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Guest editorial

Sensorimotor gating deficits in schizophrenia: Advancing our understanding of the phenotype, its neural circuitry and genetic substrates

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1. Introduction

In her 1936 report of paired-pulse blink inhibition in 13 Yale undergraduate men, Helen Peak described "quantitative variation in amount of inhibition of the second response incident to changes in intensity of the first stimulus which precedes by different intervals of time" (Peak, 1936). These observations appeared to lay dormant for much of the next 30 years, but there was a resurgence of interest in startle modulation in the 1960's, based primarily on findings from Howard Hoffman's group (e.g. Hoffman and Fleshler, 1963). Almost four decades after Peak's first report, and more than 100 years after prestimulus-induced reflex inhibition was first described by the Russian scientist, Sechenov, Frances Graham summarized the growing literature of weak prestimulation effects on startle magnitude and latency (e.g. Hoffman and Searle, 1968) in her 1974 Presidential Address to the Society for Psychophysiological Research (Graham, 1975; see Ison and Hoffman (1983) for more historical background). This set the stage for David Braff's 1978 report of findings from Enoch Callaway's laboratory, extending Graham's parametric findings of startle inhibition, and demonstrating a relative loss of prestimulus effects on startle in 12 schizophrenia patients (Braff et al., 1978). Braff and colleagues interpreted this loss to be "consistent with a dysfunction in… early protective mechanisms which would correlate with information overload and subsequent cognitive disruption in schizophrenia." They also noted that deficits observed in patients might reflect a range of issues not specific to schizophrenia, including "global psychopathology… stress of hospitalization… [and] antipsychotic medications."

In the 80 years since Peak's systematic studies of blink inhibition, and the 40 years since Braff's published observation of impaired prepulse inhibition (PPI) in schizophrenia patients, PPI has been studied in many thousands of patients, and PPI findings have been reported in approximately 3000 Medline publications. While a relationship between deficient lead stimulus inhibition and "information overload" has not been demonstrated, it is clear from reading the articles in this Special Issue of *Schizophrenia Research* that many other themes of these early studies of startle inhibition – parametric sensitivity, transdiagnostic psychopathology, "trait vs. state" factors including antipsychotic medications and stress – remain critically important to our understanding of the phenomenon of impaired sensorimotor gating in schizophrenia, and its clinical and biological underpinnings. Also represented in this issue is the theme of the genetic regulation of PPI in health and pathology, inspired by promising (though not yet actionable) developments in psychiatric genetics over the past 4 decades.

2. The phenotype

Reduced PPI as a phenotype of schizophrenia has now been reported in several dozen different published studies, conducted in many different laboratories, countries, continents and cultures. We open this Special Issue with an "internal replication" of this finding, from the 5-site Consortium on the Genetics of Schizophrenia (COGS; PI: D. Braff). This report compares PPI across two "waves" of subjects tested over 3.5 years: "Wave 1" consisting of almost 1400 subjects, reported in 2014 (Swerdlow et al., 2014), and "Wave 2" consisting of over 600

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new subjects, reported here (Swerdlow et al., 2017). Balancing the added power produced by a 5-site study vs. the added variability associated with multi-site acquisition of a complex phenotype, this report extends themes from Peak (1936), Graham (1975), Braff et al. (1978) and others (Kumari et al., 1999; Swerdlow et al., 2006; Weike et al., 2000) by focusing on the sensitivity of the "PPI phenotype" to startle stimulus parameters, antipsychotic medications and other factors. Cumulatively, these COGS reports represent the largest published sample of PPI in healthy subjects and schizophrenia patients, and significant group differences were detected, with effect sizes ranging from small ($d = 0.11$) to medium ($d = 0.57$), depending on specific startle response criteria (e.g. low startle magnitude) and patient characteristics (e.g. sex, smoking, antipsychotic use). Across the many single-site reports of PPI deficits in schizophrenia cohorts, medium effect size differences (approximately $d = 0.5$) indicate that about 69% of schizophrenia patients exhibit PPI levels below the group mean of healthy comparison subjects. While we describe strategies to limit the impact of low reflex magnitude on PPI variability, our current report underscores some limitations of PPI as an experimental measure, as we have discussed elsewhere (Swerdlow et al., 2008, 2014). Specifically, "While these known effects of sex, smoking and medications on PPI can be incorporated statistically into models that test group differences, it is important that they cannot easily be extricated from an individual subject's PPI value, and thereby complicate the genomic and neurobiological signal provided by this endophenotype."

Despite the challenges in the use of PPI as an endophenotype for multi-site genetic studies, single-site studies continue to report significant PPI deficits in schizophrenia patients. Takahashi and Kamio (2017) review for the first time a list of studies conducted in Japan and China, with a cumulative sample of several hundreds of schizophrenia patients and healthy subjects, demonstrating a consistent pattern of deficient PPI in patients, comparable to what is generally reported in single-site studies from Western countries. Importantly, such cross-cultural confirmation is not as predictable as one might imagine with a basic reflex response, since blink magnitude is modified by features of facial musculature that differ across ethnic groups (Swerdlow et al., 2005), and because there appear to be ethnic differences in the functional impact of polymorphisms thought to moderate PPI (Wang et al., 2013; also see article by Quednow et al. (2017), later in this issue). While complicating moderating factors of both stimulus parameters and medications are discussed, Takahashi and Kamio (2017) clearly make the case that reduced PPI is a "global" schizophrenia phenotype, evident in both predominantly Caucasian Western countries as well as single ethnicity Asian countries.

Another issue raised by Takahashi and Kamio (2017) is the potential utility of PPI and other startle phenotypes in the study of children with Autism Spectrum Disorders (ASDs). While the "jury is still out" on the presence of PPI deficits in ASDs – and Takahashi and Kamio (2017) note the absence of such differences in their Japanese sample – the authors make the important point that reduced PPI is not a phenotype that is specific to schizophrenia. In fact, relatively reduced PPI distinguishes many groups of healthy subjects (e.g. women vs. men; children vs. adults); beyond this, studies have reported that PPI is impaired in patients with OCD (Swerdlow et al., 1993a; Hoenig et al., 2005; Ahmari et al., 2012; Kohl et al., 2015), Tourette Syndrome (Castellanos et al., 1996; Swerdlow et al., 2001b; Zebardast et al., 2013; Baldan et al., 2014; Buse et al., 2016), Huntington's Disease (Swerdlow et al., 1995; Muñoz et al., 2003; Valls-Sole et al., 2004), nocturnal enuresis (Ornitz et al., 1992), Asperger's Syndrome (McAlonan et al., 2002; Howlin and Murphy, 2002), 22q11 Syndrome (Sobin et al., 2005), Kleinfelter Syndrome (van Rijn et al., 2011), Fragile-X Syndrome (Frankland et al., 2004; Yuhas et al., 2011; Renoux et al., 2014), and blepharospasm (Gomez-Wong et al., 1998). As discussed elsewhere in this issue (e.g. Schwabe and Krauss (2017)), the forebrain regulation of PPI involves interconnected neural circuitry that appears to be relevant to many different disorders, and perhaps particularly relevant to disorders of neurodevelopmental origin. Conceivably, disturbances at any one of several nodes within this circuitry mind produce a "deficient PPI" phenotype, together with a range of different clinical conditions. Perhaps it is equally important to note that sensorimotor gating, as measured by PPI, appears to remain relatively intact, or at least functional, in a number of other serious brain disorders, including attention deficit disorder (ADHD: Castellanos et al., 1996; Ornitz et al., 1992; Ornitz et al., 1999; Conzelmann et al., 2010; Feifel et al., 2009; Hanlon et al., 2009), bipolar disorder (Barrett et al., 2005 (euthymic); Carroll et al., 2007 (manic or mixed episode); but see Sánchez-Morla et al., 2016 and Giakoumaki et al., 2007), and major depressive disorder (Ludewig and Ludewig, 2003; Perry et al., 2004; Quednow et al., 2006), while evidence from chronic substance use disorders is mixed (e.g. Quednow et al., 2004; Schellekens et al., 2012).

The impairment of PPI in psychosis can also be complicated by comorbid disorders; this fact is underscored by Sedgwick et al. (2017) in this issue, who report that in a population of violent men in a high-secure forensic psychiatric hospital, with or without psychosis, PPI is impaired among individuals meeting criteria for an antisocial personality disorder (specifically, the ICD-10 classification of Dissocial Personality Disorder (DPD)). This observation is generally consistent with several points raised elsewhere within this issue, i.e. the fact that impaired PPI is not uniquely a function of schizophrenia; that among psychotic patients, other factors (here the presence of a personality disorder in a violent, institutionalized cohort) appear to moderate the expression of reduced PPI; and that early developmental stress (in this case, early psychosocial deprivation, including physical and sexual abuse) may be a strong determinant of the adult PPI phenotype, even independent of the diagnosis of schizophrenia.

Fargotstein et al. (2017) provide the important reminder that PPI is not the only startle reflex parameter that is impaired in schizophrenia patients. They report slowed startle reflex peak latency in their sample of schizophrenia patients — a common though not ubiquitous finding (see Discussion in Fargotstein et al. (2017)). This phenotype was most pronounced in their subgroup of unmedicated schizophrenia patients, suggesting that – as with PPI in many studies – antipsychotics may partially correct this slow-latency phenotype, or that other factors associated with unmedicated status may also contribute to prolonged reflex latency. Importantly, in this report as in many others, latency *facilitation* – the normal reduction in reflex latency on prepulse + pulse trials – was intact in patients, including those who were unmedicated. This intact form of prepulse modification of startle suggests that even unmedicated patients are "processing" the prepulse – i.e. it is altering brain function by "speeding up" the reflex – and yet the prepulse is *not normally inhibiting reflex magnitude* (in Fargotstein et al., this PPI deficit was detected only among unmedicated patients). In this way, the presence of intact latency facilitation, together with impaired magnitude suppression (PPI), argues *against* a generalized failure of reflex modification in schizophrenia, and *for* a more specific deficit of PPI. Fargotstein and colleagues also point out the high heritability of startle latency, its potential value in predicting conversion to psychosis and its association with specific genes thought to confer risk for schizophrenia. These facts, together with the very low variance evident in measures of reflex latency, argue for its utility as a schizophrenia endophentype.

3. Neural circuitry

Another important theme in this Special Issue is that – as much, or more, than most other complex human neurobehavioral phenomenon – the biology of sensorimotor gating, measured operationally by PPI, has been elucidated by convergent findings from human and infrahuman studies. Rodent studies of lead stimulus modification of startle by Howard Hoffman, Jim Ison and others were heavily cited in Fran Graham's 1974 SPR Presidential Address as foundational for the evolving human startle literature. Animal studies first linked Braff's observation of deficient PPI to an anatomical (ventral striatum) and

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