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Review

Update: Studies of prepulse inhibition of startle, with particular relevance to the pathophysiology or treatment of Tourette Syndrome

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ABSTRACT

Prepulse inhibition of the startle reflex (PPI) is an operational measure of sensorimotor gating, in which the motor response to an abrupt, intense stimulus is inhibited by a weak lead stimulus. PPI is reduced in several brain disorders, including Tourette Syndrome (TS); it is regulated by forebrain circuitry, including portions of the basal ganglia implicated in the pathophysiology of TS, and is also heritable and under strong genetic control. PPI has been the focus of numerous translational models, because it is expressed by most mammalian species, with remarkable conservation of response characteristics and underlying neural circuitry between rodents and primates. Several of these models have recently explored causative factors in TS – from genes to specific basal ganglia perturbations – as well as potential TS therapeutics, including novel pharmacological and neurosurgical interventions. With the focus on Comprehensive Behavioral Interventions for Tics (CBIT) in the evolving treatment model for TS, future studies might apply PPI as a predictive measure for CBIT response, or for identifying medications that might augment CBIT efficacy. In the end, a measure based on a simple pontine-based reflex will have limitations in its ability to explicate any complex behavioral phenotype.

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1. Introduction

The startle reflex is a constellation of responses to sudden, relatively intense stimuli. In humans, the blink reflex component of startle is measured using electromyography of orbicularis oculi; in laboratory animals, whole-body startle is quantified by assessing the downward force resulting from the contraction of the skeletal muscles. Prepulse inhibition (PPI) occurs when a weak prestimulus 30–500 ms prior to the startling stimulus inhibits the startle response; this inhibition is an operational measure of sensorimotor gating (Graham, 1975). While the inhibitory effect of the prepulse on the startle reflex is exerted in the pons, studies have described the limbic forebrain circuitry and descending pontine projections that regulate the inhibitory "tone" within the pons and determine the degree to which the prepulse inhibits the subsequent motor response (cf. Swerdlow et al., 2001a, 2008). PPI thus appears to reflect the activation of "hard-wired", centrally mediated behavioral inhibitory processes that are regulated by forebrain neural circuitry.

PPI is a useful experimental measure for understanding brain mechanisms for a number of reasons. It is tested in an automated apparatus, under tight stimulus control, and stimulus parameters can be easily modified by the experimenter to elicit optimal response characteristics for studying a number of different aspects of this measure. Because PPI is a form of startle plasticity, it is measured using a "fight-or-flight" behavior that is simple, robust, and exhibited across all mammalian species tested to date. Of relevance to the present discussion, PPI is easily studied in animal models, including mice (Carter et al., 1999; Francis et al., 2003; Frankland

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et al., 2004), rats (Swerdlow et al., 2001a), guinea pigs (Vaillancourt and Boksa, 2000), pigs (Lind et al., 2004), and infrahuman primates (Linn et al., 2003), using stimulus parameters and equipment for stimulus delivery and response acquisition that are similar or identical to what are used in humans. While there appear to be differences in the neurochemical regulation of PPI across species (cf. Swerdlow et al., 2008), the basic parametric properties of PPI exhibit striking similarities from rodents to humans (e.g. Swerdlow et al., 1994), and PPI is under significant genetic control in both rodents (Francis et al., 2003) and humans (Greenwood et al., 2007).

This review focuses specifically on the results of studies of PPI in Tourette Syndrome, related clinical conditions, and relevant animal models. Broader reviews of PPI have appeared in this journal (e.g. Li et al., 2009), and more comprehensive analyses of our current understanding of TS pathophysiology can be found in accompanying articles in this special issue.

2. PPI and Tourette Syndrome

Despite its advantages as a laboratory measure of simple brain processes, PPI would likely be a scientific footnote were it not for the fact that it is reduced in a number of different brain disorders. Compared with matched controls, PPI is deficient in patients with schizophrenia (e.g., Braff et al., 1978; Swerdlow et al., 2006b), Huntington's Disease (Swerdlow et al., 1995; Valls-Sole et al., 2004), Obsessive Compulsive Disorder (OCD) (Swerdlow et al., 1993; Hoenig et al., 2005; Ahmari et al., 2012), nocturnal enuresis (Ornitz et al., 1992), Asperger's Syndrome (McAlonan et al., 2002), 22q11 Syndrome (Sobin et al., 2005), Kleinfelter Syndrome (van Rijn et al., 2011), Fragile-X Syndrome (Frankland et al., 2004) and blepharospasm (Gomez-Wong et al., 1998), as well as in patients with TS (Castellanos et al., 1996; Swerdlow et al., 2001b). PPI deficits in TS are one of several forms of reduced "paired pulse inhibition" exhibited in this disorder: TS individuals also exhibit deficits in measures of "blink recovery cycle" (also called "blink excitability"; Smith and Lees, 1989) and "intracortical inhibition" (Ziemann et al., 1997). In each of these measures, the response to a target stimulus ("pulse" or "S2") is reduced by the presentation of a lead stimulus ("prepulse" or "S1"), and this reduction is blunted in TS patients.

Overlapping neural substrates? PPI deficits in TS are of particular interest, because the forebrain substrates regulating PPI appear to overlap somewhat with those implicated in the pathophysiology of TS. Thus, two of the neural mechanisms that figure most prominently in current models of TS neuropathology are: (1) disturbances in basal forebrain dopamine (DA) function, and (2) abnormalities within intrinsic striatal circuitry (cf. McNaught and Mink, 2011; Kalanithi et al., 2005; Kataoka et al., 2010; Steeves et al., 2010); similarly, basal forebrain DA potently regulates PPI in laboratory animals, and PPI is potently reduced by experimentally-induced damage to intrinsic striatal circuitry (cf. Swerdlow et al., 2008; Kodsi and Swerdlow, 1994; Baldan Ramsey et al., 2011a; see below). It is important to acknowledge, however, that there is no clearly elucidated mechanistic link between the various different forms of basal ganglia disturbances noted in different samples of TS patients. In fact, it is conceivable that different forms of TS might reflect distinct, causally and mechanistically *unrelated* forms of basal ganglia pathology. It is well beyond the scope of this review, or of any report based on our current state of knowledge, to attempt to link at a causal or mechanistic level the myriad reported disturbances of basal ganglia function in TS – e.g. hyperdopaminergic innervation of the ventral striatum in TS (Albin et al., 2003), striatal volumetric reductions in this disorder (Peterson et al., 2003), anti-putamen antibodies (Singer et al., 1998), aberrant distribution of intrinsic basal ganglia cells (Kalanithi et al., 2005; Kataoka et al., 2010) and abnormal neural activation through basal ganglia structures (Wang et al., 2011). Of most relevance to the present review, however, is the loss of PPI detected in a range of models that reproduce aspects of many different forms of reported TS basal ganglia pathology.

Some evidence suggests that the ventral striatum may be one site of convergence between the neural disturbances in TS and the neural substrates of PPI: (1) neurochemical imaging studies in TS patients have suggested increased dopaminergic innervation of this region (Albin et al., 2003), and DA levels in this region are strong determinants of PPI levels (Swerdlow et al., 1992; Zhang et al., 2000); (2) preliminary volumetric and morphometric measures in TS sib-pairs detected significantly reduced ventral striatal volume and density with robust familial patterns (Frey, 2006), and experimentally reduced ventral striatal volume and density is associated with PPI deficits in rodents (Kodsi and Swerdlow, 1994) as are "familial" strain-based differences in ventral striatal gene expression (Swerdlow et al., 2012); (3) recent reports (discussed below) suggest TS symptom response to deep brain stimulation (DBS) within either the ventral striatum (nucleus accumbens; e.g. Neuner et al., 2009) or within one ventral striatal output field in the internal globus pallidus (Welter et al., 2008), while DBS within an analogous region in rats prevents the PPI-disruptive effects of DA agonists (Posch et al., 2012; see below). Thus, evidence from pharmacologic, neurochemical and volumetric imaging studies, as well as emerging therapeutic reports, suggest an overlap between the many reported (but potentially mechanistically unrelated) brain disturbances in TS and the neurobiology of PPI. Of course, it is highly likely that – as the potentially long list of genetic and non-genetic etiologies of TS is identified – different forms of this syndrome will be differentially associated with disturbances in neuronal function and DA neurotransmission within striatal subregions.

Overlapping psychophysiological substrates? An intriguing conceptual connection between TS and PPI relates to their psychophysiological underpinnings. PPI is an operational measure of sensorimotor gating, a process of central inhibition that has both automatic (preconscious) and volitional (attentionally sensitive) components. Over the past 20 years, it has become clear that the visible or audible tics in TS, in many instances, may be integrally connected to a form of failed automatic "gating" of sensory information, that is experienced as bothersome, unwanted internal sensory or psychic experiences (Bliss, 1980; Cohen and Leckman, 1992; Leckman et al., 1993, 1994; Miguel et al., 1997, 2000; Hollenbeck, 2003). Thus, it is conceivable that the pathological processes responsible for the loss of PPI in TS patients may also be related to, and even contribute to, the processes responsible for intrusive sensory phenomena in this disorder.

In truth, the association of a physiological abnormality such as reduced PPI, with a disorder likely to have multiple different genetic and non-genetic causes, might be based on a number of structurally different biological relationships e.g. mediating, moderating, independent or interactive. The simplest case, which is almost certainly not relevant to most (or even any) brain disorders, is that pathological genes code for neural circuitry that generates deficient PPI, and this PPI deficit causes the symptoms of the disorder. Patients simply do not present to the clinic complaining of "too little PPI", or that they "startle too much, even when there are prepulses." A more likely association between PPI and a brain disorder would reflect the fact that pathological genes code for neural circuitry that regulates PPI, and which also regulates other fundamental behavioral or neurocognitive processes. A "simple" example of such an association *might* underlie PPI deficits in disorders related to pontine dysfunction or developmental delay, such as enuresis, based on the apparent role of neighboring pontine structures in both the control of PPI and bladder function (cf. Swerdlow et al., 2001a); conceivably, such a relationship might also underlie PPI deficits in TS, based on a contribution of striatal dysfunction to both of these "phenotypes." Certainly, there are more complex and interactive models

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for an association between PPI and a disorder like TS; for example, TS might be manifested most intensely (or positively moderated) in individuals who also carry genes coding for reduced neural control of a psychophysiological process – sensorimotor gating – that results in a reduced level of motor inhibition in response to sensory input; studies by Wang et al. (2011) suggest such a loss of activity in inter-connected cortico-striatal circuitry that exerts a top-down control of motor activity in TS. The key point is that the experimental association of reduced PPI and TS tells us very little about the biological relationship between these two phenomena; this does not, however, mean that such a relationship will not be a useful one, for testing hypotheses and potential etiologies, and even for developing novel therapeutics.

3. Update of recent PPI findings of relevance to TS

A number of past reviews have described PPI and its applications toward understanding TS (e.g. Swerdlow and Sutherland, 2005, 2006). More recent developments in this field have come from several novel uses of PPI in TS-related models; these studies share a common measure (PPI) and target disorder (TS), but otherwise cover a range of different topics:

A. *Striatal regulation of PPI in mice*: Based on the ability to easily study molecular manipulations in mice, they are the species of favor for modeling genetic contributions to human disorders such as TS. In truth, however, most of the neurobiology of PPI was initially identified in rats, and not in mice (cf. Swerdlow et al., 2001a). While the default assumption had been that the neural regulation of PPI in mice should be quite similar to that found in rats, there is already evidence for species differences in this circuitry, particularly among systems of direct relevance to TS (Ralph and Caine, 2005). A number of mutant mice are being used in gene-based models for TS, and it will thus be increasingly important to understand the neural circuit regulation of PPI in mice. In one important recent finding, Baldan Ramsey et al. (2011a) reported that excitotoxic lesions of the dorsomedial striatum in C57Bl/6J mice profoundly disrupted PPI, suggesting that basal ganglia circuitry regulate PPI in mice, in a manner consistent with similar findings in rats (Kodsi and Swerdlow, 1995) and with findings in humans with known striatal pathology (Swerdlow et al., 1995). While there is no guarantee that these findings will generalize across all mouse strains (Ralph et al., 2001), or relevant brain regions, they establish at least one background strain with striatal-regulated PPI on which the effects of genetic manipulations could then be interpreted.

B. *PPI deficits in histidine carboxylase-deficient TS patients and mice*: In a recent use of mutant mice to model TS-related PPI deficits, Baldan Ramsey et al. (2011b) studied PPI in a two-generation TS human pedigree characterized by a nonsense mutation in the histidine decarboxylase (HDC) gene, HDC W317X, and in HDC knockout (KO) mice. PPI was significantly reduced among the nine TS patients carrying the HDC nonsense mutation, compared to control subjects, and in the HDC KO mice, compared to wild type mice; mice heterozygous for the HDC mutant allele exhibited intermediate PPI levels. Neuroimaging and biochemical analyses confirmed midbrain and forebrain D2/3 receptor abnormalities in these TS patients and in HDC KO mice. While these findings do not suggest that HDC is a common causative gene in either TS or its associated PPI deficits, they do provide convergent evidence that across species, HDC deficiencies are associated with reduced PPI. More generally, the use of PPI as a cross-species model to study the neurobiology of HDC mutations exemplifies the potential utility of this measure in investigating the numerous other genes that will ultimately be implicated in the complex genetics of TS.

C. *Noradrenergic regulation of PPI in forebrain regions of relevance to TS*: In addition to the proposed role of forebrain DAergic systems in tic genesis and therapeutics, there is also both clinical and preclinical evidence for a role of frontal noradrenergic transmission in these processes (cf. Leckman et al., 2010). Consistent with such a role, our group and others have reported effects of noradrenergic drugs in both reducing and restoring PPI in rats. For example, PPI in rats is disrupted by cirazoline, an agonist at the α1 NE receptor (Carasso et al., 1998). We reported that these effects of cirazoline are opposed by acute administration of the alpha-2 agonist, clonidine (Swerdlow et al., 2006a), which after chronic administration, is an effective antitic medication (Leckman et al., 1991). Thus, it is conceivable that antitic properties of noradrenergic agents might be predicted by their ability to reverse the gating-disruptive effects of cirazoline. More recently, Alsene et al. (2011) "mapped" the forebrain noradrenergic regulation of PPI in Sprague-Dawley rats, via intracerebral infusions of a mixture of the α1 NE agonist, phenylephrine plus the β-receptor agonist isoproterenol. PPI was significantly reduced after infusion of the NE agonist "cocktail" into the posterior medial prefrontal cortex, nucleus accumbens shell, bed nucleus of the stria terminalis, basolateral amygdala, and the mediodorsal thalamus (MD) disrupted PPI, with particularly strong effects in MD. Several other sites did not support PPI disruptions after NE agonist infusion, but did so after infusion of the dopamine D2 receptor agonist, quinpirole. These findings begin to define a network of forebrain NE terminal fields in which either basal- or stress-induced increases in NE transmission might disrupt PPI in disorders such as TS; conceivably, this circuitry may interface with PPI-regulatory mechanisms in many brain regions, including the nucleus accumbens, where α1 NE receptors are known to regulate DAergic activity (Mitrano et al., 2012).

D. *PPI models applied toward TS therapeutics*: Several recent studies have utilized PPI in efforts to understand and advance novel TS therapeutics. In one such study, Devoto et al. (2012) utilized PPI to explicate the neural mechanisms that might account for an observed reduction in tic severity in a series of 10 adult male TS patients treated with the 5α-reductase inhibitor, finasteride (FIN) (Muroni et al., 2011). In rats, FIN was shown to prevent the PPI-disruptive effects of DA agonists after systemic, intraventricular and intracerebral administration, the latter being into the nucleus accumbens (NAC) core or shell subregions. FIN infusion into a number of other brain regions failed to prevent DA agonist effects on PPI. The authors interpreted their findings to suggest that FIN effects on PPI in rats – and by extrapolation, potentially its effects on TS symptoms – reflect its actions on cells within the NAC. Here, DA-disrupted PPI was used as a sort of surrogate model for TS symptoms, to understand the clinical observation of positive FIN effects on TS patients.

   A similar use of PPI was reported in studies designed to understand and potentially map circuitry for DBS sites of value to severe, treatment-refractory TS and other disorders. Posch et al. (2012) demonstrated that high frequency DBS of the rat entopeduncular nucleus (EPN) – a rodent analog of the human globus pallidus interna (GPi), an effective site for DBS in TS patients (Welter et al., 2008) – prevented the PPI-disruptive effects of the DA agonist, apomorphine (APO). Taken together with the above findings of Devoto et al. (2012), these effects of DBS underscore that DA-induced PPI deficits can be opposed via interventions at multiple levels of interconnected forebrain circuits, conceivably recapitulating the therapeutic impact of DBS administered to multiple sites within these same circuits.

E. *PPI in disorders relevant to TS*: Because PPI abnormalities are observed in numerous brain disorders, they are clearly not diagnostically specific. Because of the common comorbidity of TS, it is important that previous findings have determined that – in small

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numbers of patients – PPI deficits in TS are not dependent on the common comorbid conditions of Attention Deficit Hyperactivity Disorder (ADHD) or Obsessive Compulsive Disorder (OCD) (Castellanos et al., 1996; Swerdlow et al., 2001b). However, to the degree that TS is a disorder that shares clinical, neuroanatomical and potentially genetic elements with these and other neurodevelopmental disorders, the findings of PPI deficits within the "TS spectrum" can be informative regarding their relevance to TS. For example, Ahmari et al. (2012) recently confirmed that PPI is deficient in unmedicated OCD patients – as it had been previously reported in smaller groups of medicated OCD patients (Swerdlow et al., 1993; Hoenig et al., 2005). Ahmari et al. (2012) detected significantly reduced PPI in OCD patients vs. comparison subjects, and also identified 3 individuals with a history of tics, whose PPI levels were reduced, on average, well below the levels of the other 19 OCD patients. While a comprehensive review of recent reports of PPI deficits among neurodevelopmental disorders is not within the scope of this paper, it is worth noting that among these disorders, PPI is being applied toward the development of novel therapeutics (e.g. Levenga et al., 2011; Olmos-Serrano et al., 2011), and toward the diagnostic and pathophysiological dissociation of clinical subtypes (e.g. Eggert et al., 2012).

F. *Sensory phenomena and TS psychotherapeutics*: Some intriguing recent developments in our understanding of TS relate to the sensory phenomenology associated with this disorder. Among the most important breakthroughs in all of TS therapeutics to date has been the recent multi-site finding of the therapeutic benefits of a modified Habit Reversal Therapy protocol – termed "Comprehensive Behavioral Interventions for Tics (CBIT)" – in children with TS (Piacentini et al., 2010), and in TS adults (Wilhelm et al., 2012). The efficacy of CBIT in reducing tics is comparable to, or exceeds, that of known antitic medications. Importantly, while this effective "new" therapy does not rely on any models for the molecular or genetic basis of TS, it is critically dependent on our understanding of the TS clinical phenotype, and particular the sensory and premonitory symptoms described by Leckman et al. (1993) and by many subsequent groups. In CBIT, patients identify these sensory events as the antecedent of the motor or phonic event, and initiate a competing opposing response. Thus, the intrusive sensory information plays an important role in the therapeutic impact of CBIT, and indeed, the inability to recognize such sensory events can hinder CBIT's efficacy.

Based in part on their new, central role in TS therapeutics, TS-related sensory phenomena have become a focus of several recent studies. Sutherland Owens et al. (2011) characterized features of sensory phenomena in TS patients. In addition to the discrete sensory tics and premonitory urges, they reported that TS patients endorse difficulties in specific sensory gating processes, including: (1) the ability to modulate stimulus intensity and prevent perceptual inundation, (2) the ability to focus attention or prevent distractibility, (3) a low threshold of perception (over-inclusion and hyperawareness), and (4) a vulnerability to perceptual and attentional anomalies during periods of fatigue and stress (Sutherland Owens et al., 2011). Belluscio et al. (2011) reported complementary findings, with 80% of their adult TS sample reporting heightened sensitivity to sensory stimulation. Importantly, however, direct assessment of tactile and olfactory thresholds revealed no differences between TS and control subjects, suggesting that subjective sensitivity differences in TS patients reflected altered central information processing rather than enhanced peripheral sensory detection.

The sensitivity of TS symptoms to CBIT depends heavily on the ability of an individual to detect a premonitory event, and to initiate an appropriate preventative response. Structurally, this process is analogous to that used in traditional cognitive and behavioral therapy (CBT), where individuals identify an event (a negative thought, obsession, delusion, etc.) and interrupt the typical consequence (rumination, avoidance, etc.) by initiating a preventative cognitive or behavioral process. Over time, with consistent, effortful application, the volitional components of this inhibitory process become more automatic, integrated into the "default" behavioral profile; conceptually, the regulation of this inhibition shifts from cortical to subcortical circuitry. This structural similarity between CBIT and CBT is of interest because PPI has been reported to be a potent predictor of the therapeutic impact of CBT in schizophrenia patients (Kumari et al., 2012). While PPI has not yet been assessed as a predictor of CBIT response, previous studies of response predictors for Habit Reversal Therapy in TS demonstrated that improvement from HRT correlated significantly with levels of inhibition in a conceptually-related visuospatial priming (VSP) paradigm (Deckersbach et al., 2006); an animal model of this VSP paradigm, and its pharmacologic sensitivity, is reported herein by Amitai et al. (2012).

Because of the link between CBIT, sensory phenomena, and motor inhibition, as well as the new evidence that PPI predicts the therapeutic response to CBT (Kumari et al., 2012), it is worth considering how PPI or related measures might be of utility in the application of CBIT or other behavioral interventions for TS. One emerging concept involves the identification of "pro-cognitive therapy" medications that can specifically enhance the therapeutic impact of a cognitive or behavioral intervention, by enabling patients to better meet the specific cognitive demands of that therapy (cf. Swerdlow, 2011). A "proof of concept" for such a paradigm comes from the use of the pro-extinction drug, D-cycloserine (DCS), to enhance the therapeutic benefits of CBT in several different brain disorders, including OCD; this ability of DCS was first predicted based on its ability to facilitate extinction of the fear-potentiated acoustic startle reflex (cf. Davis, 2011). In the case of TS, such "pro-CBIT" interventions might be specific to both the patient's symptoms and their cognitive capabilities. In a simple example, one might hypothesize that TS patients with comorbid ADHD are particularly challenged by the attentional demands of CBIT (Woods et al., 2008); in these individuals, stimulants might augment the therapeutic impact of CBIT, even above their independent antitic properties (The Tourette's Syndrome Study Group, 2002). While such synergy has not yet been tested, one small study failed to detect a synergistic effect of acute methylphenidate administration with tic suppression (not CBIT per se); one likely explanation for this outcome appeared to be a floor effect – i.e. near-maximal tic reduction with either tic suppression or methylphenidate (Lyon et al., 2010). Clearly, tic activity after CBIT does not always reach "floor" levels (Piacentini et al., 2010), and there is ample range to assess the potential synergistic impact of medications with CBIT.

One might envision medication-enhanced behavioral interventions for TS via drug effects on other neurocognitive processes. For example, it is indeed conceivable that extinction of the premonitory sensation – which often serves as a "trigger" for tics – might be accelerated with DCS, similar to its ability to enhance extinction of the psychic discomfort associated with obsessions in OCD. Should such a process "disconnect" the urge from the subsequent motor tic, it might obviate a need to initiate a competing event. Alternatively, drugs that enhance sensorimotor gating – assessed by increases in PPI – might potentiate an individual's ability to suppress the motor (tic) response to the sensory (premonitory) event. Individuals with low levels of PPI are particularly sensitive to PPI-enhancing effects of a number of drugs from different chemical classes – including atypical antipsychotics (Swerdlow et al., 2006b; Vollenweider et al., 2006), direct (Bitsios et al., 2005) or indirect DA agonists (Talledo et al., 2009), the catechol-O-methyl-transferase

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inhibitor, tolcapone (Giakoumaki et al., 2008) and the low-potency NMDA antagonists, memantine (Swerdlow et al., 2009) and amantadine (Swerdlow et al., 2002; Bitsios et al., 2005). Conceivably, by identifying an individual's sensitivity to drug-enhanced PPI in the laboratory, it might be possible to predict pharmacological strategies for augmenting sensorimotor gating processes that would potentiate their ability to assert volitional control over semi-automatic motor responses. Whether such a strategy can be applied toward identifying "pro-CBIT" medications, and whether PPI, VSP, "Go–No Go" (e.g. Deckersbach et al., 2006) or related measures of behavioral inhibition can play a predictive role in the development or application of this strategy, are worthwhile topics for future investigation.

Understanding the limits of PPI: It is important to have realistic expectations for what can, and cannot be learned, from the use of any laboratory measure, and PPI is no exception to this rule (Swerdlow et al., 2008). As we have noted previously, PPI and its relative deficiencies are not diagnostic of TS or any other condition; levels of PPI do not predict clinical course, specific symptoms, or individual treatment responses (Swerdlow et al., 2008), with the possible exception of one recent report with CBT (Kumari et al., 2012). It appears that PPI is reduced in TS, in a manner that is: (1) independent of stimulus modality and co-morbid conditions; (2) evident in the "general" TS population and in at least one group of individuals whose TS is associated with a specific genetic mutation, as well as in a proposed isomorphic animal model; (3) reproducible in other animal models that appear to be informative about TS neurobiology, and potentially, its treatments. Some applications of this measure are relatively "low-cost/high-yield", such as its use in a cross-species platform to assess models of genetics and neurobiology. Other uses – particularly those with direct clinical applications – remain under investigation, and in the foreseeable future may remain "a bridge too far." To some degree, it is astonishing that a laboratory measure of plasticity in a pontine-based reflex has had any utility in the study of the pharmacology, neurobiology and genetics of complex and uniquely human brain disorders like TS; PPI remains an experimental tool of value that should continue to be informative if applied in a rational manner, within its limits of resolution.

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