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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 - 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 2001-2016, 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.

Keywords

catechol-O-methyl transferase; prepulse inhibition; sensorimotor gating; startle

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 et al.

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2001b), and is impaired in several major psychiatric disorders, including schizophrenia (cf. Swerdlow et al. 2008, 2016b).

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 et al. 2002a, 2003, 2006b, 2009a,b, 2016a; Talledo et al. 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 et al. 2001b), 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 sizable 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.

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 (Figure 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 hours of menses onset). A schematic diagram of a typical screening day schedule is seen in Figure 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 et al. 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 < 40 dB(A) at 1000 Hz.

Startle was measured as previously described (e.g. Swerdlow et al. 2006a). Broadband noise (70 dB(A)) preceded active stimuli by 3 minutes 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 et al. 2002b)). 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 et al. 2006a) and does not correlate with key startle measures (Swerdlow et al. 2002c). Stimulus rise time was near-instantaneous. The variable inter-trial interval averaged 15 s (range 10-20 s). Total test time was 15 minutes. 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 (Graham 1975, Braff et al. 1992). Onset latency was defined by a shift of 6 digital units from baseline during the 18 to 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 1991); 2) the Sensation Seeking Scale (SSS)

(Zuckerman et al. 1990); and 3) the Eysenck Personality Questionnaire (EPQ) (Eysenck and Eysenck 1975) (e.g. see Ebstein et al. 1997; Noble et al. 1998; Kuhn et al. 1999; Benjamin et al. 2000; Hutchison et al. 1999; Strobel et al. 1999; Kumari et al. 2008a). Based on one report of PPI differences associated with sexual orientation (Rahman et al. 2003), this factor was assessed using either the Heterosexual-Homosexual Rating Scale (HHRS; Kinsey et al., 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 (Figure 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. Roussos et al. 2008; Giakoumaki et al. 2008; Gensler et al. 2013), only data from rs4680, COMT SNPs rs174696 and rs174697, and GRID2 SNPs rs2870699 and rs1583337 are reported herein. For analyses of racial differences in startle variables (e.g. Hasenkamp et al. 2008; Swerdlow et al. 2005), self-reported race was recorded for the following groups: White (not Hispanic) and White (Hispanic) (collectively, “European Americans”), Black / African American, Asian, Native American, Pacific Islander, and “multiple races”; based on sample size, only some subgroups were used in specific analyses as described in the Results. Subjects self-identified as Asian were also asked to identify a country of ancestry, based on reports of differential COMT effects among individuals of Chinese Han vs. European ancestry (Wang et al. 2013).

Data Analysis

A total of 30/487 (6.2%) of screened subjects were excluded from analysis based on startle magnitude < 10 digital units (n=17), positive urine toxicology or pregnancy test (n=7) and electrode asymmetry (n=6). For the remaining subjects, startle magnitude, peak startle latency and %PPI were treated as continuous measures and analyzed with repeated measure analyses of variance (ANOVAs) with appropriate post-hoc comparisons. %PPI was calculated based on the formula: 100 × [reflex magnitude to pulse alone minus reflex magnitude to (prepulse + pulse)] / reflex magnitude to pulse alone. Primary analyses were limited to assessing the impact of specific variables on PPI and other startle measures where

past reported provide a basis for an a priori hypothesis; in these cases, potential moderating factors were treated as categorical or continuous variables, and their relationships with startle variables were tested via repeated measure ANOVAs or simple regression analyses. Secondary analyses are reported in Supplemental Materials. In some cases, analyses involved very different sample sizes, comparing small subgroups to the larger remaining test sample; for these comparisons, effect sizes (*d*) are used as metrics of group differences (Cohen 1988). Alpha for planned comparisons and empirical findings were set at 0.05 and 0.005, respectively.

Results

Subject Demographics

As seen in Table 2, the subjects were generally young adults, well-educated, mostly non-smokers and moderate caffeine consumers.

Stability of dependent measures over time

Analyses assessed the stability of the key startle measures – PPI, startle magnitude on pulse alone trials and peak startle latency on pulse alone trials (PSL) - across the 15 year test period (2001 - 2016) (Figure 2). Because women were included only during the second half of this project (10/6/2009 – 5/25/2016), stability among male and female cohorts was assessed separately. Analyses revealed stable values of PPI and PSL across the 15 years of testing, but a linear decline in startle magnitude over this period (Table 3). Analyses revealed a highly significant negative correlation between test order (1 through 457) and startle magnitude ($p<0.0001$); no such relationship even approached statistical significance for %PPI (either averaged across the 5 prepulse intervals, or at each individual interval) or PSL. Analyses suggest that “shrinking” startle magnitude in this sample paralleled increasing subject age over the 15 years of testing, as healthy subjects were matched by age to older patient samples being tested in parallel studies; however, age overall was not significantly correlated with startle magnitude ($r = -0.08$, NS). Other changes in subject characteristics over the 15 years of testing included unexpected robust and linear reductions in the highly inter-correlated measures of Novelty Seeking and Sensation Seeking (Table 3; Figure S1), each of which correlated significantly with startle magnitude (r’s = 0.17 and 0.18 respectively; p’s ≤ 0.001). Both caffeine use and years of education also increased among subjects over the 15 years of testing (Table 3), but neither correlated significantly with startle magnitude. When these 5 independent variables that changed significantly across the 15 years of testing were entered into a multiple regression analysis of startle magnitude, none contributed independently to the decline in startle magnitude. Analyses linked to the dates when a second test system and new amplifier were added did not account for this drift in startle magnitude. Other potential cohort effects, such as differences in racial representation over time (Swerdlow et al. 2005), also did not account for declining startle magnitude in this sample. Finally, EMG activity during “Nostim” trials did not correlate significantly with test order ($r = -0.08$, NS), suggesting that EMG sensitivity changes could not easily account for the observed “drift” in startle magnitude.

Variables moderating startle magnitude (Table 4)

In addition to age (above), we were able to evaluate two physiological factors that have been empirically and/or conceptually associated with startle magnitude: self-reported race and eye color. In 2005, we reported reduced startle magnitude among 47 Asian-American vs. 127 White-American men (Swerdlow et al. 2005). Analyses confirmed this finding among this inclusive database, and among the 277 subjects tested subsequent to our 2005 report. An indirect relationship links eye color to startle magnitude via the intermediate construct of "behavioral inhibition" (BI). Studies have reported both qualitative and quantitative evidence of increased startle magnitude among high BI infants and children (Barker et al. 2014), as well as higher BI scores among children with blue vs. brown eye color (Rosenberg & Kagan 1989). Blue-eyed adults have also been reported to have higher reactivity and lower detection thresholds in response to a range of diferent sensory stimuli (Hood et al. 1976; Herbener et al. 1989; Barrenas & Hellstrom, 1996; Henderson et al. 2005; Acosta et al. 2006). In the present sample, eye color was recorded for 261 subjects, blind to hypothesis. Among these subjects, startle magnitude was elevated among adults with blue vs. brown eye color, but this effect was accounted for by the fact that 100% of the lower-startling Asian subgroup had brown eyes. Among White subjects, there was no relationship between eye color and startle magnitude.

Caffeine (typically after acute administration) has also been reported to moderate several startle variables, though these relationships may be complicated by levels of daily use and effects of caffeine withdrawal under placebo conditions (Andrews et al. 1998; Swerdlow et al. 2000). Here, we were able to assess the relationship between startle magnitude and self-reported caffeine intake patterns in 395 individuals (1 additional individual reported caffeine consumption > 8 SD above the group mean, and > 350 mg/d above the next largest consumer, and was excluded on this basis). Analyses revealed no significant relationship between self-reported caffeine intake and either startle magnitude or PSL; a marginal relationship with PPI ($r = 0.10$, $p<0.05$ ($Rs = 0.11$, $p<0.035$)) did not achieve the more rigorous threshold required absent an a priori prediction (Table 4).

Variables moderating peak startle latency (PSL) (Table 4)

PSL is a highly heritable phenotype, that is slowed in several brain disorders, including schizophrenia (Braff et al. 1978; Swerdlow et al. 2014) and Huntington's Disease (Swerdlow et al. 1995b). PSL has been reported to correlate with startle reflex magnitude (Hoffman & Searle, 1968); here, we detected a small but statistically significant negative correlation between startle magnitude and PSL ($r = -0.15$; $p<0.0015$); latency facilitation (faster peak latency under prepulse + pulse vs. pulse alone conditions) was not significantly moderated by startle magnitude. One study (Gensler et al. 2013) identified a significant association between PSL and the single nucleotide polymorphism (SNP), rs1912718, in the GRID2 gene, which regulates the glutamate ionotropic receptor delta-type, subunit 2. While s1912718 was not studied in the present cohort, two other functional GRID2 SNPs, rs2870699 and rs1583337, were not associated with PSL in our sample.

Variables moderating prepulse inhibition

PPI is moderated by stimulus parameters as well as subject characteristics. PPI has a non-linear relationship with prepulse interval; using the current stimulus configuration, PPI is generally detected with the shortest (10 ms) prepulse intervals, with a nadir of minimal or no inhibition detected with 20-30 ms prepulse intervals, and increasingly robust PPI evident with 60-120 ms intervals (Figure 3A). There was no significant effect of eye side. For most subsequent analyses of PPI herein, except where specified otherwise, PPI was collapsed across intervals and eye sides to generate a single value of "mean %PPI". Mean PPI levels did not correlate significantly with levels of startle magnitude (Table 4).

Sex differences in PPI were evident in this sample (Figure 3B), as is commonly (though not always) reported in the literature (children: Ornitz et al. 1991; adults: Swerdlow et al. 1993; cf. Kumari 2011), with prepulse potentiation (greater startle magnitude on prepulse+pulse vs. pulse alone trials) evident in women at 20-30 ms prepulse intervals. In this sample (limited to the time period when both men and women were tested), the sex difference had an effect size (*d*) of 0.35 for the full cohort, with larger effect sizes when samples are limited to child-bearing years (0.41) or to non-smokers (0.44). Moderating effects of sexual orientation on PPI in women, but not men, were reported in one prospective published study (Rahman et al. 2003). In the present cohort, two different self-report measures of sexual orientation were used in several studies, yielding some information on sexual orientation for 282 of our test subjects, 48 of whom self-identified as something other than exclusively heterosexual in their orientation. Despite using a variety of criteria to define sexual orientation, no clear moderating effects were detected in women, though this might clearly reflect the small representation of women who self-identified as "strictly homosexual".

Age effects on PPI have been reported in children (PPI increases with age; Ornitz et al. 1991) and adults ("inverted-U" relationship; Ellwanger et al. 2003); here we detected a significant positive correlation of age (18-55) and PPI, calculated as a mean collapsed across prepulse intervals (Table 4), as well as separately for 10, 20, 30 and 60 ms prepulse intervals.

Racial differences have been reported in startle measures, including PPI, with African American > European American PPI levels detected in healthy subjects for 30-120 ms prepulse intervals (Hasenkamp et al. 2008). A similar pattern was detected in the present sample using these prepulse intervals (Figure 3C).

PPI has been reported to be moderated by the gene for catechol-O-methyl transferase (COMT), and particularly by the COMT SNP rs4680. Specifically, several reports from studies in male Greek Army conscripts have detected a gradient of PPI at 60-120 ms prepulse intervals, based on the rs4680 SNP: Met/Met > Val/Met >Val/Val (Roussos et al. 2008; Giakoumaki et al. 2008). Among the 143 subjects in this sample with a known rs4680 genotype, we failed to detect such a pattern using all prepulse intervals, or using only the 60-120 ms prepulse intervals (Figure 3D, left). We explored alternative approaches to identifying rs4680-based patterns of PPI similar to those reported previously, and did detect sex-dependent effects of rs4680 on PPI, with lower PPI among men carrying one or more valine alleles ($d = 0.47$), and the opposite pattern in women ($d = 0.48$; Figure 3D, right). This pattern could not be easily explained by differences in startle magnitude or

demographic variables among these SNP-carrying subgroups; based on reported racial differences in rs4680 effects on COMT activity (Wang et al. 2013), analyses excluding subjects with self-reported Chinese family origin somewhat increased the effect sizes of these opposite SNP effects in men and women.

Another factor moderating PPI in several reports is smoking status (Della Casa et al. 1998). Our sample included very few smokers, based on the demographics recruited for several of our drug studies. Nonetheless, consistent with the general literature of nicotine effects on PPI, self-reported active smokers exhibited significantly more PPI than non-smokers (Figure 3E).

In 2002, we reported a significant negative correlation between PPI and resting blink rate, among 79 men tested in the initial phase of the present cohort. Resting blink rate were subsequently recorded from an addition 275 subjects in this cohort, including 44 women. Analyses confirmed this relationship in the subjects tested subsequent to this report, as well as the inclusive sample (Figure 3F), and determined that this relationship was not sex-specific (*d* for lowest vs. highest quartile blink rate for men vs. women = 0.37 vs. 0.48).

A number of reports have identified moderating effects of personality features on PPI (Swerdlow et al. 1995a; Hutchison et al. 1999; Kumari et al. 2008a; Takahashi et al. 2012); we previously failed to detect such a relationship using the TPQ, among 83 men tested in the initial phase of the present cohort (Swerdlow et al. 2002c), but did report that personality measures moderated PPI sensitivity to both amphetamine and memantine (Swerdlow et al. 2009b; Talledo et al. 2009). We were able to collect additional personality scale scores from sizable subgroups of the present cohort, including the Sensation Seeking Scale (SSS; n=337) (Zuckerman et al. 1990) and the Eysenck Personality Questionnaire (EPQ; n=215) (Eysenck and Eysenck 1975), along with an TPQ ratings from an additional 347 subjects (total n=430). Unlike startle magnitude (see above), no significant relationships were detected between PPI and any of the 3 TPQ subscales (Novelty Seeking, Harm Avoidance, Reward Dependence), SSS total or Disinhibition subscale, or TPQ total or Psychoticism subscale (Table 4).

Discussion

One dilemma faced by every investigator in choosing an experimental design reflects the pragmatic balance between maintaining sufficient constancy in experimental parameters to benefit from a foundation of a priori empirical evidence, vs. the need to modify experimental parameters to address novel questions. Here we present data collected over 15 years of this imperfect balancing process, reflecting relative constancy in the assessment of a key set of dependent measures – particularly PPI of acoustic startle - across many discrete studies that addressed different questions, that in turn required the collection of different independent measures. This database is fraught with the frailties of longitudinal drift in machinery, methods and personnel; in addition, some independent measures were collected via self-report rather than more rigorous and time consuming approaches, based on pragmatic limitations of time and resources. Despite this, at a time when our experimental efforts are moving elsewhere, we thought it potentially worthwhile to use this large cohort to assess the

reproducibility and robustness of findings from smaller reports related to startle and PPI, many of which have become “foundational” in the way our field thinks about these measures, and their relationship to brain mechanisms in health and pathology.

Over the 15 years of data collection represented in the present cohort, we detected a downward drift in startle magnitude, along with substantial stability in both PPI and startle latency. The basis for the gradual decline in startle magnitude is unclear, and the independent contributions of 5 separate independent variables that also changed across this 15-year period (age, NS score, SSS score, caffeine intake and education) could not be confirmed. The rate of this decline in startle magnitude (approximately 5 startle units per year, or 4.5% of the average startle signal per year) was such that, across any given study (typically lasting about 1 year), minimal change in startle magnitude would be noticed. Perhaps of more relevance, the stability of both PPI, startle latency and Nostim EMG activity in the face of this declining startle magnitude reinforces findings from both infrahuman and human studies that these measures are often independent from changes in startle magnitude.

While the main focus of our work has been PPI, we were able to assess several variables as potential moderators of startle magnitude and peak startle latency, based on past reports from our group and others. Relatively reduced startle magnitude among Asian and African American vs. European American participants was clearly evident in this inclusive sample; this Asian vs. White difference had been reported in a small subset of this sample (Swerdlow et al. 2005), and the African American vs. White difference had been reported previously by others (Hasenkamp et al. 2008). Elevated startle magnitude among our subjects with blue vs. brown eyes seemingly parallels reports by others (Barker et al. 2014; Rosenberg & Kagan 1989); however, unlike these previous reports in White children, in our present multi-racial adult sample, this difference was accounted for entirely by the skewed racial distribution of eye colors. Across the entire sample, peak startle latency exhibited a very small but statistically significant negative correlation with startle magnitude, with the latter variable accounting for 2.3% of the variance in PSL; this relationship was evident across racial groups.

With regards to PPI, the present sample reproduced reports of several different moderating variables. Ornitz et al. reported less PPI among girls vs. boys (1991), and we reported similar PPI sex differences in adults in 1993 (Swerdlow et al. 1993); these findings have been widely reproduced in both humans and infrahumans (e.g. Lehmann et al. 1999; Kumari et al. 2008b; cf. Kumari et al. 2011), with some less common exceptions in human reports, perhaps attributable to the fact that these sex differences are moderated by menstrual phase (Swerdlow et al. 1997; Jovanovic et al. 2004) and other factors potentially related to reproductive hormones (e.g. Bannbers et al. 2010; Kumari et al. 2010; Comasco et al. 2015, 2016). Male > female PPI was evident in the present sample, and this group difference increased modestly when samples were limited to women of child-bearing years and to non-smokers.

Racial differences in PPI have been reported previously, and while the present sample was relatively limited in diversity, our findings support those reported previously by Hasenkamp

et al. (2008), that PPI is elevated in African American vs. European American healthy adults. While it is impossible to rule out a contribution of startle magnitude differences to this observation, it is evident that comparably lower startle magnitude in Asian American vs. European American subjects was not accompanied by differences in PPI.

Four previous studies have reported rs4680 Met/Met > Val/Val PPI levels in distinct cohorts, including: 1) male Greek army conscripts (total n=116 across two studies; Roussos et al. 2008; Giakoumaki et al. 2008), 2) male and female white schizophrenia patients (n = 68; Quednow et al. 2010), 3) male white healthy subjects (HS) (n=45; Quednow et al. 2010) but not female white HS, and 4) healthy pregnant women (n=154; Comasco et al. 2015) but not healthy post-partum women (n=128; Comasco et al. 2016). The PPI-moderating effects of rs4680 have been reported using a range of prepulse intensities (e.g. Comasco et al. 2015) and intervals (e.g. Roussos et al. 2008); cohorts in these studies have generally been young and almost exclusively white, and either of European or Greek origin. Interestingly, “strain” differences in the physiological or PPI-moderating effects of COMT have been reported in both humans (Wang et al. 2013) and rodents (Shilling et al. 2008). While we could not reproduce the most common report of Met/Met > Val/Val PPI levels, the present study provides at least modest support for a moderating role of rs4680 in PPI in HS: we detected lower PPI among men carrying one or more rs4680 valine alleles, and the opposite pattern in women. In addition to rs4680, COMT has several other polymorphisms that are thought to impact enzyme activity and hence PFC DA levels; two of these SNPs (rs174696 and rs174697) were assessed in about 110 individuals in the current cohort, and while minor allele frequencies preclude any definitive conclusion, there was no obvious relationship between these SNPs and %PPI, either independently or as an interaction with sex.

A number of studies have reported that PPI is elevated among active smokers (Kumari et al. 1996; Della Casa et al. 1998; Duncan et al. 2001; Swerdlow et al. 2006a) and among non-smokers after acute nicotine challenge (Kumari et al. 1997; Drobes et al. 2013). Because of this, smokers are generally excluded from our drug challenge studies, though more recently this criterion has been removed in order to more closely match the smoking histories of healthy subjects with those of patients. The present sample included only 24 active smokers who, by self-report, smoked about 10 cigarettes per day. Nonetheless, PPI was elevated among these smokers vs. the non-smokers in this sample, with a medium-to-large effect size. Obviously, without cotinine levels, or evidence for the time between testing and last cigarette, this observation is practically anecdotal, but it is nonetheless consistent with other reports in more carefully controlled studies.

The relationship of resting blink rate to PPI was initially investigated based on evidence from infra-human primates and humans that blink rate was regulated by forebrain dopamine activity (e.g. Karson 1988; Elsworth et al. 1991), and specifically with dopamine content in the rostral ventromedial caudate nucleus (Taylor et al. 1999). Because PPI was known to be reduced after experimental stimulation of dopamine activity in this area, we hypothesized that higher resting blink rates would be associated with lower levels of PPI. This hypothesis was confirmed in 79 healthy men, and the present study confirmed this observation, and extended it to women. There is no independent evidence from this study that the link between blink rate and PPI has anything to do with dopamine; blink rates correlated

significantly with specific personality scales (some of which were reported previously in our smaller sample (Swerdlow et al. 2002c)), but none that accounted for significant variance in PPI measures.

We have alluded to some of the limitations of the present data as an evidence-base for understanding the variables that moderate startle and PPI, including issues related to longitudinal drift in machinery, methods and personnel, the potential inaccuracy of self-report data, the large number of different variables assessed driving an inflated risk of false positive findings, and the challenges of interpreting findings from large samples in which differences of very small effect size can nonetheless yield robust statistical significance. To address some of these potential flaws, analyses were limited to ones for which there was a reasonable a priori hypothesis based on other empirical reports – some by our group, but more by others. For example, while we identified a statistically significant positive relationship between caffeine consumption and PPI (Table 4), absent a strong a priori hypothesis, we view this weak association to likely reflect a spurious artifact of a large sample subjected to numerous analyses. Because different interdependent variables were assessed in distinct subgroups of this 15-year cohort, it was not feasible to conduct a meaningful multivariate / pathway analysis in this large sample, but some attempts were made to isolate effects of variables via multiple regression analyses and by matching groups, e.g. based on age, startle magnitude, testing date, etc. With these limitations and analytic strategies in mind, the present findings support reported PPI-moderating effects of sex, race, smoking status, resting blink rate, and – in men – age. The present evidence related to rs4680 as a PPI moderator might be best viewed as “inconclusive”; certainly, this failure to replicate the most cited reports of such a role of rs4680 might reflect differences in cohorts (e.g. the Greek conscript cohort of Roussos et al. (2008) included more smokers, and heavier smokers, than were included herein).

A conundrum faced in interpreting studies of PPI reflects the fact that inhibition of the reflex is not uniformly produced by each lead stimulus condition, and it is reasonable to question whether analyses of “prepulse inhibition” should include conditions – e.g. prepulse intensities, intervals, frequencies, etc. – that do not generate startle magnitude inhibition. In some cases, lead stimulus characteristics are selected specifically to *potentiate* reflex responses (sometimes called “prepulse potentiation”), and this form of prepulse modification is studied by design (e.g. Kumari et al. 2004). But in most cases, as was true here, lead stimulus and other parameters are selected to produce a broad range of inhibition, to enable investigators to probe the basis for inter-individual differences in sensitivity to response inhibition; in effect, this approach is agnostic to any mechanistic differences responsible for the “sign” of change in reflex magnitude, instead viewing “0% PPI” as an arbitrary threshold within a physiological range of inhibition and potentiation. The decision to include, or exclude, from analysis the conditions that do or do not consistently generate response inhibition is a complex one: for example, in our inclusive sample, significant inhibition was generated by prepulse intervals of 10, 30, 60 and 120 ms, but not 20 ms, yet for many subgroups (e.g. males, African Americans, smokers, etc.), significant response inhibition was generated at all 5 prepulse intervals. Even among other subgroups, e.g. women, there are many individuals for whom significant inhibition was generated by all prepulse intervals, and still others for whom inhibition was not generated at any interval. In fact, among

individuals, there are trials where the same prepulse either does or does not generate inhibition; and metrics such as “response probability” are sometimes used to capture the likelihood of inhibition rather than the magnitude or percent inhibition, per se. Perhaps most importantly, a decision to limit analyses to conditions that produce inhibition would, in effect, preclude precisely the kinds of comparisons that this study sought to perform. Thus, because our experimental goal was to examine variables that might account for inter-individual and inter-subgroup differences in the magnitude of response inhibition, we opted to include all trial conditions in our analyses. However, all subgroup comparisons included prepulse interval as a within-subgroup repeated measure, that enabled us to detect and report examples in which a significant main effect was dependent on the disproportionate influence of one or some of the prepulse intervals over the others.

Mechanisms underlying at least some of these moderating effects have been discussed elsewhere and in some cases have been the focus of direct experimentation, but most remain obscure. While the present results cannot clarify these mechanisms, they do support the potential value of such mechanistic studies, since these effects appear to be sufficiently robust to be detected in this large sample. More generally, while each of these moderating variables accounts only for a fraction of the variance in PPI, the present results underscore the fact that studies of PPI with more limited samples might consider ways to constrain this variance, to the degree that this does not restrict their ability to test their hypotheses of interest.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Startle and prepulse inhibition (PPI) were tested in 487 subjects over 15 years;
- PPI and startle latency were stable but startle magnitude declined over 15 years;
- Moderating effects of specific variables on PPI largely supported published reports;
- PPI is reliable, and variables are known that can constrain uncontrolled variance.

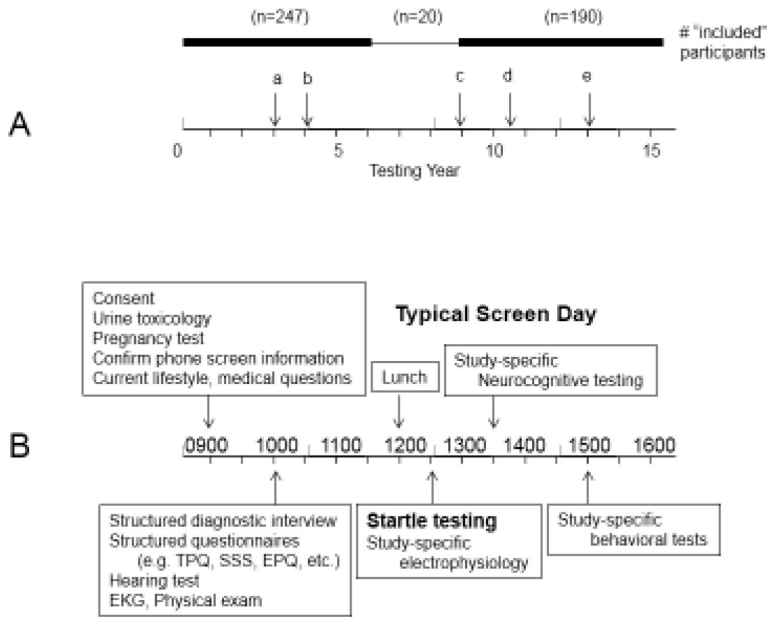

Fig 1.

A. Schematic of testing activity during the 15 years of data collection represented in this report. Testing was continuous through this period but most active in the initial and final 6 year periods. Arrows indicate changes in our testing protocol during this period: a. addition of second startle testing unit; b. replacement of one stimulus delivery amplifier; c. inclusion of women; d. increased age limits to match patient recruitment; e. laboratory moved from 3rd to 1st floor of our building. **B.** Schematic of "typical" screen day activities. Timing differed slightly across studies, based on duration of study-specific electrophysiology, neurocognitive and behavioral tests.

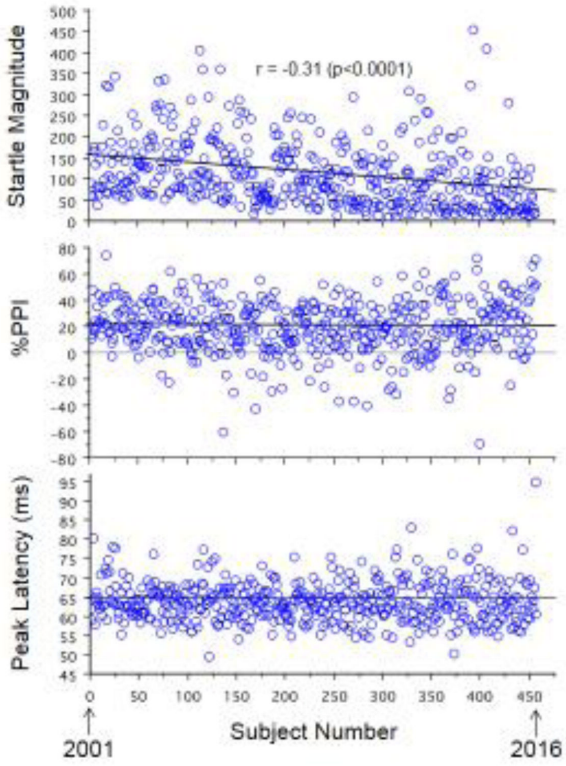

Fig 2.

Changes in startle magnitude, %PPI and peak startle latency in 457 subjects tested over a 15 year period.

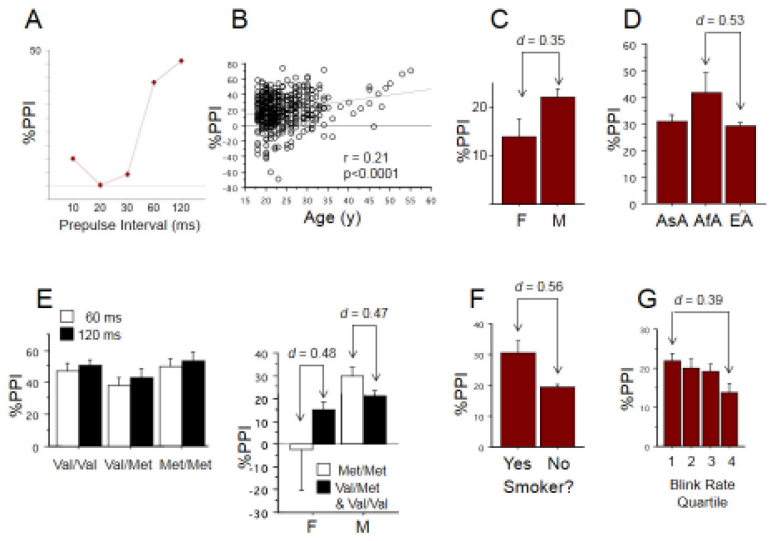

Fig 3.

Summary of major findings. A. Mean (+/− SEM) PPI across 10-120 ms prepulse intervals, collapsed across 457 subjects. B. Significant positive correlation of PPI and age in this 18-55 year age range. C. Sex difference in PPI, collapsed across 10-120 ms intervals ($F=5.62$, df 1,204, $p<0.02$; data included only from years when both men and women were tested (10/2009 - 2016). D. Racial differences in PPI, collapsed across 30-120 ms intervals, as per Hasenkamp et al. (2008) (EA vs. Afa: $F=4.65$, df 1,296, $p<0.035$). E. No effect of rs4680 status on PPI collapsed across men and women, when analyzed by genotype as in Roussos et al. (2008) (left), but significant sex × genotype interaction ($F=5.44$, df 1,133, $p<0.025$) with medium effect size, opposite genotype effects in women vs. men, when analyzed based on presence or absence of any Val allele (right). F. Higher PPI among smokers vs. non-smokers ($F=7.08$, df 1,446, $p<0.009$). G. Inverse relationship of PPI to resting blink rate (ANOVA by quartile: $F=2.85$, df 3,354, $p<0.04$; lowest vs. highest quartile, $p<0.007$; second lowest vs. highest quartile: $p<0.03$).

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 & 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	Hassenkamp et al. 2008
	Rs4680	Roussos et al. 2008
	Smoking	Della Casa et al. 1998
	Resting blink rate	Swerdlow et al. 2003
	Personality Scales	Kumari et al. 2008

Table 2

Subject characteristics

Age (y: mean (range)):		23.87 (18-55)
M:F		398:59
Weight (lbs: mean (SEM)):		167.27 (1.52)
Race (n):	White (not Hispanic)	255
	White (Hispanic)	29
	African American	14
	Asian	112
	American Indian / Alaskan Native	12
	Hawaiian / Pacific Islander	3
	Multiple Races	11
	Other / Not Declared	21
Education (y (SEM)):		14.48 (0.08)
Eye color (n):	brown / black	185
	blue	43
	green / hazel	33
Daily Caffeine (mg (SEM)):		83.09 (6.07)
Marital Status (n):	single	218
	married	29
	separated / divorced	10
Employment (n):	employed	122
	unemployed	50
	student	285
Smoking (n):	current	24
	nonsmoker	424
	unknown	9
Personality Scale Scores (mean (SEM):		
TPQ Novelty Seeking Scale		16.32 (0.25)
TPQ Harm Avoidance		7.88 (0.26)
TPQ Reward Dependence		19.09 (0.21)
Sensation Seeking Scale (Total)		20.33 (0.34)
EPQ (Psychoticism Subscale)		2.45 (0.12)
EPQ (Total)		20.90 (0.32)
Eye blinks/ 3 min (mean (SEM))		49.34 (1.93)
Rs4680 (Met/Met : Val/Met : Val/Val)		31 : 52 : 60

Table 3

Changes in dependent and independent measures over years of testing

Variable	r vs. time (test order)	Interpretation: Over time, our subjects…
Age	0.34 (p<0.0001)	… were older
Weight	0.03	
Education	0.11 (p<0.02)	… had more years of education
Daily Caffeine	0.16 (p<0.002)	… consumed more caffeine
TPQ Novelty Seeking Scale	−0.35 (p<0.0001)	… were less “novelty seeking”
TPQ Harm Avoidance	0.02	
TPQ Reward Dependence	−0.05	
EPQ (Psychoticism Subscale)	0.00	
Sensation Seeking Scale	−0.26 (p<0.0001)	… were less “sensation seeking”
EPQ Total	−0.07	
Eye blinks/ 3 min	−0.02	
Startle magnitude	−0.31 (p<0.0001)	… had lower startle magnitude
Peak startle latency	0.00	
Nostim magnitude	−0.08	
PPI: Mean	−0.01	
10 ms interval	−0.03	
20 ms interval	−0.06	
30 ms interval	0.02	
60 ms interval	0.05	
120 ms interval	−0.03	

Table 4

Variables potentially moderating startle magnitude, latency and %PPI

	Startle Magnitude	Peak Latency	%PPI[1]
Age	NS	NS	r = 0.21, p<0.0001
M:F [2]	NS	NS	M > F, p<0.02
Race [3]	EA > AsA, p<0.0001 EA > AfA, p<0.035	AsA > EA, p<0.0001 Afa > EA, p<0.0005	AfA > EA, p<0.035
Eye color [4]	Blue > Brown, p<0.04	NS	NS
Daily Caffeine	NS	NS	r = 0.10, p<0.05 (Rs = 0.11, p<0.035)
Smoking	NS	NS	Smokers > Non-Smokers, p<0.009
TPQ NS	r = 0.17, p<0.0005	NS	NS
TPQ HA	NS	NS	NS
TPQ RD	NS	NS	NS
SSS Total	r = 0.18, p = 0.001	NS	NS
EPQ (Psychoticism Subscale)	NS	NS	NS
EPQ Total	NS	r = − 0.11, p<0.05	NS
Eye blinks	NS	NS	NS
Rs4680[5]		NS	r = − 0.13, p<0.015 genotype × sex interaction, p<0.025 Men: Met/Met > others (d = 0.47) Women: Met/Met < others (d = 0.48)

[1] Mean %PPI across 10, 20, 30 60 and 120 ms intervals

[2] 10/09 – present

[3] Race: European America (EA); Asian American (AsA); African American (AfA)

[4] Blue vs. Brown

[5] (Val/Val, Val/Met) vs. (Met/Met)