were in all ways "invisible" to the subject.

Most subjects completed several questionnaires based on reported relationships between specific scale scores and dopaminergic function and/or PPI, including: 1) the Tridimensional Personality Questionnaire (TPQ) (Cloninger, Przybeck, & Svrakic, 1991); 2) the Sensation Seeking Scale (SSS) (Zuckerman, 1990); and 3) the Eysenck Personality Questionnaire (EPQ) (Eysenck & Eysenck 1975) (e.g. see Benjamin et al., 2000; Ebstein, Nemanov, Klotz, Gritsenko, & Belmaker, 1997; Hutchison, Wood, & Swift, 1999; Kuhn et al., 1999; Kumari, Antonova, & Geyer, 2008; Noble et al., 1998; Strobel, Wehr, Michel, & Brocke, 1999). Based on one report of PPI differences associated with sexual orientation (Rahman, Kumari, & Wilson, 2003), this factor was assessed using either the Heterosexual-Homosexual Rating Scale (HHRS; Kinsey, Pomeroy, & Martin, 1948) or the Sell Assessment of Sexual Orientation (SOQ3; Sell & Petrulio, 1996). A number of other demographic and physiological variables were assessed, based on reports that they moderate either startle magnitude or PPI (Table 1).

Across the 15 years of laboratory testing, two major changes were made to our startle testing equipment, aside from regular servicing or replacement of electrodes and headphones (Fig. 1A). First, testing involved only one startle system for the first 2 years of this test period, but a second system was added in years 3 through 15. Second, the amplifier in the first startle system was replaced, 4 years into this testing period. Analyses assessed the stability of the key startle variables, with these equipment changes in mind. Other subtle changes to equipment (e.g. earphone, electrodes, calibration system, etc.) or test environment (e.g. chair type, fluctuations in room illumination or background noise level, room configuration, etc.) were recorded but not factored into the present analyses. Acoustic stimulus calibration was done monthly during periods of high utilization and quarterly during periods of lower testing activity; testing activity using this specific test session was greatest in years 1–6 and 9–15 of this 15 year span, with regular but less frequent testing occurring in years 7–8.

DNA was extracted from whole blood in a subset of subjects (n = 143) and genotyping of 14 SNPs was conducted, as described in the Supplemental Methods; based on specific a priori hypotheses (e.g. Gensler et al., 2013; Giakoumaki, Roussos, & Bitsios, 2008;