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Prepulse Inhibition Deficits in Obsessive-Compulsive Disorder are More Pronounced in Females

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Obsessive-compulsive disorder (OCD) is a disabling and chronic psychiatric disorder, but despite its severity and prevalence, relatively little is known about its neurobiology. Substantial evidence suggests that abnormalities in structure and function of cortico-striato-thalamo-cortical (CSTC) circuits underlie OCD pathophysiology (Ahmari and Dougherty 2015). This fact highlights the need to identify probes of CSTC circuits that are consistently abnormal in OCD patients, in order to facilitate translational studies. In pursuit of this goal, in a previous study (Ahmari *et al*, 2012) we found that unmedicated adults with OCD had deficits in sensorimotor gating as measured by prepulse inhibition (PPI) of the acoustic startle response at three different prepulse intensities (74, 78, and 86 dB; $n=22$ OCD, 22 controls). Exploratory analyses suggested that OCD patients with a history of tics had lower PPI than those without tics.

Owing to recent studies highlighting potential sex differences in both OCD genetic substrates (Taylor 2013) and clinical course (Torresan *et al*, 2013), the known effects of hormonal state on PPI (Jovanovic *et al*, 2004), and increasing recognition of the importance of sex effects in psychiatric pathophysiology (see NIH NOT-OD-15-102: Consideration of Sex as a Biological Variable in NIH-funded Research; Clayton and Collins 2014), we reanalyzed our PPI data to examine males and females separately (see original manuscript for demographics and clinical details). In light of past literature demonstrating increased prevalence of tic-related OCD in males (Leckman *et al*, 1994), we hypothesized that male OCD patients were driving the observed PPI deficits in our study. Surprisingly, when male and female patients were analyzed separately, we found that PPI deficits were more pronounced in female patients (*Females*: OCD ($n=10$) *vs* control ($n=10$): F (1,18) = 4.539; $p<0.047$, Cohen's $d=0.88$; *Males*: OCD ($n=12$) *vs* control ($n=12$): F (1,22) = 2.269; $p>0.146$, Cohen's $d=0.65$). This effect was even more striking when patients with tics ($n=3$ males) were removed from the male sample (*Males without tics*: OCD *vs* control: F (1,19) = 0.380; $p>0.545$, Cohen's $d=0.27$), and was most prominent at higher prepulse intensities (Figure 1). In females, re-analysis of timing of PPI measurements relative to menstruation revealed that although all subjects signed consent within days 1-10 of the menstrual cycle, 5 HC and 4 OCD were tested outside this window, yielding a range of cycle day 4-17 in HC and 1-17 in OCD (ie, follicular/ovulation phase); average menstrual cycle day was the same in both groups (OCD = 9.5 ± 5.1; HC = 9.5 ± 5.9). There was no statistically significant correlation between day of menstrual cycle and PPI (R^2: HC = 0.017; OCD = 0.031; F values: HC = 0.14; OCD = 0.19). Exploratory analyses testing the association between the consolidated PPI measure for each sex and clinical variables (OCD severity; age of OCD onset; or any of the five symptom dimensions) using Spearman's correlation indicated that females with OCD had a trend towards lower percent PPI (ie, larger deficits) with older age of OCD onset ($p<0.089$). No other significant associations were observed in either females (all p-values >0.25) or males (all p-values >0.33) with OCD.

The observed differential effect of sex suggests that pathophysiologic processes may be distinct in females and males with OCD, and that these differences may potentially be localized to the neural substrates underlying PPI, a well-established method for probing functional status of cortico-striato-pallidal circuitry in humans and rodents. Because this is a *post hoc*, exploratory analysis with multiple moderators in a relatively small data set, and therefore would not survive correction for multiple comparisons, these findings need to be replicated in a study in which sex effects are examined from the outset. Though the neurobiological underpinnings of this effect are unknown, the trend in females towards larger deficits when OCD onset is after typical age of menarche suggests pubertal-related circuit changes. One explanation for these changes could include a shift in the prepulse inhibition/facilitation curve towards facilitation in post-pubertal women, via increased circulating estrogen, leading to increased excitatory/inhibitory balance (Aasen *et al*, 2005). Dissecting the mechanisms leading to

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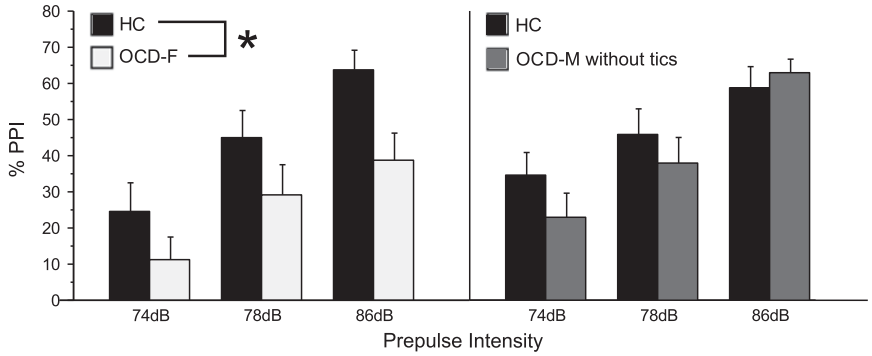

Figure 1 PPI deficits are more pronounced in female OCD subjects. Bar graph demonstrates percent PPI (mean ± SEM) at 74, 78, and 86 dB prepulse intensities. Female OCD patients (left panel) demonstrate more pronounced PPI deficits than males, particularly when patients with a history of tics ($n = 3$ males) are removed (right panel). *Females*: OCD ($n = 10$) *vs* control ($n = 10$): F (1,18) = 0 4.539; $p < 0.047$. *Males without tics*: OCD ($n = 9$) *vs* control ($n = 12$): F (1,19) = 0.380; $p > 0.545$. HC, healthy control subjects; OCD-F, female OCD subjects; OCD-M without tics, male OCD subjects without tics. * indicates significance at $p < 0.047$.

increased PPI deficits in female OCD patients could ultimately lead to discovery of targets for sex-specific, tailored OCD treatments.

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