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Functional neural mechanisms of sensory phenomena in obsessive-compulsive disorder

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Abstract

Sensory phenomena (SP) are aversive or uncomfortable sensations that accompany and/or drive repetitive behaviors in obsessive-compulsive disorder (OCD). Although SP are associated with significant distress and may respond less well to standard treatments than harm-related obsessions, little is known about their underlying neurobiology. The present study used functional magnetic resonance imaging (fMRI) to measure brain functioning related to severity of SP during a "body-focused" videos task designed to elicit activation in sensorimotor brain regions. Regression analysis examined the relationship between severity of SP and activation during task using permutation analysis with threshold-free cluster enhancement, corrected for multiple comparisons (family-wise error rate $p<0.05$). The distribution of SP severity was not significantly different from normal, with both high- and low-severity scores represented in the OCD sample. Severity of SP was not correlated with other clinical symptoms in OCD including general anxiety, depression, or harm avoidance. When viewing body-focused videos, patients with greater severity of SP showed increased activity in the mid-posterior insula, a relationship that remained significant when controlling for other clinical symptoms, medication status, and comorbidities. At uncorrected thresholds, SP severity was also positively related to somatosensory, mid orbitofrontal, and lateral prefrontal cortical activity. These data suggest that SP in OCD are dissociable from other symptoms in the disorder and related to hyperactivation of the insula. Future work examining neural mechanisms of SP across different disorders (tics, trichotillomania) as well as with other

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imaging modalities will be needed to further understand the neurobiology of these impairing symptoms.

Keywords

neuroimaging; somatosensory; insula; sensorimotor; urges; not-just-right experiences

Introduction

Obsessive-compulsive disorder (OCD) is characterized by the presence of obsessions, defined as thoughts, impulses, or images that cause anxiety and are experienced as intrusive and inappropriate, and/or compulsions, which are repetitive behaviors typically performed to relieve anxiety caused by obsessions. Despite this rather straightforward definition, OCD is a highly heterogeneous disorder, with clusters of symptoms likely derived from differing neural etiologies. Although the classic example is of a fearful and harm-avoidant patient who performs compulsions to prevent a dreaded event (i.e., a patient who checks the stove to prevent the house from catching fire), a significant portion of patients experiences “sensory phenomena” (SP) consisting of aversive or uncomfortable sensations or perceptions that drive repetitive behaviors in addition to, or instead of, fear of harm. Approximately 60–70% of OCD patients have some form of sensory symptom not associated with a specific feared consequence (Ferrao et al., 2012; Lee et al., 2009; Rosario et al., 2009; Shavitt et al., 2014). OCD patients with touching, counting, and repeating compulsions report sensory-based urges preceding their repetitive behaviors, including approximately 30% of patients who report physical sensations in their muscles/joints or extremities (Lee et al., 2009; Shavitt et al., 2014). SP are also prominent in patients with symmetry/ordering and checking compulsions, which are frequently performed until the patient achieves the sensation or perception that things are “just right” or “complete” (Coles et al., 2003; Ferrao et al., 2012; Pietrefesa and Coles, 2009; Rosario et al., 2009; Summerfeldt, 2004). SP can additionally manifest as tactile or visceral sensations of contamination associated with feelings of disgust (rather than fear of illness or disease) that drive washing and cleaning compulsions (Ferrao et al., 2012; Rosario et al., 2009). Although SP have been associated with some OCD dimensions (i.e. symmetry/ordering) more than others (Coles et al., 2003; Ferrao et al., 2012; Rosario et al., 2009), they cut across traditional subtype boundaries (Ecker and Gonner, 2008; Ferrao et al., 2012; Rachman, 1994; Tallis, 1996) and can be distinguished from harm avoidance as the motivation for repetitive behaviors (Ecker and Gonner, 2008; Pietrefesa and Coles, 2008, 2009; Summerfeldt, 2004; Summerfeldt et al., 2014). Interestingly, SP are transdiagnostic and also prominent in tic disorders, skin picking, and trichotillomania (Ferrao et al., 2009; Flessner and Woods, 2006; Miguel et al., 2000; Miguel et al., 2005; Neziroglu et al., 2008; Prado et al., 2008). Not surprisingly, the prevalence of SP is quite high (>80%) among OCD patients with comorbid tics (Miguel et al., 2000; Shavitt et al., 2014). SP are clinically assessed using the Sensory Phenomena Scale (SPS (Rosario et al., 2009)), which is a semi-structured interview containing a checklist composed of examples of different types of SP preceding or occurring at the same time as repetitive behaviors. The SPS checklist includes items encompassing all previous descriptions in the literature, including physical sensations, “not just right” sensations, incompleteness, general energy or inner tension buildup, and urges. Following the checklist, severity of SP is measured through ratings of frequency, distress, and interference.

Patients with SP report that they are highly distressing (Cohen and Leckman, 1992; Leckman et al., 1993; Prado et al., 2008), and there is some evidence that they are not well addressed by standard treatments in OCD (Abramowitz et al., 2003; Foa et al., 1999; Smits et al., 2002; Stein et al., 2007; Summerfeldt, 2004). Over the past few decades, much important work has identified several clinical and demographic factors associated with SP (Coles et al., 2003; Ferrao et al., 2012; Leckman et al., 1994; Miguel et al., 2000; Prado et al., 2008; Rosario et al., 2009; Rosario-Campos et al., 2001; Shavitt et al., 2014), yet very little is known about their underlying neurobiology. One recent study found increased gray matter volume in sensorimotor cortex in a group of OCD patients with SP compared to OCD patients without SP (Subira et al., 2015). This finding is interesting in light of neuroimaging studies investigating "urges-for-action", which are sensations that drive an individual to perform a behavior, such as the urge to blink, swallow, or scratch. These commonplace urges-for-action may be phenomenologically similar to sensory-related urges in psychiatric disorders (Berman et al., 2012; Jackson et al., 2011) and are associated with activation in somatosensory cortex as well as the insula (Berman et al., 2012; Holle et al., 2012; Jackson et al., 2011; Lerner et al., 2009; Mazzone et al., 2011). Motor and premotor regions are also frequently associated with the buildup of sensory urges (Berman et al., 2012; Holle et al., 2012; Lerner et al., 2009; Mazzone et al., 2011) – even in the absence of overt movement – illustrating the critical link between sensation and action that is highlighted by a disorder such as OCD.

The present investigation explored the relationship between SP and activation of the insula and sensorimotor cortical regions in a sample of OCD patients exhibiting varying severity of SP. Patients performed a functional magnetic resonance imaging (fMRI) task that has been shown to elicit activity in these circuits (Schaefer et al., 2012; Stern et al., 2018). This work represents a first step toward identifying the functional neural mechanisms of SP, with the long-term goal of identifying brain circuitry that could be targeted by future treatments for these impairing symptoms.

Materials and Methods

Subjects and Procedure

Twenty-seven patients with OCD were recruited into the study and signed consent forms approved by the Icahn School of Medicine at Mount Sinai Institutional Review Board. Eight patients were subsequently excluded (3 due to subclinical OCD, 1 due to severe alcohol use disorder, 3 patients changed their mind about participating after the screening visit, and 1 patient's head could not fit comfortably under the head coil). Final data were analyzed from 19 patients. All patients met DSM-5 criteria for OCD and were excluded for lifetime presence of bipolar disorder, schizophrenia spectrum disorder, or autism spectrum disorder. Fourteen patients had at least one comorbid Axis I disorder (with 8 patients exhibiting multiple comorbidities) including generalized anxiety disorder (GAD, n=7), attention deficit hyperactivity disorder (ADHD, n=5), excoriation/skin picking disorder (n=3), panic disorder (n=2), agoraphobia (n=2), and one each of major depressive disorder, trichotillomania, body dysmorphic disorder, post-traumatic stress disorder, social anxiety disorder, and hoarding disorder. Ten out of the 19 patients were taking psychotropic medications including serotonin reuptake inhibitors (SRIs, n=10), risperidone (n=1), trazodone (n=1), and benzodiazepines as needed (n=2, which both patients refrained from taking on the day of study visits). Diagnoses were made by a trained rater using the Mini International Neuropsychiatric Interview (M.I.N.I., Sheehan et al., 1998). Sensory phenomena were assessed using the Sensory Phenomena Scale (SPS, Rosario et al., 2009). After individuals endorse specific checklist items, total SP frequency, distress, and interference are rated on 6-point scales (0–5). Possible total scores range from 0 (no SP) to 15 (severe SP). The SPS shows excellent convergent validity with an open clinical interview (the gold standard), very good discriminative validity, and high inter-rater reliability (Rosario et al., 2009), and has been used to measure severity of SP in several OCD patient samples (Ferrao et al., 2012; Lee et al., 2009; Miguel et al., 2000; Prado et al., 2008; Rosario et al., 2009; Rosario-Campos et al., 2001; Shavitt et al., 2006; Subira et al., 2015).

Overall severity of obsessive-compulsive symptoms was measured using the total score from the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS (Goodman et al., 1989). The Y-BOCS consists of a checklist of different obsessive-compulsive symptoms followed by severity ratings (time occupied, distress, interference, resistance, and control) for all symptoms endorsed. In order to ensure we captured all the various manifestations of OCD symptoms reported in the literature (including thoughts, fears, images, impulses, sensory phenomena, and any associated compulsions), we combined checklist items from the Y-BOCS with those from the Dimensional Y-BOCS (DY-BOCS, (Rosario-Campos et al., 2006), which has a large and comprehensive list of OCD-related symptoms. Following the layout of the DY-BOCS, our checklist used a self-report format with multiple examples per item that was reviewed in detail between the patient and a trained rater prior to assessing severity of endorsed symptoms using the rating scales from the Y-BOCS.

In order to determine the specificity of any identified associations between brain activity and SP, we quantified general anxiety and depressive symptoms using the Beck Anxiety Inventory (Beck et al., 1988) and the Quick Inventory of Depression Severity (Rush et al., 2003), respectively. We measured trait harm avoidance using the Obsessive-Compulsive Trait Core Dimensions Questionnaire (OCTCDQ-HA, Summerfeldt et al., 2014). We also assessed severity of OCD symptoms based on subtype or dimension using the Dimensional Obsessive-Compulsive Scale (Abramowitz et al., 2010). The DOCS is a self-report scale where patients rate time occupied, avoidance, distress, interference, and difficulty disregarding/resisting symptoms separately for four categories of OCD symptoms: concerns about germs and contamination; concerns about responsibility for harm, injury, or bad luck; unacceptable thoughts; and concerns about symmetry, completeness, and the need for things to be "just right".

Body-Focused Videos (BFV) Task

Patients performed an fMRI task that elicits activation in brain regions involved in interoception and sensorimotor processing (Stern et al., 2018). In the task, subjects view videos depicting body movements/sensation ("body-focused videos") or control videos in

15s blocks. Previous work has shown that observing body touch and sensation (i.e., by viewing a video showing a brush stroking a hand as was done in (Schaefer et al., 2012; Stern et al., 2018)) elicits activation in insula, somatosensory, and premotor regions similar to actually experiencing sensation, effects that have been attributed to a sensory “mirror neuron” system (MNS) (Keysers and Gazzola, 2009; Schaefer et al., 2012). In contrast to tasks that engage interoceptive and sensorimotor regions by asking subjects to attend to their internal body sensations, this approach is less challenging for the subject and does not depend as heavily on compliance. Three different body-focused videos depicted different scenarios: a brush stroking the underside of a hand (Figure 1), a close-up of a throat while swallowing, and a medical illustration of a heart beating. The event depicted in each scenario repeated several times, with the number of repetitions varying between presentations (e.g., separate videos depict a brush stroking a hand 3, 4, or 5 times). Each body-focused video had an associated control video showing repeating non-body-related events: the tip of a brush moving across a table (Figure 1), a ball sliding through a tube, and a colored rectangle increasing and decreasing in height. After watching each video, subjects reported the number of repetitions using a 5-point scale (3.5s) in order to ensure that attention was focused on the videos throughout the task. A jittered inter-trial interval (ITI) consisting of a fixation cross was then displayed for 2–6s, after which a new video began. In total, each of the 6 videos (3 body-focused and 3 control) were presented 9 times (for each video there were 3 different numbers of repetitions, with each repetition presented 3 times each) for a total of 54 blocks comprised of 27 body-focused and 27 control videos. The reader is referred to Stern et al. (Stern et al., 2018) for data showing greater engagement of interoceptive and sensorimotor regions during body-focused compared to control videos using the same task in a group of healthy controls.

Neuroimaging data acquisition and preprocessing

MRI scanning occurred on a Siemens 3T Skyra scanner. Functional BOLD data were acquired using a 32-channel head coil with a high-resolution multiband-accelerated echo-planar sequence for full brain coverage (TR=1000ms, TE=35ms, flip angle=60°, FOV=228mm, 70 slices, 2.1-mm thickness, acceleration factor=7). A high-resolution T1-MPRAGE structural image was acquired for co-registration (TR=2400ms; TE=2.06ms; flip angle=8°; FOV=256mm, 0.8-mm thickness). Preprocessing was performed using Statistical Parametric Mapping (SPM) v.12 and scripts taken from the Human Connectome Project (HCP) preprocessing pipeline (Glasser et al., 2013) and included gradient non-linearity distortion correction, realignment of functional images, normalization of functional images to an MNI template, and spatial smoothing with a 6-mm kernel.

Data Analysis

A general linear model (SPM v.12) was used to specify regressors for all body-focused and control videos separately with duration set to block length (15s). A regressor for the rating period was included to capture variance, with duration set equal to response time. Six realignment parameters were included to further reduce error variance associated with residual movement after realignment. Additional motion and artifact correction was conducted through spike-regression (Ciric et al., 2017). We first identified volumes showing framewise displacement over 2 mm (translation) or 1 degree (rotation), or global signal over

9 standard deviations from the mean, using ART (www.nitrc.org/projects/artifact_detect) and then regressed these volumes out of the data by specifying them as covariates of no interest the subject-level models. Two primary contrasts focused on the comparisons of body-focused videos with implicit baseline (consisting of ITI time points) and control videos with implicit baseline. Due to our *a priori* interest in insula and sensorimotor cortex, data were examined within a large region-of-interest (ROI) mask consisting of bilateral insula, somatosensory cortical regions (postcentral gyri, paracentral lobule), and premotor/motor cortical regions (precentral gyri, supplementary motor area), created with Wake Forest University's pickatlas tool (Maldjian et al., 2003) by specifying the above-listed automated anatomical labels (AAL) and including Brodmann's areas 1, 2, 3, 4, 5, 6, 13, and 43. Group-level regression analyses examined the relationship between brain activity during contrasts of interest and SPS total score. Stringent correction for false positives using permutation testing was implemented with palm software (Winkler et al., 2014) to identify clusters with a corrected family-wise error rate less than 5% (i.e. $p<0.05$) within the ROI using a voxelwise threshold of $p<0.001$, as suggested by Eklund et al. (2016). Due to the preliminary nature of the investigation, we also explore whole-brain activations obtained through permutation testing using an uncorrected voxelwise threshold of $p<0.001$, cluster extent $(k)>10$.

Results

Relationships between clinical measures

The mean total score on the SPS was 7.45 (SD: 3.16) and the range was between 2 and 14, importantly indicating that both high and low SP severity patients were represented in the sample (Figure 2A). The distribution of SPS scores was not significantly different from normal (Shapiro-Wilk test statistic=0.96, p=0.50). SPS score was positively correlated with the total Y-BOCS score (r=0.67, p=0.002), indicating that greater overall obsessive-compulsive symptom severity was associated with increased severity of sensory phenomena, which would be expected given that several types of SP ('not just right' experiences, symmetry and ordering compulsions, sensitivity to physical sensations) are also assessed in the checklist that we used for the Y-BOCS rating scales, which included items from both the Y-BOCS and DY-BOCS checklists and intended to encompass all possible OCD-related symptoms including thoughts, fears, images, impulses, sensory phenomena, and their associated compulsions. Interestingly, SPS score was not correlated with general symptoms of anxiety (r=0.16, p=0.52), depression (r=−0.28, p=0.26), harm avoidance (r=−0.09, p=0.71), DOCS severity of concerns about germs and contamination (r=−0.06, p=0.80), DOCS severity of responsibility for harm (r=−0.07, p=0.77), or DOCS severity of unacceptable thoughts (r=−0.37, p=0.12), indicating that SP are dissociable from these other symptoms and clinical characteristics. Not surprisingly, SPS scores were significantly correlated with DOCS severity of symmetry, completeness, and "just right" symptoms (r=0.73, p<0.001).

ROI analysis

For body-focused videos, there was a significant positive relationship between severity of SP in the OCD sample and activity in left mid-posterior insula (x=−38, y=−2, z=−4, k=65, family-wise error-corrected p-value=0.04, k=65) (Figure 2B). For control videos, there were no relationships with SP severity that achieved statistical significance when correcting for multiple comparisons.

Exploratory whole-brain analysis

For body-focused videos, in addition to the left mid-posterior insula activation reported in the ROI analysis, there were also positive correlations between SP severity and activity in right mid-anterior insula, bilateral postcentral gyri, bilateral middle OFC, left lateral PFC, and left posterior middle/superior temporal gyri at an uncorrected threshold of $p<0.001$ ($k>10$) (Table 1, Figure 2C). For control videos, a region of left mid-posterior insula was positively correlated with SP severity (x=−36, y=−2, z=2, k=10, uncorrected p-value [uncorrp]=0.0004), as well as an area of left fusiform gyrus in the temporal lobe (x=−38, y=−40, z=−22, k=38, uncorrp=0.0001) and middle occipital cortex (x=−46, y=−68, z=−16, k=26, uncorrp=0.0001).

Specificity to SP

We sought to determine whether the relationships with brain function were unique to SP by performing partial correlation analyses between SP and activation in the reported clusters, controlling for the other clinical measures. The left mid-posterior insula cluster remained highly significant when controlling for Y-BOCS score (partial $r=0.71$, $p=0.001$). The other regions reported in Table 1 also remained significantly associated with SPS score when controlling for Y-BOCS score ($0.55<\text{partial } r<0.73$, $0.02<p<0.001$). Similarly, activity in all regions remained significantly related to SP when controlling for anxiety, depression, or harm avoidance ($0.53<\text{partial } r<0.78$, $0.03<p<0.001$), as well as for the three DOCS dimensions not correlated with SPS scores (concerns about germs and contamination; concerns about responsibility for harm; unacceptable thoughts) ($0.56<\text{partial } r<0.81$, $0.02<p<0.001$). These data suggest that the reported relationships are unique to SP and do not merely reflect general severity of the disorder (as measured by the Y-BOCS or DOCS scores) or other disorder-relevant clinical characteristics (general anxiety, depression, harm avoidance).

In order to further explore the contribution of overall symptom severity as assessed by the Y-BOCS to the relationship between SPS score and activation in the insula, we ran a series of regression analyses predicting insula activity in the most significant cluster (x=−38, y=−2, z=−4, k=65) from SPS score alone, Y-BOCS score alone, and when both SPS and Y-BOCS scores were predictors in the model. A model with the SPS score as the only predictor revealed that it significantly predicted insula activation ($t=4.91$, $p<0.001$), explaining 58.6% of the variance. A model where the Y-BOCS score is the only predictor shows that it is marginally significant ($t=1.97$, $p=0.065$) and accounts for 18.6% of the variance. Consistent with the small amount of variance explained by the Y-BOCS, the model with both the SPS and Y-BOCS scores as predictors revealed a significant effect of the SPS predictor ($t=4.06$, $p=0.001$) but not the Y-BOCS predictor ($t=-0.70$, $p=0.49$), with 59.9% of the variance in insula activation explained by the full model.

Controlling for medication and comorbidities

There was no significant difference in SP severity between medicated and unmedicated patients (t_{17}=1.1, p=0.29) or between patients with and without the two most frequent comorbidities in our sample (OCD patients with and without GAD and OCD patients with and without ADHD, t_{17}=0.80, p=0.44 and t_{17}=0.95, p=0.36, respectively). Furthermore, the relationship between SP severity and activation in the clusters from Table 1 remained significant when conducting partial correlations controlling for medication status, GAD, or ADHD as categorical (yes/no) variables (0.51<partial r<0.76, 0.03< p< .001). This indicates that the relationships between brain activity and SP severity were not due to differences between low and high SP patients in medication status or the presence of comorbidities.

Discussion

In this investigation of sensory phenomena in OCD, we found that severity of SP was not significantly related to measures of general anxiety, depression, or harm avoidance, consistent with prior research showing a distinction between incompleteness (a type of SP) and harm avoidance (Ecker and Gonner, 2008; Pietrefesa and Coles, 2008, 2009; Summerfeldt et al., 2014). Neurally, SP severity was positively related to activation in left mid-posterior insula as well as right mid-anterior insula, bilateral somatosensory cortex (postcentral gyri), left posterior temporal cortex, bilateral middle OFC, and left dorsal prefrontal regions. These relationships remained significant when controlling for other symptoms, comorbidities, and medication, suggesting that SP in OCD are behaviorally and neurally dissociable from other clinical characteristics.

Prior work indicates that everyday “urges-for-action”, such as the urge to blink, swallow, or scratch, may be phenomenologically similar to SP (Berman et al., 2012; Jackson et al., 2011) and are associated with activation of insula, somatosensory, and premotor regions (Berman et al., 2012; Holle et al., 2012; Jackson et al., 2011; Lerner et al., 2009; Mazzone et al., 2011). The one prior study investigating the neurobiology of SP found increased volume of somatosensory and premotor cortical areas in OCD patients with SP compared to patients without SP (Subira et al., 2015). Our results showing an association between somatosensory activation and SP severity are consistent with these findings, which together suggest that somatosensory areas are both functionally and structurally related to SP in OCD.

Among those regions that have been linked to sensory-based urges, the insula has been shown to be involved in the detection and integration of signals from within the body, a process known as interoception (Caseras et al., 2013; Critchley et al., 2004; Farb et al., 2013; Khalsa et al., 2018; Simmons et al., 2013; Stern et al., 2017; Wiebking et al., 2014; Zaki et al., 2012) (see Schulz, 2016, for meta-analysis). The insula is a heterogeneous cortical structure extending 50–60 mm horizontally (from approximately y=+30 to y=−30) at the intersection of the frontal, temporal, and parietal lobes, with an antero-posterior segregation of function (Cauda et al., 2012; Kurth et al., 2010; Wager and Barrett, 2004). While the posterior section of the insula is thought to hold the initial cortical representation of the physical state of the body (Craig, 2002; Singer et al., 2004), reciprocal intrainsular connections transfer information between posterior, mid, and anterior regions (Almashaikhi et al., 2013). Anterior insula has been proposed to integrate body state information (from posterior and mid insula areas) with emotional signals from limbic/paralimbic regions (such as the amygdala) and cognitive/motor plans processed in dorsal frontal cortex (Chang et al., 2013; Kurth et al., 2010; Wager and Barrett, 2004). The correlations with SP that were identified in this study were located in both mid-posterior insula (in the left hemisphere with peak activation at y=−2) as well as a more ventral mid-anterior region (in the right hemisphere with peak activation at y=+8), suggesting that SP may involve hyper-responsivity in an intermediate insular zone that bridges the gap between purely sensory processing (at the posterior end) and emotion/cognition integration (at the anterior end). Previous case-control studies in OCD have also implicated the mid-posterior insula in the disorder (Becker et al., 2014; Jung et al., 2011; Kwon et al., 2003; Nakao et al., 2009; Roth et al., 2007; Schienle et al., 2005; Stein et al., 2006); the present study extends these prior findings by specifically linking activation of this region to the severity of sensory phenomena in the disorder.

The strongest relationship was between mid-posterior insula and SP during the body-focused videos condition, yet a weaker (uncorrected) relationship was found in the same area during the control videos as well. It is possible that the insula of high-SP patients is more generally reactive than low-SP patients, which becomes particularly apparent during conditions when the insula is engaged (i.e., body-focused videos) but is also present during conditions that are not specifically designed to elicit interoceptive/sensorimotor processing (i.e., control videos). Taking this a step further, it is possible that insula hyperreactivity to control videos in high-SP patients reflects a misperception or interpretation of non-interoceptive/non-sensory stimuli as sensory in nature. Although the reason for the correlation between SP severity and insula activation during control videos remains unclear, this finding highlights the importance of this region for SP and suggests that active engagement of the interoceptive/sensorimotor circuit (as in the body focused videos condition) may not be required in order to observe this relationship.

We also found a relationship between SP severity and activation of bilateral middle regions of orbitofrontal cortex (BA 11), which is consistent with prior work finding hyperactivation of this area in meta-analyses in OCD (Menzies et al., 2008; Rotge et al., 2008) as well as hyperconnectivity in resting-state functional connectivity studies (Abe et al., 2015; Beucke et al., 2013). OFC has also been associated with interoception (Craig, 2002; Critchley et al., 2004), perhaps due to connections with posterior sensory systems involved in somatosensation, taste, olfaction, and vision (Kringelbach, 2005; Ongur and Price, 2000; Price, 2007; Rolls, 2000), an observation that has led several authors to propose that OFC is a multimodal integration area processing the motivational significance of incoming sensory information (Critchley and Harrison, 2013; Kringelbach, 2005; Ongur and Price, 2000; Price, 2007; Rolls, 2000). One possible explanation for the OFC finding is that patients with higher SP may find the body-focused videos to be more motivationally salient than patients with lower SP; while we believe this is a reasonable suggestion given the task that was used and the purported functions of OFC, it is speculation that requires further testing to confirm.

Given that we have linked SP severity to activity in regions involved in interoception and sensorimotor processing (i.e. insula, somatosensory cortex, OFC), it is tempting to theorize that patients with high SP have an abnormality of interoception (see Stern, 2014). However, the current study focused only on identifying neurocircuitry and did not probe for behavioral measures of interoception; as such, these results cannot speak directly to this question and caution must be taken not to infer psychological processes from brain activations (a fallacy known as reverse inference). Indeed, very few studies have directly examined interoception in OCD. One recent study found that patients with OCD more accurately monitored their own heartbeat than individuals without OCD, while showing no difference when monitoring an external sound (Yoris et al., 2017). This is in contrast to findings from Lazarov and colleagues showing that OCD patients (Lazarov et al., 2014) and undergraduates with high "OC tendencies" (Lazarov et al., 2012, as measured from the obsessive-compulsive inventory [Foa et al., 2002]) were less accurate and requested external feedback more often than those without OCD (or individuals with low OC tendencies) when generating different levels of muscle tension, which was interpreted as reflecting reduced access to internal states and increased reliance on external information ("proxies") to guide behavior. Although it is difficult to interpret these seemingly conflicting findings from the literature, it is possible that the discrepancy is partly related to the fact that symptom variability, and in particular, sensory phenomena variability, in the OCD cohorts were not investigated in relation to interoception measures. As we have shown (Figure 2), even among diagnosed OCD patients there is considerably variability in sensory phenomena severity, and it is conceivable that the distribution of sensory symptoms could vary between studies and unduly influence group differences even if the OCD samples appear to be diagnostically similar. Highlighting the importance of considering SP variability when studying interoception, Ganos et al. (2015) found that greater frequency of premonitory urges (a type of SP) in Tourette's disorder patients was associated with increased accuracy when counting heartbeats despite the fact that, as a group, patients were actually less accurate than control subjects. Given the limited amount of available data, it is too early to make conclusions about whether SP and SP-related brain activations are related to the ability to consciously detect or access internal body states. To answer this question, future work will need to measure interoception directly and in relation to SP severity and neural circuitry.

This study raises additional questions for future work. It is a limitation that we did not obtain a healthy control sample to compare to the OCD group. Although we would predict that patients with high severity of SP would show greater activity in the insula (and other regions identified in this study, i.e., somatosensory cortex, OFC) when compared to controls, at present this remains speculative and future work should seek to compare high and low SP patients to control subjects. Furthermore, the sensory phenomena scale covers several types of sensory-related symptoms ranging from those that are mostly physical in nature (i.e., sensations of dirtiness, the need to tense muscles or touch items to achieve a specific sensation) to mostly mental (i.e., the need to engage in repeititive behaviors to achieve an inner sense of completeness). 'Not just right' experiences encompass multiple sensory domains including not only somatosensatory and interoceptive but also auditory and visual (Rosario et al., 2009). Although these different types of SP all share the characteristic that they drive repetitive behaviors (rather than fear), it is possible that different manifestations of SP could be associated with dissociable mechanisms. The present work represents a first step in identifying functional neurocircuitry that may cut across different types of SP, but future work may wish to further segregate these symptoms in order to better understand their underlying mechanisms. Furthermore, although our mid-posterior insula finding was significant when statistically corrected for multiple comparisons within our region of interest, the other reported clusters were not and should be interpreted with caution, pending replication in a larger sample. Finally, it will be important to study SP in other disorders characterized by sensory urges, including Tourette's/tic disorders, trichotillomania, and skin picking (Ferrao et al., 2009; Flessner and Woods, 2006; Miguel et al., 2000; Miguel et al., 2005; Neziroglu et al., 2008; Prado et al., 2008), in order to determine whether the mechanisms underlying SP are similar across diagnostic categories. Prior work has found mid insula and sensorimotor activation during the few seconds prior to the onset of a tic, a time period typically associated with the build-up of a premonitory sensory urge (Bohlhalter et al., 2006). This data suggests that the neural circuitry of SP may be similar across diagnoses, although future work using the same measures and tasks across different disorders will be needed.

Despite these limitations, this investigation probed the functional neural correlates of sensory phenomena in a sample of OCD patients showing symptom variability, revealing that SP are dissociable both behaviorally and neurally from other clinical symptoms. The identification of a significant relationship between mid-posterior insula and SP severity suggests that future treatments for SP may wish to specifically target the functioning of this brain area.

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References

Abe Y, Sakai Y, Nishida S, Nakamae T, Yamada K, Fukui K, Narumoto J, 2015 Hyper-influence of the orbitofrontal cortex over the ventral striatum in obsessive-compulsive disorder. Eur Neuropsychopharmacol 25(11), 1898–1905. [PubMed: 26395293]

Abramowitz JS, Deacon BJ, Olatunji BO, Wheaton MG, Berman NC, Losardo D, Timpano KR, McGrath PB, Riemann BC, Adams T, Bjorgvinsson T, Storch EA, Hale LR, 2010 Assessment of obsessive-compulsive symptom dimensions: development and evaluation of the Dimensional Obsessive-Compulsive Scale. Psychol Assess 22(1), 180–198. [PubMed: 20230164]

Abramowitz JS, Franklin ME, Schwartz SA, Furr JM, 2003 Symptom presentation and outcome of cognitive-behavioral therapy for obsessive-compulsive disorder. J Consult Clin Psychol 71(6), 1049–1057. [PubMed: 14622080]

Almashaikhi T, Rheims S, Ostrowsky-Coste K, Montavont A, Jung J, De Bellescize J, Arzimanoglou A, Kosal PK, Guenot M, Bertrand O, Ryvlin P, 2013 Intrainsular Functional Connectivity in Human. Human Brain Mapping epub ahead of print

Beck AT, Epstein N, Brown G, Steer RA, 1988 An inventory for measuring clinical anxiety: psychometric properties. J Consult Clin Psychol 56(6), 893–897. [PubMed: 3204199]

Becker MP, Nitsch AM, Schlosser R, Koch K, Schachtzabel C, Wagner G, Miltner WH, Straube T, 2014 Altered emotional and BOLD responses to negative, positive and ambiguous performance feedback in OCD. Soc Cogn Affect Neurosci 9(8), 1127–1133. [PubMed: 23893850]

Berman BD, Horovitz SG, Morel B, Hallett M, 2012 Neural correlates of blink suppression and the buildup of a natural bodily urge. Neuroimage 59(2), 1441–1450. [PubMed: 21906689]

Beucke JC, Sepulcre J, Talukdar T, Linnman C, Zschenderlein K, Endrass T, Kaufmann C, Kathmann N, 2013 Abnormally high degree connectivity of the orbitofrontal cortex in obsessive-compulsive disorder. JAMA Psychiatry 70(6), 619–629. [PubMed: 23740050]

Bohlhalter S, Goldfine A, Matteson S, Garraux G, Hanakawa T, Kansaku K, Wurzman R, Hallett M, 2006 Neural correlates of tic generation in Tourette syndrome: an event-related functional MRI study. Brain 129(Pt 8), 2029–2037. [PubMed: 16520330]

Caseras X, Murphy K, Mataix-Cols D, Lopez-Sola M, Soriano-Mas C, Ortriz H, Pujol J, Torrubia R, 2013 Anatomical and functional overlap within the insula and anterior cingulate cortex during interoception and phobic symptom provocation. Hum Brain Mapp 34(5), 1220–1229. [PubMed: 22162203]

Cauda F, Costa T, Torta DME, Sacco K, D'Agata F, Duca S, Geminiani G, Fox PT, Vercelli A, 2012 Meta-analytic clustering of the insular cortex Characterizing the meta-analytic connectivity of the insula when involved in active tasks. NeuroImage 62(1), 343–355. [PubMed: 22521480]

Chang LJ, Yarkoni T, Khaw MW, Sanfey AG, 2013 Decoding the Role of the Insula in Human Cognition: Functional Parcellation and Large-Scale Reverse Inference. Cereb Cortex 23(3), 739–749. [PubMed: 22437053]

Ciric R, Wolf DH, Power JD, Roalf DR, Baum GL, Ruparel K, Shinohara RT, Elliott MA, Eickhoff SB, Davatzikos C, Gur RC, Gur RE, Bassett DS, Satterthwaite TD, 2017 Benchmarking of participant-level confound regression strategies for the control of motion artifact in studies of functional connectivity. Neuroimage 154, 174–187. [PubMed: 28302591]

Cohen AJ, Leckman JF, 1992 Sensory Phenomena Associated with Gilles-De-La-Tourettes Syndrome. J Clin Psychiat 53(9), 319–323.

Coles ME, Frost RO, Heimberg RG, Rheaume J, 2003 "Not just right experiences": perfectionism, obsessive-compulsive features and general psychopathology. Behaviour research and therapy 41(6), 681–700. [PubMed: 12732376]

Craig AD, 2002 How do you feel? Interoception: the sense of the physiological condition of the body. Nat Rev Neurosci 3(8), 655–666. [PubMed: 12154366]

Critchley HD, Harrison NA, 2013 Visceral Influences on Brain and Behavior. Neuron 77(4), 624–638. [PubMed: 23439117]

Critchley HD, Wiens S, Rotshtein P, Ohman A, Dolan RJ, 2004 Neural systems supporting interoceptive awareness. Nature neuroscience 7(2), 189–195. [PubMed: 14730305]

Ecker W, Gonner S, 2008 Incompleteness and harm avoidance in OCD symptom dimensions. Behav Res Ther 46(8), 895–904. [PubMed: 18514616]

Eklund A, Nichols TE, Knutsson H, 2016 Cluster failure: Why fMRI inferences for spatial extent have inflated false-positive rates. Proc Natl Acad Sci U S A 113(28), 7900–7905. [PubMed: 27357684]

Farb NAS, Segal ZV, Anderson AK, 2013 Attentional Modulation of Primary Interoceptive and Exteroceptive Cortices. Cereb Cortex 23(1), 114–126. [PubMed: 22267308]

Ferrao YA, Miguel E, Stein DJ, 2009 Tourette's syndrome, trichotillomania, and obsessive-compulsive disorder: how closely are they related? Psychiatry Res 170(1), 32–42. [PubMed: 19801170]

Ferrao YA, Shavitt RG, Prado H, Fontenelle LF, Malavazzi DM, de Mathis MA, Hounie AG, Miguel EC, do Rosario MC, 2012 Sensory phenomena associated with repetitive behaviors in obsessive-compulsive disorder: an exploratory study of 1001 patients. Psychiatry research 197(3), 253–258. [PubMed: 22361443]

Flessner CA, Woods DW, 2006 Phenomenological characteristics, social problems, and the economic impact associated with chronic skin picking. Behav Modif 30(6), 944–963. [PubMed: 17050772]

Foa EB, Abramowitz JS, Franklin ME, Kozak MJ, 1999 Feared Consequences, Fixity of Belief, and Treatment Outcome in Patients with Obsessive-Compulsive Disorder. Behavior therapy 30, 717–724.

Foa EB, Huppert JD, Leiberg S, Langner R, Kichic R, Hajcak G, Salkovskis PM, 2002 The Obsessive-Compulsive Inventory: development and validation of a short version. Psychol Assess 14(4), 485–496. [PubMed: 12501574]

Ganos C, Garrido A, Navalpotro-Gomez I, Ricciardi L, Martino D, Edwards MJ, Tsakiris M, Haggard P, Bhatia KP, 2015 Premonitory urge to tic in Tourette's is associated with interoceptive awareness. Mov Disord 30(9), 1198–1202. [PubMed: 25879819]

Glasser MF, Sotiropoulos SN, Wilson JA, Coalson TS, Fischl B, Andersson JL, Xu J, Jbabdi S, Webster M, Polimeni JR, Van Essen DC, Jenkinson M, Consortium WU-MH, 2013 The minimal preprocessing pipelines for the Human Connectome Project. Neuroimage 80, 105–124. [PubMed: 23668970]

Goodman WK, Price LH, Rasmussen SA, Mazure C, Fleischmann RL, Hill CL, Heninger GR, Charney DS, 1989 The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. Archives of General Psychiatry 46(11), 1006–1011. [PubMed: 2684084]

Holle H, Warne K, Seth AK, Critchley HD, Ward J, 2012 Neural basis of contagious itch and why some people are more prone to it. P Natl Acad Sci USA 109(48), 19816–19821.

Jackson SR, Parkinson A, Kim SY, Schuermann M, Eickhoff SB, 2011 On the functional anatomy of the urge-for-action. Cogn Neurosci 2(3–4), 227–243. [PubMed: 22299020]

Jung WH, Kang DH, Han JY, Jang JH, Gu BM, Choi JS, Jung MH, Choi CH, Kwon JS, 2011 Aberrant ventral striatal responses during incentive processing in unmedicated patients with obsessive-compulsive disorder. Acta Psychiat Scand 123(5), 376–386. [PubMed: 21175552]

Keysers C, Gazzola V, 2009 Expanding the mirror: vicarious activity for actions, emotions, and sensations. Curr Opin Neurobiol 19(6), 666–671. [PubMed: 19880311]

Khalsa SS, Adolphs R, Cameron OG, Critchley HD, Davenport PW, Feinstein JS, Feusner JD, Garfinkel SN, Lane RD, Mehling WE, Meuret AE, Nemeroff CB, Oppenheimer S, Petzschner FH, Pollatos O, Rhudy JL, Schramm LP, Simmons WK, Stein MB, Stephan KE, Van den Bergh O, Van Diest I, von Leupoldt A, Paulus MP, Interoception Summit, p., 2018 Interoception and Mental Health: A Roadmap. Biol Psychiatry Cogn Neurosci Neuroimaging 3(6), 501–513. [PubMed: 29884281]

Kringelbach ML, 2005 The human orbitofrontal cortex: linking reward to hedonic experience. Nat Rev Neurosci 6(9), 691–702. [PubMed: 16136173]

Kurth F, Zilles K, Fox PT, Laird AR, Eickhoff SB, 2010 A link between the systems: functional differentiation and integration within the human insula revealed by meta-analysis. Brain Struct Funct 214(5–6), 519–534. [PubMed: 20512376]

Kwon JS, Kim JJ, Lee DW, Lee JS, Lee DS, Kim MS, Lyoo IK, Cho MJ, Lee MC, 2003 Neural correlates of clinical symptoms and cognitive dysfunctions in obsessive-compulsive disorder. Psychiatry Res 122(1), 37–47. [PubMed: 12589881]

Lazarov A, Dar R, Liberman N, Oded Y, 2012 Obsessive-compulsive tendencies may be associated with attenuated access to internal states: evidence from a biofeedback-aided muscle tensing task. Conscious Cogn 21(3), 1401–1409. [PubMed: 22841959]

Lazarov A, Liberman N, Hermesh H, Dar R, 2014 Seeking proxies for internal states in obsessive-compulsive disorder. J Abnorm Psychol 123(4), 695–704. [PubMed: 25133987]

Leckman JF, Grice DE, Barr LC, de Vries AL, Martin C, Cohen DJ, McDougle CJ, Goodman WK, Rasmussen SA, 1994 Tic-related vs. non-tic-related obsessive compulsive disorder. Anxiety 1(5), 208–215. [PubMed: 9160576]

Leckman JF, Walker DE, Cohen DJ, 1993 Premonitory Urges in Tourettes-Syndrome. Am J Psychiat 150(1), 98–102. [PubMed: 8417589]

Lee JC, Prado HS, Diniz JB, Borcato S, da Silva CB, Hounie AG, Miguel EC, Leckman JF, do Rosario MC, 2009 Perfectionism and sensory phenomena: phenotypic components of obsessive-compulsive disorder. Comprehensive psychiatry 50(5), 431–436. [PubMed: 19683613]

Lerner A, Bagic A, Hanakawa T, Boudreau EA, Pagan F, Mari Z, Bara-Jimenez W, Aksu M, Sato S, Murphy DL, Hallett M, 2009 Involvement of insula and cingulate cortices in control and suppression of natural urges. Cereb Cortex 19(1), 218–223. [PubMed: 18469316]

Maldjian JA, Laurienti PJ, Kraft RA, Burdette JH, 2003 An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. Neuroimage 19(3), 1233–1239. [PubMed: 12880848]

Mazzone SB, Cole LJ, Ando A, Egan GF, Farrell MJ, 2011 Investigation of the neural control of cough and cough suppression in humans using functional brain imaging. The Journal of neuroscience : the official journal of the Society for Neuroscience 31(8), 2948–2958. [PubMed: 21414916]

Menzies L, Chamberlain SR, Laird AR, Thelen SM, Sahakian BJ, Bullmore ET, 2008 Integrating evidence from neuroimaging and neuropsychological studies of obsessive-compulsive disorder: the orbitofronto-striatal model revisited. Neurosci Biobehav Rev 32(3), 525–549. [PubMed: 18061263]

Miguel EC, do Rosario-Campos MC, Prado HS, do Valle R, Rauch SL, Coffey BJ, Baer L, Savage CR, O'Sullivan RL, Jenike MA, Leckman JF, 2000 Sensory phenomena in obsessive-compulsive disorder and Tourette's disorder. The Journal of clinical psychiatry 61(2), 150–156; quiz 157. [PubMed: 10732667]

Miguel EC, Leckman JF, Rauch S, do Rosario-Campos MC, Hounie AG, Mercadante MT, Chacon P, Pauls DL, 2005 Obsessive-compulsive disorder phenotypes: implications for genetic studies. Molecular psychiatry 10(3), 258–275. [PubMed: 15611786]

Nakao T, Nakagawa A, Nakatani E, Nabeyama M, Sanematsu H, Yoshiura T, Togao O, Tomita M, Masuda Y, Yoshioka K, Kuroki T, Kanba S, 2009 Working memory dysfunction in obsessive-compulsive disorder: A neuropsychological and functional MRI study. J Psychiatr Res 43(8), 784–791. [PubMed: 19081580]

Neziroglu F, Rabinowitz D, Breytman A, Jacofsky M, 2008 Skin picking phenomenology and severity comparison. Prim Care Companion J Clin Psychiatry 10(4), 306–312. [PubMed: 18787665]

Ongur D, Price JL, 2000 The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. Cereb Cortex 10(3), 206–219. [PubMed: 10731217]

Pietrefesa AS, Coles ME, 2008 Moving beyond an exclusive focus on harm avoidance in obsessive compulsive disorder: considering the role of incompleteness. Behav Ther 39(3), 224–231. [PubMed: 18721636]

Pietrefesa AS, Coles ME, 2009 Moving beyond an exclusive focus on harm avoidance in obsessive-compulsive disorder: behavioral validation for the separability of harm avoidance and incompleteness. Behav Ther 40(3), 251–259. [PubMed: 19647526]

Prado HS, Rosario MC, Lee J, Hounie AG, Shavitt RG, Miguel EC, 2008 Sensory phenomena in obsessive-compulsive disorder and tic disorders: a review of the literature. Cns Spectrums 13(5), 425–432. [PubMed: 18496480]

Price JL, 2007 Definition of the orbital cortex in relation to specific connections with limbic and visceral structures and other cortical regions. Ann N Y Acad Sci 1121, 54–71. [PubMed: 17698999]

Rachman S, 1994 Pollution of the mind. Behav Res Ther 32(3), 311–314. [PubMed: 8192629]

Rolls ET, 2000 The orbitofrontal cortex and reward. Cereb Cortex 10(3), 284–294. [PubMed: 10731223]

Rosario MC, Prado HS, Borcato S, Diniz JB, Shavitt RG, Hounie AG, Mathis ME, Mastrorosa RS, Velloso P, Perin EA, Fossaluza V, Pereira CA, Geller D, Leckman J, Miguel E, 2009 Validation of the University of Sao Paulo Sensory Phenomena Scale: initial psychometric properties. Cns Spectrums 14(6), 315–323. [PubMed: 19668122]

Rosario-Campos MC, Leckman JF, Mercadante MT, Shavitt RG, Prado HS, Sada P, Zamignani D, Miguel EC, 2001 Adults with early-onset obsessive-compulsive disorder. Am J Psychiatry 158(11), 1899–1903. [PubMed: 11691698]

Rosario-Campos MC, Miguel EC, Quatrano S, Chacon P, Ferrao Y, Findley D, Katsovich L, Scahill L, King RA, Woody SR, Tolin D, Hollander E, Kano Y, Leckman JF, 2006 The Dimensional Yale-Brown Obsessive-Compulsive Scale (DY-BOCS): an instrument for assessing obsessive-compulsive symptom dimensions. Mol Psychiatry 11(5), 495–504. [PubMed: 16432526]

Rotge JY, Guehl D, Dilharreguy B, Cuny E, Tignol J, Bioulac B, Allard M, Burbaud P, Aouizerate B, 2008 Provocation of obsessive-compulsive symptoms: a quantitative voxel-based meta-analysis of functional neuroimaging studies. J Psychiatry Neurosci 33(5), 405–412. [PubMed: 18787662]

Roth RM, Saykin AJ, Flashman LA, Pixley HS, West JD, Mamourian AC, 2007 Event-related functional magnetic resonance imaging of response inhibition in obsessive-compulsive disorder. Biol Psychiat 62(8), 901–909. [PubMed: 17511967]

Rush AJ, Trivedi MH, Ibrahim HM, Carmody TJ, Arnow B, Klein DN, Markowitz JC, Ninan PT, Kornstein S, Manber R, Thase ME, Kocsis JH, Keller MB, 2003 The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. Biol Psychiatry 54(5), 573–583. [PubMed: 12946886]

Schaefer M, Heinze HJ, Rotte M, 2012 Embodied empathy for tactile events: Interindividual differences and vicarious somatosensory responses during touch observation. Neuroimage 60(2), 952–957. [PubMed: 22306799]

Schienle A, Schafer A, Stark R, Walter B, Vaitl D, 2005 Neural responses of OCD patients towards disorder-relevant, generally disgust-inducing and fear-inducing pictures. International journal of psychophysiology : official journal of the International Organization of Psychophysiology 57(1), 69–77. [PubMed: 15935263]

Schulz SM, 2016 Neural correlates of heart-focused interoception: a functional magnetic resonance imaging meta-analysis. Philos Trans R Soc Lond B Biol Sci 371(1708).

Shavitt RG, Belotto C, Curi M, Hounie AG, Rosario-Campos MC, Diniz JB, Ferrao YA, Pato MT, Miguel EC, 2006 Clinical features associated with treatment response in obsessive-compulsive disorder. Comprehensive psychiatry 47(4), 276–281. [PubMed: 16769302]

Shavitt RG, de Mathis MA, Oki F, Ferrao YA, Fontenelle LF, Torres AR, Diniz JB, Costa DL, do Rosario MC, Hoexter MQ, Miguel EC, Simpson HB, 2014 Phenomenology of OCD: lessons from a large multicenter study and implications for ICD-11. J Psychiatr Res 57, 141–148. [PubMed: 25012187]

Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC, 1998 The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. The Journal of clinical psychiatry 59 Suppl 20, 22–33;quiz 34–57.

Simmons WK, Avery JA, Barcalow JC, Bodurka J, Drevets WC, Bellgowan P, 2013 Keeping the body in mind: insula functional organization and functional connectivity integrate interoceptive, exteroceptive, and emotional awareness. Hum Brain Mapp 34(11), 2944–2958. [PubMed: 22696421]

Singer T, Seymour B, O'Doherty J, Kaube H, Dolan RJ, Frith CD, 2004 Empathy for pain involves the affective but not sensory components of pain. Science 303(5661), 1157–1162. [PubMed: 14976305]

Smits JA, Telch MJ, Randall PK, 2002 An examination of the decline in fear and disgust during exposure-based treatment. Behav Res Ther 40(11), 1243–1253. [PubMed: 12384321]

Stein DJ, Andersen EW, Overo KF, 2007 Response of symptom dimensions in obsessive-compulsive disorder to treatment with citalopram or placebo. Rev Bras Psiquiatr 29(4), 303–307. [PubMed: 18200396]

Stein DJ, Arya M, Pietrini P, Rapoport JL, Swedo SE, 2006 Neurocircuitry of disgust and anxiety in obsessive-compulsive disorder: a positron emission tomography study. Metab Brain Dis 21(2–3), 267–277. [PubMed: 16850255]

Stern ER, 2014 Neural circuitry of interoception: New insights into anxiety and obsessive-compulsive disorders. Current Treatment Options in Psychiatry 1, 235–247.

Stern ER, Grimaldi SJ, Muratore A, Murrough J, Leibu E, Fleysher L, Goodman WK, Burdick KE, 2017 Neural correlates of interoception: Effects of interoceptive focus and relationship to dimensional measures of body awareness. Hum Brain Mapp 38(12), 6068–6082. [PubMed: 28901713]

Stern ER, Shahab R, Grimaldi SJ, Leibu E, Murrough JW, Fleysher L, Parides MK, Coffey BJ, Burdick KE, Goodman WK, 2018 High dose ondansetron reduces activation of interoceptive and sensorimotor brain regions. Neuropsychopharmacology

Subira M, Sato JR, Alonso P, do Rosario MC, Segalas C, Batistuzzo MC, Real E, Lopes AC, Cerrillo E, Diniz JB, Pujol J, Assis RO, Menchon JM, Shavitt RG, Busatto GF, Cardoner N, Miguel EC, Hoexter MQ, Soriano-Mas C, 2015 Brain structural correlates of sensory phenomena in patients with obsessive-compulsive disorder. J Psychiatry Neurosci 40(4), 232–240. [PubMed: 25652753]

Summerfeldt LJ, 2004 Understanding and treating incompleteness in obsessive-compulsive disorder. J Clin Psychol 60(11), 1155–1168. [PubMed: 15389620]

Summerfeldt LJ, Kloosterman PH, Antony MM, Swinson RP, 2014 Examining an obsessive-compulsive core dimensions model: Structural validity of harm avoidance and incompleteness. Journal of Obsessive-Compulsive and Related Disorders 3, 83–94.

Tallis F, 1996 Compulsive washing in the absence of phobic and illness anxiety. Behav Res Ther 34(4), 361–362. [PubMed: 8871369]

Wager TD, Barrett LF, 2004 From affect to control: Functional specialization of the insula in motivation and regulation Published online at PsychExtra.

Wiebking C, Duncan NW, Tiret B, Hayes DJ, Marjanska M, Doyon J, Bajbouj M, Northoff G, 2014 GABA in the insula - a predictor of the neural response to interoceptive awareness. Neuroimage 86, 10–18. [PubMed: 23618604]

Winkler AM, Ridgway GR, Webster MA, Smith SM, Nichols TE, 2014 Permutation inference for the general linear model. Neuroimage 92, 381–397. [PubMed: 24530839]

Yoris A, Garcia AM, Traiber L, Santamaria-Garcia H, Martorell M, Alifano F, Kichic R, Moser JS, Cetkovich M, Manes F, Ibanez A, Sedeno L, 2017 The inner world of overactive monitoring: neural markers of interoception in obsessive-compulsive disorder. Psychol Med 47(11), 1957–1970. [PubMed: 28374658]

Zaki J, Davis JI, Ochsner KN, 2012 Overlapping activity in anterior insula during interoception and emotional experience. Neuroimage 62(1), 493–499. [PubMed: 22587900]

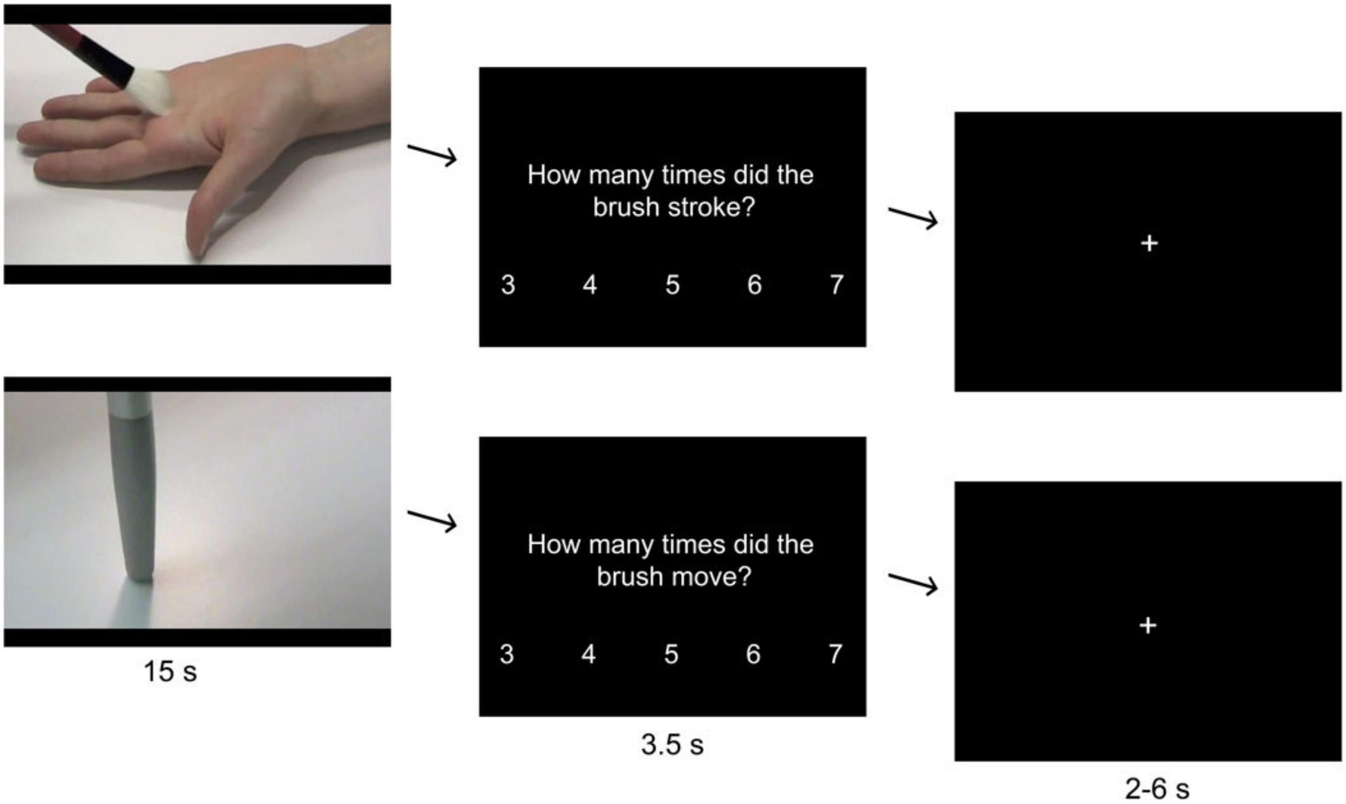

Figure 1.
Examples of body-focused videos (top) and control videos (bottom) blocks in the task.

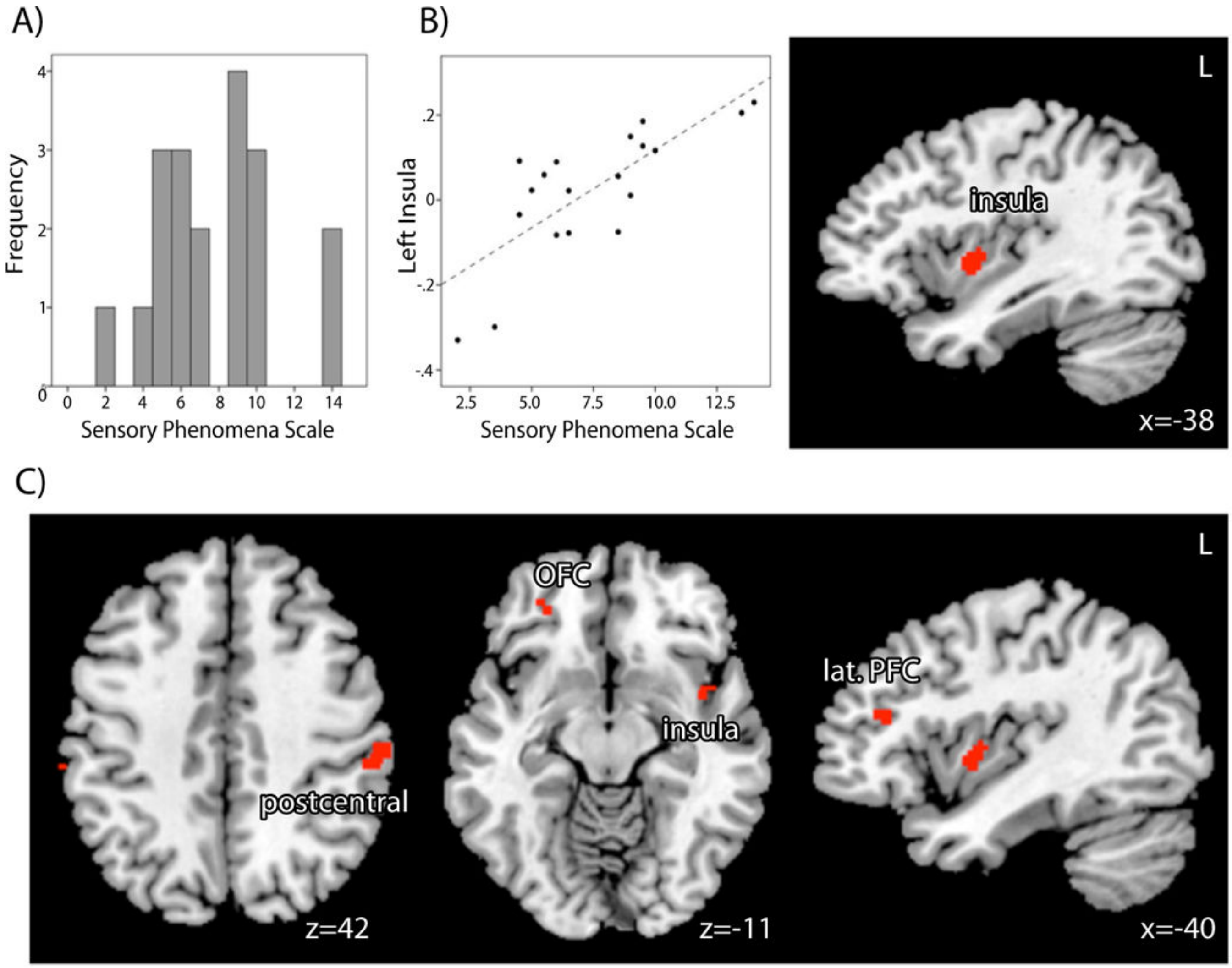

Figure 2.

A) Distribution of sensory phenomena scale (SPS) scores in the OCD sample, B) Region of mid-posterior insula showing a significant positive correlation with SPS score during body-focused videos, corrected for multiple comparisons within region-of-interest mask using permutation testing C) Whole-brain positive correlations with SPS score during body-focused videos, thresholded at voxelwise p<0.001, uncorrected. L=left.

Table 1.

Brain regions positively correlated with sensory phenomena (SP) severity during the body-focused videos condition.

	BA	k	x	y	z	Max p
Insula (mid-posterior) (L)	13	90	−38	−2	−2	0.0001
Postcentral gyrus (R)	1, 2, 3, 4	42	58	−28	42	0.0001
Postcentral/supramarginal gyrus (L)	2, 40	21	−62	−30	34	0.0001
Orbitofrontal (L)	11	16	−28	42	−12	0.0001
Middle frontal (L)	n/a	16	−24	32	22	0.0004
Insula (mid-anterior)	13	14	46	8	−14	0.0001
Dorsolateral prefrontal (L)	46	13	−40	34	18	0.0001
Orbitofrontal (R)	11	12	26	38	−10	0.0004
Posterior middle/superior temporal (L)	39	11	−46	−62	22	0.0004

BA=Brodmann's areas; k=cluster extent; Max p=maximum uncorrected p-value; R=right, L=left, B=bilateral; coordinates are in MNI space.