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## Deficient prepulse inhibition in schizophrenia in a multi-site cohort: Internal replication and extension

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### ABSTRACT

**Background:** The Consortium on the Genetics of Schizophrenia (COGS) collected case-control endophenotype and genetic information from 2457 patients and healthy subjects (HS) across 5 test sites over 3.5 years. Analysis of the first “wave” (W1) of 1400 subjects identified prepulse inhibition (PPI) deficits in patients vs. HS. Data from the second COGS “wave” (W2), and the combined W(1 + 2), were used to assess: 1) the replicability of PPI deficits in this design; 2) the impact of response criteria on PPI deficits; and 3) PPI in a large cohort of antipsychotic-free patients. **Methods:** PPI in W2 HS (n = 315) and schizophrenia patients (n = 326) was compared to findings from W1; planned analyses assessed the impact of diagnosis, “wave” (1 vs. 2), and startle magnitude criteria. Combining waves allowed us to assess PPI in 120 antipsychotic-free patients, including many in the early course of illness. **Results:** ANOVA of all W(1 + 2) subjects revealed robust PPI deficits in patients across “waves” (p < 0.0004). Strict response criteria excluded almost 39% of all subjects, disproportionately impacting specific subgroups; ANOVA in this smaller cohort confirmed no significant effect of “wave” or “wave x diagnosis” interaction, and a significant effect of diagnosis (p < 0.002). Antipsychotic-free, early-illness patients had particularly robust PPI deficits. **Discussion:** Schizophrenia-linked PPI deficits were replicable across two multi-site “waves” of subjects collected over 3.5 years. Strict response criteria disproportionately excluded older, male, non-Caucasian patients with low-normal hearing acuity. These findings set the stage for genetic analyses of PPI using the combined COGS wave 1 and 2 cohorts.

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### 1. Introduction

Prepulse inhibition (PPI) of startle is a reliable, quantitative operational measure of sensorimotor gating that is deficient in several neuropsychiatric disorders, including schizophrenia (SZ) (Braff et al., 1978;

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Swerdlow et al., 2008). PPI deficits in SZ patients have been reported from a large number of laboratories in many different countries, using a variety of stimuli to elicit and inhibit startle, both within and across stimulus modalities (Aggernaes et al., 2010; Braff et al., 1978, 1999, 2001; Csomor et al., 2009; Hammer et al., 2011, 2013; Hong et al., 2007; Kishi et al., 2012; Kumari et al., 1999, 2007; Kunugi et al., 2007; Light et al., 2012; Ludewig et al., 2003; Mackeprang et al., 2002; Martinez-Gras et al., 2009; Meincke et al., 2004; Molina et al., 2011; Moriwaki et al., 2009; Oranje and Glenthøj, 2013; Preuss et al., 2011; Quednow et al., 2006; Rabin et al., 2009; Takahashi et al., 2008; Wang et al., 2013; Weike et al., 2000; Xue et al., 2012). PPI has robust heritability (Greenwood et al., 2007), and genes associated with PPI in SZ patients and healthy comparison subjects (HS) have been identified (Hong et al., 2008a; Petrovsky et al., 2010; Quednow et al., 2011; Greenwood et al., 2011, 2012; Roussos et al., 2016).

The Consortium on the Genetics of Schizophrenia (COGS) was designed to identify genes associated with SZ endophenotypes, using five geographically dispersed data collection sites. From July 2010, to February 2014, neurocognitive and neurophysiological endophenotypes as well as genetic material were collected from 1405 carefully characterized SZ patients and 1052 HS. Despite significant efforts in quality control and equipment and procedural standardization, this large, multi-site study presented challenges not faced in smaller, single-site studies of PPI in SZ, including site-based differences in sample demographics, methodologies and test conditions. Our quality assurance plan included an interim (circa January 2013) analysis of PPI data from the “first wave” of 1400 COGS subjects.

The results of the “first wave” (W1) analysis of PPI (Swerdlow et al., 2014) confirmed significant deficits in PPI in SZ patients. These deficits were sensitive to several moderating variables as previously reported in numerous “single site” PPI studies (e.g. Hong et al., 2008a, 2008b; Kumari et al., 1999, 2004; Swerdlow et al., 2006a; Weike et al., 2000), including prepulse interval (deficits at 60 ms, but not 30 or 120 ms) and medications (deficits blunted by antipsychotics (“APs”). We discussed opportunities and challenges created by PPI assessment in this multi-site platform. For example, embedded within this multi-site sample was the largest subgroup of AP-free SZ patients in which PPI had been tested, providing the opportunity for potentially novel insights into the nature of SZ-linked PPI deficits independent of drugs that are known to alter PPI. We also reported differences in the magnitude of PPI and SZ-linked PPI deficits across the 5 COGS sites, which created interpretative challenges, and at least in part may have reflected site-specific patterns of racial stratification.

Another challenge emerged from this W1 analysis: the use of strict response inclusion criteria (a “non-responder” defined as reflex magnitude < 10 units (1.31  $\mu\text{V}/\text{digital unit}$ ) for either of the two trial blocks during which PPI was analyzed) resulted in the exclusion of over 40% of the test subjects. While PPI deficits were evident with or without the use of these exclusion criteria based on a minimal startle response magnitude, this large attrition rate became important in subsequent COGS analyses, when multiple endophenotypes were integrated across subjects to identify endophenotype “factors” or “pathways” (Seidman et al., 2015; Millard et al., 2016; Thomas et al., 2017). Conceivably, this substantive loss of subjects may also negatively impact the design and interpretation of upcoming COGS genetic analyses, in which PPI data will be used, together with results from all other COGS endophenotypes.

Multi-site PPI assessment in the COGS “second wave” (W2) was completed in February 2014. Here, we present the results of the inclusive W1 and W2 PPI assessments, with three goals: 1. To assess the replicability, over time, of SZ-linked PPI deficits within a multi-site study; 2. To assess the impact of reflex response magnitude exclusion criteria on usable sample size and predicted patterns of PPI; 3. Absent evidence of significant W1 vs. W2 differences, to combine W(1 + 2) samples to achieve adequate power to conduct informative analyses of moderating variables in larger subgroups of potential interest, including patients who were unmedicated and early in their illness.

## 2. Methods

Other than collection date, methods and procedures for W2 subject ascertainment and collection of W2 data were identical to that for W1. As described previously, COGS participants were recruited and tested at 5 sites: Mount Sinai School of Medicine, University of California Los Angeles, University of California San Diego, University of Pennsylvania and University of Washington. Participants were 18–65 years old and fluent in English. Inclusion and exclusion criteria for W2 subjects were identical to those previously reported for W1 (Swerdlow et al., 2014), designed to exclude participants whose startle data was likely to be confounded by factors that interfere with startle signal acquisition or analysis (e.g. subjects with hearing impairment were not tested; subjects with zero measurable response to startle stimuli, or whose data was entirely missing from one eyeblink side or trial block – generally reflecting electrode removal or failure – were not included in analyses) and those whose PPI might have been altered on the basis of clinical factors unrelated to SZ per se (e.g. subjects with a history of recent substance abuse or electroconvulsive therapy were not tested). Local IRB boards of each testing site approved the study, and all participants provided signed informed consent before study participation (UCSD HRPP #080435). Diagnostic and clinical assessments (Andreasen, 1984a, 1984b; Faraone et al., 1999; First et al., 1995, 1996; Hall, 1995) were identical to those used in W1 (Swerdlow et al., 2014) and in earlier COGS studies (Calkins et al., 2007). As part of the initial structured clinical assessment, a list of all current medications was composed and reviewed with the test subject; it was then confirmed to be correct on the day(s) of testing. For patients whose medications were dispensed via a treatment or structured living facility, medication lists were typically confirmed with that facility. Patients were considered to be “antipsychotic-free” if no antipsychotic agents (including long-acting injectable forms) were included in those confirmed lists.

The full COGS test schedule was described previously (Swerdlow et al., 2015), and in W2 was divided over 2 days in 263 subjects (196 of whom were from test site 2), but the test sequence was maintained. For startle testing, as in W1, the eyeblink component of the acoustic startle response was measured using an EMG system that recorded 250 1-ms epochs, starting with startle stimulus onset. The session lasted 23.5-min, beginning with a 5-min acclimation period with 70-dB(A) SPL noise that continued throughout the session. The acclimation period was followed by 74 active trials, with 18 no stimulation (“nostim”) trials interspersed throughout the session. Startle “pulses” were 40-ms 115-dB(A) SPL noise bursts (near-instantaneous rise time, est. 1 ms). Prepulses were 20 ms noise bursts 15-dB above a 70-dB(A) SPL noise background, initiated 30, 60 or 120 ms prior to pulse onset; using slightly more intense 16 dB prepulses with this startle system, prepulse-associated EMG activity is < 0.5% of startle stimulus-induced levels (Swerdlow et al., 2006b). Five startle pulses were presented at the start (Block 1) and end of the session (Block 4) to assess habituation. In Blocks 2–3, pulse presented alone and preceded by each of the 3 prepulse trial types were pseudo-randomly intermixed (9 trials per condition per blocks; inter-trial intervals 11–19 s (mean = 15 s)). For “nostim” trials, data were recorded without stimulus presentation, to assess basal EMG activity. Filters, amplification, calibration, scoring and training procedures were described previously (Braff et al., 1992; Calkins et al., 2007; Graham, 1975; Swerdlow et al., 2007).

Patterns of subject “attrition” based on exclusion criteria are seen in Table 1S. Of the 660 W2 subjects for whom startle data were uploaded to the COGS database, 641 had a non-zero startle response, and 621 had sufficient startle data to allow calculation of the key dependent measure (60 ms PPI). Of these 621 subjects, 373 (195 HS, 178 patients) met the strict inclusion criteria for startle magnitude generally applied in single-site PPI studies, and applied with W1 data (“responder” defined as “mean startle magnitude for both PPI blocks  $\geq$  10 digital units (1.31  $\mu\text{V}/\text{unit}$ ”) in addition to other criteria listed in Table 2S. Of the 884 subjects for whom these startle magnitude exclusion criteria were

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