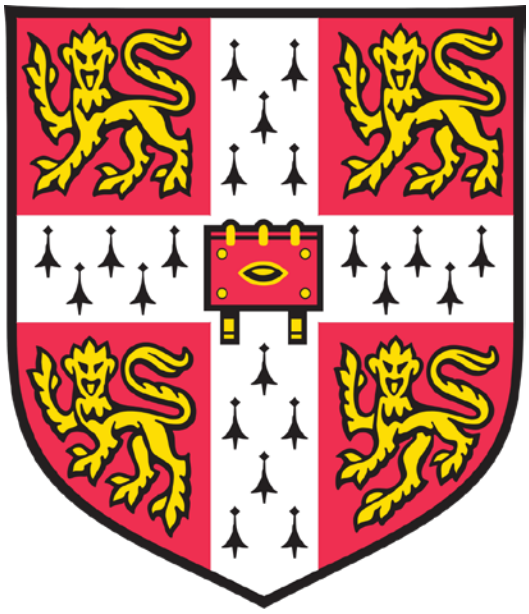
“Vicarious Exposure”: Experimental Studies Towards Developing Novel Therapies for Obsessive-Compulsive Disorder



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Preface

This dissertation is the result of my own work and includes nothing which is the outcome of work done in collaboration except as declared in this Preface and specified in the text. Study 1 and Study 2 were conducted at Harvard University and McLean Hospital; under the supervision of Professor Richard J. McNally and in collaboration with Professor V. S. Ramachandran (UC San Diego) and Dr. Jason Elias. The same OCD patients were used in Study 1 and Study 2 (i.e., tested by research assistants at McLean Hospital). From March to April, 2016, and June to September, 2018, I was a "work away" student conducting these studies for my PhD in the Department of Psychology at Harvard University.

This dissertation is not substantially the same as any that I have submitted, or, is being concurrently submitted for a degree or diploma or other qualification at the University of Cambridge or any other University or similar institution except as declared in the Preface and specified in the text. I further state that no substantial part of my dissertation has already been submitted, or, is being concurrently submitted for any such degree, diploma or other qualification at the University of Cambridge or any other University or similar institution except as declared in the Preface and specified in the text. It does not exceed the prescribed word limit for the Degree Committee for the Faculties of Clinical Medicine and Veterinary Medicine.

Primary supervisor: Professor Barbara J. Sahakian
Secondary supervisor: Professor Trevor W. Robbins
External supervisors: Professor V. S. Ramachandran and Professor Richard J. McNally

“Vicarious Exposure”: Experimental Studies Towards Developing Novel Therapies for Obsessive-Compulsive Disorder

By Baland Jalal

Forty percent of obsessive-compulsive disorder (OCD) patients fail to respond to any kind of treatment. Developing novel therapies for OCD—the aim of this thesis—therefore represents an urgent unmet need. Study 1 examined vicarious contamination sensations and relief in OCD. Study 2 explored the therapeutic utility of the “rubber hand illusion” (RHI) and multisensory processing in OCD. Study 3 tested two novel smartphone interventions in subclinical OCD.

In Study 1, OCD patients (n = 29) reported greater contamination sensations when watching the experimenter contaminating himself than healthy volunteers (n = 34). But more notably, patients, upon first contaminating themselves, reported significant disgust reductions by watching the experimenter washing his own hands, relative to control conditions (unlike anxiety and washing urges); and displayed a (nonsignificant) tendency towards disgust reductions during vicarious handwashing relative to control conditions, compared to healthy volunteers. Finally, an exploratory analysis found that patients with moderate symptoms, unlike severe patients, reported greater reductions in disgust and handwashing urges from vicarious handwashing relative to control conditions, compared to healthy controls. In Study 2, in patients with OCD (n = 27) “dummy contamination” during the RHI resulted in greater contamination reactions than the control (contrary to expectations, after the fake hand had been contaminated for 5 min.); assessed via disgust facial expressions and *in vivo* exposure. Surprisingly, patients failed to reject the RHI during the “gold-standard” control condition. In Study 3, subclinical individuals (n = 93) either watched a video recording of themselves: engaging in handwashing (intervention 1), touching a disgust-inducing object (intervention 2), or performing sequential hand movements (control), on a smartphone four times a day, for one week. As hypothesized, the two interventions, unlike the control, improved OCD symptoms and cognitive flexibility.

These studies demonstrate, for the first time, vicarious contamination sensations and relief in OCD; suggest sensory assimilation of contamination sensations into the body image via the RHI and show aberrant self-referential processing in OCD. Finally, two novel smartphone interventions improved OCD symptoms and cognitive function, after only one week in subclinical individuals. Taken together, these results have important clinical implications for the treatment of OCD.

For my parents, Parwin Murad and Samal Jalal

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Publications during PhD

Jalal, B. (in preparation). OCD—contaminations fears and novel treatments: A review. (Background, introductory, and discussion sections of this thesis)

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Jalal, B., Brühl, A., O’Callaghan, C., Piercy, T., Cardinal, R. N., Ramachandran, V. S., & Sahakian, B. J. (2018). Novel smartphone interventions improve cognitive flexibility and obsessive-compulsive disorder symptoms in individuals with contamination fears. *Scientific Reports*, *8*(1), 14923. https://doi.org/10.1038/s41598-018-33142-2

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(Note: [†] references are to work thematically related to my thesis done prior to my PhD studies under the supervision of Professor V. S. Ramachandran at UC San Diego; [*] this manuscript was revised and published during my PhD studies.)

“Out, damned spot! out, I say!
…All the perfumes of Arabia will not sweeten this little hand.”
—Shakespeare

1. Background

1.1.1 Obsessive-compulsive disorder diagnostic criteria and comorbidities

Obsessive-compulsive disorder (OCD) is a deeply enigmatic neuropsychiatric disorder that has puzzled artists and scientists for centuries. This cruel condition is highly debilitating, costly and associated with immense suffering worldwide (Eaton et al., 2008; Stein, 2002). Once thought rare, OCD is now considered one of the most common psychiatric conditions, afflicting 2-3 percent of the general population (Robins et al., 1984; Ruscio, Stein, Chiu, & Kessler, 2010). OCD is characterized by obsessions (recurrent and intrusive thoughts, images and impulses), and/or compulsive rituals (excessive washing, checking, arranging/ordering of objects), which may include covert mental compulsions (neutralizing cognitions such as counting or visualizations etc.) (Abramowitz, Taylor, & McKay, 2009). One of the most common and striking types of OCD, affecting up to 46 percent of patients, is characterized by severe contamination fears and excessive washing behaviors (Markarian et al., 2010; Rachman, 2004). These patients feel anxious even after incidents of minor “contamination” (for example, touching a door knob), and may spend hours painstakingly washing and scrubbing their hands, sometimes causing bleeding and skin damage (Jalal, McNally, Elias, Potluri, & Ramachandran, in press). In some cases, these exasperating cleansing routines result in patients being unable to leave their home (e.g., Cyr, 2007).

The disorder is traditionally classified into distinct subtypes based on symptom presentation: (1) as noted, contamination fears and compulsive cleaning; (2) obsessive thoughts about causing harm and compulsive checking rituals; (3) obsessions with symmetry and compulsive ordering; (4) obsessions with collecting useless objects and compulsive hoarding (Abramowitz et al., 2009; Stein, 2002; for a review see also, McKay et al., 2004). A purely obsessional subtype has been proposed with mixed empirical support, characterized by unwanted thoughts about sex, violence and blasphemy (Baer, 1994; Williams et al., 2011). Moreover, according to a recent view hoarding compulsivity which affects around 30 percent

of sufferers, may be etiologically distinct from other subtypes of OCD. Accordingly, it was categorized in the latest edition of the Diagnostic and Statistical Manual of Mental Health Disorders (DSM-5) as a disorder on its own (i.e., "hoarding disorder"), within the OCD and related disorders spectrum (American Psychiatric Association, 2013; Ayers, 2017; Chen et al., 2017; Samuels et al., 2002). Interestingly, one factor-analysis of OCD symptoms in a large child and adolescent sample did not find hoarding to separate from other key symptoms (e.g., obsessions and/or compulsions about harm/sex, symmetry, contamination/cleaning), suggesting that hoarding symptomatology perhaps does not become distinct from other factors (i.e., OCD subtypes) until post-adolescence (Højgaard et al., 2017).

The diagnosis of OCD relies on clinical assessment. Specific diagnostic criteria according to the DSM-5 include having obsessions or compulsions that are time-consuming (e.g., take an hour or more per day), cause considerable distress or interfere with everyday activities (e.g., social and occupational functioning). These symptoms must not be a consequence of substance abuse or a health condition (Hirschtritt, Bloch, & Mathews, 2017). The fact that the DSM stipulates that having either obsessions *or* compulsions is sufficient for a diagnosis (not both) suggests that these are autonomous. It challenges the notion of a fixed functional/causal relationship between them, where obsessions must precede compulsions (for evidence that anxiety is not always causal in triggering compulsive-like behaviors, but that they may arise as a post hoc rationalization, see Gillan et al., 2014). (Abramowitz & Jacoby, 2014; Robbins, Vaghi, & Banca, 2019).

The DSM-5 includes a specifier about the level of insight into obsessions and compulsions (i.e., awareness of their senselessness); that OCD patients have varying degrees of insight (i.e., delusionality), with some patients having *good* or *fair insight* whereas others *poor insight* and even *absent insight/delusional beliefs* (Abramowitz & Jacoby, 2015). This specifier may enhance diagnostic classification as it, e.g., stresses that OCD patients can have outright delusional beliefs, not attributable to schizophrenia etc. (Abramowitz & Jacoby, 2014). Interestingly, OCD patients' level of insight may differ for specific symptoms (they might have ample insight into certain obsessions and lack complete insight into others); and levels of delusionality may shift over time (Abramowitz & Jacoby, 2015).

Notably, while overarching OCD diagnostic criteria—vis-à-vis obsessions and compulsions—have largely remained the same since the 1980s, in DSM-5 OCD is no longer classified as an anxiety disorder, but an "obsessive-compulsive and related disorder" (OCRD). This category includes, as noted, hoarding disorder, and also, body dysmorphic disorder, trichotillomania (hair-pulling disorder) and excoriation (skin-picking) disorder etc. (Abramowitz & Jacoby, 2015). The OCRDs clustering reflects a better understanding of the neurobiological substrate underlying these disorders of compulsivity (e.g., conditions associated with basal ganglia abnormality; Fineberg, Saxena, Zohar, & Craig, 2007) (Marras, Fineberg, & Pallanti, 2016). Akin to the DSM-5, the latest edition of the World Health Organization's International Classification of Diseases (ICD-11) has likewise shifted OCD into a new OCRD category (previously a "Neurotic, Stress-related, and Somatoform Disorder"). In spite of this new classification, the DSM-5 and ICD-11 still recognize the strong link between the OCRDs and the anxiety disorders; evident by the fact that the two chapters appear next to each other in both classification systems (Reddy, Simpson, & Stein, 2018). All in all, this new regrouping may pave the way for more empirically grounded psychiatric classification (e.g., nosology underpinned by neuroscience and genetics); and have clinical applicability (Marras et al., 2016; Stein, 2019). As the OCRDs tend to co-occur, it may lead to early detection; once one condition is identified, the clinician might further inquire about other OCRDs (Fineberg et al., 2018).

OCD often co-occurs with other psychiatric disorders, with lifetime comorbidity rates as high as 50-60 percent (Denys, Tenney, van Megen, de Geus, & Westenberg, 2004). Common co-occurring disorders include depression (66 percent), specific phobia (22 percent), social anxiety disorder (18 percent), eating disorder (17 percent), alcohol dependence (i.e., "alcohol use disorder" per DSM-5) (14 percent), and panic disorder (12 percent) (Fineberg et al., 2007; on OCD comorbidity see also, Pigott, L'Heureux, Dubbert, Bernstein, & Murphy, 1994). In spite of the frequent comorbidity between OCD and the anxiety disorders, one study found that OCD patients are more likely to report lifetime OCD spectrum disorders (e.g., trichotillomania, skin-picking disorder, and tic-related disorders) relative to those with

social anxiety and panic disorder; broadly in line with the new DSM-5 OCRD category (Richter, Summerfeldt, Antony, & Swinson, 2003; see too, Fineberg et al., 2007).

1.1.2 OCD neuropathology

Research has implicated parallel cortico-striato-thalamo-cortical (CSTC) circuits in the pathophysiology of OCD (Milad & Rauch, 2012; see also, van den Heuvel et al., 2016); i.e., responsible for the computation of reward- and motivational-related processes, executive function, motor and response inhibition, and habit-based behavior (Fineberg et al., 2018). CSTC circuits project from frontal-cortical regions to the striatum, and then onward to thalamic sites, from where they loop back to the cortex (Milad & Rauch, 2012). The direct and indirect pathways within these circuits have opposing net effects on the thalamus, resulting in either increased (i.e., direct pathway) or decreased cortical excitation (i.e., indirect direct pathway). An imbalance between these two pathways is thought to contribute to OCD pathology; i.e., overactivity in the direct pathway (critical for initiation and suppression of behavior) creating a positive feedback loop resulting in CSTC circuit hyperactivity (Saxena, Bota, & Brody, 2001; see also, Maia, Cooney, & Peterson, 2008; Ting & Feng, 2011) (van den Heuvel et al., 2016; Vahabzadeh & McDougle, 2014).

Studies have revealed structural abnormalities in CSTC circuits, particularly those implicating the orbitofrontal cortex (OFC); i.e., reduced volume of this region (e.g., Atmaca, Yildirim, Ozdemir, Tezcan, & Poyraz, 2007); and, less consistently, reduced volume of the striatum in OCD (e.g., Robinson et al., 1995; for a review see Menzies et al., 2008). Moreover, research has shown enhanced activation of these CSTC circuits in OCD patients. In particular, OCD is linked to increased activation of the OFC and striatum, including the caudate (Saxena et al., 1999; for a review see, Robbins et al., 2019; for a meta-analysis see, Whiteside, Port, & Abramowitz, 2004). Conversely, CSTC hyperactivation may normalize following pharmacological and psychological treatment (Baxter et al., 1992; Saxena et al., 1999; see also, Fineberg et al., 2018). Interestingly, disrupting these loops using surgical intervention (e.g., anterior cingulotomy) may lead to reduced volume of the caudate nucleus (Rauch et al., 2000), and improvement in OCD symptomatology (Fineberg et al., 2018; Jenike, 1998; Stein, 2002). And repeated stimulation (over several days) of the OFC and

ventromedial striatum (VMS) within CSTC circuits using optogenetics triggers OCD-like grooming behaviors in mice (i.e., mirroring compulsivity seen in OCD patients with contamination fears) (Ahmari et al., 2013).

Over the years several disease models have been proposed and revised, implicating specific CSTC circuits in OCD pathology (van den Heuvel et al., 2016; Menzies et al., 2008; Milad & Rauch, 2012). One model stresses the OFC, grounded in extensive research implicating its role in OCD, as noted above (Menzies et al., 2008; Milad & Rauch, 2012). This is the so-called "orbito-frontal striatal model" (i.e., the circuit projecting from the OFC to the striatum, onwards to the thalamus before looping back to the OFC; Menzies et al., 2008). A modified model later proposed dysfunction in three functionally distinct CSTC circuits in OCD (Milad & Rauch, 2012): (1) "the affective circuit" involved in emotion and reward-associated processing; it projects from the anterior cingulate cortex (ACC) and the ventromedial prefrontal cortex (vmPFC) to the nucleus accumbens, and then on to the thalamus, before looping back to the ACC and vmPFC. (2) The "dorsal cognitive circuit" is pertinent to executive function including working memory; projecting from the dorsolateral prefrontal cortex (dlPFC) to the caudate nucleus, then the thalamus before looping back. (3) The "ventral cognitive circuit" is responsible for motor and response inhibition, starting from the anterolateral OFC, then going to the putamen, thalamus, and then back to the original cortical region. Additionally, in light of the recent shift in thinking about OCD as a "disorder of compulsivity," a (4) "sensorimotor circuit" has been proposed; projecting from premotor cortical regions to the putamen, and then thalamus, and back to the cortex. This circuit is involved in habit (automatic stimulus-response) based behavior thought to contribute to compulsivity (van den Heuvel et al., 2016; see also, Fineberg et al., 2018). Taken together, dysfunction in CSTC circuits, important for emotion and reward-associated processing, executive function, motor and response inhibition, and habit formation may mediate inflexible thoughts and behaviors (e.g., inhibitory deficits) underlying OCD symptoms like compulsivity.

Notably, early on these CSTC circuits were considered to be fully closed (i.e., segregated). But a more recent understanding (including of their structural overlap) points to considerable

functional interactions between them (van den Heuvel et al., 2016; Milad & Rauch, 2012). For instance, cross-talk between the "affective circuit" and "sensorimotor circuit" is crucial for the formation of habitual behaviors and associated compulsivity (on CSTC between-circuit interplay see van den Heuvel et al., 2016; Robbins, Gillan, Smith, de Wit, & Ersche, 2012). Likewise, the earliest CSTC account did not factor in the affective function of limbic centers, including the amygdala implicated in fear and anxiety (Milad & Rauch, 2012). This is relevant given the strong anatomical link between the amygdala and striatum (with amygdaloid projections to large areas of the striatum; on cortico-amygdala-striatal circuits see, Cho, Ernst, & Fudge, 2013) (van den Heuvel et al., 2016). Fittingly, however, limbic regions, including the basolateral amygdala and hippocampus well-connected to the OFC, were incorporated in a later orbito-frontal striatal model; i.e., more aligned with our contemporary understanding of the involvement of these limbic centers in emotional states (Menzies et al., 2008; on the amygdala in OCD, see van den Heuvel et al., 2016). Finally, the initial CSTC account did not make any distinction between OFC sub-areas. However, it is now established that the lateral and medial OFC have different functions (vis-à-vis processing of affective-, reward- and fear-related information); i.e., being either hyperactive or hypoactive in OCD depending on the specific experimental context (Robbins et al., 2019; one model per se proposes a hyper-lateral versus a hypo-medial OFC in OCD, see Milad & Rauch, 2012).

1.1.3 Pharmacological drugs for OCD and putative mechanisms of action

First-line pharmacological treatments for OCD are the serotonin (5-HT) reuptake inhibitors (SRIs), which include all the selective serotonin reuptake inhibitor (SSRI) drugs (e.g., citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline) and the tricyclic antidepressant (TCA) drug clomipramine (Dougherty, Rauch, & Jenike, 2004; Fineberg et al., 2015; for meta-analyses see, Jefferson, Kobak, Katzelnick, & Serlin, 1995; Soomro, Altman, Rajagopal, & Browne, 2008; Stein, Spadaccini, & Hollander, 1995; for a review see Fineberg & Gale, 2005). In cases where OCD patients are unresponsive to such treatment, antipsychotic agents are sometimes added as an adjunct to SRIs (for a meta-analysis see Fineberg et al., 2006; see also, Sareen, Kirshner, Lander, Kjernisted, Eleff, & Reiss, 2004).

SRI drugs work by inhibiting serotonin reuptake at the level of the synapse thereby increasing serotonin availability (Goddard, Shekhar, Whiteman, & McDougle, 2008). Their effects on OCD have resulted in a "serotonin hypothesis" implicating the serotonin system in the pathophysiology of the disorder (Barr, Goodman, & Price, 1993; Fineberg, Brown, Reghunandanan, & Pampaloni, 2012; Insel, Alterman, Linnoila, & Murphy, 1985). Although to date there is no overarching model of serotoninergic dysfunction in OCD and the mechanisms whereby SRIs ameliorate symptoms are not well understood (Fineberg et al., 2012; Stein, 2002), suggestions have been made.

SRIs might improve OCD symptomatology by modulating orbito-frontal striatal function (Maia & Cano-Colino, 2015). For example, an early study showed that administration of the SSRI drug paroxetine for 8-12 weeks resulted in reduced activity of the right anterolateral OFC and right caudate nucleus (Saxena et al., 1999). OFC function per se is greatly modulated by serotonin (e.g., Clarke, Dalley, Crofts, Robbins, & Roberts, 2004). The OFC is well-connected to the raphe nucleus, including the dorsal raphe nucleus (Maia & Cano-Colino, 2015), which may have the greatest number of serotonin neurons in the brain (Liu, Van Den Pol, & Aghajanian, 2002). One key impairment linked to aberrant OFC activity concerns the ability to appropriately switch behavior to a change in reward and punishment values of stimuli (i.e., a reversal in stimulus-reward contingencies); so-called reversal learning (Maia & Cano-Colino, 2015). Research in primates has shown that selective serotonin depletion of the PFC results in impairments on an OFC-reliant reversal learning task (Clarke et al., 2004). Another (likewise marmoset) study showed that selective dopamine depletion in the OFC did not lead to such reversal learning deficits, illustrating neurochemical specificity for serotonin (Clarke, Walker, Dalley, Robbins, & Roberts, 2007). Relatedly, research in humans has revealed that acute administration of the SSRI citalopram leads to impairments in reversal learning (Chamberlain, Fineberg, Blackwell, Robbins, & Sahakian, 2006). (Of note, acute SSRI administration is thought to result in serotonin reduction, unlike chronic administration, due to auto-receptor activity. For example, in guinea pigs with a similar subtype of terminal serotonin auto-receptors as humans [Bergqvist, Bouchard, & Blier, 1999], unlike 3 weeks, 8 weeks of the SSRI paroxetine leads to elevated serotonin release in the OFC; owing to desensitization of 5-HT_{1D} auto-receptors. This mirrors

the delayed time course for the effects of SSRIs during OCD treatment [El Mansari, Bouchard, & Blier, 1995; see also, El Mansari & Blier, 2006].) Notably, OCD individuals and their (OCD-free) first-degree relatives display decreased activation of the lateral OFC, during a reversal learning task. This suggests that such OFC-dependent reversal learning-type hypoactivity constitutes an OCD endophenotype; a brain-marker in those with genetic susceptibility (Chamberlain et al., 2008).

As mentioned, antipsychotic agents (such as quetiapine) can often be successfully added as an adjunct to SRIs to treat refractory OCD. Antipsychotic drugs (used in such augmentation intervention for OCD) are usually potent serotonin 2a receptor (5-HT_{2A}R) antagonists (Fineberg et al., 2006; Marek, Carpenter, McDougle, & Price, 2003). Marek and colleagues (2003) have suggested that the benefits of combining SRIs and antipsychotic drugs may arise from a particular synergistic effect namely: the activation of a number of 5-HT receptors (i.e., via serotonin reuptake inhibition exerted by SRIs), in conjunction with a specific 5-HT_{2A} receptor antagonism (i.e., exerted by antipsychotics). This seems to explain the beneficial effects of antipsychotics that are strong 5-HT_{2A} receptor antagonists (e.g., quetiapine and risperidone) but not antipsychotics with higher affinity instead for D_2 receptors relative to 5-HT_{2A} (e.g., haloperidol) (Fineberg et al., 2006).

While clinical observation points to the involvement of the 5-HT_{2A}R in OCD, imaging research has also examined these receptors via positron emission tomography (PET) in OCD. For example, Adams and colleagues (2005) showed that unmedicated OCD patients had enhanced 5-HT_{2A}R binding in the caudate nuclei; and argued that this may possibly be due to the compensatory effects of low availability of serotonin within CSTC circuits. Another study, however, did not find elevated 5-HT_{2A} binding in the OFC in OCD (also in unmedicated patients); but did show that an earlier onset of the disorder was linked to increased 5-HT_{2A}R availability in this cortical region (Simpson et al., 2011). Taken together, research regarding 5-HT_{2A}R binding is intriguing but inconclusive (Maia & Cano-Colino, 2015), and the exact role of 5-HT in OCD remains elusive (Stein, 2002; Westenberg, Fineberg, & Denys, 2007); further complicated by the fact that only around 40-60 percent of patients improve following SRI intervention (Dougherty et al., 2004) (Menzies et al., 2008).

The fact that antipsychotic drugs that modulate dopamine activity may improve OCD symptoms (when combined with SRIs), suggests dopamine involvement in OCD pathophysiology (for reviews see Denys, Zohar, & Westenberg, 2004; Koo, Kim, Roh, & Kim, 2010). This is consistent with imaging studies in OCD revealing increased dopamine concentrations in the basal ganglia (Denys et al., 2004). For example, one study showed that unmedicated OCD patients had enhanced dopamine transporter binding ratios in the right basal ganglia relative to healthy volunteers (Kim et al., 2003). Relatedly, another study found increased dopamine transporter density in the left caudate and left putamen in unmedicated OCD patients compared to healthy controls, again compatible with CSTC models of OCD pathology (van der Wee et al., 2004). Finally, dopamine agonists can generate OCD-like behaviors in both animals (Szechtman, Sulis, & Eilam, 1998), and humans (Borcherding, Keysor, Rapoport, Elia, & Amass, 1990), indicative of a possible role of dopamine in OCD (see also, Stein, 1996).

Another neurotransmitter implicated in OCD pathology is glutamate; the main excitatory neurotransmitter within CSTC loops (Marinova, Chuang, & Fineberg, 2017). Imaging research has shown that OCD patients (i.e., an unmedicated pediatric sample) have raised glutamate concentrations in the caudate relative to healthy individuals. Interestingly, this study showed that caudate glutamate concentrations normalized post 12 weeks of SSRI (paroxetine) treatment (Rosenberg et al., 2000). This suggests that an elevation in serotonin levels may inhibit abnormally raised caudate glutamate activity (Moore, MacMaster, Stewart, & Rosenberg, 1998). That is, SSRI-induced serotonin alterations in the frontal cortex may impact cortical-striatal glutamate projections in OCD (i.e., with great fronto-cortical glutamatergic innervations to the caudate; Rosenberg et al., 2000); whereas the absence of these inhibitory effects of serotonin within CSTC circuits might allow for elevated glutamate activity within these loops (Goddard et al., 2008). Moreover, in line with the idea of glutamate dysfunction in OCD, research has revealed increased glutamate concentrations in cerebrospinal fluid (CSF) of (unmedicated) OCD patients (Chakrabarty, Bhattacharyya, Christopher, & Khanna, 2005). Unsurprisingly, given this glutamate imbalance hypothesis, glutamatergic agents have become a focus of interest, particularly for treatment-resistant

OCD. Notwithstanding promising findings (e.g., for glutamate modulators like memantine), this research is still preliminary (Pittenger, 2015; see also, Marinova et al., 2017). On the whole, future research will need to shed light on the exact role of glutamate in OCD.

1.1.4 Learning-based models of OCD

Learning-based models of OCD (derived from Mowrer's two-process model of fear [1960]) posit that obsessional fear acquisition (via classical conditioning) and extinction are crucial in the etiology and subsequent treatment of OCD (Foa, 2010; McGuire et al., 2016; Shafran, 2005; Taylor, Abramowitz, & McKay, 2007; Tracy, Ghose, Stecher, McFall, & Steinmetz, 1999). Fear and obsessive thoughts are acquired through the pairing of a neutral stimulus (e.g., a doorknob) with a distressing event; e.g., contracting a sexually transmitted disease (unconditioned stimulus) after touching a contaminated doorknob (conditioned stimulus) in a public restroom. Later encounters with the conditioned stimulus (doorknob) can now trigger a conditioned response (e.g., excessive contamination concerns) (Foa, 2010; McGuire et al., 2016; Taylor et al., 2007). The individual later learns that repetitive cleansing and avoidance behaviors ameliorate the obsessions and contamination fears. Indeed, these behaviors are negatively reinforced by distress reduction (via operant conditioning); in turn, the obsessional fears are never subject to extinction (Shafran, 2005; Taylor et al., 2007; Tracy et al., 1999). Next, stimulus generalization takes place where the learned fear response is generalized to other stimuli (e.g., a toilet seat), associated with the conditioned stimulus (Dunsmoor, Martin, & LaBar, 2012; McGuire et al., 2016). These thus become secondary conditioned stimuli (Rachman, 1977). Of interest, anxiety-related pathology may be characterized by excessive stimulus generalization (McGuire et al., 2016).

While conditioned fear responses are generally robust over time (Butcher, Mineka, & Hooley, 2008), extinction occurs when the individual is repeatedly exposed to the conditioned stimulus (e.g., touching a dirty doorknob) without the aversive outcome (unconditioned stimulus; e.g., contracting herpes); and prevention from performing compulsive acts (e.g., excessive handwashing) (McGuire et al., 2016). As a result, the pathological association is degraded or a new non-threatening stimulus-response link is

established effectively suppressing the previous aberrant association (Jacoby & Abramowitz, 2016; McGuire et al., 2016; Tracy et al., 1999).

Ostensible strengths of the learning-based models of OCD have been highlighted in the literature. For example, research has shown—as the theory would predict—that exposure to obsession-related stimuli raises anxiety levels and that subsequent engaging in compulsive rituals lowers such distress; *prima facie* indicating a causal relationship between obsessive ideation and compulsions (Foa, 2010; Shafran, 2005). Another suggested strength is that such models assume learning-based mechanisms driving obsessions and compulsions in OCD are not pathological as such. This dovetails with research showing that the vast majority of people in the general population occasionally have obsessive-like intrusive thoughts that bear resemblance to clinical obsessions (Rachman & de Silva, 1978; Shafran, 2005). Arguably, however, the most obvious strength is that these models have provided a theoretical framework for the preeminent psychological therapy for OCD to date: the behavioral intervention called exposure and response prevention (ERP) (Shafran, 2005; Taylor et al., 2007; Tracy et al., 1999). ERP entails exposure to anxiety-inducing objects and the prevention of ritualistic safety behaviors (Foa, 2010; Shafran, 2005).

However, learning-based models of OCD have notable limitations. For instance, they assume that obsessions are primary and drive compulsions (secondary epiphenomena); that these—seemingly purposeful and goal-directed—acts are performed to ameliorate obsessional distress (Gillan & Robbins, 2014). But these models cannot explain the fact that OCD patients often are cognizant that compulsive rituals make no sense; i.e., they are ineffective and excessive hence the condition is often described as ego-dystonic (as noted, there are cases where patients do lack insight; Gillan & Robbins, 2014). Compulsions in OCD seem to be disconnected from the overall goal of the activity; they appear to have become undesired and insistent habits (Fineberg et al., 2018). Indeed, research on habit formation in OCD has shown that anxiety is not always causal in triggering compulsive-like behaviors (Gillan et al., 2014) (see also, Robbins et al., 2019). This indicates the presence of an exclusively behavioral deficit that does not rely on obsessional symptoms (Gillan & Robbins, 2014). Other pitfalls of these models include a failure to explain why OCD patients often do not have any memory (history) of pertinent fear conditioning episodes that may account for their

obsessional concerns (e.g., illness occurring after contamination) (Jones & Menzies, 1998; Taylor et al., 2007). Also, OCD patients' obsessions and compulsions can shift over time. A patient at one point might excessively wash after shaking hands, and a few months later, instead, engage in compulsive cleansing of household items (Taylor et al., 2007).

1.1.5 Behavior therapy for OCD

The first-line non-pharmacological treatment for OCD, including the contamination subtype—the focus of this thesis—is a form of cognitive behavior therapy (CBT) as noted called "exposure and response prevention" (ERP). ERP was first reported by Meyer (1966) (see also, Abramowitz, 1996; Foa et al., 1983; Rasmussen & Eisen, 1997; Stanley & Turner, 1995). During ERP, the patient is first "contaminated" (e.g., touches a toilet bowl) which can trigger an acute spike in anxiety, and then prevented from performing the compulsive ritual (e.g., washing hands). This procedure may help the patient experience a subsequent decrease in anxiety, resulting in habituation (Abramowitz et al., 2009; Jalal et al., in press). That is, by preventing the patient from performing the neutralizing ritual extinction can occur (e.g., Schruers, Koning, Luermans, Haack, & Griez, 2005).

ERP may work by decoupling habit-driven stimulus-response links through repeated exposure and ritual prevention procedures (e.g., Gillan, Robbins, Sahakian, van den Heuvel, & van Wingen, 2016). This is consistent with studies revealing that caudate nucleus overactivation is associated with habits in OCD (Gillan et al., 2015), and that such caudate hyperactivity can improve in response to ERP (Baxter et al., 1992). Notably, research has found a dose-effect relationship for exposure interventions such that the greater amount of therapy (i.e., hours) the more recovery from OCD (Fisher & Wells, 2005). This dovetails with the notion that ERP mitigates symptoms by gradually breaking down stimulus-response associations, which typically requires repetition. Indeed, ERP often necessitates as many as 15-20 sessions to have beneficial effects (van der Heiden, van Rossen, Dekker, Damstra, & Deen, 2016).

Unsurprisingly many OCD patients do not benefit from ERP (Kozak, 1999); the notion of being contaminated in this crude fashion is simply too unbearable. Alarmingly, 50 percent of

patients who start ERP do not improve, 25 percent are asymptomatic following treatment, 20 percent drop out prematurely and 25 percent refuse to initiate therapy (Abramowitz, 2006; Fisher & Wells, 2005; Kozak, 1999; Schruers et al., 2005), mainly due to fear of exposure protocols (Maltby & Tolin, 2005) (Jalal et al., in press).

Restricted accessibility is another key limitation of CBT; complicated by the fact that ERP requires many hours for improvement, which is costly for patients and time-consuming for therapists (van der Heiden et al., 2016). Unsurprisingly, therefore, many patients treated with CBT do not receive adequate amounts (Stobie, Taylor, Quigley, Ewing, & Salkovskis, 2007). Limited accessibility—high cost, being time-consuming, inconvenience of delivery (e.g., participant travel), and geographical isolation (e.g., impacting rural areas)—is thus a major weakness of ERP (Boisseau, Schwartzman, Lawton, & Mancebo, 2017; Harris, Drummond, & Fineberg, 2019; van der Heiden et al., 2016; Wootton, 2016).

Another limitation of ERP pertains to the context-specificity of fear extinction. That is, if fear conditioning takes place in one context and extinction in another that means a conditioned fear response may return in the initial fear acquisition context (McNally, 2007). Indeed, extinction occurring in the artificial environment of the clinic may not fully generalize to real-life settings (Butcher et al., 2008). One way to address this issue of context-specificity has been via conducting imaginal exposures, where patients imagine the real-life anxiety-provoking events in the clinician's office (like touching a contaminated doorknob in a public restroom) (Gillihan, Williams, Malcoun, Yadin, & Foa, 2012; Jacoby & Abramowitz, 2016). In a seminal study, Foa, Steketee and Grayson (1985) examined the efficacy of imaginal exposure relative to *in vivo* exposure (without response prevention) in OCD patients with compulsive checking symptoms. Patients received 15 sessions of exposure (2 hours/session) over the course of three weeks. Although both methods yielded improvement in OCD symptoms, at-post treatment *in vivo* exposure showed advantages: unlike imaginal exposure, those in the *in vivo* exposure group tended to continue to improve (Foa, 2010; Gillihan et al., 2012).

An advantage of *in vivo* exposure compared to imaginal exposure is that it allows for real-life confrontation with distressing objects thus proper fear disconfirmation; i.e., direct (physical) contact with the conditioned stimulus (e.g., a contaminated doorknob) without materialization of the feared outcome (e.g., illness) (Gillihan et al., 2012). Indeed, unlike imaginal exposure, *in vivo* exposure provides sensory feedback; e.g., tactile and visual input (such as actually *seeing* the confrontation). Sensory input (a vivid visual representation) may ensure that exposures are sufficiently real-life-like which might modulate extinction effects (e.g., enhance emotional saliency). Finally, although patients during imaginal exposure imagine themselves confronting feared objects and events in real-world scenarios, it is still conducted in the clinic. Thus, like *in vivo* exposure, extinction may not fully apply to real-life (non-imaginary) contexts (Butcher et al., 2008).

Arguably, the most notable limitation of ERP is the distressing nature of the procedure. It has been suggested that the judicious use of safety behaviors might reduce treatment-related fears (Rachman, Radomsky, & Shafran, 2008). The practice of abstaining from safety behaviors post exposure is a key component of learning-based models of OCD (Shafran, 2005); shown to be efficacious in the treatment of anxiety-related pathology (Rachman et al., 2008). But few studies have directly demonstrated that treatments employing safety behaviors maintain OCD pathology (Rachman et al., 2008; see too Levy & Radomsky, 2014). Research has shown that incorporating safety behaviors into interventions does not always interfere with treatment—but to the contrary can be clinically beneficial—and improve acceptability (e.g., Levy & Radomsky, 2014). For example, research in a nonclinical sample with elevated contamination fears showed that two sessions of exposure plus safety behavior (i.e., cleansing using hygienic wipes) completed two weeks apart resulted in significant reductions in contamination, danger, fear, and disgust reactions (Rachman, Shafran, Radomsky, & Zysk, 2011). Others have replicated this finding (van den Hout, Engelhard, Toffolo, & van Uijen, 2011). Similarly, a study of OCD patients with contamination concerns showed that a single session of exposure plus safety behavior was as effective as standard exposure in reducing contamination fears (Levy & Radomsky, 2016). Taken together, research challenges the prevailing view (derived from orthodox learning-based models) that safety behaviors are invariably countertherapeutic (van den Hout et al., 2011). Conceivably, the strategic use of

safety behaviors during treatment may offer a sense of perceived control, leading to a more comfortable approach to confronting aversive objects (e.g., yielding less avoidance behavior), and thus increased fear disconfirmation overall (Levy & Radomsky, 2016; Rachman et al., 2008) (Jalal et al., in review).

1.1.6 Health anxiety

Health anxiety is characterized by excessive fear or belief that one has a serious medical condition, and is a defining feature of hypochondriasis (Abramowitz, Olatunji, & Deacon, 2007; Warwick & Salkovskis, 1990); in fact, the two terms (i.e., health anxiety and hypochondriasis) are often used interchangeably in the literature (e.g., Tyrer et al., 2011). Health anxiety or hypochondriasis symptomatology is seen in those with chronic pain (Tang et al. 2007), multiple sclerosis (Kehler & Hadjistavropoulos, 2008), and overlaps with certain anxiety disorders, such as panic disorder (Abramowitz et al., 2007), and some forms of OCD (Abramowitz, 2005). (In spite of the shared symptomatology between clinical health anxiety/hypochondriasis and OCD, they significantly differ on diagnosis-specific symptoms [e.g., Greeven, van Balkom, van Rood, Oppen, & Spinhoven, 2006].)

In patients with contamination-related OCD, health anxiety presents as an extreme fear of germs (bacteria and viruses in the environment), resulting in intrusive thoughts about contamination, avoidance behaviour (e.g., avoiding public restrooms or shaking hands), and washing compulsions (e.g., handwashing) to prevent illness (Abramowitz et al., 2007). Indeed, one subtype of contamination-related OCD arises mainly from health anxiety. According to Rachman (1994) OCD patients with washing compulsions can be classified into three subtypes: (1) one that results from a “sense of being dirty” (e.g., the fear of transmitting dirt to clean items and people, what has been referred to as “contact contamination”; Abramowitz et al., 2014; Rachman, 2004; on “transmitting contamination”, see also Riskind, Abreu, Strauss, & Holt, 1997); (2) another that arises from purely psychological (internal) factors, that is, “mental pollution” (or “mental contamination”) (i.e., even in the absence of physical contact with contaminants); and finally, (3) a subtype that arises primarily from health anxiety. Consistent with Rachman (1994), Feinstein and colleagues (2003) have shown that there are at least two distinct types of washing compulsions in OCD: (1) one that is

characterized by contamination fears (e.g., disgust-driven fears) without fearing illness; these individuals engage in excessive neutralizing cleansing rituals to reduce contamination-related ideation. (2) Another type is characterized by health anxiety; that is, specific fears about the consequences of a potential contamination, such as the spreading of germs resulting in illness. In addition, Tallis (1996) suggested that a fourth category of washing compulsions can be attributed to the personality trait of perfectionism; such individuals are comfortable with the idea of being physically contaminated and do not have elevated health anxiety.

Research on the treatment of health anxiety has focused on those with hypochondriasis, and the use of psychosocial treatments (e.g., CBT) and pharmacological interventions (e.g., SSRIs) to reduce symptoms (e.g., Barsky & Ahern, 2004; Buwalda, Bouman, & van Duijn, 2007; Fallon et al., 1993; Fallon et al., 2003; Greeven et al., 2007; McManus, Surawy, Muse, Vazquez-Montes, & Williams, 2012; Sørensen, Birket-Smith, Wattar, Buemann, & Salkovskis, 2011; Visser & Bouman, 2001; for a meta-analysis see also, Olatunji et al., 2014). Research indicates that this patient population prefers psychological interventions over pharmacological ones; indeed, up to 48 percent of patients only accept psychological treatment (Walker, Vincent, Furer, Cox, & Kjernisted, 1999).

1.1.7 The role of disgust in OCD

Disgust is a basic emotion that may serve the adaptive function of protecting humans from contamination which could result in illness (Rozin & Fallon, 1987). It evokes a unique physiological (e.g., nausea), subjective (e.g., feelings of revulsion), and behavioral response, including distancing-related behavior; and a particular facial expression (Ludvik, Boschen, & Neumann, 2015; Rozin & Fallon, 1987). Although disgust and contamination aversion overlap, they are distinct concepts. As opposed to disgust, contamination fears arise from post hoc interpretive processes; e.g., triggered by disgust, or related emotions like anxiety (Ludvik et al., 2015; Rachman, 2004) (Jalal et al., in press).

Disgust plays a notable role in OCD (Ludvik et al., 2015). Research suggests that there is an association between OCD symptoms including contamination fears (and compulsive washing), and disgust (Mancini, Gragnani, & D'Olimpio, 2001; Muris, Merckelbach,

Nederkoorn, Rassin, Candel, & Horselenberg, 2000; Olatunji, Sawchuk, Lohr, & De Jong, 2004; Sawchuk, Lohr, Tolin, Lee, & Kleinknecht, 2000; Schienle, Stark, Walter, & Vaitl, 2003; Thorpe, Patel, & Simonds, 2003). It has specifically been shown that disgust sensitivity and anxiety are two independent factors driving contamination fears. For instance, one study found disgust sensitivity to predict contamination related fears after controlling for trait anxiety and anxiety sensitivity (Olatunji, Sawchuk, Arrindell, & Lohr, 2005) (for a theoretical model on the structure of disgust in relation to contamination fears and excessive washing, see too Olatunji, Williams, Lohr, & Sawchuk, 2005). Unsurprisingly, given this link between disgust sensitivity and contamination fears, research has shown that individuals with contamination fears have difficulties disengaging from both fear and disgust stimuli (Cisler & Olatunji, 2010). This is consistent with the finding that disgust sensitivity is associated with attention bias towards disgust stimuli (Charash & McKay, 2002).

Certain cognitive mechanisms may contribute to excessive disgust reactions (Ludvik et al., 2015) such as *sympathetic magic*. This entails irrational thoughts about how contamination is transmitted from one object to another (Tolin, Worhunsky, & Maltby, 2004). Two principles drive sympathetic magic: the "law of contagion" and "law of similarity." The law of contagion dictates that once an object has contacted a disgust-inducing item, it becomes permanently contaminated (e.g., disgust-induced avoidance of drinking from a now-clean cup that once contained urine; Bhikram, Abi-Jaoude, & Sandor, 2017; Ludvik et al., 2015; Tolin et al., 2004). The law of similarity posits that a non-contaminated object's visual likeness to a disgust-provoking item renders it contaminated (Ludvik et al., 2015) exemplified by reluctance to eat chocolate shaped like feces (Bhikram et al., 2017; Rozin, Millman, & Nemeroff, 1986). Hence, principles driving the effects of sympathetic magic illustrate how disgust reactions can override top-down factual knowledge (Jalal et al., in review).

Patients with contamination-related OCD are prone to disgust-related cognitive errors (i.e., sympathetic magic beliefs; Ludvik et al., 2015). In one investigation, OCD patients observed as an experimenter touched a non-contaminated pencil to a perceived contaminated object; thereafter, another (non-contaminated) pencil was put in contact with the initial pencil; repeated for 12 pencils total. Interestingly, unlike non-anxious control participants and those

with panic disorder, OCD patients rated all 12 pencils as being equally contaminated (Tolin et al., 2004). This study demonstrates how contamination may be perceived as rapidly transmitting in OCD. Indeed, it shows how the law of contagion works in a dynamic and escalating fashion; allowing for an irrational transference of contagion across a chain of items many degrees removed from the original contaminated item (Tolin et al., 2004; see too, Bhikram et al., 2017) (Jalal et al., in review).

Aberrant disgust processing in the brain may contribute to the pathophysiology of OCD (Husted, Shapira, & Goodman, 2006); in particular, the insula cortex (Knowles, Jessup, & Olatunji, 2018; Ludvik et al., 2015). This is a large cortical region with sub-areas important for computing various functions, e.g., processing interoceptive bodily and visceral states (particularly the right anterior insula; Critchley, Wiens, Rotshtein, Öhman, & Dolan, 2004), as well as disgust (Royet, Plailly, Delon-Martin, Kareken, & Segebarth, 2003; Wicker et al., 2003) (Husted et al., 2006; Knowles et al., 2018). Research has shown elevated activation of the insula in OCD (Berlin et al., 2017; Shapira et al., 2003; Stein, Arya, Pietrini, Rapoport, & Swedo, 2006). For instance, patients with contamination-related OCD exhibit enhanced activation of the right insula cortex when exposed to disgust-inducing pictures compared to healthy controls (Shapira et al., 2003).

The insula is well-connected to the OFC; important for the integration and appraisal of reinforcement association of incoming sensory stimuli (e.g., processing of aversive expectations); and executing and planning behaviors accordingly (Bhikram et al., 2017; Husted et al., 2006; Rolls, 2004). One account posits (i.e., consistent with LeDoux's [2000] model of fear processing) that interactions between the insula cortex and OFC may help explain the role of disgust in OCD (Brady, Adams, & Lohr, 2010). It argues that when faced with a possible contaminant, at first an automatic (non-interpretive gut-level) disgust reaction is triggered; a warning mechanism resulting in, e.g., nausea and revulsion, and insula activation. Next, sensory input is passed on from disgust centers (e.g., the insula) to the OFC for evaluation of its danger. If the OFC renders the object as threatening this will lead to fear (e.g., amygdala activation); and execution of appropriate behaviors (like handwashing) (Bhikram et al., 2017). In OCD, CSTC (including OFC) hyperactivity may result in an

exaggerated response to aversive stimuli. Effectively, disgusting objects are readily mislabeled as dangerous culminating in obsessions and execution of inflexible and repetitive behaviors (i.e., compulsions) (Bhikram et al., 2017). Moreover, disgust-related vulnerabilities in OCD may contribute to such enhanced "false contamination alarm." For example, given OCD patients have increased levels of disgust proneness means they are more likely to have a disgust experience in the first place which can be misconstrued as a danger signal. Likewise, that OCD patients tend to perceive disgust experiences as highly negative events means an overall amplified disgust response possibly increasing the probability that the OFC mislabels the signal as a sign of danger (Brady et al., 2010).

In light of this model, accurately dismissing disgust sensations as nonthreatening would lead to a reduction in contamination fears (Brady et al., 2010). Notably, research suggests that disgust reactions in individuals with clinical contamination fears (i.e., OCD), are amenable to exposure therapy (McKay, 2006). In fact, OCD patients are likely to experience overall symptom improvement, if treatments reduce disgust propensity (Knowles et al., 2018; see also, Athey et al., 2015). As such, developing novel treatments that target disgust systems in OCD represents a promising avenue for future research (see Bhikram et al., 2017).

1.1.8 Cognitive flexibility

Compulsive symptoms such as excessive washing behaviors are believed to be mediated by cognitive inflexibility (impaired "set shifting"). This is perhaps the most striking cognitive/executive impairment in OCD, characterized by the inability to shift attentional focus (e.g., Chamberlain, Blackwell, Fineberg, Robbins, & Sahakian, 2005). Indeed, growing evidence shows that cognitive inflexibility represents a core feature and biomarker of the neurocognitive profile of OCD (for meta-analyses see, Abramovitch, Abramowitz, & Mittelman, 2013; Snyder, Kaiser, Warren, & Heller, 2015) and a candidate neurocognitive endophenotype (Chamberlain et al., 2007b) (see also Jalal et al., 2018).

A key measure of cognitive flexibility on which OCD patients perform less well than healthy controls is the Intradimensional-Extradimensional Set Shift task (IED) (Downes et al., 1989; on set shifting see also, Grant & Berg, 1948) of the well-validated Cambridge

Neuropsychological Test Automated Battery (CANTAB) (e.g., Sahakian & Owen, 1992) (for a review on the IED task in OCD see, Olley, Malhi, & Sachdev, 2007). A series of studies have demonstrated that performance on the crucial extradimensional shift (EDS) stage of the IED task (conceptually similar to the Wisconsin Card Sort Test [WCST; Berg, 1948]), is impaired in OCD (Chamberlain et al., 2006; Vaghi et al., 2017; Veale, Sahakian, Owen, & Marks, 1996; Watkins et al., 2005), making it a sensitive marker of cognitive flexibility. Cognitive flexibility or set shifting deficits in OCD are mediated by abnormal activation of fronto-striatal circuitry (e.g., dorsolateral/ventrolateral prefrontal and striatal regions) (Bersani, Quartini, Ratti, Pagliuca, & Gallo, 2013; Vaghi et al., 2017). Interestingly, fronto-striatal dysfunction in OCD is amenable to treatment (Freyer et al., 2011). Moreover, several studies have shown that set shifting in particular in OCD may improve following behavioral therapy (Bolton, Raven, Madronal-Luque, & Marks, 2000; Katrin Kuelz et al., 2006; Moritz, Kloss, Katenkamp, Birkner, & Hand, 1999; for a review see Vandborg et al. 2012).

1.1.9 Visuospatial memory

Memory impairment plays a role in OCD (e.g., Penadés, Catalán, Andrés, Salamero, & Gastó, 2005). This is consistent with the clinical observation that OCD patients often complain about forgetting whether they have performed certain actions, resulting in repetitive ritualistic behaviours such as checking and cleaning (Muller & Roberts, 2005). One key example of a memory impairment in OCD is that of nonverbal visuospatial memory, which involves maintaining and processing visual and spatial information (Nikolova & Macken, 2015). Indeed, one meta-analysis concluded that OCD patients exhibit severe and consistent visuospatial memory impairments compared to healthy controls (Shin, Lee, Kim, & Kwon, 2014; for another meta-analysis see, Abramovitch et al., 2013; see also, Katrin Kuelz et al., 2006; Vandborg, Hartmann, Bennedsen, Pedersen, & Thomsen, 2015).

The Paired Associates Learning test (PAL; Sahakian et al., 1988) is a sensitive marker of visuospatial memory, in which participants have to remember the location of various distinct abstract shapes. A number of studies have shown that patients with OCD perform less well than healthy controls on the PAL (Bersani et al., 2013; Gottwald et al., 2018; Morein-Zamir

at al., 2010), indicating possible abnormal involvement of the prefrontal cortex and medial temporal regions. Research has yielded mixed results as to whether visuospatial memory is amenable to non-pharmacological treatment in OCD. One study found that nonverbal visuospatial memory improved in OCD patients after 12 weeks of CBT treatment (Katrin Kuelz et al., 2006). Another study to the contrary, did not find an effect of CBT on visuospatial memory, and concluded that such a cognitive impairment in OCD might be trait-related as opposed to state-dependent (Vandborg et al., 2015).

1.1.10 Response inhibition

Response inhibition refers to the ability to suppress a prepotent motor response, a neurocognitive domain related to impulsivity (Aron & Poldrack, 2005; Bari & Robbins, 2013; Logan, Cowan, & Davis, 1984; Tannock, Schachar, Carr, Chajczyk, & Logan, 1989; on impulsivity see also, Dalley, Everitt, & Robbins, 2011; Dalley & Robbins, 2017; Dalley & Roiser, 2012; Sonuga-Barke, Lea, & Webley, 1989; on the neurobiology of impulsivity see, Dalley, Mar, Economidou, & Robbins, 2008). It has been suggested that the intrusive thoughts and repetitive rituals in OCD may reflect an inability to control and inhibit these cognitions and behaviours, and that as such, OCD can be seen as a disorder of cognitive and behavioural inhibitory failures (Chamberlain et al., 2005). Consistent with this view, meta-analyses have found response inhibition impairments in OCD (e.g., Abramovitch et al., 2013; Snyder et al., 2014).

One measure of response inhibition is the Stop Signal Task (SST; Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003). The SST assesses the ability to stop an already triggered motor response. Response inhibition deficits measured on the SST have been reported in OCD patients (Chamberlain et al., 2006; Penadés et al., 2007), and their first-degree relatives without the disorder (Chamberlain et al., 2007b), suggesting that motor disinhibition may be an endophenotypic marker for brain dysfunction in OCD. To date there is little available research on the impact of treatment on response inhibition in OCD (van Velzen, Vriend, de Wit, & van den Heuvel, 2014); although research has shown that pharmacological treatment can improve response inhibition in patients with other OCD-spectrum (“fronto-stratial”) disorders such as attention deficit/hyperactivity disorder (ADHD) (Chamberlain et al., 2007a;

on response inhibition in ADHD see also, Castellanos, Sonuga-Barke, Milham, & Tannock, 2006; Demurie, Roeyers, Wiersema, & Sonuga-Barke, 2016). However, one longitudinal study did find that in OCD patients with response inhibition impairments, such deficits were not improved once their OCD symptoms reached remittance, suggesting perhaps this cognitive-motor impairment may possibly be treatment resistant (Bannon, Gonsalvez, Croft, & Boyce, 2006).

1.2.1 Goal-directed versus habitual control

Compulsions in OCD such as ritualistic handwashing behaviours seem to be disconnected from the overall goal of the activity (hygiene/avoiding contamination). Patients are cognizant that repetitive handwashing makes no sense—is ineffective and excessive—vis-à-vis the desired outcome. Yet they are unable to stop (e.g., washing hands until they bleed). Such behaviours appear to have become undesired and insistent habits (Fineberg et al., 2018). Based on this clinical observation, it has been proposed that the stereotyped behaviours seen in OCD may be controlled by habitual brain systems involving cortico-basal ganglia circuits (Graybiel & Rauch, 2000). Dual-system theories of instrumental behaviour posit two dissociable brain systems influencing actions (Dickinson & Balleine, 1993; de Wit & Dickinson, 2009). Goal-directed systems drive purposeful and flexible behaviours performed to achieve a certain desired outcome; for instance, washing hands once after using the restroom to avoid contamination. In contrast, washing hands 10 times (inflexibly and thoughtlessly) after using the restroom indicates an automatized response under the influence of habitual neural systems. In the latter case the repetitive handwashing is overall insensitive to a specific outcome (e.g., hygiene) (Fineberg et al., 2018).

Research supports the idea that OCD patients rely more so on habits (automatized behaviour) as opposed to goal-directed behaviour compared to healthy individuals. In one study Gillan and colleagues (2011) using the Fabulous Fruit Game task, trained OCD patients to respond to cues by pressing keys on a computer to win points. During a later stage of the task the patients were told that some of the cues were no longer valuable (i.e., did not gain points). Yet, they continued to press the keys in response to the no longer valuable outcomes (referred to as “slips-of-action”), indicating a bias towards habitual and automatic responding (for a

related study on habit bias in OCD using a shock avoidance paradigm see, Gillan et al., 2014; for a study on functional neuroimaging of habits in OCD, see Gillan et al., 2015; for a review, see Gillan & Robbins, 2014). Research on goal-directed behaviour versus habitual control in OCD is relatively recent. For this reason, to the best of my knowledge, there are no published studies on whether habitual bias in OCD may improve as a result of treatment. However, it is possible that SSRI treatments could reduce habitual bias and associated compulsive behaviours indirectly by ameliorating anxiety and stress that induce them (Gillan et al., 2016). On the other hand, as noted, ERP therapy might through repeated exposure to "contaminants" improve habits in OCD by decoupling habitual stimulus-response associations (for a review see Gillan et al., 2016).

One recently developed measure to assess habit bias is the "Aversive Stimulus Snack" task on which patients with schizophrenia display deficits in goal-directed action (Morris, Quail, Griffiths, Green, & Balleine, 2015). In this task, subjects are trained to liberate snacks from a virtual vending machine; and, accordingly, awarded the actual snack to eat in real life. But after some time, the snack is devalued: a video shows the snack infested with cockroaches. Thereafter, participants again have the opportunity to tilt the virtual vending machine to win snacks. This paradigm appears particularly relevant to contamination-related OCD because the outcome devaluation entails a contamination procedure; making it a well-suited comparator to the Fabulous Fruit Game. It can potentially shed light on whether disgust-based devaluation per se influences habitual behaviour.

1.2.2 Subclinical OCD

Research has shown that a significant proportion of the general population experience noteworthy levels of obsessive-compulsive (OC) symptoms without meeting full diagnostic criteria for OCD (Ruscio et al., 2010). According to one study conducted in a sample of 4181 individuals, the 12-month prevalence rate for subclinical OCD was 4.5 percent (Adam, Meinlschmidt, Gloster, & Lieb, 2012; on subclinical prevalence rates see also, Fineberg et al., 2013a; Grabe et al., 2000). Individuals with subclinical OCD experience greater distress than healthy controls (De Bruijn, Beun, De Graaf, Ten Have, & Denys, 2010), exhibit overall impairment in psychosocial functioning and quality of life (Grabe et

al., 2000), and according to some research, increased treatment seeking behavior (Adam et al., 2012; Fineberg et al., 2013a). Also, OCD symptoms within the general population, akin to clinical OCD, are associated with elevated prevalence rates of psychiatric conditions, including anxiety, mood and bipolar disorder (Fineberg et al., 2013b).

There is evidence that OC symptoms in subclinical and clinical OCD are of similar qualitative nature. That is, such symptoms in the two populations appear to be of dimensional (rather than categorical) character, differing in level of severity and frequency (Abramowitz et al., 2014). In terms of symptom presentation, research has shown that the overall themes of intrusive thoughts and types of neutralizing behaviors (washing, checking, counting etc.) are the same in the two populations (e.g., García-Soriano, Belloch, Morillo, & Clark, 2011; Purdon & Clark, 1993). The OC symptoms in both populations also have the same etiologies (for a meta-analysis of twin-studies, see Taylor, 2011), causal, developmental and maintenance factors (for a review see, Abramowitz et al., 2014), such as certain dysfunctional beliefs that are predictive of these symptoms (e.g., Abramowitz, Khandker, Nelson, Deacon, & Rygwall, 2006). For instance, OC symptoms arising from mental pollution (i.e., purely psychological triggers as opposed to physical contact with contaminants; Abramowitz et al., 2014; Rachman, 1994, Rachman, 2004) exist in both clinical (e.g., Coughtrey, Shafran, Knibbs, & Rachman, 2012), and non-clinical groups (e.g., Herba & Rachman, 2007; Radomsky & Elliott, 2009).

Unlike OCD patients who show clear neuropsychological impairment, research has yielded mixed results as to whether there are reliable neuropsychological deficits in subclinical populations. Some studies have shown that individuals with subclinical symptoms are impaired on the WCST, a set shifting measure, compared to healthy controls (e.g., Goodwin & Sher, 1992; Kim, Jang, & Kim, 2009). Other investigations in subclinical OCD groups have not found such impairments in executive function on this measure (e.g., Mataix-Cols et al., 1999). One study assessed set shifting performance and visuospatial memory in subclinical OCD using the CANTAB battery, and found no impairments on the IED (including the EDS measure), the Spatial Recognition Memory (SRM) and the Spatial Working Memory (SWM) test (Johansen & Dittrich, 2013). Another study likewise found

no impairments on the Stroop test of response inhibition in this subclinical population (Mataix-Cols et al., 1999).

Unsurprisingly given the body of research showing that OC symptoms in subclinical populations are milder but phenomenologically similar to those of clinical OCD, subthreshold groups are often used as analogue samples. Subclinical analogue studies commonly test the initial efficacy of novel treatment protocols (e.g., Cougle, Wolitzky-Taylor, Lee, & Telch, 2007; Najmi & Amir, 2010; Olatunji, Wolitzky-Taylor, Willems, Lohr, & Armstrong, 2009).

1.2.3 OCD treatment

There are currently few effective treatments for OCD. As noted, the first-line psychological treatment for OCD is ERP, as recommended by the National Institute for Health and Care Excellence (NICE, 2005) (Knopp, Knowles, Bee, Lovell, & Bower, 2013). Indeed, several meta-analyses have found ERP to be effective for OCD (Abramowitz, 1998; Abramowitz, Franklin, & Foa, 2002; Rosa-Alcázar, Sánchez-Meca, Gómez-Conesa, & Marín-Martínez, 2008). In terms of pharmacological intervention, SSRIs and clomipramine are efficacious; confirmed by a large recent network meta-analysis (Skapinakis et al., 2016; see too, Harris et al., 2019). This meta-analysis also reported that the efficacy of SSRIs and clomipramine does not differ and that the efficacy of individual SSRI drugs is comparable. But given that SSRIs are associated with milder side-effects relative to clomipramine, SSRIs are considered the first-line pharmacological treatment for OCD (NICE, 2005) (Fineberg et al., 2015; Harris et al., 2019; Skapinakis et al., 2016). While some clinics provide combined pharmacological (SSRI or clomipramine) and psychological treatment (CBT), there is inadequate evidence to conclude that combined treatment is superior to either drugs or CBT alone (Fineberg et al., 2015; Skapinakis et al., 2016). As noted, when OCD patients are unresponsive to treatment, antipsychotic agents can be added to SRIs; effective according to meta-analyses (Veale, Miles, Smallcombe, Ghezai, Goldacre, & Hodsoll, 2014; see too Fineberg et al., 2006). In cases of extreme debilitating and refractory OCD, neurosurgery interventions (associated with risks due to their invasive nature) are available. These include procedures like dorsal anterior cingulotomy, anterior capsulotomy, and deep brain stimulation (DBS); the latter

being less risky with 60 percent of OCD patients responding to this approach according to one meta-analysis (Alonso et al., 2015) (see also, Harris et al., 2019; Tyagi et al., 2019).

In spite of the favourable effects of pharmacotherapy not all OCD patients benefit. According to some estimates, around 40-60 percent of patients improve following SRI intervention (Dougherty et al., 2004). Moreover, one potential drawback of pharmacological treatment is the undesired side effects. One study found that up to 33.3 percent of OCD patients who received the TCA drug clomipramine for 12 weeks reported drowsiness as an adverse side effect (versus 11.5 percent in the placebo group); likewise, 27.8 percent of patients experienced sedation (versus 3.8 percent in the placebo group), and 22.2 percent had sexual dysfunction side effects (versus 3.8 percent in the placebo group) (Foa et al., 2005). While the SSRIs are better tolerated than clomipramine (Zohar & Judge, 1996), they too can come with side effects such as nausea, insomnia, restlessness, diarrhoea and sexual dysfunction (Fineberg & Brown, 2011).

To improve upon ERP, cognitive elements have been added to the treatment or been applied as a separate "cognitive therapy" modality (Rosa-Alcázar et al., 2008). This approach entails targeting cognitive errors. These include: (1) "heightened responsibility": having a distinct ability to precipitate and/or responsibility to avert aversive outcomes; (2) "over-emphasis on thought": for instance, that merely thinking of an event increases the likelihood of its occurrence; (3) "controlling thoughts": that full control and regulation of one's thinking is attainable and essential; (4) "overestimation of threat": that aversive outcomes have a high probability of occurring and disastrous consequences; (5) "perfectionism": that actions have to be done exactly the "right way," and overall intolerability towards errors; (6) "intolerance of uncertainty": for instance, a need to be fully reassured that aversive events will not unfold (Abramowitz, 2006). Mirroring learning-based models, according to cognitive theorists these biases and faulty beliefs give rise to obsessional anxiety. Compulsive acts are then performed to ameliorate intrusive thoughts and anxiety; e.g., to ward off aversive outcomes (Abramowitz, 2006; Abramowitz, Taylor, & McKay, 2005; Gillan & Robbins, 2014). Cognitive therapy typically involves teaching patients about the implausibility and maladaptive nature of these cognitions (i.e., how they give rise to obsessions); that intrusions

are not inherently dangerous but rely on the patient's interpretation (Abramowitz, 2006; Abramowitz et al., 2005; Fama & Wilhelm, 2005). The clinician often employs Socratic dialogue to challenge the underlying logic of faulty cognition; e.g., by posing questions about the utility and evidence corroborating maladaptive cognitions and beliefs (Fama & Wilhelm, 2005).

One meta-analysis examined the effectiveness of ERP, cognitive therapy and their combination: Abramowitz, Franklin and Foa (2002) reported mean effect sizes for ERP (d = 1.50), cognitive therapy (d = 1.19), and combined ERP and cognitive therapy (d = 0.99); i.e., revealing a larger effect size for ERP (relative to control conditions), than either cognitive therapy or their combination; yet suggesting benefits across all three approaches (Abramowitz et al., 2005; see too, Rosa-Alcázar et al., 2008). Furthermore, this meta-analysis showed that ERP led to greater reductions in OCD symptomatology than did cognitive therapy or ERP + cognitive therapy. Overall, these results are in line with the view that ERP should constitute the psychological treatment of choice for OCD (Abramowitz et al., 2005). They also dovetail with other meta-analyses showing that behavioral therapies for OCD tend to have greater efficacy than cognitive ones (Eddy, Dutra, Bradley, & Westen, 2004). However, in spite of the efficacy of behavioral therapy it has serious limitations (for details see Section 1.1.5).

To address barriers to traditional treatment (i.e., improve accessibility) research has explored remotely delivered forms of CBT (Abramowitz, Blakey, Reuman, & Buchholz, 2018; Boisseau et al., 2017; Harris et al., 2019; Wootton, 2016). These include video-conference administered CBT (vCBT), where treatment is provided through a videoconference call, as an analog to in-person CBT; and telephone-delivered CBT (tCBT), similar to vCBT, except the patient is visually unobserved. These CBT applications are delivered in real-time and usually require comparable clinician-patient interaction as in-person treatment (Wootton, 2016). Controlled trials support the effectiveness of both vCBT (Vogel et al., 2014) and tCBT (Lovell et al., 2006).

Other remotely delivered CBT methods include computerized CBT (cCBT) and internet-based CBT (iCBT). These may involve reading modules about the rationale of CBT and receiving instructions to conduct *in vivo* exposure, on a computerized device; either offline (cCBT) or online (iCBT) (e.g., Andersson et al., 2012; Wootton, 2016). One iCBT intervention (10 weeks), provided by Andersson and colleagues (2012), included elements like psychoeducation, cognitive restructuring, constructing an exposure hierarchy, and instructions to do *in vivo* ERP. In this study, iCBT was effective, yielding greater improvements in OCD symptoms than the control intervention (internet-based non-directive supportive treatment); i.e., reporting a large (between-group) effect size (d = 1.12).

Taken together, OCD patients appear willing to incorporate technology-based intervention into their daily lives. One recent meta-analysis found that remote interventions for OCD are efficacious and as effective as in-person CBT (Wootton, 2016). Although promising in terms of widening the reach of OCD intervention, remote-CBT applications have limitations. For instance, computers such as laptops are not fully transportable. They do not always allow for easy and instant access to treatment as patients go about their daily lives (i.e., in places where symptoms naturally arise); e.g., the gym, grocery store, park or the bus or train (Boisseau et al., 2017).

The rise in smartphone technology offers an exciting new avenue for overcoming accessibility challenges. Indeed, smartphones are now widely used by most members of society (Pew Research Center, 2018). In spite of such widespread smartphone use, few apps have been developed for treating OCD (Boisseau et al., 2017). That is, available apps include CBT-type interventions with very limited empirical support (see Van Ameringen, Turna, Khalesi, Pullia, & Patterson, 2017). For example, the Mayo Clinic Anxiety Coach for anxiety disorders and OCD entails components like psychoeducation, construction of fear hierarchies, progress tracking, and guidance to conduct exposure exercises (Van Ameringen et al., 2017; Whiteside, Ale, Vickers Douglas, Tiede, & Dammann, 2014; see too, Abramowitz et al., 2018). Case reports suggest this app is effective, showing overall acceptability for children with OCD (Whiteside et al., 2014; Whiteside et al., 2019). Another example is “LiveOCDFree,” a self-help app-guided ERP treatment for OCD. This app

provides guidance on ERP and includes specific components such as help designing an exposure schedule, setting up an ERP hierarchy and reminders for ERP exercises (Boisseau et al., 2017). One open trial (non-controlled) provided preliminary data in support of its efficacy and acceptability; the first study to assess the efficacy of a smartphone intervention for OCD. The study found the app (i.e., 12-week intervention) improved OCD and anxiety symptomatology (Boisseau et al., 2017). All in all, very limited empirical research is available on app-based intervention for OCD. Nonetheless, preliminary findings are promising, suggesting smartphone approaches could potentially improve OCD treatment.

1.2.4 Smartphone technology

Innovative technology-based therapies (Insel et al., 2013; Perna, Grassi, Caldirola, & Nemeroff, 2018; Sahakian, 2014), for example using smartphones— "technology-based personalized medicine" (or TPM for short)—have the potential to transform psychiatry, including the treatment of OCD. By moving therapy out of the clinician's office and into the hands of the patients themselves, these interventions can be tailored to the specific needs of individual patients, which may ultimately improve treatment outcomes. Such interventions, unlike standard CBT treatments, are inexpensive, highly scalable, and can facilitate psychotherapy by making it readily available to patients as they go about in their daily lives, and encourage them to take a more active role in their treatment strategies. Likewise, it can make therapy more available to members of lower SES communities and developing countries with insufficient access to mental health care (Collins et al., 2011). Smartphone interventions can also give patients direct feedback about their treatment progress, provide insight about their condition, as well as pave the way for clinicians to monitor patients' progress in real-time and intervene swiftly if necessary (Luxton, McCann, Bush, Mishkind, & Reger, 2011; Perna et al., 2018). Indeed, smartphone interventions are especially well-suited for modern societies where people, more than ever, are becoming reliant on such technology. Smartphone technology is now adopted by most members of society regardless of social status, and across wide age groups, including preadolescents and the elderly (Pew Research Center, 2018). According to one report there were 3.9 billion smartphone subscribers globally in 2016; the overall number of smartphone subscribers is expected to rise dramatically by the year 2022 (Barboutov et al., 2017) (see also, Jalal et al., 2018).

2. Project aims

2.1 OCD treatment: summary and future directions

At present, as many as 40 percent of OCD patients fail to respond to any kind of treatment, including CBT and/or SRI drugs (Haverkampf, 2014; Fineberg et al., 2018). Developing novel treatments for OCD therefore represents an urgent unmet need. In particular, it is important to design interventions that can target compulsive symptoms in the early stages of the disorder. That is, stimulus-response associations which may drive compulsions often become crystalized by the time patients typically receive a diagnosis and begin treatment. Indeed, similar to other disorders of compulsivity (e.g., addiction) OCD becomes harder to treat during later stages (Gillan et al., 2016). Currently, OCD patients on average initiate effective treatments 17 years after the onset of the disorder (Hollander et al., 1997), stressing the need for early intervention.

As we have seen, a notable limitation of existing psychological therapies for OCD like ERP includes fear of treatment. This results in high rates of treatment refusal and drop-out. There is thus a pressing need for gentler treatments that do not require patients to touch highly anxiety-inducing objects (e.g., indirect approaches). Future treatments may likewise benefit from the strategic incorporation of safety-like behaviors. As reviewed, cautious use of safety behaviors is therapeutically beneficial and may reduce treatment-related fears (i.e., improve acceptability).

Future approaches should also address the limited accessibility of conventional treatment. They should overcome obstacles like high cost, inconvenience of delivery, and geographical isolation. In light of such barriers, unsurprisingly patients treated with CBT often do not receive adequate amounts (Stobie et al., 2007). Currently, around 60 percent of OCD patients stay untreated (i.e., based on a review of epidemiology studies; Kohn, Saxena, Levav, & Saraceno, 2004) (Wootton, 2016); highlighting the need for accessible and cost-effective interventions.

Smartphone interventions may help overcome limitations of conventional treatment. They are cost-effective, efficient (do not require frequent visits to the clinic), can readily reach remote geographical regions, and improve privacy (address stigma concerns) (Boisseau et al., 2017). Such technology is highly transportable. It allows for instantaneous access to treatment in real-life contexts where contamination fears naturally arise. As discussed, context-specific treatment is crucial. In spite of these advantages, few smartphone apps are available for OCD with limited empirical support. Critically, these apps are based on distressing ERP principles.

In sum, the great gap between symptom onset and treatment prolongs the chronicity of OCD (Skoog & Skoog, 1999), results in poorer treatment outcomes (Dell'Osso, Buoli, Hollander, & Altamura, 2010), and unnecessary suffering. As such, it is all the more problematic that a quarter of patients refuse behavioral therapies at the outset mainly due to intolerability issues (Kozak, 1999; Maltby & Tolin, 2005; Schruers et al., 2005). Arguably, the lack of timely access to effective therapy is the foremost problem faced by OCD patients today. Thus, to improve the chronicity, course and ultimately the high disease burden of OCD, it is critical to develop tolerable, accessible and cost-effective therapies (i.e., that can reduce the onset-to-treatment gap). Ideally, such interventions should be tailored to the individual needs of patients ("personalized medicine"), encourage patients to take an active role in their recovery, and promote the learning of adaptive strategies to help eradicate compulsive urges (e.g., Gillan et al., 2016).

We recently conducted two studies that may inform novel tolerable, accessible and low-cost treatments for OCD. In one study, we found that participants with OCD symptoms reported experiencing disgust when watching someone else touching a contaminated object (e.g., fake feces). More intriguingly, after the participants had contaminated themselves, they obtained relief from merely watching someone else washing their own hands. We refer to this effect, that is, the inducing of emotions and sensations vicariously (e.g., disgust and relief), as "vicarious exposure" (Jalal & Ramachandran, 2017). If vicarious observation of certain behaviours can play a comparable functional role for patients as performing them, this may inform novel smartphone interventions for OCD (see Study 3). For instance, if they view video footage of themselves washing hands, on a smartphone when feeling contaminated

(a safety-like behavior) this may trigger sufficient relief to eradicate the urge to engage in handwashing. Short-term handwashing relief might over time lead to the realization that abstaining from the compulsive act brings no harm, thus uncoupling the act from the stimulus. Likewise, if contamination sensations can be induced vicariously, this could inform a smartphone desensitization treatment. Indeed, if patients watch video footage of themselves touching disgust-inducing objects this might over time lead to habituation (for details see Study 1 and Study 3) (Jalal et al., 2018).

In another investigation in healthy volunteers, we explored OCD-like disgust reactions via the "rubber hand illusion" (RHI) (Jalal, Krishnakumar, & Ramachandran, 2015). The RHI is a multisensory effect in which tactile sensations are perceived as arising from a fake hand (Botvinick & Cohen, 1998). Specifically, we found that contaminating the fake hand during the RHI resulted in greater disgust reactions relative to the (illusion attenuating) control condition. Indeed, if contaminating a fake hand during the RHI provokes contamination reactions (akin to ERP) via an immersive multisensory mechanism, this may pave the way for a simple and tolerable treatment technique for OCD (see Study 2) (Jalal et al., in press).

Although this research conducted in a non-clinical population is promising, several key issues remain unresolved. For example, it is known that contamination may be perceived as irrationally spreading in OCD (see Section 1.1.7). Yet there has been no standardized investigation of whether contamination sensations can be induced vicariously in this population. Similarly, no study has assessed whether relief can be induced in OCD (i.e., by watching someone else washing hands). Indeed, if the principle of vicarious exposure is to form the basis for novel smartphone treatments, research should establish whether contamination sensations and relief can be induced vicariously in OCD patients. In the same vein, if the RHI is to form the basis of a novel treatment, research must examine this basic "RHI contamination effect" in OCD. Likewise, if such dummy exposure triggers contamination reactions in OCD, research should explore whether this eventually leads to habituation akin to ERP (Jalal et al., in press). Finally, research should test whether these proposed smartphone interventions can improve OCD symptoms and cognitive function.

2.2 Overall thesis goals

The current PhD thesis explored innovative treatments for OCD with potential to overcome challenges of existing therapies. In light of the reviewed literature, in three programmatic studies the following key research questions were addressed:

(1) Can contamination sensations (e.g., handwashing urges) be induced vicariously in patients with OCD (i.e., by merely watching someone else contaminating himself)? And can relief (e.g., reduction in washing urges) be induced vicariously in OCD (i.e., by simply watching someone else washing his own hands)?
(2) Does "contaminating" the fake hand during the RHI trigger greater contamination sensations as compared to the asynchronous control condition in patients with OCD? And does such dummy exposure over time lead to habituation (akin to ERP)?
(3) If individuals with subclinical contamination fears watch a brief video recording of themselves engaging in handwashing on a smartphone (several times a day, for a week), will this improve OCD symptoms? Similarly, if they watch a video recording of themselves repeatedly touching a disgust-inducing object on a smartphone, will this improve OCD symptoms? As reviewed, given the role of cognitive inflexibility in mediating compulsivity in OCD, found to improve following behavioral therapy, would such smartphone interventions improve cognitive flexibility?

In sum, in light of these overarching scientific objectives, Study 1 examined an indirect form of "exposure" ("vicarious exposure") in a clinical OCD group. It specifically tested whether OCD patients can experience contamination sensations and relief merely by watching an experimenter contaminating himself and washing his own hands. In a thematically related experiment, Study 2 examined the therapeutic utility of the RHI in patients with OCD; i.e., if "contaminating" the dummy during the RHI provokes greater contamination sensations as compared to the asynchronous control condition; and if such contamination eventually results in habituation. Finally, based on the principle of "vicarious exposure," Study 3 investigated whether two novel smartphone interventions (over one week) can improve OCD symptoms and cognitive flexibility relative to a placebo intervention in individuals with subclinical OCD. All in all, this thesis explored innovative yet simple low-cost solutions for treating

OCD—that lend themselves to transportable and highly accessible personalized medicine which allows for optimized targeted therapies. (Detailed study aims, secondary aims, and exploratory aims [e.g., assessing multisensory processing in OCD], as well as explicit hypotheses, are provided in the introductory sections of each of the three studies respectively.)

3. Study 1

Abstract

Obsessive-compulsive disorder (OCD) is a puzzling neuropsychiatric condition that has baffled clinicians and scientists for centuries. It is associated with worldwide suffering. Indeed, OCD patients often feel like they are trapped in a nightmare and their lifestyle is severely compromised. We recently conducted some novel experiments on OCD-like contamination fears with potential treatment implications. Surprisingly, subjects with OCD symptoms reported similar levels of disgust when watching an experimenter touching a "contaminated" object and also when they themselves touched it. More intriguingly however, after subjects had contaminated themselves they experienced relief from merely watching the experimenter washing his own hands. We refer to this effect, the induction of emotions and sensations vicariously, as "vicarious exposure." In the current study, we examined whether contamination sensations and relief can be induced vicariously in severe OCD patients (n = 29) (i.e., undergoing intensive residential treatment) relative to healthy volunteers (n = 34). We found that OCD patients reported greater disgust, anxiety, and handwashing urges when watching the experimenter contaminating himself (i.e., touch a foul-smelling feces replica) than healthy control subjects. But more strikingly, OCD patients, upon first contaminating themselves, reported significant disgust reductions (comparable to actual handwashing) by watching the experimenter washing his own hands, relative to control conditions; and displayed a (nonsignificant) tendency towards disgust reductions during vicarious handwashing relative to control conditions, compared to healthy volunteers. Finally, an exploratory analysis found that patients with moderate symptoms, unlike severe patients, reported greater reductions in disgust and handwashing urges from vicarious handwashing relative to control conditions, compared to healthy controls; and a tendency towards anxiety reductions during vicarious handwashing. This study is the first to demonstrate that patients with OCD can experience contamination sensations (e.g., handwashing urges) and relief merely by observing an experimenter contaminating himself and washing his own hands. These highly counterintuitive results may pave the way for innovative therapies for OCD using smartphone technology.

Reference: Jalal, B., McNally, R. J., Elias, J., & Ramachandran, V.S. (in review). “Vicarious exposure”—"spooky action” at a distance in obsessive-compulsive disorder.

3.1 Study aims

Jalal and Ramachandran (2017) recently revealed the impact of vicarious, rather than direct, exposure on OCD-like contamination fears, with potential implications for therapy (see pages 31-32). These findings are consistent with research showing that brain regions involved in the processing of disgust (such as the insula) become activated not only when people experience this emotion themselves (Royet et al., 2003), but also when they watch someone else experience disgust (Wicker et al., 2003) (Jalal et al., 2018).

This type of empathetic response has been found to activate the anterior cingulate cortex, and is thought to be mediated by the activity of the mirror neuron system (MNS) (Wicker et al., 2003; on the MNS, see also Iacoboni et al., 2005; Rizzolatti, 2005). The MNS is purportedly involved in various aspects of human social cognition (Gallese, Keysers, & Rizzolatti, 2004). Mirror neurons are cells that become activated both when performing a certain action and when observing someone else performing the same action (Rizzolatti, Fogassi, & Gallese, 2001). While single-unit recording studies have revealed the activity of mirror neurons in the macaque (Gallese, Fadiga, Fogassi, & Rizzolatti, 1996), there is indirect evidence of a MNS in humans (e.g., Iacoboni et al., 1999; although the existence of these mirror-like cells in humans has been debated by researchers; for a review see, Heyes, 2010). Research on the function of the MNS in humans has focused both on action/execution (e.g., Hari et al., 1998), and emotion—that is, feeling the same emotion as others (e.g., Pfeifer, Iacoboni, Mazziotta, & Dapretto, 2008).

If vicarious observation of repetitive behaviors can play a functional role for OCD patients that is similar to actually performing them, it may inform novel smartphone interventions (i.e., using “vicarious exposure” procedures). It is plausible that OCD patients may experience relief from watching a video recording of themselves washing hands, on a smartphone as they go about their daily lives. Such a procedure could possibly be used as part of a treatment regimen. It would be particularly helpful in cases where cleansing routines

prevent patients from leaving their home or excessive washing rituals result in skin damage. Over time, the intervention might eliminate the compulsive ritual (decouple the ritual from the stimulus) or replace it—become a "benign substitute compulsion." Similarly, if OCD patients were to watch video footage of themselves touching a disgust inducing object on a smartphone, this could form a novel type of desensitization therapy (i.e., lead to habituation). As this intervention is conducted in a real-life setting, unlike the artificial environment of the clinic, it might accelerate stimulus generalization, enhancing therapeutic efficacy (Jalal et al., 2018).

Such interventions have the potential to overcome limitations of existing therapies for OCD; such as, cost, inconvenience of delivery, and intolerability of the treatment procedures (Abramowitz, 2006; Whittal, Thordarson, & McLean, 2005). In contrast to ERP, they do not involve patients touching highly disgust-provoking "contaminants." They may therefore provide a tolerable route to the treatment of OCD due to the "vicarious" approach (i.e., lack of direct skin contamination), which might appeal to the many patients who fear ERP. Indeed, up to a quarter of OCD patients refuse behavioral therapies chiefly due to intolerability issues (Kozak, 1999; Maltby & Tolin, 2005 Schruers et al., 2005). These interventions may be ideal for targeting compulsions during the early stages of the disorder before symptoms worsen (stimulus-response links crystalize) and become hard to treat (Gillan et al., 2016).

In the current study—building on the findings of Jalal and Ramachandran (2017) regarding "vicarious exposure"—the primary aim was to examine whether patients with OCD can experience contamination sensations (e.g., handwashing urges) merely by observing an experimenter contaminating himself. And whether patients upon first contaminating themselves can experience relief by simply watching an experimenter washing his own hands.

3.2 Hypotheses

If college students with elevated OCD symptoms experience disgust when watching someone else touching a contaminated object (Jalal & Ramachandran, 2017), this should also hold true

for OCD patients with contamination obsessions. As noted, OCD is associated with heightened disgust, including a propensity towards cognitive errors such as sympathetic magic. Indeed, the law of contagion suggests these patients may experience contamination from watching someone else contaminating himself. Moreover, the law of similarity implies that OCD patients should experience contamination when touching artificial contaminants known to be fake (e.g., fake feces). Given *in vivo* exposure triggers anxiety and cleansing urges (Cougle et al., 2007; Rachman, 2004), and disgust drives contamination fears (for a review see Olatunji, Cisler, McKay, & Phillips, 2010), vicarious contamination should increase anxiety and washing urges as well as disgust. Hence, OCD patients should experience greater vicarious contamination sensations than should healthy volunteers who are less prone to disgust- and contamination-related vulnerabilities.

Furthermore, given that college students with subclinical OCD symptoms experience vicarious relief from contamination, OCD patients should, too. Indeed, reminiscent of patients with OCD, these students sometimes describe highly idiosyncratic and perfectionistic methods of vicarious de-contamination that must be performed for them to feel "just right" (Jalal & Ramachandran, 2017; see also, Abramowitz, 2006; Abramowitz et al., 2009). This suggests that clinical urges, too, can be interrupted via vicarious cleansing. Moreover, research favors *in vivo* over imaginal exposure for OCD (Foa et al., 1985), implying the importance of sensory input during treatment (e.g., visual feedback). That is, merely imagining distressing scenarios seems less effective than experiencing them in a fully sensorial manner. Thus, vicarious observation of handwashing (after self-contamination), should trigger greater relief than imagining ritualized handwashing. Also, given contamination feelings in OCD initially intensify (e.g., 45 min. of exposure may be required for habituation; see Jalal et al., in press), visual distraction (watching arbitrary hand-motions), unlike vicarious handwashing, should not reduce contamination sensations. Finally, OCD patients should experience greater vicarious handwashing relief than should healthy volunteers after self-contamination, especially when participants know the contaminants are not authentic. This hypothesis is based on the fact that unlike OCD patients, healthy individuals do not experience intense contamination fears and compulsive urges, rendering them largely insensitive to such (fake) contamination and vicarious relief procedures. Taken

together, assuming that: (1) contamination sensations can arise vicariously in OCD and (2) relief can be induced via vicarious washing in this group, we advanced the following hypotheses:

Vicarious contamination: we hypothesized that OCD patients would report greater disgust, anxiety, and handwashing urges when watching the experimenter contaminate himself (repeatedly touch the disgust stimulus, i.e., known to be fake) compared to non-anxious controls (NACs).

Vicarious relief: we hypothesized that OCD patients, upon contaminating themselves, would report greater relief (i.e., lower disgust, anxiety and handwashing urges) when watching the experimenter wash his hands, compared to the control conditions (watching the experimenter do sequential hand movements or imagining the experimenter washing his hands), relative to NACs.

We also explored if symptom severity would impact vicarious handwashing relief; that is, whether patients with moderate symptoms or more severe patients (divided based on empirically derived clinical classification; Storch et al., 2015) would experience greater vicarious relief. Compulsive symptoms become crystalized over time, becoming increasingly difficult to interrupt. Indeed, entrenched and severely pathological associations are more immune to extinction, which is why OCD increasingly becomes harder to treat (Gillan et al., 2016). Thus, it is plausible that patients with moderate symptoms will experience greater vicarious relief compared to severe patients. It might be more difficult to disrupt stimulus-response links in the latter group; i.e., by introducing a "benign substitute compulsion"—vicarious ritualizing.

Moreover, in two exploratory conditions, we examined whether disgust, anxiety, and handwashing urges would differ when participants first watched the experimenter contaminate himself and then watched the same experimenter wash his hands versus watching a different experimenter wash his hands. Given college students with OCD symptoms, after watching one experimenter contaminating himself experience relief by

observing another experimenter washing hands—suggesting disgust reactions can override cognitive inferences—this should also hold for OCD patients; particularly in view of the role of disgust in OCD. Because these inquiries were exploratory, we did not propose a priori directional hypotheses.

3.3 Methods

3.3.1 Participant selection

OCD patients undergoing intensive residential treatment (IRT) were recruited for research participation at the Obsessive-Compulsive Disorder Institute (OCDI) at McLean Hospital, a psychiatric facility affiliated with Harvard Medical School. At the OCDI patients receive intensive (2-4 hours daily) of cognitive-behavioural therapy and psychopharmacological management; i.e., by a team of behavioural and family therapists, and psychiatrists etc. Medications are used on case-to-case basis (i.e., determined during weekly psychiatric assessment), and often include, SSRIs (e.g., venlafaxine and clomipramine), and antipsychotics (i.e., as an adjunct to SSRIs). Although, treatment duration is based on individual need, patients on average remain at the OCDI for 45 days, with 25 percent of patients for at least 12 weeks (Athey et al., 2015). Inclusion criteria for admission to the OCDI include major OCD-related functional impairment and lack of response to treatment in other settings. The program does not have official exclusion criteria, but patients are not admitted if they have a condition that would interfere with treatment; e.g., severe intellectual disability (mental retardation or neurodevelopmental disorders etc.), current substance abuse, and active psychosis (see also Stewart, Stack, Farrell, Pauls, & Jenike, 2005) (Jalal et al., in press).

In the current study, all participants were diagnosed with OCD by an expert clinician on staff as part of standard clinical procedures based on DSM-IV or DSM-5 criteria and had disgust- and/or contamination-related obsessions. The presence of disgust- and contamination-related symptoms were defined by elevated scores on the Disgust Propensity and Sensitivity Scale-Revised (DPSS-R; van Overveld et al., 2006) and endorsement of contamination obsessions on the Dimensional Obsessive-Compulsive Scale (DOCS; Abramowitz et al., 2010) (completed as part of an admission's battery of questionnaires). This clinical

assessment was not based on a specific cut-off score but whether such symptoms were present (i.e., akin to the Yale-Brown Obsessive-Compulsive Scale symptom checklist; Goodman et al., 1989) (Jalal et al., in press).

The above noted OCDI selection criteria were applied. As such, patients on medication (e.g., SSRIs and antipsychotic agents) were not excluded. None currently was psychotics. Given all patients were undergoing intensive residential treatment, they were only selected for participation insofar that it would not interfere with their treatment (Jalal et al., in press).

Information regarding comorbid psychiatric diagnoses was available for 27 patients (i.e., out of 30). (Comorbidity data were missing due to logistic reasons, e.g., patients discharging prior to program completion or unavailability of staff to conduct interviews to determine co-occurring conditions.) Of these 27 patients, 92.6 percent (25/27) had OCD as a primary diagnosis and 3.7 percent (1/27) as a secondary diagnosis (data regarding whether OCD or a related mood disorder was primary was unavailable for one patient). Individuals who did not have a primary diagnosis of OCD were diagnosed with an obsessive-compulsive related disorder (e.g., body dysmorphic disorder: 3.7 percent; 1/27) or a related mood disorder (e.g., bipolar disorder I: 3.7 percent; 1/27) (Jalal et al., in press).

Moreover, 74.1 percent (20/27) of participants had at least one comorbid axis I diagnosis. Frequencies of most co-occurring disorders were: major depressive disorder (29.6 percent; 8/27), dysthymic disorder/persistent depressive disorder (18.5 percent; 5/27), post-traumatic stress disorder (18.5 percent; 5/27), and generalized anxiety disorder (14.8 percent; 4/27); followed by eating disorder NOS/other specified feeding or eating disorder (11.1 percent; 3/27), specific phobia (11.1 percent; 3/27), excoriation/skin-picking disorder (7.4 percent; 2/27), panic disorder (7.4 percent; 2/27), hoarding disorder (7.4 percent; 2/27), bulimia nervosa (3.7 percent; 1/27), illness anxiety disorder (3.7 percent; 1/27), body dysmorphic disorder (3.7 percent; 1/27), depressive disorder NOS (3.7 percent; 1/27), and trichotillomania (3.7 percent; 1/27). Participants' past diagnoses (i.e., prior to attending the OCDI), included (but were not restricted to): alcohol abuse, eating disorder NOS, major depressive disorder, specific phobia, anorexia nervosa, excoriation/skin-picking disorder, and

stimulant use disorder etc. Finally, for these 27 patients for which comorbidity information was available, no patient endorsed autism spectrum disorder (i.e. on a self-reported diagnosis checklist) (Jalal et al., in press).

Healthy control participants, without a history of OCD and other anxiety disorders, were recruited from the local community via advertisement, and through the Harvard Study Pool comprising participants from the Cambridge-Boston area as well as students at the university. Control participants interested in participating received a brief phone screen to ascertain their eligibility. During this phone screen potential volunteers were administered the OCD and other anxiety disorder modules from the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) to ensure that none had current or past OCD or anxiety disorders. If eligible, control participants were tested in our lab in the Department of Psychology at Harvard University. All participants had to range in age between 18 and 65 years old, and all had to be proficient in English.

Although OCD patients were undergoing IRT, relying on a community-based sample of healthy controls was appropriate for several reasons. The OCDI IRT program often includes refractory individuals but is a level beneath inpatient treatment; reserved for the severely debilitated patients (e.g., at suicide risk; Veale et al., 2016). The OCDI is specifically suited for "individuals with moderate to severe or treatment-resistant OCD" (https://www.mcleanhospital.org/treatment/ocd-institute), who are relatively well-functioning (e.g., do not require constant monitoring) (see too, Veale et al., 2016). Moreover, patients in this study were doing reasonably well overall, evident by the fact that they were willing to participate; indeed, the decision to invite them was decided in coordination with the patient's treatment team at the OCDI that vouched for their suitability. Thus, the current OCD sample is best characterized as moderate to severe; with one analysis explicitly dividing the group into a "moderate" and combined "moderately-severe and severe" OCD subgroup. In brief, our patients (although often refractory and severe) were insufficiently distinct from OCD outpatients to form a meaningful comparison group. Accordingly, we recruited a healthy community-based comparison group.

3.3.2 Procedure

The protocol was approved by Harvard University's Committee on the Use of Human Subjects, and McLean Hospital's institutional review board formally ceded review to Harvard's committee. All participants provided written informed consent prior to participation in the study and received $20 for their time.

OCD participants and NACs were matched for age and sex. The experiment consisted of a baseline assessment and 6 conditions involving 2 steps (each step 30 seconds in duration). At baseline the participant viewed the disgust stimulus (i.e., fake feces in a bedpan placed on a table in front of the participant) for 30 seconds. Condition 1: the participant repeatedly touches the disgust stimulus (Step 1), and then washes his own hands (i.e., with soap and water at a basin) (Step 2). Condition 2: the participant touches the disgust stimulus (Step 1), and then watches the experimenter washing his own hands (Step 2). Condition 3: the participant touches the disgust stimulus (Step 1), and then watches the experimenter doing arbitrary hand movements (Step 2). Condition 4: the participant touches the disgust stimulus (Step 1), and then closes his eyes and imagines the experimenter washing his own hands (Step 2). Condition 5: the participant watches the experimenter ("A") touching the disgust stimulus (Step 1), and then watches the same experimenter ("A") washing his own hands (Step 2). Condition 6: the participant watches the experimenter ("A") touching the disgust stimulus (Step 1), and then watches a different experimenter ("B") washing his own hands (Step 2). Promptly after the completion of each step (i.e., Step 1 and Step 2 in all conditions including baseline assessment), the experimenter asked the participant to provide subjective ratings of disgust, anxiety and handwashing urge levels on a 10-point Likert scale. The experimenter also rated the participant's facial expression of disgust (either present or not).

After completion of each condition (i.e., conditions 1 to 6), the experimenter removed the disgust stimulus from the testing area such that it was no longer visible to the participant (e.g., taken to the adjacent room). There was a natural (untimed) brief break between each condition (i.e., with the disgust stimulus completely out of sight). Before starting each condition, the experimenter explicitly asked the participant if he or she was ready to proceed to the next step (e.g., from Condition 1 to Condition 2). The experimenter told the participant,

“We will now bring in the same object [disgust stimulus] and we would like you to lightly touch it just as before. I will be asking you questions again. And just as before, we’d like you to continue touching and looking at the object as you answer. Do you feel ready to proceed?” The order in which the participants completed conditions 1 to 6 was counterbalanced, such that half the participants started with Condition 1 and the other started with Condition 6. Conditions 3 and 4 served as control procedures to rule out that merely watching someone else doing arbitrary hand movements or imagining someone else washing their hands (i.e., in the absence of visual feedback) would generate vicarious relief. During Conditions 5 and 6 the experimenter exhibited a facial expression of disgust while touching the disgust stimulus (i.e., Step 1). An overview of the conditions is shown in Figure 3.1.

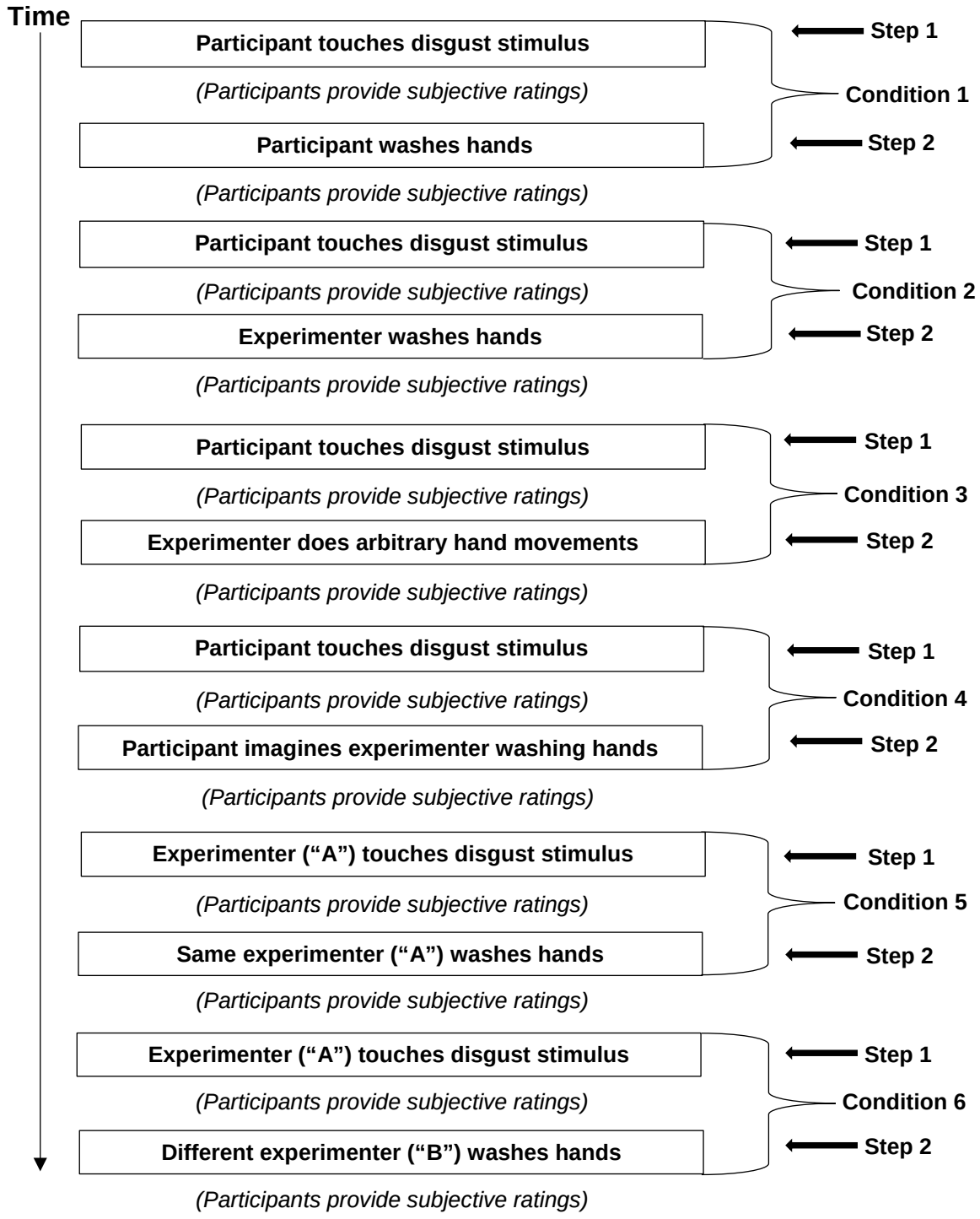

Figure 3.1 Overview of the Conditions

[a] The order of conditions 1 to 6 was reversed for half of the participants.

In Condition 3, the arbitrary hand movements consisted of a cutting motion, then a fist, followed by palm down with fingers extended ("cut, fist, and slap"; Luria, 1970). To avoid inducing (vicarious) contamination distress the sequential hand movements were made in mid-air, without the experimenter's hands touching the surface of the table (see Figure 3.2).

Figure 3.2 Arbitrary Hand Movements (Control Procedure)

3.3.3 Materials and measures

Yale-Brown Obsessive-Compulsive Scale (Y-BOCS)

The Y-BOCS (Goodman et al., 1989) assesses severity of obsessions and compulsions. Scores are generated from a total of 10 items, each rated on a 5-point Likert scale. Scores range from 0 to 40. In the current study, the self-report version of the Y-BOCS was used (Steketee, Frost, & Bogart, 1996).

Disgust stimulus

The disgust stimulus comprised a mixture of chocolate and peanut butter, sprayed with a joke-shop odor. It had both the visual appearance and smell of genuine feces, and was placed in a bedpan. Unlike our previous methodology (e.g., Jalal et al., 2015; Jalal & Ramachandran, 2017), participants were informed before partaking in the study that the stimulus was in fact not genuine feces (see Figure 3.3). (According to research, healthy volunteers are hesitant to eat chocolate shaped as feces, even when told that the objects are food items [Rozin et al., 1986], illustrating how disgust reactions can override such top-down factual knowledge.)

Figure 3.3 Disgust Stimulus

Disgust, anxiety, and handwashing urge ratings

Participants provided ratings of disgust, anxiety and handwashing urges on a 10-point Likert scale ranging from 1 (not at all) to 10 (extremely), during the following 7 steps: when the participant (1) views the disgust stimulus, (2) touches the disgust stimulus, (3) washes his own hands with soap and water, (4) observes the experimenter washing his own hands, (5) observes the experimenter making sequential hand movements, (6) closes his/her eyes and imagines the experimenter washing his own hands, (7) observes the experimenter touching the disgust stimulus. To further assess participants' disgust reactions, we observed and noted

whether their facial expression indicated disgust (or not) during each of these steps. (The universal facial expression of disgust includes, closing the nostrils and opening the mouth, facial areas involved in smelling and rejecting food [e.g., Rozin & Fallon, 1987; see, also Ekman, 1993; Tottenham et al., 2009].)

3.3.4 Statistical analyses

The study included a quantitative between-subject cross-sectional design comparing two groups (OCD patients and NACs) on the experimental and control procedures. It assessed various types of exposure including, vicarious contamination and vicarious relief; focusing on both the within-subject and between-subject effects. The study targeted the following primary outcome variables: self-reported ratings of disgust, anxiety, and handwashing urges. Participants' disgust facial expression (rated by the experimenter) constituted a secondary outcome measure of disgust reactions.

Specific hypotheses (i.e., pertaining to vicarious contamination and relief) were tested using contrast analysis (Rosenthal & Rosnow, 1985). For exploratory analyses, dependent variables were analyzed using contrast analysis, multivariate analysis of variance (MANOVA) and mixed MANOVA; followed up with either discriminant function analysis or one-way ANOVAs. The chi-square and the McNemar tests were used to analyze the facial expression of disgust dependent variables. The McNemar test was not corrected for continuity; such adjustment can be too conservative (Lui, 2001), and the test is robust even without this correction (Yang, 2013).

To control for possible Type I errors, we used Benjamini and Hochberg's (1995) false discovery rate (FDR) (e.g., McDonald, 2014), for all analyses testing a priori hypotheses, including one-tailed *t* tests and *z* tests. The FDR was set at $q < 0.15$ consistent with other studies (e.g., Skandali et al., 2018) and recommendations in the field (e.g., Genovese, Lazar, & Nichols, 2002). The Benjamini-Hochberg adjusted significance level was 0.067. *P*-values displayed in the text are raw (non-adjusted) but labelled as either significant or nonsignificant per the multiplicity correction (e.g., McDonald, 2014). Given the high volume of tests, exploratory (non-hypothesis driven) analyses (e.g., baseline tests) were

not corrected for multiple comparisons. Multiplicity adjustment is unnecessary when one labels such tests as exploratory (Bender & Lange, 2001).

For all measures, the distribution of residuals was checked with Q-Q plots and the Shapiro-Wilk test. Preliminary examination showed that residuals often departed from normality. These dependent variables were subjected to a $\log_{10}(x + 1)$ and a square-root transformation to test whether these improved matters (Myers & Well, 2003). In a few cases, transformations were impossible, as dependent variables had negative values (i.e., computed difference scores). As the *F* test and *t* test generally are robust to minor violations (Blanca, Alarcón, Arnau, Bono, & Bendayan, 2017), we overall report findings for untransformed data. Finally, on all figures (i.e., box plots) a circle (o) signifies an individual data point, a cross (+) denotes the sample mean, and an asterisk (*) a statistically significant result.

3.4 Results

Thirty OCD patients and 34 NACs completed the study. Data on some measures (i.e., subjective ratings of disgust, anxiety and handwashing urges, and facial expression of disgust) were not obtained for a few participants during some of the conditions. One OCD patient did not provide consent for their demographic and Y-BOCS data to be used (Y-BOCS, $n = 28$). Likewise, one OCD patient was excluded from analyses for not exhibiting an adequate contamination fear response throughout the experiment (e.g., with average contamination ratings as low as 2 out of 10 in intensity when both viewing and touching the disgust stimulus at baseline [i.e., Condition 1]). The final sample size for each analysis is displayed directly in the text below. For demographic and clinical characteristics of the final sample, see Table 3.1.

Table 3.1 Demographic and Clinical Characteristics of Participants[a]

Group	**OCD**		**NAC**		***Comparison***
	***(n = 28)**		**(*n* = 34)**		
	μ	**(*SD*)**	μ	**(*SD*)**	F_{df}
Age	26.57	(6.67)	26.03	(7.50)	† $F_{1,60} < 1$, NS
Y-BOCS	26.36	(6.29)	-	-	-
	n	**(%)**	***n***	**(%)**	X^2_{df}
Sex (*n*/% female)	22	(78.6)	30	(88.2)	$X^2_1 = 1.06$, $p = 0.30$

[a]μ, mean; *SD*, standard deviation; *n*, sample size; *F*, *F* statistic; X^2, chi-square statistic; *df*, degrees of freedom; *p*, *p* value; NS, non-significant; OCD, obsessive-compulsive disorder; NAC, non-anxious control; Y-BOCS, Yale-Brown Obsessive-Compulsive Scale; (*) One OCD patient did not provide consent for their demographic and Y-BOCS data to be shown; (†) After applying a $\log_{10}(x + 1)$ transformation.

Baseline ratings

Viewing the disgust stimulus

A MANOVA compared ratings of disgust, anxiety and handwashing urges in the OCD (n = 29) and NAC group (n = 34) when viewing the disgust stimulus. As expected, the MANOVA revealed that OCD participants reported significantly higher contamination sensations overall (i.e., disgust, anxiety and handwashing urges) when viewing the disgust stimulus compared to NACs ($F_{3,59} = 20.40$, $p = 3.44 \times 10^{-9}$). The MANOVA was followed up with a discriminant function analysis that revealed one discriminant function, which significantly differentiated the OCD and NAC group (Wilks' lambda $\lambda = 0.49$, $\chi^2_3 = 42.34$, $p = 3.40 \times 10^{-9}$). A canonical correlation of 0.71 showed that the model explained 51 percent of the variation in the group variable. The discriminant function analysis revealed that anxiety ratings had the highest standardized canonical discriminant function coefficient ($\beta = 1.22$) indicating the greatest contribution to the model (i.e., the best discriminator between the two groups); followed by disgust ($\beta = -0.46$) and then washing urge ratings ($\beta = 0.07$). Finally, a

chi-square test showed that a lower proportion of OCD participants (n = 28) exhibited a facial expression of disgust when viewing the disgust stimulus compared to NACs (n = 34) (46.4 percent versus 76.5 percent; $\chi^2_1 = 5.94$, $p = 0.01$).

Self-contamination

A repeated measures MANOVA was conducted on the disgust, anxiety and handwashing urge ratings during Step 1 of Conditions 1 to 4 (i.e., participants touch the disgust stimulus). The effect of Condition was nonsignificant in both the OCD group (n = 29; $F_{9,20} = 1.75$, p = 0.14) and the NAC group (n = 34; $F_{9,25} = 1.37$, $p = 0.25$). Finally, a chi-square test confirmed that an equal proportion of OCD participants (n = 28) exhibited a facial expression of disgust when touching the disgust stimulus in Conditions 1 to 4, ($\chi^2_3 = 1.75$, $p = 0.63$) as did the NACs (n = 34) ($\chi^2_3 = 1.70$, $p = 0.64$).

Self-contamination and handwashing

To examine levels of disgust, anxiety and handwashing urges when OCD participants (n = 29) and NACs (n = 33) first contaminated themselves (i.e., repeatedly touched the disgust stimulus) (Step 1), and then washed their hands (Step 2), we conducted a two-way MANOVA on the dependent variables. A 2 (Step: 1, 2) × 2 (Group: OCD, NAC) analysis revealed a main effect of Step ($F_{3,58} = 30.41$, $p = 6.09 \times 10^{-12}$) and a main effect of Group ($F_{3,58} = 21.05$, $p = 2.39 \times 10^{-9}$). None of the remaining effects was significant, including the Step × Group interaction ($ps \geq 0.135$). A McNemar test revealed a reduction in the proportion of participants who exhibited a facial expression of disgust from Step 1 (touching the disgust stimulus) to Step 2 (washing hands) in the OCD group (n = 28) (i.e., 50.0 percent versus 21.4 percent; $\chi^2_1 = 4.57$, $p = 0.03$), as well as the NAC group (n = 33) (i.e., 60.6 percent versus 0 percent; $\chi^2_1 = 20.00$, $p = 8.00 \times 10^{-6}$).

Self-contamination versus vicarious contamination

A MANOVA tested levels of disgust, anxiety and handwashing urges when participants touched the disgust stimulus (self-contamination) versus when participants observed the experimenter touch the disgust stimulus (vicarious contamination), in the OCD (n = 29) and NAC group (n = 34). A 2 (Exposure-type: direct-exposure, vicarious-exposure) × 2 (Group:

OCD, NAC) two-way MANOVA revealed direct exposure provoked more intense responses than vicarious exposure ($F_{3,59} = 18.41$, $p = 1.51 \times 10^{-8}$) and that the OCD group reported more intense responses than the NAC group did, ($F_{3,59} = 22.34$, $p = 8.67 \times 10^{-10}$). The Exposure-type × Group interaction was nonsignificant ($F_{3,59} = 1.40$, $p = 0.25$).

Self-contamination versus vicarious contamination in the OCD group

A repeated measures MANOVA tested levels of disgust, anxiety and handwashing urges when OCD participants ($n = 29$) touched the disgust stimulus (self-contamination) versus when they observed the experimenter touch the disgust stimulus (vicarious contamination). The analysis revealed a main effect of Exposure-type ($F_{3,26} = 6.33$, $p = 0.002$). Follow-up one-way ANOVAs showed that levels of disgust ($F_{1,28} = 1.09$, $p = 0.30$) and anxiety ($F_{1,28} < 1$, NS) did not differ during self-contamination and vicarious contamination; however, handwashing urge levels were significantly higher during self-contamination versus vicarious contamination ($F_{1,28} = 13.32$, $p = 0.001$) (see Figure 3.4). Finally, a chi-square test showed that an equal proportion of participants in the OCD group ($n = 29$) exhibited a facial expression of disgust during self-contamination versus vicarious contamination ($\chi^2_1 < 1$, NS).

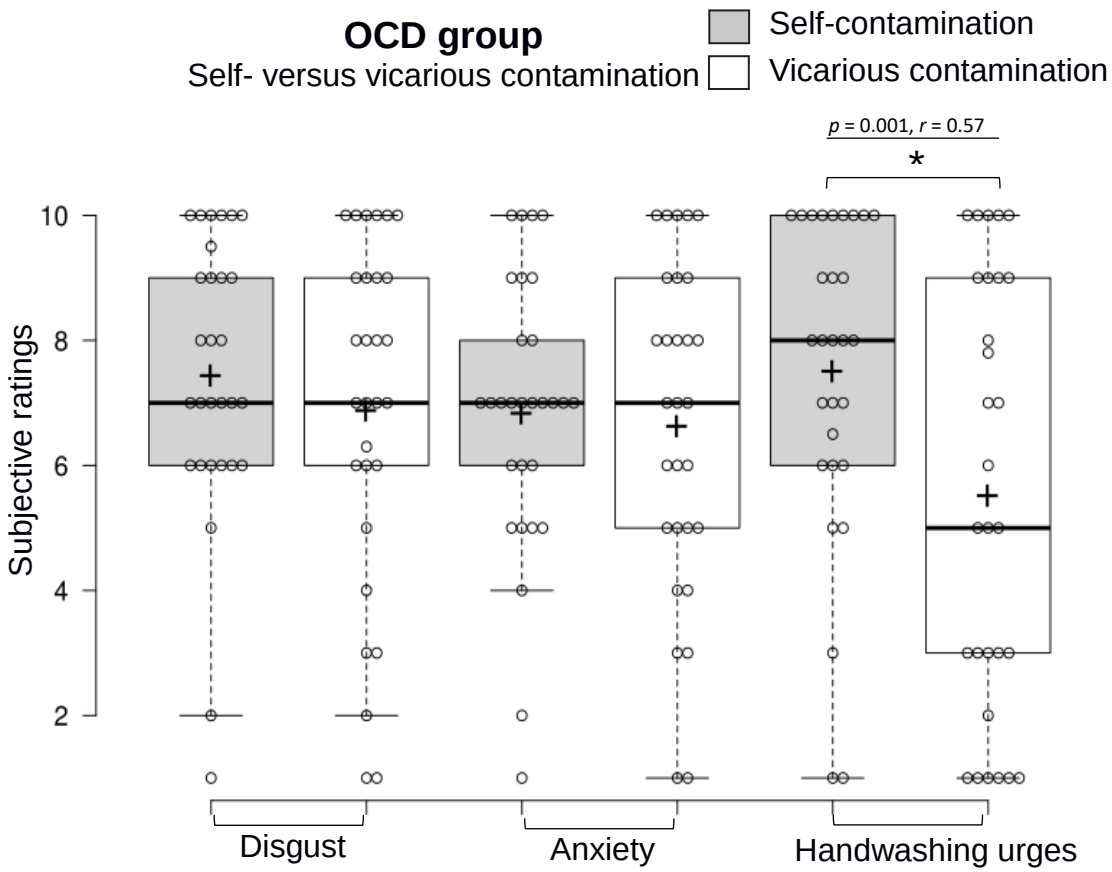

Figure 3.4 Self-Contamination Versus Vicarious Contamination in the OCD Group[a]

[a]Disgust and anxiety did not differ during self-contamination versus vicarious contamination; however, handwashing urge levels were significantly higher during self-contamination versus vicarious contamination.

Vicarious contamination

We used one-tailed, single degree of freedom, focused contrast analyses and computed effect size *r*, to test the hypothesis that OCD patients (n = 29) would report higher disgust, anxiety and handwashing urges when watching the experimenter touch the disgust stimulus (i.e., vicarious contamination) than would NACs (n = 34). This hypothesis was supported for disgust (t_{61} = 3.75, p = 0.0002, one-tailed, r = 0.43, Benjamini-Hochberg corrected), anxiety (t_{61} = 6.63, $p = 9.94 \times 10^{-9}$, one-tailed, r = 0.65, Benjamini-Hochberg corrected) and

handwashing urges ($t_{48.56}$ = 3.89, p = 0.0003, one-tailed, r = 0.49, Benjamini-Hochberg corrected) (see Figure 3.5). Finally, an equal proportion of OCD (n = 29) and NAC participants (n = 34) exhibited a facial expression of disgust during vicarious contamination (z_2 = -0.24, p = 1.62, one-tailed, r = 0.03, Benjamini-Hochberg corrected).

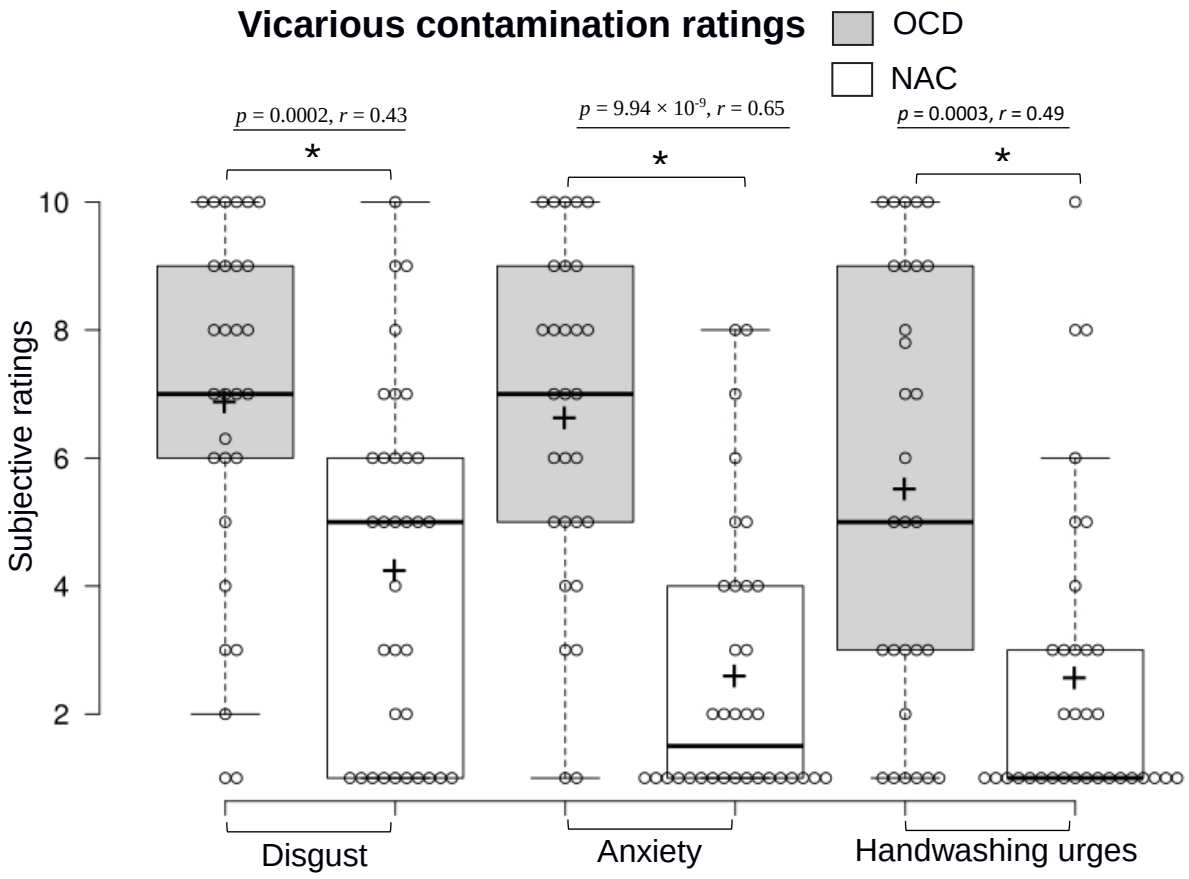

Figure 3.5 Vicarious Contamination Ratings in the OCD and NAC Group[a]

[a]Disgust, anxiety and handwashing urge levels were significantly higher for OCD participants versus NACs during vicarious contamination.

Vicarious handwashing relief

Next, using focused contrasts, we compared the active vicarious handwashing condition—that is, participants first contaminate themselves (Step 1) and then watch the experimenter wash his own hands (Step 2) (Condition 2)—to the two placebo control conditions (i.e.,

participants first contaminate themselves [Step 1], and then either watch the experimenter do complex hand movements [Condition 3], or imagine the experimenter wash his own hands [Condition 4]). We first computed difference scores from participants' contamination ratings (disgust, anxiety and handwashing urges) during the two time points to reflect a relief score: Step 1 minus Step 2 (e.g., in Condition 2: ratings during self-contamination minus ratings during vicarious handwashing). We used contrast weights of 2, -1 and -1 to test the hypothesis that OCD participants (n = 29) would report greater relief (reductions in disgust, anxiety, and handwashing urges) during vicarious handwashing (after self-contamination) compared to the two control conditions. As hypothesized, OCD participants reported greater disgust-related relief (i.e., reductions in disgust) during the active vicarious handwashing condition compared to the two control conditions (t_{28} = 1.62, p = 0.058, one-tailed, r = 0.29, Benjamini-Hochberg corrected) (see Figure 3.6); however, the active condition did not differ from the control conditions vis-à-vis anxiety-related relief (t_{28} = 0.15, p = 0.44, one-tailed, r = 0.03, Benjamini-Hochberg corrected), and handwashing urge-related relief (t_{28} = -0.15, p = 1.76, one-tailed, r = 0.03, Benjamini-Hochberg corrected). A z test using contrast weights of -2, 1 and 1, showed that an equal proportion of OCD participants (Cond. 2: n = 28, Cond. 3: n = 29, Cond. 4: n = 28) exhibited a facial expression of disgust during the vicarious handwashing condition versus the two control conditions (i.e., Step 2), (z_2 = 0.42, p = 0.34, one-tailed, r = 0.05, Benjamini-Hochberg corrected). (An exploratory follow-up t test showed that in the OCD group [n = 29] disgust-related relief did not significantly differ during actual handwashing [Condition 1] versus vicarious handwashing [Condition 2], but revealed a trend [t_{28} = 1.54, p = 0.13, two-tailed, r = 0.28]; similarly, the proportion of OCD participants who displayed a facial expression of disgust during actual handwashing and vicarious handwashing did not differ [$\chi^2_1 < 1$, NS].)

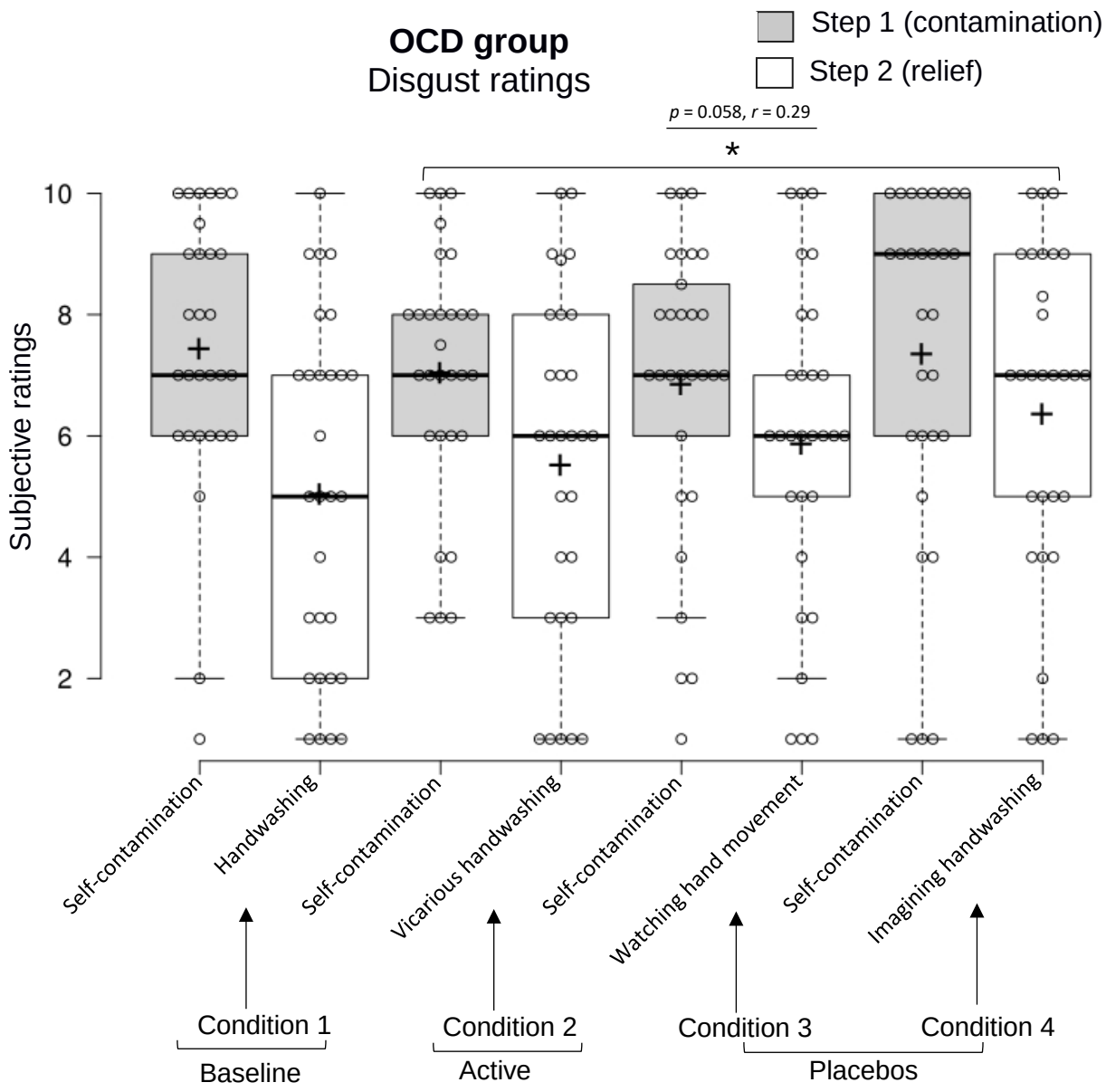

Figure 3.6 Disgust Ratings During Conditions 1 to 4 in the OCD Group[a]

[a]OCD participants reported significantly greater disgust-related relief during vicarious handwashing compared to placebo conditions.

Next, using contrast analysis, we tested the hypothesis that the OCD group (n = 29) would report greater relief during the vicarious handwashing condition (Condition 2) relative to the

two control conditions (i.e., Condition 3 and Condition 4), compared specifically to the NAC group (n = 34) (i.e., a more focused approach to a 3 [Condition] x 2 [Group] repeated-measures ANOVA). This analysis was done only for disgust-related relief, as anxiety and handwashing urge-based relief did not differentiate the active condition and the control conditions in the OCD group (as reported above). Using contrast weights of 2, -1 and -1, we found a nonsignificant tendency for the OCD participants to show disgust-related relief (i.e., disgust reductions) during vicarious observation of handwashing relative to the two control conditions, compared to the NACs (t_{61} = 1.05, p = 0.15, one-tailed, r = 0.13, Benjamini-Hochberg corrected).

OCD severity and vicarious relief

In an exploratory follow-up analysis, we divided patients into two groups based on empirically derived Y-BOCS criteria (i.e., benchmarks for clinical severity): moderate OCD (Y-BOCS = 14-25) versus combined moderately-severe and severe OCD (Y-BOCS ≥ 26), (Storch et al., 2015). (One patient met criteria for mild OCD [Y-BOCS = 0-13] but was included in the moderate group.) Contrast analysis showed that moderate OCD patients (n = 11; μ = 20.55, SD = 5.63) reported significantly greater disgust-related (t_{43} = 2.56, p = 0.007, one-tailed, r = 0.36) and handwashing-related relief (t_{43} = 2.51, p = 0.008, one-tailed, r = 0.36), during vicarious handwashing relative to the two control conditions, compared to NACs (n = 34); and tended to report greater anxiety-related relief (t_{43} = 1.35, p = 0.09, one-tailed, r = 0.20), (for ratings during self-contamination and vicarious handwashing in the OCD and NAC group, see Figure 3.7). In contrast, for the severe OCD group (n = 17; μ = 30.12, SD = 2.96), disgust-related (t_{49} = -0.33, p = 1.48, one-tailed, r = 0.05), anxiety-related (t_{49} = -1.07, p = 0.58, one-tailed, r = 0.15), and handwashing urge-related relief (t_{49} = 0.48, p = 0.32, one-tailed, r = 0.07), did not differ during vicarious handwashing relative to the control conditions, compared to NACs.

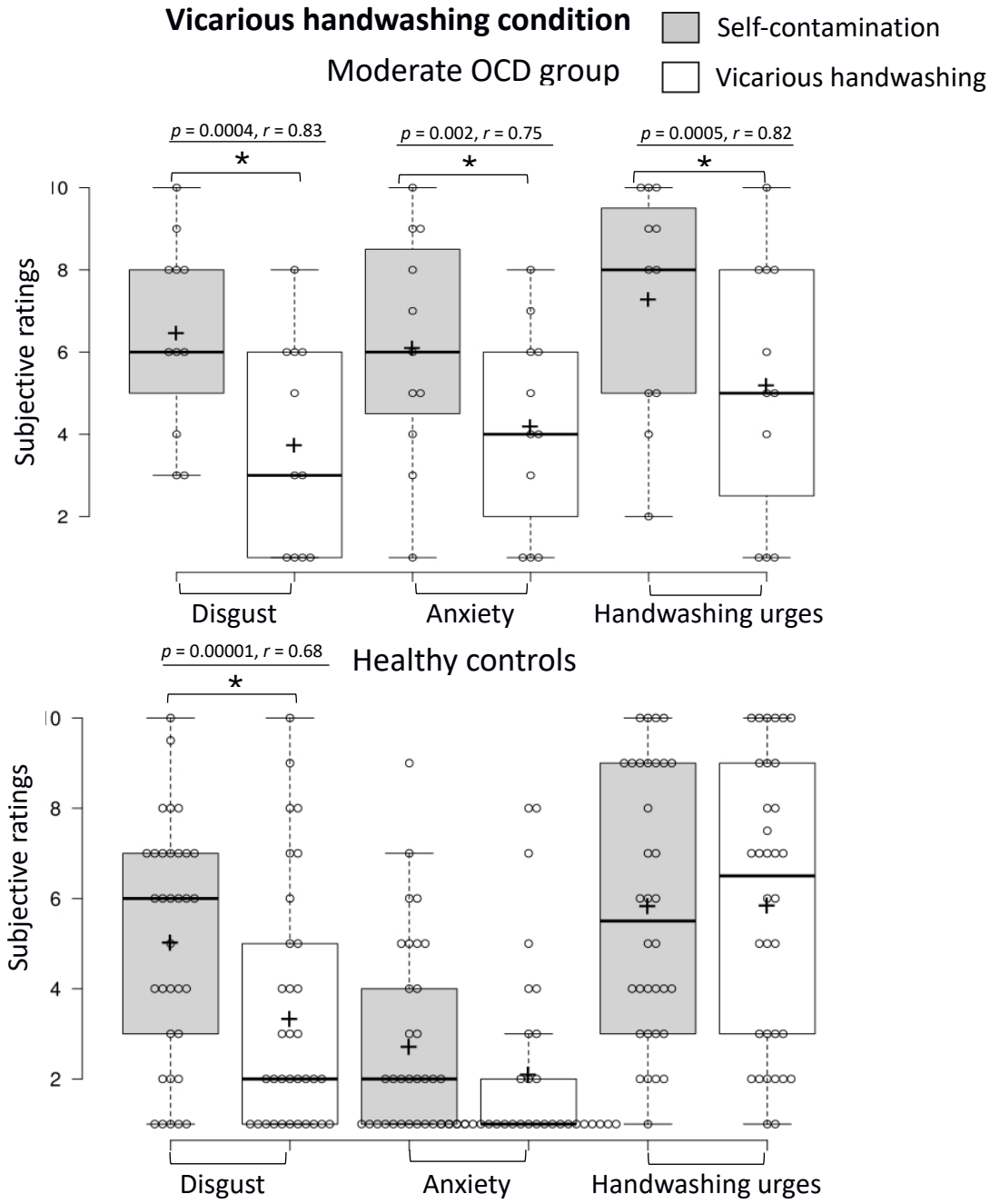

Figure 3.7 Disgust, Anxiety and Handwashing Urge Ratings During Self-Contamination and Vicarious Handwashing in the OCD and NAC Group[a]

[a]*P* values and *r* effect sizes are shown for one-tailed paired samples *t*-tests for disgust, anxiety and handwashing urge ratings for each group (for results of the contrast analysis see main text).

Second-person versus third-person vicarious contamination and relief

To explore whether contamination sensations would differ when OCD participants (n = 29) and NACs (n = 33) first watched the experimenter ("A") contaminate himself (Step 1), and then either watched the same experimenter ("A") wash his hands (Step 2) (Condition 5), or a different experimenter ("B") wash his hands (Condition 6), we conducted a three-way MANOVA on the dependent variables. A 2 (Condition: 5, 6) × 2 (Step: 1, 2) × 2 (Group: OCD, NAC) analysis revealed a main effect of Step ($F_{3,58}$ = 18.55, $p = 1.48 \times 10^{-8}$) and a main effect of Group ($F_{3,58}$ = 27.15, $p = 4.26 \times 10^{-11}$), and a significant Step × Group interaction ($F_{3,58}$ = 4.55, p = 0.006). None of the remaining effects was significant, including the Condition × Step × Group interaction ($ps \geq 0.232$).

Next, to explore whether contamination sensations would differ when OCD participants (n = 29) first watched the experimenter ("A") contaminate himself (Step 1), and then either watched the same experimenter ("A") wash his hands (Step 2) (Condition 5), or a different experimenter ("B") (Condition 6), we conducted a two-way MANOVA on the dependent variables. A 2 (Condition: 5, 6) × 2 (Step: 1, 2) analysis revealed a main effect of Step ($F_{3,26}$ = 5.59, p = 0.004). None of the remaining effects was significant, including the Condition × Step interaction ($ps \geq 0.079$). Finally, a McNemar test showed that in Condition 5 an equal proportion of OCD participants (n = 28) exhibited a facial expression of disgust during Step 1 (experimenter "A" touches disgust stimulus) and Step 2 (the same experimenter "A" washes hands), ($\chi^2_1 < 1$, NS). However, in Condition 6, the McNemar test revealed a reduction in the proportion of OCD participants (n = 28) who exhibited a facial expression of disgust from Step 1 (experimenter "A" touches disgust stimulus) to Step 2 (experimenter "B" washes hands), (i.e., 35.7 percent versus 14.3 percent; χ^2_1 = 4.50, p = 0.03).

3.5 Discussion

We demonstrate for the first time that patients with OCD can experience contamination sensations and relief merely by observing an experimenter contaminating himself and washing his own hands. Relative to healthy comparison subjects, OCD patients reported greater disgust, anxiety, and handwashing urges when watching the experimenter contaminating himself. But more strikingly, OCD patients, upon first contaminating

themselves, reported significant disgust reductions by watching the experimenter washing his own hands, relative to control conditions. Patients also displayed a (nonsignificant) tendency to report greater disgust reductions during vicarious handwashing (after self-contamination) relative to control conditions, compared to the NAC group. In an exploratory analysis, splitting the OCD group by symptom severity (i.e., categorical classifications of the Y-BOCS; Storch et al., 2015), we found that OCD patients with moderate symptoms, unlike severe patients, reported greater reductions in disgust and handwashing urges from vicarious handwashing relative to control conditions, compared to healthy controls; and a tendency towards anxiety reductions during vicarious handwashing. Overall, these results are counterintuitive and defy common sense. Indeed, one would not expect handwashing urges and relief to arise merely from watching someone else becoming contaminated and washing their own hands. Our novel findings may pave the way for innovative therapies for OCD.

In a previous study (Jalal & Ramachandran, 2017), we found that healthy individuals with OCD symptoms reported indistinguishable levels of disgust when watching an experimenter contaminating himself and when they themselves were contaminated. But the present findings are especially surprising because of the clinical nature of the sample; the fact that severe OCD patients (undergoing intensive residential treatment) reported equivalent disgust and anxiety during indirect vicarious contamination and actual self-contamination. In this study, unlike previous research (Jalal & Ramachandran, 2017), the experimenter exhibited a disgust facial expression when contaminating himself. Doing so may have increased empathetic self-identification with the experimenter (e.g., via the mirror neuron system; Rizzolatti et al., 2001) and thus enhanced vicarious contamination sensations.

Our finding that OCD patients reported disgust reductions—comparable to engaging in actual handwashing—by watching someone else washing his hands is the most intriguing as it makes no logical sense whatsoever. It is congruent with Jalal and Ramachandran's study (2017) in which healthy volunteers with contamination fears reported disgust reductions during vicarious observation of handwashing. However, again, the current results are notable because of the clinical severity of the patients.

Unlike disgust, vicarious handwashing did not reduce anxiety and handwashing urges in the OCD group. Clinical severity may account for these findings. Vicarious handwashing represents a type of "compulsion substitution"—in effect interrupting established stimulus-response associations. Compulsive symptoms become increasingly entrenched and difficult to treat with time (e.g., Gillan et al., 2016). As noted, OCD participants in this study were under intensive residential care, reserved for the more severe patients who are unresponsive to treatment in other settings (i.e., refractory; e.g., Veale et al., 2016). Accordingly, it would be more difficult to disrupt stimulus-response links in this population (e.g., by introducing a "benign substitute compulsion"; Jalal et al., 2018) compared to less severe patients (e.g., outpatients). This explanation dovetails with the results that patients with moderate symptoms (unlike severe patients) did indeed report clear-cut disgust and handwashing urge reductions (and marginally so reductions in anxiety) from vicarious handwashing, relative to both control conditions and healthy volunteers.

In this study, we assessed disgust facial expressions (a secondary outcome) to gauge overt disgust reactions. OCD patients tended to exhibit reduced expressivity in response to the disgust stimulus compared to healthy controls. For instance, at baseline a lower proportion of patients displayed an expression of disgust when viewing the stimulus than NACs; showing a dissociation between self-reported and observable emotional responsiveness (i.e., that these measures can operate independently [e.g., Sloan, Strauss, Quirk, & Sajatovic, 1997; on subvisible emotional expressivity see, Ekman, 1993]). Likewise, an equal proportion of patients and NACs displayed expressivity during vicarious contamination (again, standing in contrast to self-reports). OCD patients also exhibited unusual facial expressions (i.e., inflexibility) in response to the relief stimulus: a noteworthy proportion of patients (21 percent) displayed expressivity when engaging in handwashing (after self-contamination) unlike NACs (0 percent); an equal proportion of patients exhibited disgust facial expressions during vicarious handwashing compared to control conditions; and during actual handwashing and vicarious handwashing. These findings suggest that OCD patients perhaps had difficulties shaking off disgust expressions—irrespective of the relief stimulus; indicative of outward emotional inertia (i.e., inflexibility of expression). Put together, our results are consistent with studies suggesting abnormal facial expression in OCD in response to

emotional stimuli (for a review see, Davies et al., 2016); a key disturbance include hypomimia (facial rigidity) (Valeriani et al., 2015), attributed to basal ganglia dysfunction (Mergl et al., 2003). Reduced facial expressivity (affective flattening) in OCD is linked to symptom severity, and resembles expressions of schizophrenic patients (Bersani et al., 2012).

In an exploratory analysis we found that both OCD patients and NACs were provoked by watching an experimenter contaminating himself. But surprisingly, it did not matter whether the same or a different experimenter washed his hands afterwards—both scenarios triggered comparable relief. In fact, for OCD patients specifically, watching a different experimenter washing hands resulted in a reduced proportion of patients exhibiting disgust facial expressions; unlike when the same experimenter washed his own hands after first contaminating himself. These curious results illustrate the elusive interface between mind and body and emotions like disgust in OCD; how gut reactions can override top-down cognitive inferences (on the noncognitive nature of disgust, see McNally, 2002). The agent performing the contamination and relief inducing behaviour is redundant—the barrier between self and other ultimately breaks down—in the face of highly visceral emotional reactions.

Overall, these results could be explained by the activity of the mirror neuron system. Mirror neurons fire not only when one performs an action, but also when merely *observing* another person performing the same action (Rizzolatti et al., 2001). In effect, they do a "virtual reality simulation" of someone else's sensory system (bridging the gap between observer and actor), by allowing you to experience his emotions and sensations as if they were yours (on mirror neurons see also, Iacoboni et al., 2005; Rizzolatti, 2005). Researchers have debated the degree of autonomy and modular organization of the human mirror neuron system; some have argued it is the same as what have previously been referred to as "action understanding" (for a review, see Heyes, 2010). This issue regarding terminology use, or the exact function of mirror neurons in humans, however, does not bear any practical significance on our results. Our findings demonstrate the cognitive impenetrability of the mirror neuron system (or "action understanding system")—how gut level empathy can override logic.

Our findings may have clinical implications for OCD. Watching a video recording of oneself touching disgust provoking stimuli, could have a desensitizing effect—a type of inexpensive virtual reality simulation of exposure therapy. Likewise, if vicarious observation of repetitive behaviors can play a similar functional role for patients as performing them, this may form a treatment intervention. Short-term vicarious relief might serve as a "compulsion substitution strategy"; over time repeated blunting of urges could trigger cognitive realization that refraining from compulsions is harmless, in effect, decoupling behaviour from stimulus. These interventions could potentially provide a cost-effective, scalable and tolerable route to the treatment of OCD (for details see Study 3).

Study limitations include not controlling for comorbid psychiatric disorders. It is conceivable that patients carried diagnoses of other psychiatric disorders which could have impacted these results. Also, because of the small number of moderate OCD patients (n = 11), findings in this subgroup require confirmation in larges samples. Moreover, it will be useful for future imaging studies to examine the activation and deactivation of the anterior cingulate cortex (a possible locus of mirror neurons; Wicker et al., 2003), as well as the insula, during vicarious contamination and vicarious handwashing. Finally, these findings regarding "vicarious exposure" (see also, Jalal & Ramachandran, 2017) may have implications for other psychiatric disorders like self-mutilation (e.g., cutting one's forearm), binge-drinking, and trichotillomania (hair pulling disorder), treating or perhaps minimally, providing symptomatic relief to patients.

4. Study 2

Abstract

Obsessive-compulsive disorder (OCD) is a deeply enigmatic psychiatric condition associated with immense suffering worldwide. Efficacious therapies for OCD, like exposure and response prevention (ERP) are sometimes poorly tolerated by patients. As many as 25% of patients refuse to initiate ERP mainly because they are too anxious to follow exposure procedures. Accordingly, we proposed a simple and tolerable (immersive yet indirect) low-cost technique for treating OCD that we call "multisensory stimulation therapy." This method involves contaminating a rubber hand during the so-called "rubber hand illusion" (RHI) in which tactile sensations may be perceived as arising from a fake hand. In the current study, we explored the therapeutic potential of this novel approach. OCD patients (n = 29) watched as their hidden real hand was being stroked together with a visible fake hand; either synchronously (inducing the RHI) (i.e., the experimental condition; n = 16) or asynchronously (i.e., the control condition; n = 13). After 5 minutes of tactile stimulation, the rubber hand was contaminated with fake feces, simulating conventional exposure therapy. Intriguingly, results suggested sensory assimilation of contamination sensations into the body image via the RHI: patients undergoing synchronous stimulation did not report greater contamination sensations when the fake hand was initially contaminated relative to asynchronous stroking. But contrary to expectations, they did so after the rubber hand had been contaminated for 5 minutes; as assessed via disgust facial expressions (a secondary outcome) and *in vivo* exposure (upon discontinuing the illusion). Further to our surprise, synchronous and asynchronous stroking induced an equally vivid and fast emerging illusion, which helps explain why both conditions initially (5 minutes after initiating tactile stimulation) provoked contamination reactions of equal magnitude. This study is the first to demonstrate heightened malleability of body image in OCD. It may pave the way for a tolerable technique for the treatment of OCD—highly suitable for poorly resourced and emergency settings, including low-income and developing countries with minimal access to high-tech solutions like virtual reality.

Reference: Jalal, B., McNally, R. J., Elias, J., Potluri, S., & Ramachandran, V. S. (in press). Contaminating rubber hands ("multisensory stimulation therapy") to treat obsessive-compulsive disorder. *Frontiers in Human Neuroscience.*

4.1 Study aims

To overcome challenges of existing exposure therapies, we recently proposed a simple and tolerable (immersive yet indirect) low-cost technique for the treatment of OCD (Jalal et al., 2015) that we call "multisensory stimulation therapy." Healthy volunteers watched as their occluded real hand was being stroked together with a visible fake hand in precise synchrony, producing the so-called "rubber hand illusion" (RHI) (Botvinick & Cohen, 1998). After 5 minutes of such tactile stimulation, we contaminated the dummy with fake feces, in effect, mimicking traditional exposure therapy. To our astonishment, participants reported disgust sensations—as if arising from the rubber hand! This finding with potential clinical utility (discussed in more detail below) has since been replicated in a large Japanese sample, suggesting the effect is both robust and cross-culturally reliable (Nitta, Tomita, Zhang, Zhou & Yamada, 2018).

One interpretation for the emergence of the RHI evokes the "Bayesian logic" of perceptual systems (e.g., Armel & Ramachandran, 2003; Jalal et al., 2015; Ramachandran, Krause, & Case, 2011). The brain's sensory system is hardwired to detect statistical correlations that provide the basis for making predictions, and ultimately, visual representations of the external world, including one's body (see also, Corlett, Honey, Krystal, & Fletcher, 2011). The brain considers it highly unlikely that the random stroking *seen* on the fake hand and *felt* on the real hand is due simply to chance; it infers therefore that the sensations must be arising from the rubber hand, however absurd. As such, the illusion is driven by bottom-up mechanisms (i.e., statistical correlations between senses) and any object in theory could become part of one's body image including a table (Armel & Ramachandran, 2003). Consistent with this account, the RHI does not occur (or is greatly diminished) following asynchronous stimulation of the real and rubber hand. This "gold standard" control procedure shows the importance of spatial and temporal congruence of the tactile and visual inputs in driving the illusion (e.g., Shimada, Fukuda, & Hiraki, 2009).

Research has explored various measures and versions of the RHI (e.g., Armel & Ramachandran, 2003; Capelari, Uribe, & Brasil-Neto, 2009; Costantini & Haggard, 2007; Ehrsson, Wiech, Weiskopf, Dolan, & Passingham, 2007; Kammers, de Vignemont, Verhagen, & Dijkerman, 2009; Ramachandran et al., 2011). The basic effect emerges fairly quickly, in most healthy volunteers usually around 10-30 seconds after the synchronized stroking begins (Ehrsson, 2012). In our own studies, we have found that the illusion is reliably induced in healthy individuals within 2.5-5 minutes of tactile stimulation (e.g., in approx. 73 percent of subjects across two separate experiments see, Jalal et al., 2015) (see also, Armel & Ramachandran, 2003). The illusion is most commonly assessed with a subjective measure of limb ownership and an objective test of proprioceptive drift, where participants after the illusion onset close their eyes and point to the direction of their real hand. Botvinick and Cohen (1998) showed that after RHI induction, participants point to the artificial hand instead of their real hand unlike in the asynchronous control condition; and that the degree of this displacement is associated with the prevalence of the RHI over time (i.e., as measured within a 30 min. stimulation period). In line with this, Tsakiris and Haggard (2005) demonstrated that continuous tactile stimulation during the RHI gradually increases such proprioceptive drift, suggesting a gradual intensifying of the illusion over time. This proprioceptive drift test correlates with the subjective vividness of the illusion (Longo, Schüür, Kammers, Tsakiris, & Haggard, 2008).

The RHI has also been examined in psychiatric groups: for example, one study found a stronger illusion and faster onset in schizophrenia, suggesting a malleable self-representation in this population (Peled, Ritsner, Hirschmann, Geva, & Modai, 2000). Comparable results were reported in patients with eating disorders, who likewise have a pronounced RHI compared to healthy volunteers (Eshkevari, Rieger, Longo, Haggard, & Treasure, 2012). In contrast, children with autism spectrum disorders (ASD) have a delayed susceptibility to the illusion (i.e., exhibit a later illusion onset compared to non-autistic children). Interestingly, children with ASD who have lower levels of empathy are less likely to experience the RHI (Cascio, Foss-Feig, Burnette, Heacock, & Cosby, 2012). Taken together, these studies

suggest that some forms of psychopathology are associated with aberrant self-referential processing as assessed on the RHI.

To date no studies have examined the RHI in OCD. The illusion may be particularly pertinent to OCD given the role of dopamine in the pathophysiology of the disorder (e.g., Denys et al., 2004; Koo et al., 2010). Although the function of dopamine in OCD is multifaceted (e.g., Fineberg et al., 2007), research has shown that dopamine antagonists (as an adjunct to SSRI drugs) can reduce OCD symptoms (i.e., augment the effects of SSRIs; Vulink, Denys, Fluitman, Meinardi, & Westenberg, 2009). In contrast, dopamine agonists can generate OCD-like behaviours in animals (Szechtman et al., 1998), and humans (Borcherding et al., 1990), providing clues about the functional role of dopamine in OCD.

Interestingly, research suggests that dopamine is a key modulator of multisensory integration as assessed via the RHI. For instance, the dopamine releaser drugs ketamine and Dexamphetamine (with potential to trigger schizophrenia-like symptoms; Angrist & Gershon, 1970; Pomarol-Clotet et al., 2006) augment the illusion during regular synchronous stroking, but curiously also, in the (illusion-attenuating) asynchronous control condition (Albrecht et al., 2011; Morgan et al., 2011). Analogously, patients with Parkinson's disease (receiving dopaminergic drugs) fail to reject the RHI in the asynchronous condition as strongly as healthy control participants do, according to the authors, possibly due to dopamine dysregulation (Ding et al., 2017). Collectively, this research is in keeping with findings that schizophrenia (a disorder of dopamine abnormality; e.g., Howes, McCutcheon, & Stone, 2015) results in heightened illusory effects, and points to the pervasive role of dopamine in self-referential processing.

Research should disclose whether OCD is associated with multisensory processing abnormalities. By beginning to probe the corporeal self in OCD, one may eventually clarify how the processes that produce a sense of body ownership differ in this disorder versus other psychiatric conditions. Efforts to establish specificity could elucidate OCD aetiology and differentially inform novel treatments (e.g., drug and behavioral interventions) aiming at restoring aspects of self-referential processing.

The illusion may be of special interest to contamination-related OCD (Jalal et al., 2015). Although the results of Jalal and colleagues (2015) comport with the literature on ERP (i.e., disgust induced by "fake hand exposure" mirrors the effects of *in vivo* exposure; e.g., McKay, 2006), several issues remain vis-à-vis the clinical utility of this RHI contamination procedure. As noted, research should extend this work to a clinical population to assess the therapeutic use of the RHI; i.e., it is important to establish the presence of this basic "RHI contamination effect" in OCD patients. Second, to the extent that such rubber hand exposure evokes clinically relevant contamination reactions in OCD, research should examine whether this eventually leads to habituation.

Such research may have important treatment implications: if contaminating a fake hand during the RHI provokes contamination reactions (akin to ERP) via an immersive multisensory mechanism, this may pave the way for a novel (tolerable) intervention. As noted, such dummy contamination may eventually (after an extended period and/or repeated trials) lead to habituation; i.e., overall global reduction in contamination fears, analogues to conventional exposure therapy. Another possibility is that contaminating a fake hand during the RHI, minimally, is useful during the initial stages of ERP (e.g., in an "exposure hierarchy"; Wolpe, 1958; see also, Abramowitz, Foa & Franklin, 2003). This technique might sufficiently desensitize patients such that they are willing to undertake ERP, providing a convenient "transitional link" (Jalal et al., 2015).

In the current study, the primary aim was to explore the therapeutic potential of the RHI for OCD. We examined whether "contaminating" the rubber hand during the illusion would result in greater contamination sensations as compared to the asynchronous control condition. We also tested whether such dummy contamination eventually resulted in habituation; assessed both during the illusion and during an *in vivo* exposure procedure immediately upon discontinuing the illusion (i.e., ceasing the stimulation of the real and rubber hand). A secondary aim of this investigation was to broadly explore multisensory processing in OCD via the RHI.

4.2 Hypotheses

If contaminating the fake hand during the RHI (5 min. after initiating stroking) provokes greater disgust than asynchronous stroking in healthy individuals (Jalal et al., 2015; Nitta et al., 2018)—given the role of disgust in OCD—this should also hold for patients with contamination obsessions. Moreover, considering that ERP targets both anxiety and washing urges (Rachman, 2004), RHI exposure should likewise evoke such contamination sensations overall (i.e., in addition to disgust). Finally, given that OCD patients dependably experience habituation following prolonged exposure to "contaminants" during ERP (on habituation see, e.g., Abramowitz, 2006; Foa et al., 1983; Rachman, 2004), RHI exposure should after an extended period lead to habituation. (This latter hypothesis is partly grounded in research showing that the RHI emerges quickly and does not wane with time [e.g., Ehrsson, 2012; Tsakiris & Haggard, 2005], preserving the realistic nature of the exposure procedure.)

Assuming that: (1) contaminating the fake hand during the RHI results in greater contamination sensations than does asynchronous stroking in OCD; and that (2) such exposure over time leads to habituation, we advanced the following hypotheses:

RHI contamination: OCD patients in the RHI condition would report greater contamination sensations (disgust, anxiety and handwashing urges), and be more likely to exhibit a disgust facial expression, when the fake hand is contaminated (i.e., 5 minutes upon initiating the real and rubber hand stroking), compared to those in the asynchronous control condition.

RHI habituation: OCD patients in the RHI condition would report lower contamination sensations (disgust, anxiety and handwashing urges), and be less likely to exhibit a disgust facial expression, 5 minutes after contaminating the dummy (i.e., 10 minutes upon initiating the real and rubber hand stroking), compared to those in the asynchronous condition.

In vivo exposure: OCD patients in the RHI condition would report lower contamination sensations (disgust, anxiety and handwashing urges) when their real hand is contaminated (i.e., immediately upon ceasing the stimulation of the real and rubber hand) compared to those in the asynchronous condition.

A secondary aim was to broadly explore multisensory processing in OCD. In view of research indicating: (1) that dopamine, implicated in OCD (e.g., Denys et al., 2004; Koo et al., 2010), is a modulator of multisensory processing (e.g., Albrecht et al., 2011; Morgan et al., 2011); and (2) suggesting aberrant somatosensory integration in psychiatric disorders more generally (see above), we tentatively hypothesized that OCD would be associated with atypical multisensory processing. For example, OCD patients would show high susceptibility to the illusion (indexed by illusion onset and intensity measures) compared to healthy populations (e.g., as reported in our own studies; Jalal et al., 2015). Given the exploratory (open-ended) nature of this inquiry, no directional hypothesis was made a priori.

4.3 Methods

4.3.1 Participant selection

Study participants were recruited from the McLean Hospital Obsessive-Compulsive Disorder Institute (OCDI), an intensive residential treatment (IRT) program affiliated with Harvard Medical School. All participants were diagnosed with OCD by an expert clinician on staff as part of standard clinical procedures based on DSM-IV or DSM-5 criteria and had disgust-related contamination obsessions. Medicated patients were not excluded and none currently was psychotics. Participation was restricted to those aged between 18 and 65 years old, and who were proficient in English. The same sample of OCD participants were used in both Study 1 and Study 2 (for selection criteria and clinical characteristics of the patients see Section 3.3.1.)

4.3.2 Procedure

Harvard University's Committee on the Use of Human Subjects approved the study protocol and McLean Hospital's Institutional Review Board formally ceded review to Harvard's committee. Participants gave written informed consent prior to initiation of any study procedure and received monetary compensation ($20) for their time.

The participant sat at a table with both hands resting on it. A vertical cardboard barrier was placed on the table, just to the left of the participant's right hand, occluding his view of his

right hand. A rubber hand was placed on the left side of the cardboard. A sheet of cloth was wrapped around the wrist of the dummy extending up to the shoulder of the right arm. This arrangement prevented the participant from viewing his right hand, giving the illusion that the fake hand was his real right hand (Figure 4.1). The experimenter stroked the participant's right hand with a paintbrush while simultaneously and synchronously stroking the rubber hand with another paintbrush. The participant was asked to indicate orally if and when he experienced touch sensations coming from the rubber hand. The simultaneous stroking of the rubber hand and real right hand produces the illusion (to the participant) that the rubber one feels like his own right hand. After five minutes of such stroking, the experimenter asked the participant to rate how much the rubber hand felt like his own hand. Next, the experimenter used a tissue to smear the disgust stimulus (fake feces) on the rubber hand while simultaneously dabbing a damp paper towel from a nearby water bowl on the participant's real right hand. Immediately thereafter, the participant was asked to provide subjective contamination ratings (i.e., disgust, anxiety and handwashing urge levels), and the experimenter rated the participant's facial expression of disgust (either present or not). The tissue that had been used to "contaminate" the rubber hand and the clean paper towel were then removed from the fake and real hand; the fake feces remained on the rubber hand. The rubber hand and the participant's real hand continued to be stroked for an additional 5 minutes, after which the participant again provided contamination ratings and the experimenter rated his facial expression. The stroking of the rubber hand and real hand then stopped (i.e., 10 minutes of rubber hand and real hand stimulation had elapsed). Immediately thereafter, the experimenter told the participant that he would place the disgust stimulus (referred to as the "object") on his right hand; and, accordingly, took a piece of the disgust stimulus and put it on the participant's real right hand. At this point, the participant provided a final set of contamination ratings.

A second group of patients underwent the same procedure except that the stimulation of the rubber hand and real right hand was asynchronous (i.e., the stroking was temporally and spatially incongruent), thereby either greatly diminishing or preventing the illusion from developing.

Figure 4.1 The Set-Up of the Rubber Hand Illusion

4.3.3 Materials and measures

Yale-Brown Obsessive-Compulsive Scale (Y-BOCS)

The Y-BOCS (Goodman et al., 1989) is widely considered the "gold standard" measure for assessing OCD symptomatology in clinical research. The Y-BOCS indexes severity of obsessions and compulsions in the past week. Scores are generated from a total of 10 items; each rated on a 5-point Likert scale, and scores range from 0 to 40. In the present study, patients completed the self-report version of the Y-BOCS (Steketee et al., 1996).

Disgust stimulus

The disgust stimulus visually resembled and smelled of genuine feces. It consisted of food items (a mixture of chocolate and peanut butter) and was sprayed with a joke-shop odor, and placed in a bedpan. Participants were told before the study began that the stimulus was not genuine feces (Figure 4.2).

Figure 4.2 Disgust Stimulus

Multisensory integration

RHI onset and intensity: the time onset of the RHI (i.e., how soon after the stroking was initiated participants felt the presence of the illusion, if at all) constituted a measure of multisensory integration. Participants were asked to indicate verbally, if and when they experienced touch sensations coming from the rubber hand.

The perceived intensity of the illusion provided another measure of multisensory processing. Participants were asked to rate how much the rubber hand felt like their own hand (5 minutes after initiating the stroking); on a 20-point Likert scale, ranging from 1 (“not at all”) to 20 (“exactly like my own hand”). A more rapid onset (measured in seconds) and higher intensity rating indicated greater susceptibility to the illusion.

RHI contamination

Participants were asked to provide ratings of contamination sensations (i.e., their level of disgust, anxiety and handwashing urges), when the rubber hand was first contaminated (i.e., 5 minutes after initiating the stroking); on a 10-point Likert scale ranging from 1 (“not at all”)

to 10 (“extremely”). Higher ratings indicated greater assimilation of contamination sensations into their body image via the RHI.

RHI habituation

Participants were asked to provide contamination ratings (i.e., disgust, anxiety and handwashing urge levels), 5 minutes after the dummy contamination procedure (i.e., 10 minutes after initiating the stroking); on a 10-point Likert scale ranging from 1 (“not at all”) to 10 (“extremely”). Lower ratings indicated greater habituation.

Disgust facial expressions: to further gauge participants’ disgust reactions, we observed and noted whether their facial expression indicated disgust (or not) when: (1) the rubber hand was initially contaminated and (2) when *RHI habituation* assessment took place (i.e., 5 minutes after the dummy contamination).

In vivo exposure habituation

Participants were asked to provide contamination ratings (i.e., disgust, anxiety and handwashing urge levels), when the experimenter contaminated the participant’s real hand (i.e., immediately after *RHI habituation* ratings were obtained); on a 10-point Likert scale ranging from 1 (“not at all”) to 10 (“extremely”). Lower ratings indicated greater habituation.

(An overview of the experimental procedures is shown in Figure 4.3.)

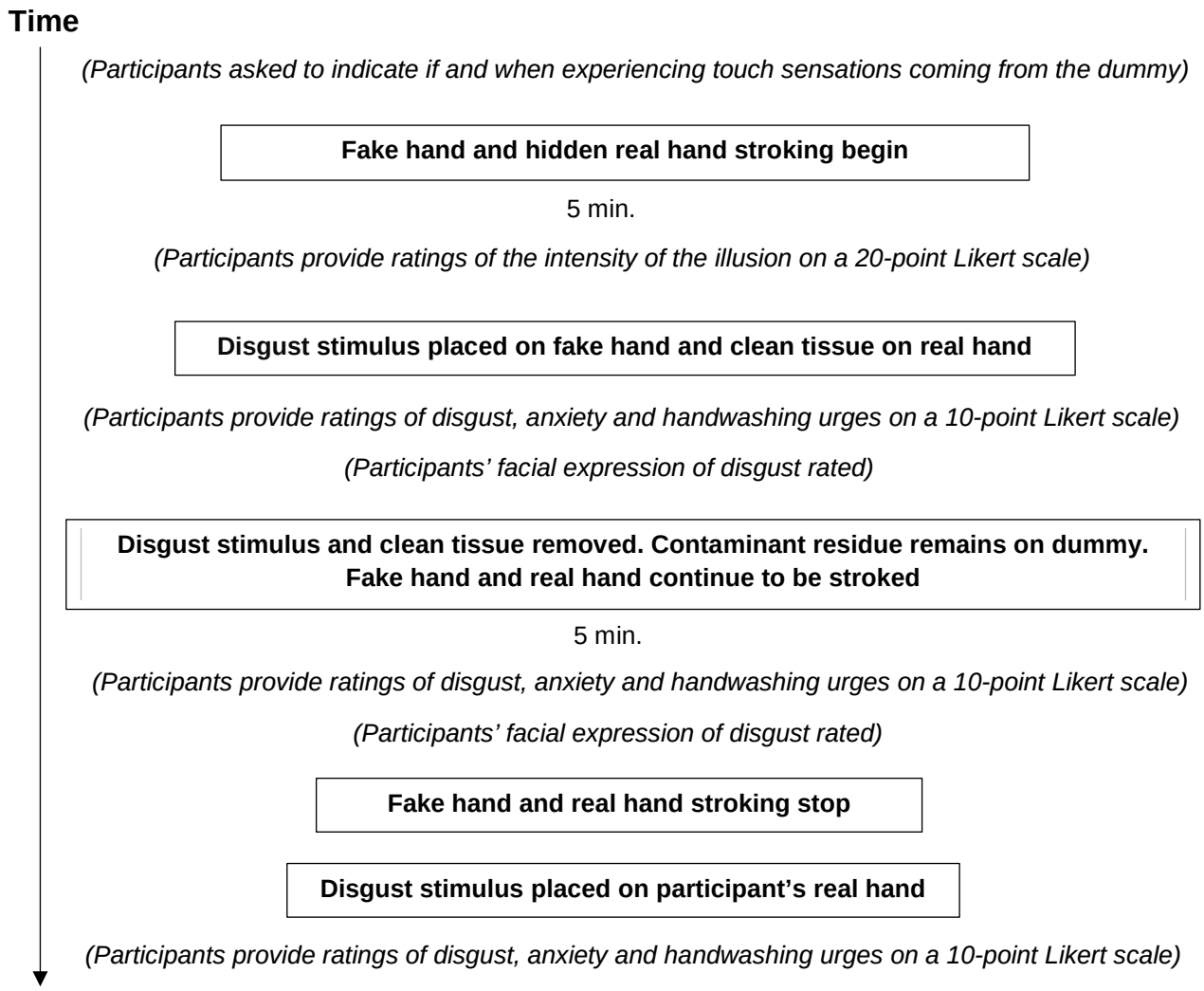

Figure 4.3 Overview of Study

4.3.4 Statistical analyses

The study included a quantitative between-subject cross-sectional design comparing two conditions (experimental versus control) on the following measures: RHI contamination sensations, RHI habituation, *in vivo* exposure habituation, and multisensory integration, focusing on the between-subject effects. The study targeted the following primary outcome variables: self-reported ratings of disgust, anxiety, and handwashing urges (assessment of RHI contamination sensations and habituation effects), and RHI onset and intensity (assessment of multisensory integration). Participants' facial expression of disgust (i.e.,

present or non-present; rated by the experimenter) constituted a secondary outcome measure of RHI contamination sensations and habituation.

RHI onset and intensity dependent variables were analyzed via one-way ANOVA. Disgust, anxiety and handwashing urge ratings dependent variables were analyzed using a one-way MANOVA test; followed up with ANOVA post-hoc tests. A chi-squared test was used to analyze disgust facial expression dependent variables.

For all analyses testing a priori hypotheses, we applied the Benjamini and Hochberg's (1995) false discovery rate (FDR) (e.g., McDonald, 2014) to control for potential Type I errors. Congruent with related studies (e.g., Skandali et al., 2018) and general guidelines (e.g., Genovese et al., 2002) the FDR was set at $q < 0.15$. In the current study, the Benjamini-Hochberg corrected significance level was 0.06. *P*-values shown in the text are uncorrected (i.e., raw) (e.g., McDonald, 2014). Exploratory analyses and post-hoc tests (i.e., following a significant omnibus MANOVA) were not adjusted for multiple comparisons. Multiplicity correction is not required when analyses are labelled exploratory (Bender & Lange, 2001).

For all dependent variables, the distribution of residuals was checked with Q-Q plots and the Shapiro-Wilk test; residuals were often found to depart from normality. Such variables were transformed with a $\log_{10}(x + 1)$ and a square-root transformation to test whether these improved matters (Myers & Well, 2003). As the *F* test is robust to minor normality departures (Blanca et al., 2017), we report untransformed data (except when otherwise specified in the text). (For details on box plots see Section 3.3.4.)

4.4 Results

Twenty-nine OCD patients completed the study. Of these, 16 were assigned to the experimental condition (i.e., to undergo the RHI) and 13 to the control (i.e., to undergo asynchronous stroking of the real and rubber hand). One OCD patient failed to provide consent for their demographic and Y-BOCS data to be used; these were thus excluded. The final sample sizes were: experimental condition $n = 16$ and control condition $n = 13$.

Additional data were missing for a few measures. Three participants did not provide an illusion time onset. One participant's data were excluded from the "RHI contamination and habituation" analyses due to an experimental error. Likewise, a participant was excluded from these analyses for not exhibiting an adequate contamination fear response throughout the experiment (e.g., with average contamination ratings as low as 1.3 out of 10 in intensity when directly exposed to the disgust stimulus during *in vivo* exposure). (For a third participant, the tissues used to stimulate the real hand and contaminate the dummy, were not removed after this experimental procedure. As this protocol deviation was trivial [i.e., unlikely to impact contamination sensations], the data were not excluded. As a precaution, the data were also analyzed while excluding this participant; the results remained unaltered.) For demographic and clinical characteristics of participants, see Table 4.1.

Table 4.1 Demographic and Clinical Characteristics of Participants[a]

Condition	**Experimental † (*n* = 15)**		**Control (*n* = 13)**		***Comparison***
	μ	**(*SD*)**	μ	**(*SD*)**	F_{df}
Age	26.60	(7.32)	27.31	(6.28)	* $F_{1,26} < 1$, NS
Y-BOCS	27.80	(3.91)	24.92	(8.21)	$F_{1,26} = 1.46$, $p = 0.24$
	n	**(%)**	***n***	**(%)**	X^2_{df}
Sex (*n*/% female)	13	(86.7)	9	(69.2)	$X^2_1 = 1.26$, $p = 0.26$

[a]μ, mean; *SD*, standard deviation; *n*, sample size; *F*, *F* statistic; X^2, chi-square statistic; *df*, degrees of freedom; *p*, *p* value; NS, non-significant; Y-BOCS, Yale-Brown Obsessive-Compulsive Scale; (†) One participant did not provide consent for their demographic and Y-BOCS data to be shown. (*) $\text{Log}_{10}[x + 1]$ transformed Y-BOCS scores. These analyses were also conducted without the two participants excluded from the RHI contamination and habituation analyses (described above); the results remained unaltered: Age ($F_{1,24} < 1$, NS), Y-BOCS ($F_{1,24} = 1.32$, $p = 0.26$), and Sex ($X^2_1 < 1$, NS).

Multisensory integration in OCD

RHI survival rate: all participants in the experimental condition ($n = 16$) reported a robust RHI effect; except one participant who did not provide an illusion onset, but rated the illusion as 5 out of 20 in intensity, which suggested he had a diminished RHI (based on our previous cut-off where an intensity rating of less than 3 out of 20 indicates no illusion; see Jalal et al., 2015). Surprisingly, all patients in the control condition ($n = 13$) also reported the RHI; except one who scored 2 out of 20 in intensity (another participant had a borderline illusion with an intensity rating of 5). Thus, the presence of the RHI did not differ in the two conditions, ($\chi^2_1 = 1.27$, $p = 0.26$).

Illusion onset: on average participants in the experimental condition reported experiencing the illusion after 65.50 seconds ($SD = 68.16$) versus 57.42 seconds ($SD = 51.16$) in the control condition (experimental $n = 14$, control $n = 12$). A one-way ANOVA was conducted on the illusion onset dependent variable (i.e., $\log_{10}[x + 1]$ transformed scores) to compare

ratings in the experimental condition and control condition. The onset of the illusion did not differ in the two conditions ($F_{1,24} < 1$, NS) (see Figure 4.4).

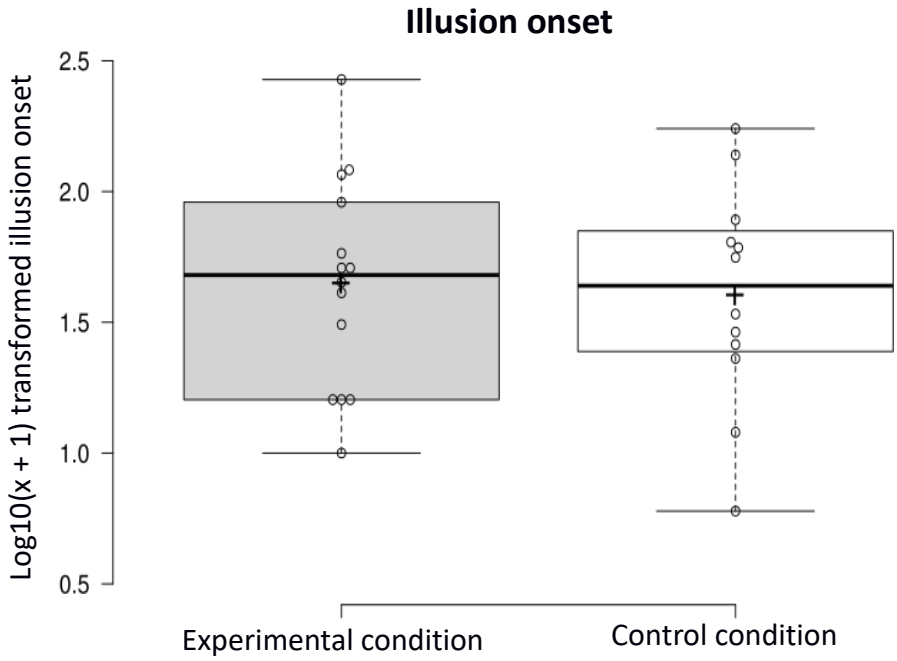

Figure 4.4 $Log_{10}(x + 1)$ Transformed Illusion Onset in the Experimental and Control Condition

Illusion intensity: a one-way ANOVA was conducted on the illusion intensity dependent variable to compare ratings in the experimental condition and control condition (experimental $n = 16$, control $n = 13$). The intensity of the illusion did not differ in the two conditions ($F_{1,27} < 1$, NS) (see Figure 4.5).

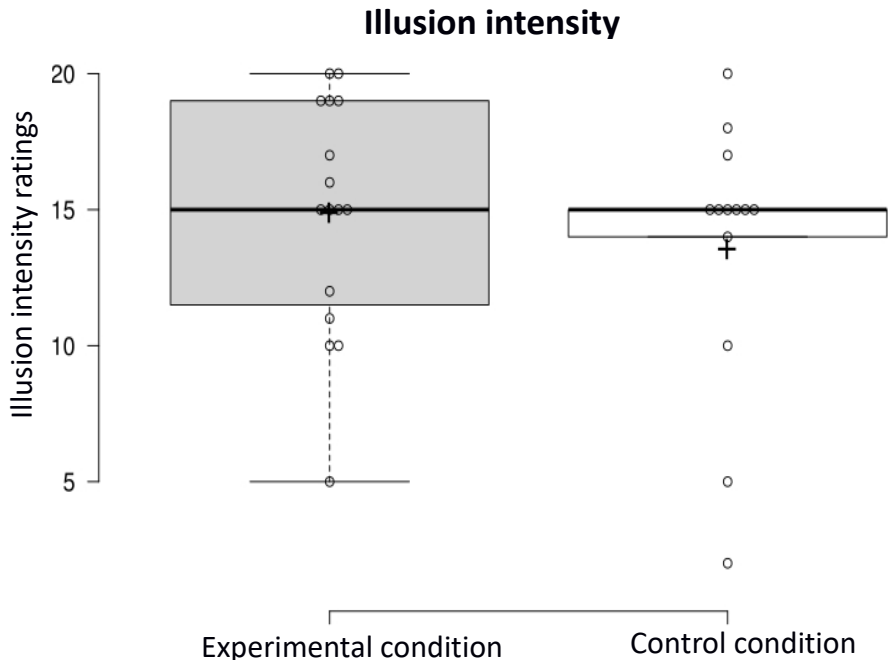

Figure 4.5 Illusion Intensity in the Experimental and Control Condition

OCD symptoms and RHI onset and intensity: an exploratory Pearson's Correlation Test showed that OCD symptom severity was not associated with how soon participants experienced the RHI (i.e., $\log_{10}[x + 1]$ transformed Y-BOCS and onset scores), (r_{11} = -0.16, p = 0.61, two-tailed), in the experimental condition; similarly, such symptom severity was not associated with the strength of the illusion (r_{13} = 0.12, p = 0.67, two-tailed). However, in the control condition, while OCD symptom severity was not associated with the illusion onset (r_{10} = 0.15, p = 0.64, two-tailed), Y-BOCS scores inversely correlated with the intensity of the illusion (r_{11} = -0.73, p = 0.004, two-tailed).

RHI contamination ("fake hand exposure")

To examine contamination sensations when the fake hand was contaminated, we conducted a one-way MANOVA on the dependent variables (experimental n = 14, control n = 13). Contamination sensations (disgust, anxiety and handwashing urges) did not differ in the two conditions when the fake hand was contaminated ($F_{3,23}$ < 1, NS, Benjamini-Hochberg

corrected) (see Figure 4.6). The proportion of participants in the experimental condition and control condition who exhibited a facial expression of disgust when the fake hand was contaminated did not differ, (experimental n = 14, control n = 13), ($\chi^2_1 < 1$, NS, Benjamini-Hochberg corrected).

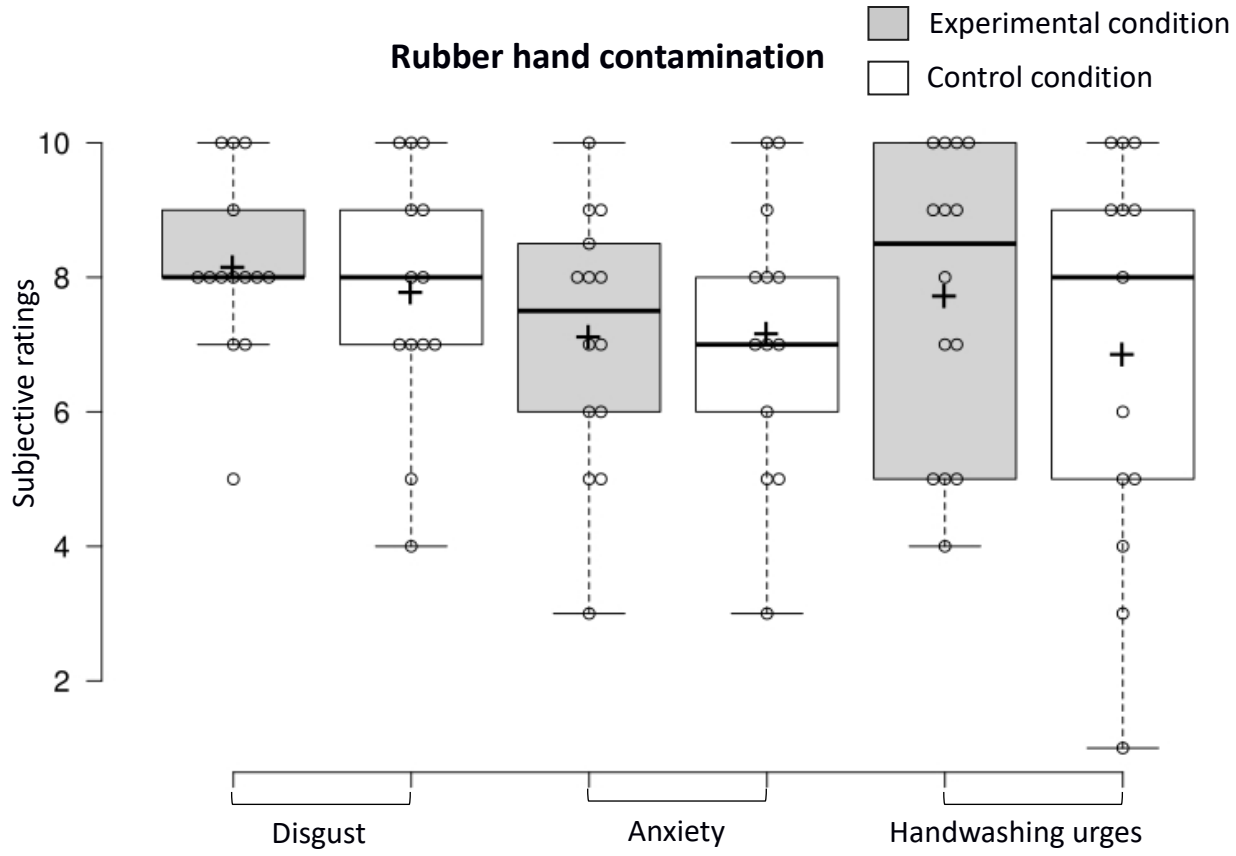

Figure 4.6 Contamination Sensations Ratings in the Experimental and Control Condition During the Rubber Hand Contamination Procedure

RHI habituation

To examine habituation 5 minutes after the fake hand was contaminated, we conducted a one-way MANOVA (experimental n = 14, control n = 13) that revealed that contamination sensations (disgust, anxiety and handwashing urges) did not differ in the two conditions ($F_{3,23}$ = 1.22, p = 0.32, Benjamini-Hochberg corrected) (see Figure 4.7). The proportion of participants who exhibited a facial expression of disgust was higher in the experimental

condition versus the control condition (experimental n = 13, control n = 13; 64.7 percent versus 35.3 percent), (χ^2_1 = 4.25, p = 0.04, Benjamini-Hochberg corrected).

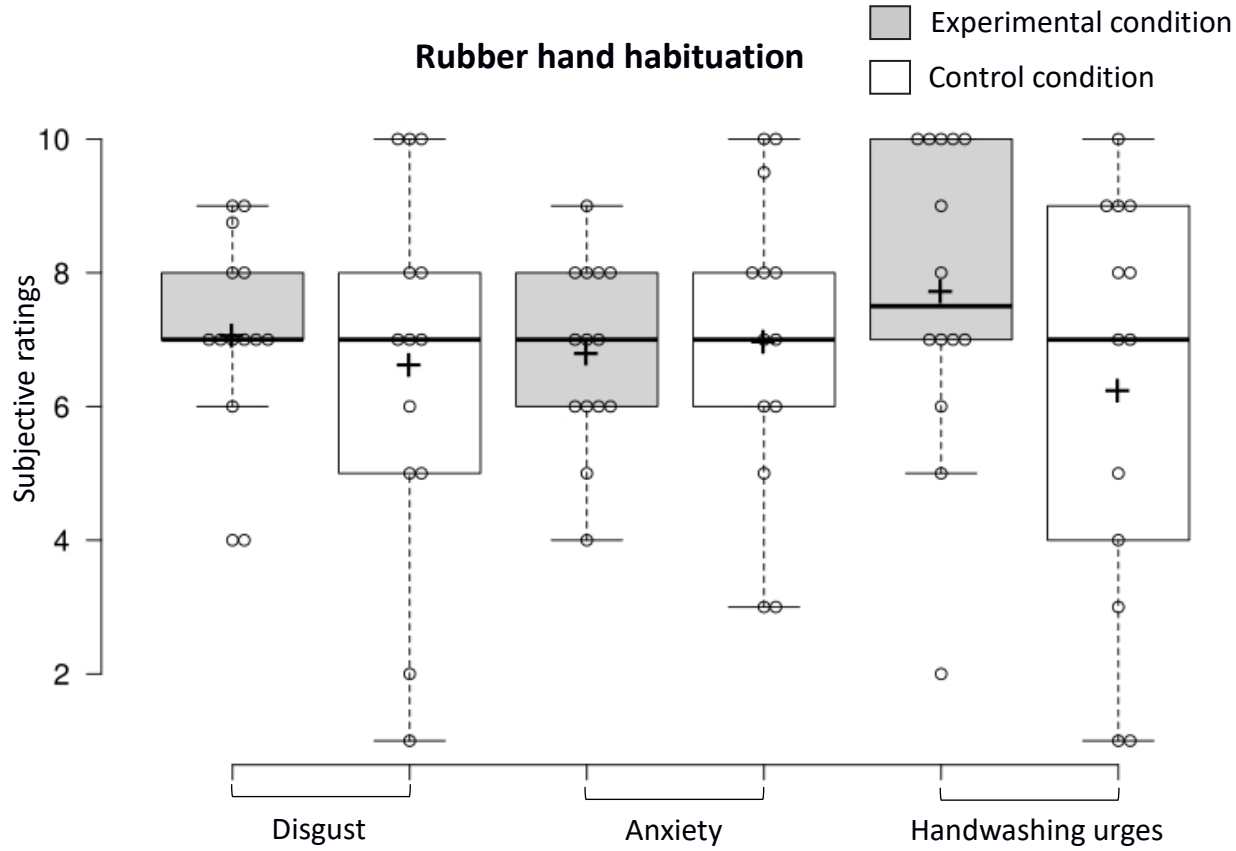

Figure 4.7 Contamination Sensations Ratings in the Experimental and Control Condition During the Rubber Hand Habituation Procedure

In vivo exposure habituation

To examine *in vivo* exposure habituation immediately upon discontinuing the stimulation of the real and rubber hand, we conducted a one-way MANOVA (experimental n = 14, control n = 13), showing that participants in the experimental condition reported higher overall contamination sensations (disgust, anxiety and handwashing urges) compared to those in the control condition ($F_{3,23}$ = 3.12, p = 0.046, Benjamini-Hochberg corrected) (see Figure 4.8). The MANOVA was followed up with a discriminant function analysis that revealed one discriminant function, which significantly differentiated the experimental and control

condition (Wilks' lambda $\lambda = 0.71$, $\chi^2_3 = 8.02$, $p = 0.046$). A canonical correlation of 0.54 showed that the model explained 29.2 percent of the variation in the condition variable. The discriminant function analysis revealed that disgust ratings had the highest standardized canonical discriminant function coefficient ($\beta = 2.40$) indicating the greatest contribution to the model (i.e., the best discriminator between the two conditions); followed by anxiety ($\beta = -1.80$) and then washing urge ratings ($\beta = -0.04$).

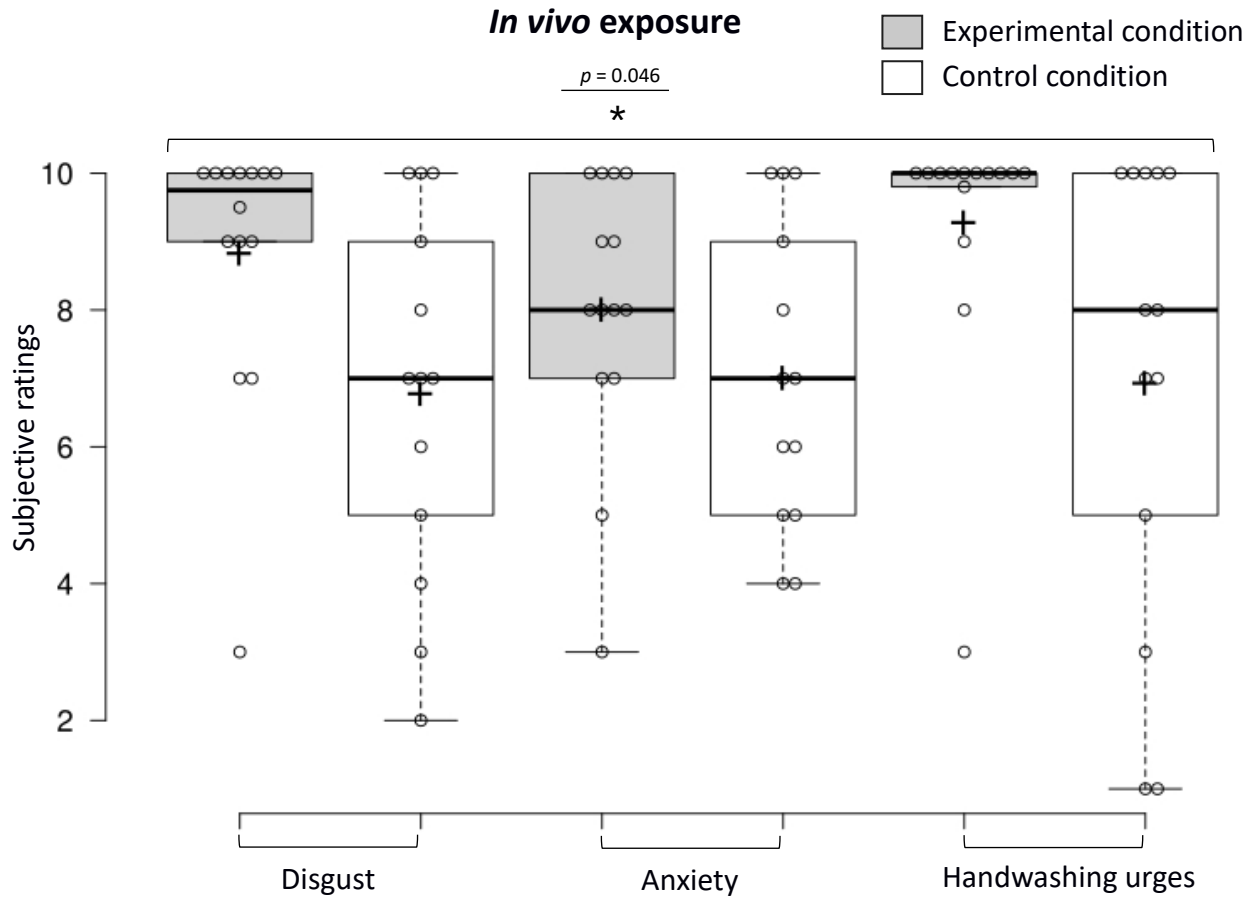

Figure 4.8 Contamination Sensations Ratings in the Experimental and Control Condition During the *In Vivo* Exposure Procedure

Dummy exposure versus in vivo exposure

In an exploratory analysis, to compare contamination sensations during dummy exposure versus *in vivo* exposure, we conducted two repeated measures one-way MANOVAs

(experimental $n = 14$, control $n = 13$); showing that while *in vivo* exposure provoked more intense responses than dummy exposure in the experimental condition ($F_{3,11} = 3.92$, $p = 0.04$), this was not the case in the control condition ($F_{3,10} < 1$, NS). (Residuals showed moderate deviation from normality but were not improved with a log or square-root transformation and were thus analyzed with those caveats.) Follow-up one-way ANOVAs showed that in the experimental condition *in vivo* contamination triggered marginally significantly greater disgust ($F_{1,13} = 3.84$, $p = 0.07$), and significantly greater anxiety ($F_{1,13} = 7.60$, $p = 0.02$) and handwashing urges ($F_{1,13} = 8.81$, $p = 0.01$) than dummy exposure.

4.5 Discussion

This study yields important new findings with clinical implications. Intriguingly, our results suggest sensory assimilation of contamination sensations into the body image via the RHI—that such feelings were curiously projected to an alien hand in patients with OCD. Patients undergoing synchronous stimulation did not report greater contamination sensations when the fake hand was initially contaminated relative to asynchronous stroking. But contrary to expectations, they did so after the dummy had been contaminated for 5 minutes; as assessed via disgust facial expressions (a secondary outcome) and *in vivo* exposure (upon discontinuing the illusion). We also found that patients failed to reject the illusion during the "gold standard" control condition. To our surprise, synchronous and asynchronous stroking induced an equally vivid and fast emerging illusion, which helps explain why both conditions initially (5 minutes after initiating tactile stimulation) provoked contamination reactions of equal magnitude. This study is the first to demonstrate heightened malleability of body image in OCD. Collectively, these results argue against a sharply localized ("hierarchical") approach to brain function, and illustrate dynamic intersensory interactions and plasticity of brain modules ("holistic mediation").

Our findings stress the importance of the temporal dimensions of the RHI; and crucially, how these can be perturbed by psychopathology. As noted, our chosen duration of tactile stimulation (i.e., 5 minutes) prior to dummy contamination was insufficient to initially differentiate the synchronous and asynchronous condition in patients with severe OCD. By comparison, we have previously shown that 5 minutes of tactile stimulation differentiates the

RHI and the control condition in healthy individuals (Jalal et al., 2015). In the current study, indeed, as both methods of stroking triggered an equally intense illusion at this time point, one would expect them to provoke comparable contamination reactions. But over time, these results suggest, synchronous stimulation more effectively assimilated the visibly contaminated rubber hand into the body image (than asynchronous stroking)—accounting for the relative rise in contamination sensations. Although we did not explicitly assess illusion intensity at a later stage, this provides a viable explanation for why synchronous stroking differentially impacted contamination reactions 10 minutes after initiating stimulation on two separate measures. As mentioned, research suggests that the RHI becomes more intense with time (i.e., duration of stimulation), as indexed on a key measure of the illusion (i.e., perceiving one's real hand drifting towards the fake one) (Tsakiris & Haggard, 2005) (on the prevalence of the RHI over time and degree of proprioceptive drift, see also Botvinick & Cohen, 1998).

The formulation of the initial hypothesis that contaminating the fake hand during the RHI results in greater contamination sensations than does asynchronous stroking in OCD, *specifically* 5 minutes after beginning the stroking, was based on prior work in healthy volunteers (Jalal et al., 2015; see also, Nitta et al., 2018). Evidently, in this study, as the RHI triggered greater contamination reactions than did the control procedure, not 5 minutes but instead 10 minutes after stroking began (consistent with the overall hypothesis, but not the timeline in which the two conditions were differentiated), our study-design was unable to capture any habituation effects.

The results of the exploratory analysis are noteworthy. They emphasize the overall finding that synchronous stroking over time exerts selective sensitizing effects (i.e., vis-à-vis contamination reactions). But more strikingly, they imply that "fake hand exposure" during asynchronous stroking provokes contamination sensations as effectively as actual real hand exposure (for details see "general discussion"; i.e., Section 9).

In this study, we found an overall amplified RHI. For instance, all patients reported the illusion during synchronous stroking. In contrast, around 85 percent of healthy volunteers experience the effect (Jalal et al., 2015). But the finding that patients failed to reject the RHI

during asynchronous stroking is more notable. It mirrors research showing that both Parkinson's disease and schizophrenia patients exhibit heightened illusory effects during asynchronous stroking compared to healthy volunteers (Ding et al., 2017; Peled et al., 2000); and that dopamine releaser drugs ketamine and Dexamphetamine enhance the RHI during both synchronous and asynchronous stimulation (Albrecht et al., 2011; Morgan et al., 2011). Taken together, these data indicate that dopamine dysregulation may boost a sense of embodiment. As noted, although the role of dopamine in OCD is admittedly complex (Fineberg et al., 2007), research has shown that dopamine antagonists can be useful in reducing OCD symptoms (as an adjunct to SSRIs) (Vulink et al., 2009), and that dopamine agonists can generate OCD-like behaviours (Borcherding et al., 1990; Szechtman et al., 1998). (Of interest, ketamine per se shows affinity for dopamine D_2 in addition to serotonin 5-HT_2 receptors [Kapur & Seeman, 2002] both blocked by quetiapine, an antipsychotic sometimes used in the treatment of refractory OCD [Gefvert et al., 2001].)

Notably, dopamine has been linked to learning (e.g., Castner & Williams, 2007; Centonze, Picconi, Gubellini, Bernardi, & Calabresi, 2001); and is found in brain areas underlying the RHI (Ehrsson, Spence, & Passingham, 2004) (on dopaminergic projections to the prefrontal cortex, see Goldman-Rakic, Lidow, & Gallager, 1990). It could therefore contribute to perceptual learning processes mediating corporeal awareness; and possibly account for an amplified illusion in OCD. But how does dopamine induce the RHI in the face of contradictory input (i.e., asynchronous stimulation)? One explanation is that dopamine overactivity underlies salience attribution: ascribing causal importance to salient events (e.g., Howes & Kapur, 2009; Kapur, Mizrahi, & Li, 2005). In the asynchronous condition, the patient focuses his attention on a dummy that resembles the patient's hand and it appears in its expected location. This attention-grabbing input violates expectations, rendering the event highly salient. As such, learning ("dopamine-encoding") might ensue; i.e., driving the illusion of ownership ("the fake hand on the table must be mine") even when incoming sensory information is incongruous; effectively, overriding internally constructed models of reality (Albrecht et al., 2011; on Bayesian prediction error, see Fletcher & Frith, 2009). Together, these findings stress how a unified sense of self may rest on a delicate balance between top-down regulation and bottom-up processes.

Counterintuitively, Y-BOCS scores inversely correlated with the intensity of the illusion but only during asynchronous stimulation. One explanation for this is that top-down attention, possibly driving the illusion during asynchronous stroking (via salience misattribution), was perturbed by anxiety states in the most severe patients. Indeed, anxiety decreases attentional control (Eysenck, Derakshan, Santos, & Calvo, 2007), and is unsurprisingly associated with OCD symptoms (e.g., Foa, Kozak, Salkovskis, Coles, & Amir, 1998). Anxiety overall may therefore have interfered with perceptual learning effects of dopamine (caused "general blunting"), which might explain why OCD severity (irrespective of condition) did not intensify the illusion.

The primary aim of this study was to explore the therapeutic potential of the RHI. Our findings may pave the way for a novel therapeutic technique for OCD (see also, Jalal et al., 2015). Practically (e.g., based on the current results), such an approach might entail 10 minutes of tactile stimulation, coupled with at least 5 minutes of continuous dummy contamination (as outlined in the Methods section). The procedure should be repeated (e.g., 3-4 times) until habituation occurs; for severe patients, possibly starting with asynchronous stroking followed by synchronous for a more immersive experience. (Analogously, a session of ERP typically lasts around 90 minutes [van der Heiden et al., 2016].)

This method we have introduced may offer a tolerable alternative to ERP, with potential to trigger clinically relevant contamination reactions. Crucially, unlike ERP, it does not require patients to touch highly aversive "contaminants." As such, it is conceivable that patients who are reluctant to engage in ERP due to fear of direct skin exposure (i.e., too frightened to confront contaminants head-on) would be more accepting of this approach. Also, as noted, it might be useful during the initial stages of exposure to help desensitize patients such that they are willing to eventually undertake ERP.

Because the RHI itself is engaging—fittingly labelled a "mind-blowing party trick" (Lawton, 2009)—our method might appeal to a younger audience. During pilot work, volunteers often express astonishment (sometimes even slight giggling) at the uncanny sensation of touch

arising from an obvious fake hand. This element of amusement (positive affect) could establish a frame for a less fearful outlook on exposure; i.e., create nonthreatening re-association to bodily contamination. All in all, this simple, immersive and cost-effective intervention might result in higher treatment uptake, lower drop-out and facilitate early intervention. It is eminently suitable for poorly resourced and emergency settings, including low-income and developing countries with minimal access to high-tech solutions like virtual reality.

Limitations of this study include not controlling for comorbid psychiatric disorders. It is plausible that co-occurring conditions may have impacted these results. Indeed, as noted, psychiatric disorders have been shown to differentially influence self-referential processing. Ideally, future studies should explore corporeal awareness in OCD using large samples of unmedicated patients without comorbidities. Moreover, double-blind placebo-controlled trials should directly compare our proposed “dummy contamination” procedure to ERP. Finally, “multisensory stimulation therapy” lends itself to other applications in psychiatry (Jalal et al., 2015)—like treating “needle phobia.” Conducting realistic exposures in this population is challenging: repeated needle injections into a real arm could result in punctured veins. Using a fake hand during the RHI, instead, may provide a clever and convenient alternative.

5. Study 3

Abstract

One type of obsessive–compulsive disorder (OCD) is characterized by contamination fears and compulsive cleansing. Few effective treatments are available for this debilitating condition. Compulsive symptoms, such as excessive washing, are believed to be mediated by cognitive inflexibility—arguably the most striking cognitive impairment in OCD. In this study, we investigated the effects of two novel smartphone interventions on cognitive flexibility and OCD symptoms in healthy individuals with OCD-like contamination fears. In the first intervention, participants watched a brief video recording of themselves engaging in handwashing on a smartphone, four times a day, for a total of one week ($N = 31$). The second intervention was similar except that participants watched themselves repeatedly touching a disgust-inducing object ($N = 31$). In a third (control) "intervention," participants watched themselves performing sequential hand movements ($N = 31$). As hypothesized, the two smartphone interventions, unlike the control, improved cognitive flexibility; as assessed on the Intradimensional-Extradimensional Set Shifting task (a sensitive marker of cognitive flexibility). The two interventions, unlike the control, also improved OCD symptoms (measured with the Obsessive–Compulsive Inventory–Revised and Yale–Brown Obsessive–Compulsive Scale). Finally, we found high levels of adherence to the interventions. These findings have significant clinical implications for OCD.

Reference: Jalal, B., Brühl, A., O'Callaghan, C., Piercy, T., Cardinal, R. N., Ramachandran, V. S., & Sahakian, B. J. (2018). Novel smartphone interventions improve cognitive flexibility and obsessive-compulsive disorder symptoms in individuals with contamination fears. *Scientific Reports, 8*(1), 14923.

5.1 Study aims

If vicarious observation of repetitive behaviors can play a functional role for the patients that is similar to actually performing them, it could be used for developing smartphone interventions for OCD using "vicarious exposure" procedures. It may be that for some OCD patients, merely watching video footage of themselves washing their hands, when feeling contaminated, brings about sufficient relief to eliminate the urge to engage in the

actual hand-cleansing behavior. Even if the cleansing urge is only partly eliminated, that would still have a potential therapeutic advantage of reducing high levels of acute stress and anxiety, known to worsen compulsive symptoms. It is conceivable that over time such short-term relief would lead to higher-level cognitive realization that refraining from the compulsion brings no harm, thus decoupling the behavior from the stimulus. Another possible application of this therapeutic procedure is that it could serve as a benign substitute compulsion. In cases of treatment-refractory OCD, for instance, this approach would be an alternative way to prevent skin damage due to excessive handwashing, and, with smartphones readily accessible, might reduce the time spent on performing compulsive behaviors (Jalal et al., 2018).

Similarly, if contamination sensations can be induced vicariously, smartphone interventions could be aimed at desensitizing OCD patients to stimuli that provoke disgust and anxiety. For example, if OCD patients repeatedly watched video footage of themselves touching disgust-inducing objects, such exposure might eventually lead to habituation—that is, diminished emotional responsiveness to the aversive stimulus. The aim of this intervention would be analogous to ERP, except that it would be inexpensive, and allow patients to complete at least part of their therapy in the absence of the therapist, making it transportable and easily accessible. This type of "vicarious desensitization therapy" is conducted in a real-life setting where patients' contamination fears and washing compulsions arise in their day-to-day lives, as opposed to the artificial environment of the clinic. This might be contextually more appropriate and accelerate stimulus generalization, potentially increasing the therapeutic efficacy (Jalal et al., 2018).

Compulsive symptoms such as excessive washing behaviors are thought to be mediated by cognitive inflexibility (impaired "set shifting"), the perhaps most striking cognitive/executive impairment in OCD (e.g., Chamberlain et al., 2005) (on cognitive flexibility see Section 1.1.8). A key measure of cognitive flexibility on which OCD patients perform less well than healthy controls is the IED (Downes et al., 1989) of the CANTAB task (e.g., Sahakian & Owen, 1992) (see also, Olley et al., 2007). In particular, research has shown that the crucial EDS stage of the IED task is impaired in OCD (Chamberlain et al., 2006; Vaghi et al., 2017;

Veale et al., 1996; Watkins et al., 2005), making it a sensitive marker of cognitive flexibility.

In the current study, we investigated the effects of two novel smartphone interventions on OCD symptoms and cognitive flexibility in healthy individuals with OCD-like contamination fears. The first intervention tested the effect of participants watching a brief video recording of themselves engaging in handwashing, four times a day, for a total of one week (washing condition). The second intervention tested the effect of participants watching a video recording of themselves repeatedly touching a disgust-inducing object, four times a day, for a total of one week ("contamination" condition). A third, control intervention was identical to the two experimental interventions, except that participants instead watched a video recording of themselves performing arbitrary hand movements.

5.2 Hypotheses

If vicarious observation of handwashing can induce relief in individuals with OCD symptoms (Jalal & Ramachandran, 2017), then watching video footage of hand-cleansing on a smartphone should likewise bring relief in this population; possibly eliminate cleansing urges. Given that abstaining from compulsive acts (e.g., excessive washing) without aversive outcomes (e.g., illness) causes extinction, viewing such footage (as a substitute for compulsions) may over time reduce OCD symptoms. Indeed, it should correct faulty cognition (i.e., not washing equals danger) and ultimately extinguish aberrant stimulus-response links. Even if watching such footage only partly eliminates compulsive urges, this should still reduce acute stress and anxiety. Considering that stress/anxiety promotes excessive habits (Schwabe & Wolf, 2011) underlying compulsivity (Gillan et al., 2011), this procedure should result in overall OCD symptom reduction. Likewise, if relief from disgust can be induced vicariously, given disgust is a driver of contamination fears (Olatunji et al., 2010), daily doses of disgust-related relief (obtained by viewing such footage) should reduce fear and OCD symptoms. Based on these reasons, if individuals with subclinical OCD watch a brief video recording of themselves engaging in handwashing on a smartphone (e.g., several times daily) this should eventually (e.g., after one week) reduce contamination fears and OCD symptoms. This hypothesis is also based

on research showing that the strategic use of safety behaviors can improve treatment (e.g., Levy & Radomsky, 2014); possibly induce a relaxed (less-agitated) state, leading to increased willingness to confront contaminants (e.g., shaking hands; see Section 1.1.5).

Next, given direct and vicarious exposure trigger comparable disgust reactions (Jalal & Ramachandran, 2017), if repeated *in vivo* exposure can improve OCD symptoms, this should also hold for vicarious exposure; e.g., viewing disgust-confrontation via smartphone footage. Relatedly, it is known that fear and OCD symptoms can be ameliorated by repeated exposure even in the absence of ritual prevention (Rachman et al., 2011). In the same vein, if merely imagining confrontation with contaminants (imaginal exposure) over time reduces OCD symptoms, then watching real-life footage of such exposure via a smartphone (another indirect approach) should likewise be effective. Indeed, this hypothesis should hold true given research tends to favor *in vivo* over imaginal exposure (Foa et al., 1985), implying the importance of sensory input vis-à-vis exposure (e.g., visual feedback) (see Section 1.1.5). In short, if individuals with subclinical OCD watch a brief video recording of themselves repeatedly touching a disgust-inducing object on a smartphone (e.g., several times/day), this should after a while (e.g., one week) reduce contamination fears and OCD symptoms. This hypothesis is also grounded in the fact that context-specificity is therapeutically important for extinction (Butcher et al., 2008; McNally, 2007). Indeed, this "vicarious desensitization therapy" is conducted in a real-life context.

Finally, if compulsive symptoms in OCD (e.g., excessive cleansing) are mediated by impaired "set shifting," and cognitive flexibility can improve in response to psychological treatment (see Section 1.1.8), these smartphone interventions should also improve cognitive flexibility (as assessed on the EDS stage of the IED task). In sum, assuming that the two smartphone interventions can improve contamination fears, OCD symptoms, and cognitive flexibility, based on the above justification the following hypotheses were advanced:

Contamination fears and OCD symptoms: if individuals with subclinical contamination fears watch a brief video recording of themselves engaging in handwashing on a smartphone (four times a day, for one week), this will improve contamination fears and OCD symptoms (as assessed on self-reported measures), unlike the control intervention. Similarly, if these participants watch a brief video recording of themselves repeatedly touching a disgust-inducing object (four times a day, for one week), this will improve contamination fears and OCD symptoms, unlike the control intervention.

Cognitive flexibility: following the two active smartphone interventions, participants will improve on the EDS stage of the IED task (a key marker of cognitive flexibility), but not following the control intervention.

5.3 Methods

5.3.1 Participant selection

Participants were recruited from the local community via online forums, flyers, newspaper adverts, mailing lists, and volunteer databases. The advert specified that our study was seeking individuals who were concerned about contamination. Given the difficulty of recruiting subjects with elevated contamination fears without a prior psychiatric history, a second recruitment approach was implemented; to accelerate recruitment and minimize the rate of false positives, a second advert was included which did not explicitly mention that we were seeking individuals with contamination fears. This advert invited healthy volunteers to initially complete a brief online pre-screening questionnaire which was composed of 6 items from the Padua Inventory Contamination Fear Subscale (PI CF; Burns, Keortge, Formea, & Sternberger, 1996) to assess contamination fear propensity and 14 items from the Barratt Impulsiveness Scale (Patton, Stanford, & Barratt, 1995). This composite questionnaire was used as the PI CF items on their own would have created an obvious focus on contamination fears.

Participants fulfilling the inclusion criterion (scoring at least 6 points on the PI CF items) based on the pre-screening, were contacted by email and invited to do a phone screening to determine their eligibility. Individuals were selected for the study if they had elevated

contamination fears, as defined by a score of at least 10 points on the PI CF during the initial telephone screening and at least 9 points on the PI CF during the first laboratory testing session. (This cut-off was selected based on the finding that the mean score of the PI CF measure for patients with OCD is 13.87 [*SD* = 7.96] [Burns et al., 1996].) Study participation was restricted to those aged between 18-65, who were proficient in English, and without a history of psychiatric disorders. During the initial phone interview potential participants were screened using the Modified Mini Screen (MMS; New York State Office of Alcoholism and Substance Abuse Services, 2002). If they endorsed any of the questions on the MMS screen, they were administered the specific diagnostic module of the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1999) relevant to their answer. If any of their answers on the MINI indicated a possible clinical diagnosis, the individual was interviewed by an experienced psychiatrist to rule out a clinical diagnosis.

5.3.2 Study timeline

The smartphone application used in this study was designed, programmed and piloted between December, 2015 and August, 2016; i.e., approx. 8 months were spent on app development. Recruitment, screening and running of participants commenced in July, 2016 and continued until June, 2018. Due to the challenge of recruiting participants with subclinical OCD without a psychiatric history, subject recruitment, screening and testing took approx. 18 months. (As noted, research has demonstrated that OCD symptoms in the general population are associated with elevated rates of psychiatric disorders [e.g., Fineberg et al., 2013b].)

5.3.3 Procedure

Participants were randomized to one of three conditions: the washing condition (smartphone intervention I), contamination condition (smartphone intervention II), or the control condition. Participants in the three conditions were actively matched for age, sex, years of education and level of contamination fears.

Participants attended two sessions, 8 days apart. This study was approved by the University of Cambridge's Psychology Research Ethics Committee and all research was performed in

accordance with the relevant guidelines and regulations. All participants provided written informed consent prior to participation in the study and received monetary compensation for their travel costs and time. In both sessions, they completed a battery of clinical measures and neuropsychological tests (described in more detail below). At the end of session one, they completed a 30-second video recording that would form the basis of the smartphone intervention.

Participants in the washing condition were recorded while washing their hands with soap at a basin. Those in the contamination condition were recorded while repeatedly touching toilet paper in a bedpan. This toilet paper was stained (using food substances) to resemble feces and placed around a fake feces-replica. An unpleasant odor was sprayed on this object to increase its authenticity. Consistent with our previous methodology participants were not informed that the feces were fake (Jalal et al., 2015; Jalal & Ramachandran, 2017). (During piloting we found that participants rated "fake feces" as more disgusting than "fake vomit" and "fake blood." This result is consistent with our previous research [Jalal & Ramachandran, 2017].) Participants in the control condition, were shown a sequence of hand movements (a cutting motion on the table, followed by a fist, and then palm down with fingers extended; Luria's Hand Sequences, i.e., "cut, fist, and slap"; Luria, 1970). They were filmed while making these movements with both hands resting on a table. All the videos were recorded such that they only showed the participants' hands and arms, and simulated the vantage point of the participants looking down at themselves (the smartphone video in each condition is shown in Figure 5.1.1).

A:

B:

C:

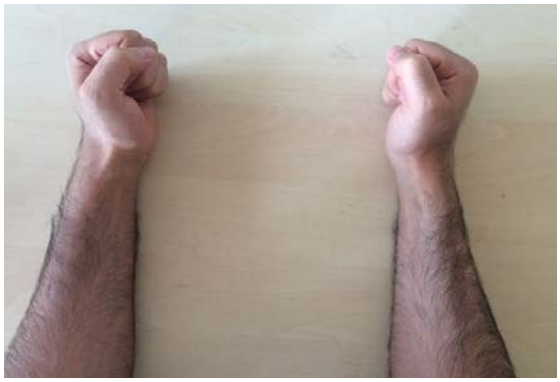

Figure 5.1.1 The Smartphone Video in Each Condition[a]

[a](A) The video footage used in the washing condition. (B) The video footage used in the contamination condition. (C) The video footage used in the control condition.

The experimenter then installed the smartphone application on the participants' smartphones and uploaded the video recording to the application. The experimenter instructed participants how to use the application, and participants completed a practice trial on their smartphones in the presence of the experimenter to ensure that they had understood the instructions. The first visit was then complete. Thereafter, participants completed the smartphone intervention for seven days, as they went about their daily lives. After a week of using the smartphone application, participants returned for a second visit and debriefing.

5.3.4 Smartphone application

The smartphone application was designed to be compatible with iPhones (model 4S or newer), iPod Touch devices and Android-based smartphones. A smartphone (Samsung Galaxy S3) and Apple iPod touch (6^{th} generation, with a 4-inch diagonal widescreen display) similar in dimensions to many widely used smartphones, were also available for participants to use during the duration of the study to avoid technical obstacles arising from running the application. The primary function of the smartphone application was to play a video recording (30 seconds) of participants either: (1) washing their hands, (2) touching a "contaminated" object, or (3) performing a sequence of arbitrary hand movements. Participants were instructed to use the application four times a day for seven days; i.e., at least once during the following time windows: 8 am to 12 pm; 12 pm to 4 pm; 4 pm to 8 pm; and 8 pm to 12 am. The default screen of the application showed a start tab at the center that participants had to touch to play the video recording; the default screen also showed what session of the day they had to complete (1-4), days remaining of the intervention (1-7), and time remaining before the next session. A virtual envelope was displayed at the top right of the screen, which participants could touch in order to email the data to the experimenter. Participants were asked to press the envelope after each session so that the experimenter could track their progress. (As the virtual envelope did not function on all smartphones and iPod devices, participants were asked in these cases to update the experimenter on their progress via email or SMS at least once a day.) To ensure that participants viewed the video at all times, while watching they were randomly presented with either one, two or three flashing circles superimposed on the video recording (approx. 2 seconds per flash). Once the video stopped playing, they were asked to indicate the number of circles they saw.

Moreover, immediately before and after watching the video, participants rated their levels of anxiety, disgust, and handwashing urges using the application. When participants had completed the session, the start tab disappeared from the screen and participants could no longer initiate a session; it would reappear once it was time to undertake a session again (for an overview of the smartphone app see Figure 5.1.2).

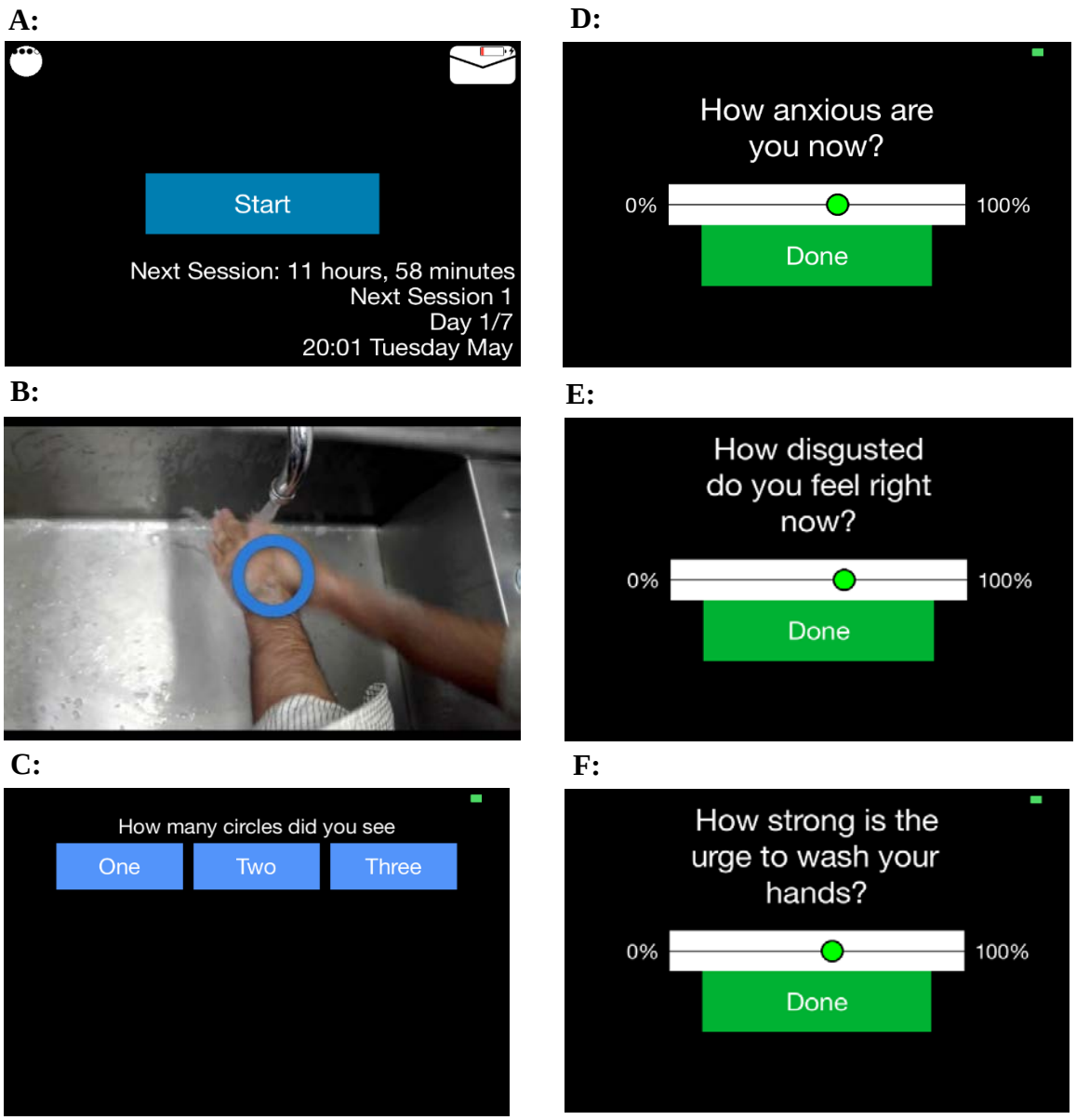

Figure 5.1.2 Overview of the Smartphone App[a]

[a](A) The "default start screen" of the smartphone application. (B) The flashing circles superimposed on the video footage to track that participants are watching. (C) The screen where participants indicate the number of circles they saw, immediately after the video finished playing. (D) Anxiety ratings before and after watching the video. (E) Disgust ratings before and after watching the video. (F) Ratings of handwashing urges before and after watching the video.

5.3.5 OCD symptomatology and mood assessment

Before and after the intervention, participants completed the following validated self-report questionnaires and clinical interviews to assess factors related to contamination fears, OCD symptomatology, mood, disgust sensitivity, and health anxiety.

Padua Inventory Contamination Fear Subscale (PI CF)

The PI CF (Burns et al., 1996) is a 10-item scale assessing the presence and severity of contamination fears and washing compulsions. Items are scored on a 5-point Likert scale and scores are generated by adding the item scores; the possible range of scores is 0-40.

The Obsessive-Compulsive Inventory-Revised (OCI-R)

The OCI-R (Foa et al., 2002) is a self-report scale that assesses distress levels associated with OCD symptoms in the last month. It consists of 18 questions rated on a 5-point Likert scale and scores are generated by adding the item scores; the possible range of scores is 0-72.

Yale-Brown Obsessive-Compulsive Scale (Y-BOCS)

The Y-BOCS (Goodman et al., 1989) is a semi-structured interview that assesses OCD symptom severity (obsessions and compulsions) and response to treatment. Scores are generated from 10 items, each rated on a 5-point Likert scale. The possible range of scores is 0-40. The version of the Y-BOCS employed in the current study ranged from 1-40 possible scores, with item 10 (measuring “degree of control over compulsive behavior”) rated on a 4-point Likert scale (1-4).

Spielberger State-Trait Anxiety Inventory (STAI-S/T)

Participants completed the STAI-S/T (Spielberger, 1983), comprising 40 items assessing state and trait levels of anxiety. Each subscale on the STAI consists of 20 items that are rated on a 4-point Likert scale. Scores are generated by adding the item scores and with a sum score ranging between 20 and 80 on each subscale.

Beck Depression Inventory-II (BDI-II)

All participants completed the BDI-II (Beck, Steer, & Brown, 1996), a 21-item self-report measure of depression rated on a 4-point Likert scale. Scores are generated by adding the item scores; the possible range of scores is 0-63.

5.3.6 Neurocognitive assessment

Before and after the intervention, the following neuropsychological measures were administered from the CANTAB battery (www.cambridgecognition.com; Sahakian & Owen, 1992) and presented on a touch-sensitive screen.

Intra/Extradimensional Set Shift task

The IED (Downes et al., 1989) is an attentional set shifting measure. The task starts with the participant seeing two colored geometric shapes. Participants are required to touch the correct shape on the screen and feedback is provided after every response. They can therefore learn which of the two shapes is correct through the process of trial and error. After six consecutive correct responses, the stimuli and/or rules are changed. These shifts are intra-dimensional as the shapes only differ on one dimension (shape). Later, white lines are superimposed on the two shapes and participants learn over the course of several stages that these lines are an irrelevant dimension. During the crucial extradimensional shift (EDS) stage, the white lines become the only relevant dimension. The EDS stage indexes cognitive flexibility; that is, assessing the ability to shift attention away from previously relevant stimulus dimensions to a novel (previously irrelevant) one. A key outcome measure on this task is errors made in the EDS stage. Another outcome measure, is pre-extradimensional shift (pre-EDS) errors; that is, errors in the stages before the extradimensional shift.

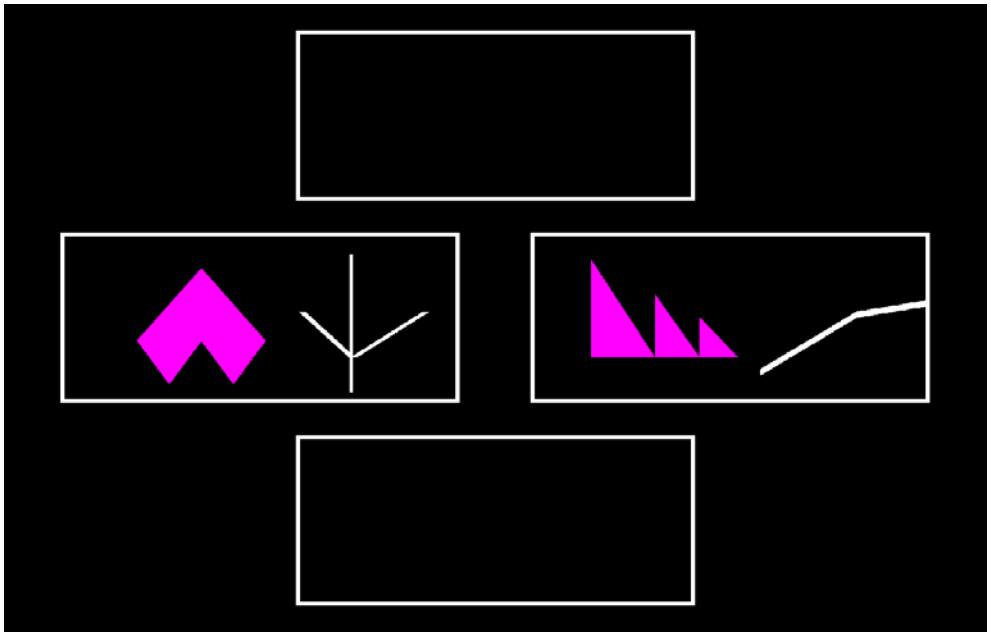

Figure 5.1.3 Illustration of the Intra/Extradimensional Set Shift Task

5.3.7 Statistical analyses

This study was done as a randomized quantitative longitudinal design (pre/post) comparing two active interventions (washing and contamination conditions) and a "placebo" control condition (neutral), focusing on both the between-subject and within-subject effects. For the IED task, we analyzed EDS errors as the primary dependent variable of interest. A secondary variable of interest was pre-EDS errors (total task errors, across all stages, minus EDS errors). Other dependent variables of interest included the PI CF, OCI-R, and Y-BOCS.

Two participants in session 1 were missing a single score each on the Y-BOCS and one participant was missing a single Y-BOCS score in session 2. Their scores were rescaled to the maximum possible total (i.e. adjusted score = full scale maximum × subject's score ÷ subject's possible maximum). The STAI-T subscale (assessing trait anxiety) of the STAI-S/T measure, was only completed at baseline. An overview of the study is shown in Figure 5.1.4.

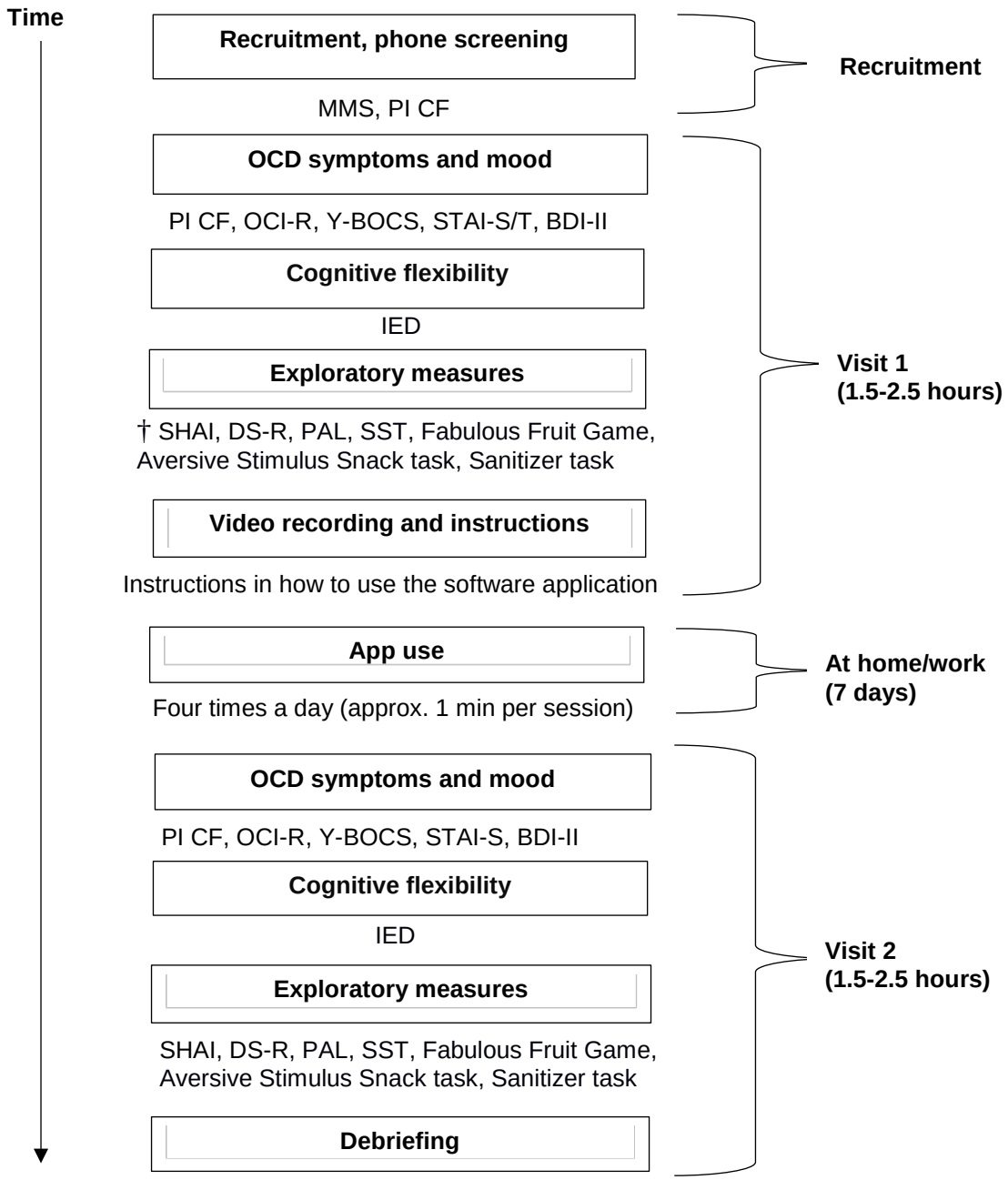

Figure 5.1.4 Overview of Study

(†) Exploratory measures are presented in Section 6. SHAI, Short Health Anxiety Inventory; DS-R, Disgust Scale-Revised; PAL, Paired Associates Learning task; SST, Stop Signal Task. The SST, Fabulous Fruit Game task, and Aversive Stimulus Snack task were completed by a subsample (n = 46).

Dependent variables before and after the intervention were analyzed with an analysis of covariance (ANCOVA). As predictors, we used the subjects' pre-intervention scores on the same task (baseline performance: a continuous covariate) and the intervention (a factor with 3 levels). An initial analysis was performed in which the covariate × factor interaction was included (a separate-slopes model). If this interaction term was not significant and the interaction model was not superior to a model without the interaction, by a χ^2 model comparison test, the simpler ANCOVA model without the interaction (a single-slope model) was used. Since subjects were randomized to interventions, with equal group sizes, sequential (type I) sums of squares (SS) were used, prioritizing treatment effects over baseline performance to maximize power. (This method differs from type II/III SS in its treatment of that portion of variance in the dependent variable potentially attributable to either the treatment effect or baseline performance, due to correlation between the two predictors. Given that subjects were randomized to equally sized groups, any such correlation is by definition random; any such variance was attributed to the treatment. This does not alter the attribution of variance attributable to the treatment but not to baseline performance, or that attributable to baseline performance but not the treatment—the latter being an important contributor, as baseline performance strongly predicts subsequent performance [Myers & Well, 2003].) Following a significant main effect of treatment, pairwise comparisons were made with separate ANCOVAs; in this specific case of pairwise comparisons used only following a significant main effect, no further family-wise error rate correction is necessary (Cardinal & Aitken, 2006); however, the sub-ANCOVAs were not constrained to use the slope from the overall ANCOVA.

For all measures, the distribution of residuals was checked with Q-Q plots and the Shapiro-Wilk test. Preliminary examination of untransformed scores showed that for some dependent variables, the residuals deviated substantially from a normal distribution, with positive skew and leptokurtosis (e.g. for EDS errors). Such variables were therefore transformed with a $\log_{10}(x + 1)$ transformation or a square-root transformation prior to final analysis (Myers & Well, 2003).

The figures pertaining to the ANCOVA analyses, show participants' scores before and after the smartphone intervention. Confidence ribbons indicate ±1 standard error. The green line

with no confidence ribbon is the $x = y$ line of "no change"; deviations from this in the control condition suggest e.g. practice effects, regression to the mean, or other nonspecific changes. The overall significance threshold for the study was set at $\alpha = 0.05$. The data were analysed using the software program R and SPSS version 25.

Correlations were checked for contamination fear and OCD symptom severity (baseline) and improvement (pre/post intervention difference scores), and performance on the IED, for each of the conditions. None of the correlations reached significance upon correcting for multiple comparisons (using the Bonferroni method) and are therefore not reported.

5.4 Results

A total of 797 study volunteers completed the online pre-screen questionnaire, of which 156 were phoned screened. Of these 156 individuals, 98 qualified for the first laboratory session. During the first laboratory session two volunteers scored less than 9 on the PI CF and thus did not qualify for the study. The initial subject pool consisted therefore of 96 participants. Three participants were subsequently excluded: one participant for missing data (i.e., 50 percent of their smartphone sessions), one participant due to a technical error on the smartphone application, and one participant for failing to show up to the final laboratory assessment due to a scheduling conflict despite completing the 7-day intervention. The final subject pool was thus comprised of 93 participants (washing $n = 31$; contamination $n = 31$; control $n = 31$). Sixty participants (64.5 percent) were female and 33 (35.5 percent) were male. The age range was 18–64 years of age ($\mu = 25.2$, $SD = 8.0$). (For demographics and baseline clinical measures, see Table 5.1).

Table 5.1 Demographic and Clinical Characteristics for the Final Randomized Groups[a]

Condition	**Washing (*n* = 31)**		**Contamination (*n* = 31)**		**Control (*n* = 31)**		***Comparison***
	μ	**(*SD*)**	*μ*	**(*SD*)**	*μ*	**(*SD*)**	F_{df}
Age	25.97	(8.88)	23.52	(3.39)	26.13	(9.98)	† $F_{2,90} < 1$, NS
Education (years)	16.74	(3.65)	16.50	(2.68)	16.39	(2.69)	† $F_{2,90} < 1$, NS
PI CF	19.10	(6.86)	19.35	(7.11)	20.19	(6.64)	$F_{2,90} < 1$, NS
OCI-R	20.55	(10.74)	20.10	(9.82)	24.48	(9.74)	$F_{2,90} = 1.77$, $p = 0.1770$
Y-BOCS	3.76	(3.19)	3.23	(3.30)	3.94	(3.36)	† $F_{2,90} < 1$, NS
STAI-T	38.87	(8.81)	36.10	(9.66)	40.61	(10.53)	$F_{2,90} = 1.71$, $p = 0.1863$
STAI-S	34.48	(8.73)	31.13	(6.75)	36.06	(10.62)	$F_{2,57.99} = 2.88$, $p = 0.0639$
BDI-II	6.97	(5.38)	8.10	(8.49)	7.16	(6.63)	† $F_{2,90} < 1$, NS
	n	**(%)**	***n***	**(%)**	***n***	**(%)**	X^2_{df}
Sex (*n*/% female)	20	(64.5)	19	(61.3)	21	(67.7)	$X^2_2 < 1$, NS

[a]*μ*, mean; *SD*, standard deviation; *n*, sample size; *F*, *F* statistic; X^2, chi-square statistic; *df*, degrees of freedom; *p*, *p* value; NS, non-significant; PI CF, Padua Inventory Contamination Fear Subscale; OCI-R, Obsessive-Compulsive Inventory–Revised; Y-BOCS, Yale-Brown Obsessive-Compulsive Scale; STAI-T, Spielberger Trait Anxiety Inventory; STAI-S, Spielberger State Anxiety Inventory; BDI-II, Beck Depression Inventory-II. (†) After applying a $\log_{10}(x + 1)$ transformation, as for the main analysis (see text).

Additional data were missing on a small number of measures. Data for the number of sessions completed and for the circle-counting control task were lost for one (control) participant due to a technical problem. For one subject (in the washing condition), the test circles were not presented in a randomized fashion due to a technical error, but as this subject's data did not deviate from that of other participants she was included. One subject's post-intervention Y-BOCS data was lost and thus not analyzed. The final sample size for the Y-BOCS before/after analysis was thus 92 (washing condition $n = 30$,

contamination $n = 31$ and control $n = 31$). One subject was excluded from the IED analyses as she only completed 2 stages (out of 9) on the task. The final sample size for the IED was therefore 92 (washing condition $n = 31$, contamination $n = 31$ and control $n = 30$).

5.4.1 Smartphone intervention

All participants completed the 7-day intervention. Participants in all three interventions successfully completed the majority of smartphone sessions ($\mu = 24.98$ out of a total of 28 sessions; $SD = 2.84$), and these did not differ by intervention (whether analyzed untransformed or squared to reduce negative skew: $F_{2,89} \leq 1.28$, $p \geq 0.283$). Overall, participants appeared to watch the video footage on the application consistently. That is, there were very few inconsistencies between the number of circles shown on the videos and subsequently reported by participants ($\mu = 2.01$ incorrect answers out of a total of 28, $SD = 2.77$), and these did not differ by intervention (following a $\log_{10}(x + 1)$ transformation, $F_{2,89} = 1.25$, $p = 0.2903$).

5.4.2 Contamination fears, OCD symptoms, and mood

Baseline performance on measures of contamination fears, OCD symptoms, and mood (PI CF, OCI-R, Y-BOCS, STAI-T, STAI-S, and BDI-II) did not differ by condition (Table 5.1).

PI CF

Neither active intervention altered contamination fear scores compared to the control (Figure 5.1.5). A single-slope ANCOVA model was used and residuals were normally distributed. There was no effect of treatment ($F_{2,89} = 2.44$, $p = 0.0928$).

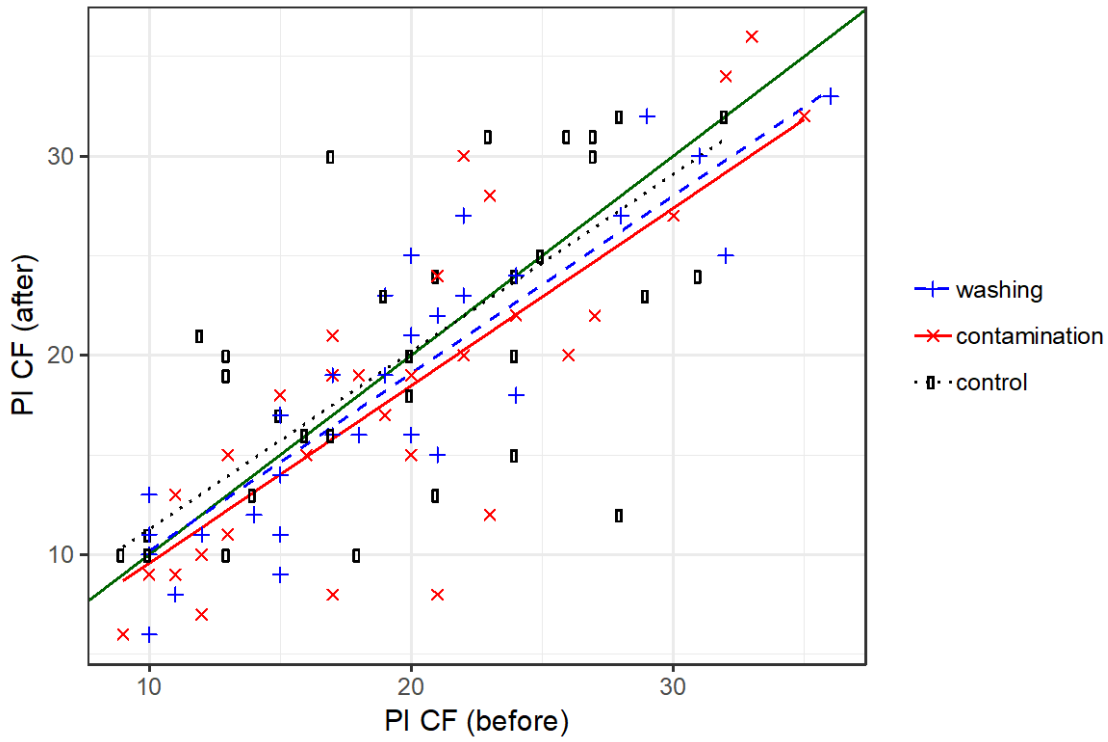

Figure 5.1.5 PI CF Scores Pre and Post Treatment[a]

[a]PI CF scores were not altered by the active interventions compared to the control.

OCI-R

Both active interventions reduced OCI-R scores compared to the control (Figure 5.1.6). A single-slope ANCOVA model was found to be preferable; residuals were normally distributed. The effect of treatment was significant ($F_{2,89} = 11.1$, $p = 5.15 \times 10^{-5}$), with differences between the washing condition and control condition ($F_{1,59} = 9.45$, $p = 0.0032$), and between the contamination condition and the control condition ($F_{1,59} = 19.3$, $p = 4.74 \times 10^{-5}$).

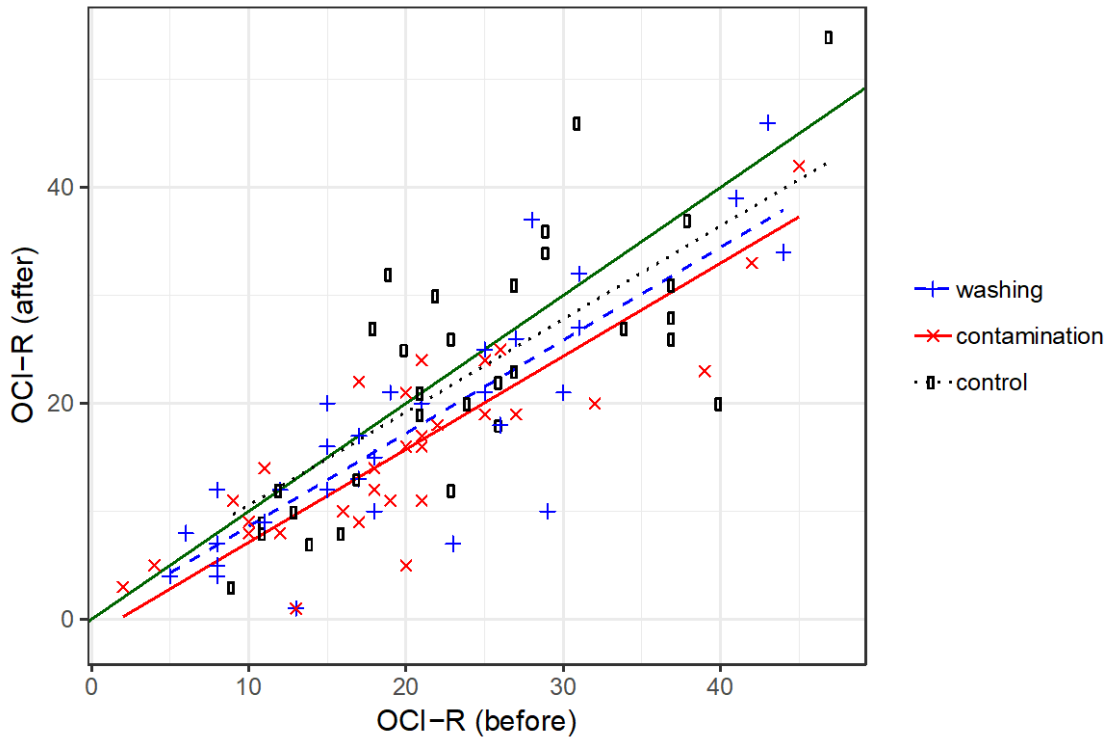

Figure 5.1.6 OCI-R Scores Pre and Post Treatment[a]

[a]OCI-R scores were reduced by both active interventions compared to the control.

Y-BOCS

Both active interventions reduced Y-BOCS scores compared to the control (Figure 5.1.7). Y-BOCS scores were subjected to a $\log_{10}(x + 1)$ transformation to reduce skew and leptokurtosis; a single-slope ANCOVA model was found to be preferable. There was a main effect of treatment ($F_{2,88} = 4.71$, $p = 0.0114$). In pairwise ANCOVA comparisons, the washing intervention differed from the control intervention ($F_{1,58} = 4.85$, $p = 0.0316$) and the contamination intervention differed from the control ($F_{1,59} = 8.11$, $p = 0.0061$).

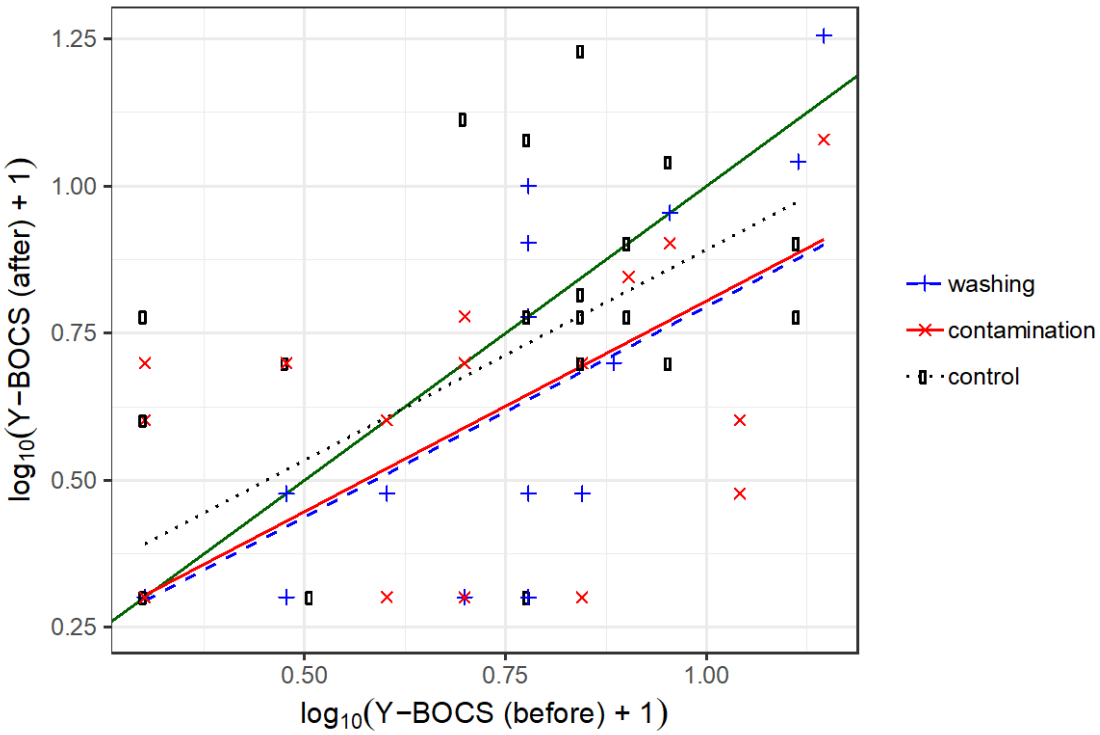

Figure 5.1.7 Y-BOCS Scores Pre and Post Treatment[a]

[a]Y-BOCS scores were reduced by both active interventions compared to the control.

STAI-S

There was no effect of the active interventions on STAI-S scores (Figure 5.1.8). STAI-S residuals showed only minor deviation from normality. A single-slope ANCOVA model was used; there was no effect of treatment ($F_{2,89} < 1$, NS).

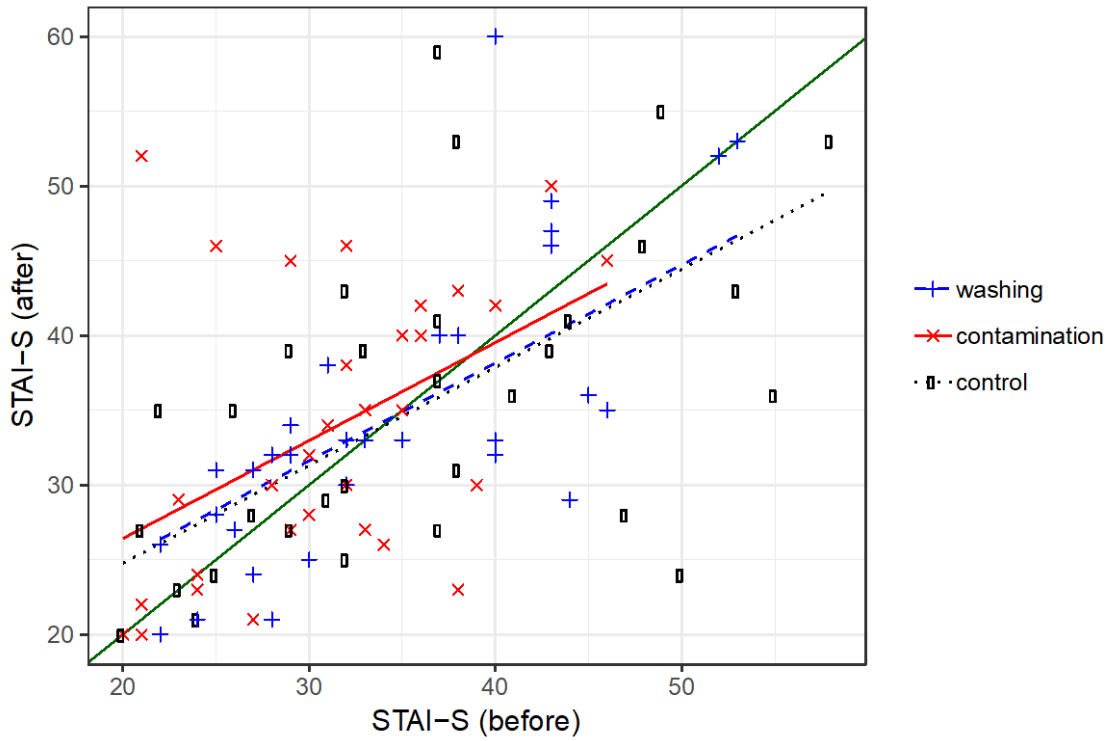

Figure 5.1.8 STAI-S Scores Pre and Post Treatment[a]

[a]STAI-S scores were not altered by the active interventions compared to the control.

BDI-II

There was no effect of the active interventions on BDI-II scores compared to the control (Figure 5.1.9). BDI-II residuals were not normally distributed, with positive skew and leptokurtosis, but satisfied normality tests following a $\log_{10}(x + 1)$ transformation; a single-slope ANCOVA model was preferred. There was no effect of treatment ($F_{2,89} = 1.99$, $p = 0.1428$).

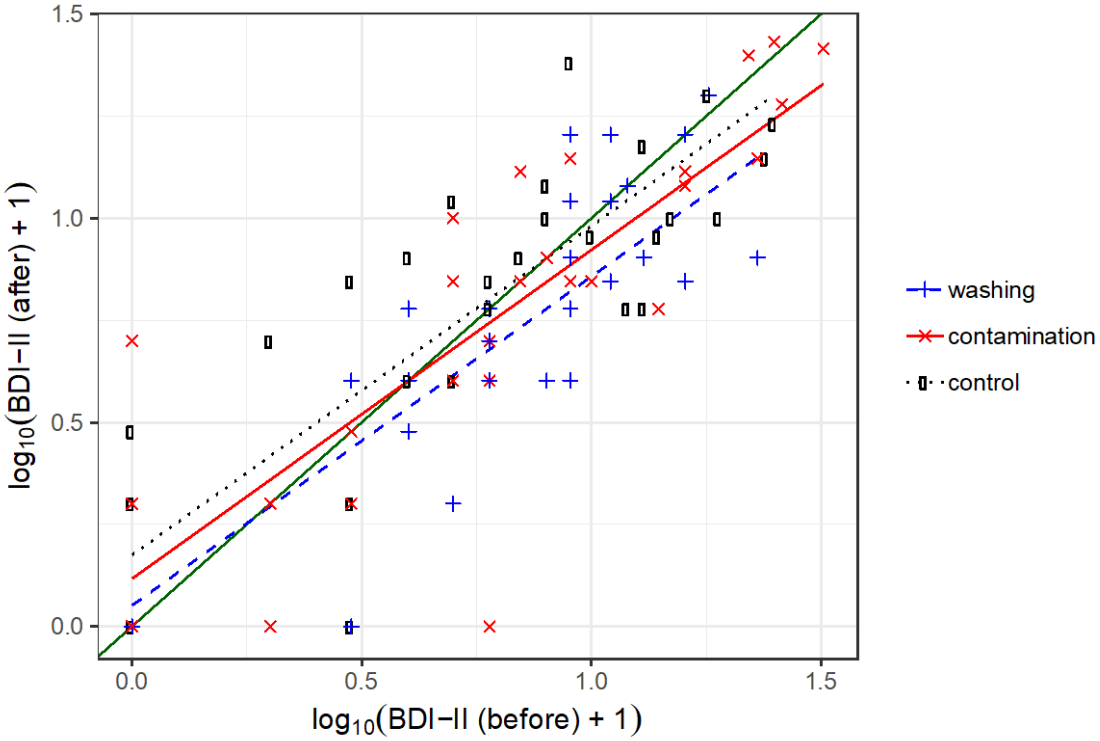

Figure 5.1.9 BDI-II Scores Pre and Post Treatment[a]

[a]BDI-II scores were not altered by the active interventions compared to the control.

5.4.3 Cognitive flexibility

Intra/Extradimensional Set Shift task

EDS errors: as hypothesized, the two active smartphone interventions improved cognitive flexibility as assessed by a reduction in EDS errors (Figure 5.1.10), whereas no significant changes were observed in the control condition. That is, both interventions (the washing and contamination condition) reduced EDS errors. A single-slope ANCOVA model was found to be preferable; residuals were normally distributed following a $\log_{10}(x + 1)$ transformation. There was a clear effect of treatment ($F_{2,88} = 4.95$, $p = 0.0092$). Pairwise ANCOVAs showed that the washing intervention reduced EDS errors compared to the control ($F_{1,58} = 5.95$, $p = 0.0178$), as did the contamination intervention ($F_{1,58} = 7.85$, $p = 0.0069$).

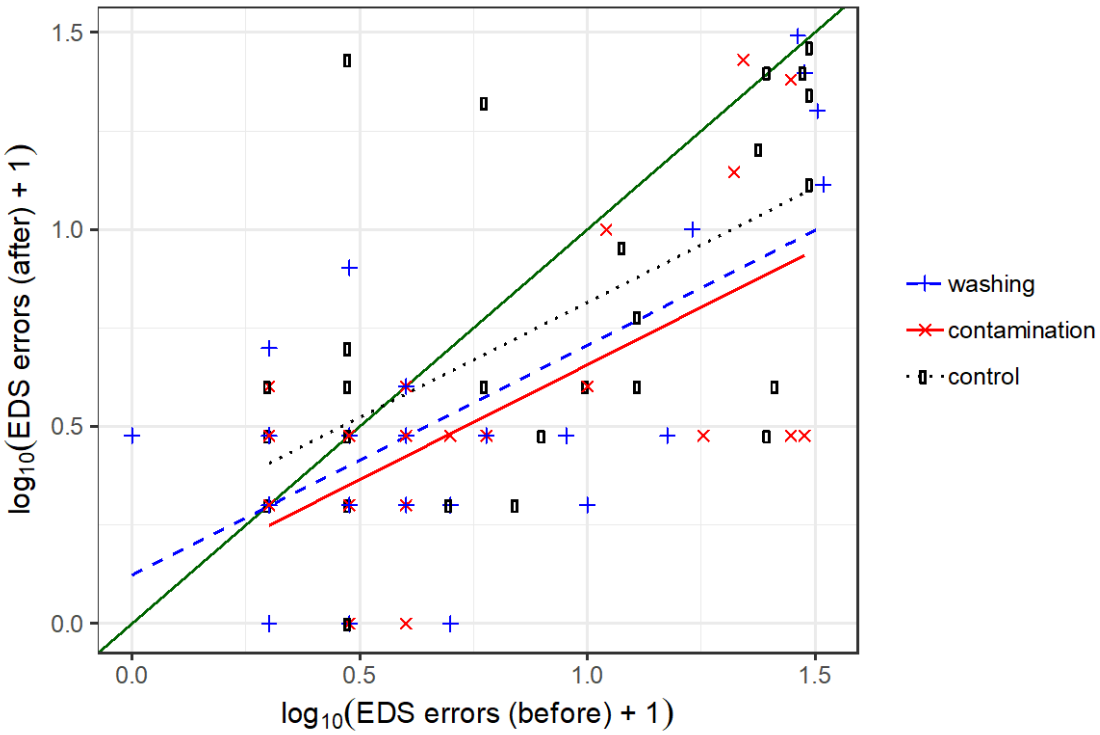

Figure 5.1.10 EDS Scores Pre and Post Treatment[a]

[a]EDS errors were reduced by both active interventions compared to the control.

Pre-EDS errors: as anticipated, neither active intervention affected pre-EDS errors (i.e., errors in the stages before the extradimensional shift) compared to the control (Figure 5.2.1). Residuals were normally distributed following a $\log_{10}(x + 1)$ transformation. The interventions had no effect on performance ($F_{2,88} < 1$, NS).

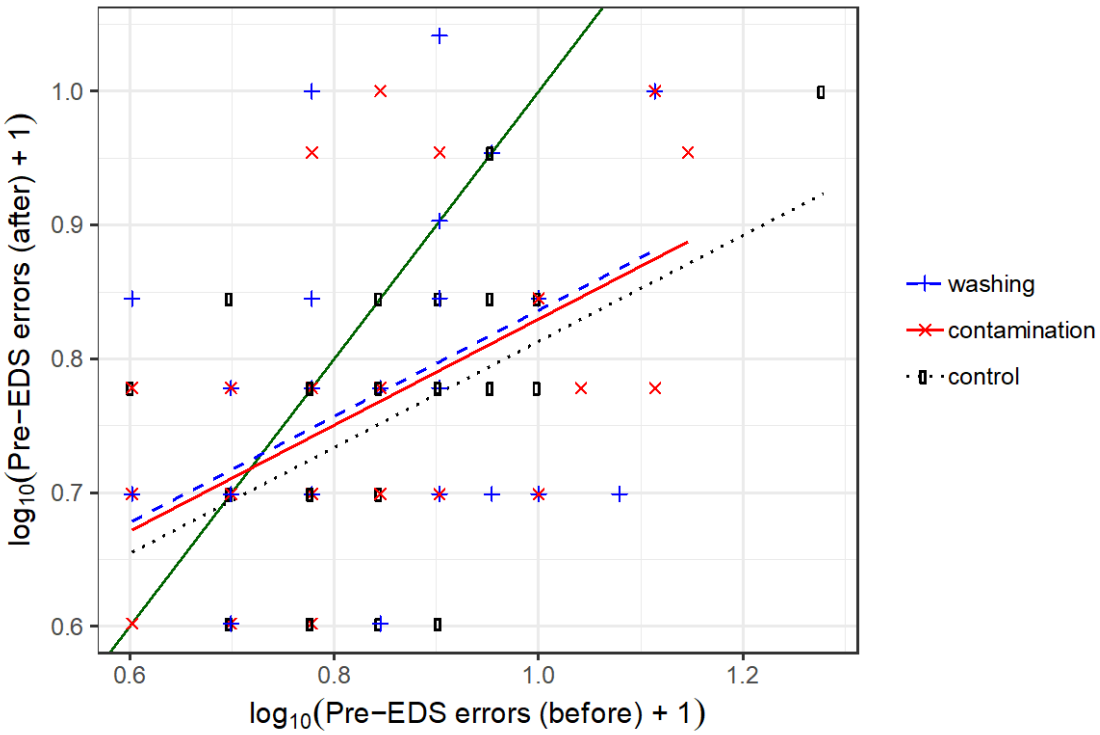

Figure 5.2.1 Pre-EDS Scores Pre and Post Treatment[a]

[a]Pre-EDS errors were not altered by the active interventions compared to the control.

5.5 Discussion

We present here two novel smartphone interventions found to improve cognitive flexibility and OCD symptoms in individuals with OCD-like contamination fears. It is striking that these changes in OCD symptomatology and executive function occurred after only one week of applying the intervention.

Improvements in cognitive flexibility, as assessed with the IED Set Shifting task, cannot be explained by practice effects, as they were not seen following the control intervention. These findings are especially intriguing as cognitive inflexibility (impaired set shifting) may represent the most prominent neuropsychological marker of OCD, emphasizing the potential clinical utility of these smartphone interventions (for meta-analyses see, Abramovitch et al., 2013; Snyder et al., 2015).

These findings are consistent with research showing that neuropsychological deficits in OCD are reversible. Indeed, several studies found that behavioral therapy (administered over the course of weeks) ameliorated neuropsychological deficits, including set shifting, in patients with OCD (Bolton et al., 2000; Katrin Kuelz et al., 2006; Moritz et al., 1999) (for a review see Vandborg et al., 2012).

In the current study, we found improvements on a task of cognitive flexibility in which poor performance is thought to reflect compulsive symptoms in OCD such as excessive washing rituals (Menzies et al., 2008). In addition, participants improved on a self-administered measure of distress associated with OCD symptoms (the OCI-R), and the Y-BOCS, which assesses OCD symptom severity. However, no changes were seen in self-reported scores of contamination fears. One possible explanation is that an intervention administered for a period of only one week (even in a clinical sample) would not directly affect self-perceived contamination fears. That is, this intervention might in many cases be too short to directly influence self-perceptions, especially if one identifies as averse to contamination (e.g., "I've always been a 'germophobe'"). On the other hand, these data suggest that the interventions, albeit short, may improve underlying OCD-type tendencies and crucial cognitive processes like cognitive rigidity, perhaps outside one's immediate awareness. Improvements in cognitive flexibility and OCD symptomatology, particularly in a clinical sample, might over time translate into detectable reductions in contamination fears.

As such, the smartphone interventions may have improved cognitive flexibility and OCD symptoms by influencing compulsive-like behaviors and propensities. The vicarious relief intervention (the washing condition) may have provided acute "doses" of relief, such that any washing urges and perhaps subsequent compulsive-like behaviors were either eliminated or reduced after using the application. This might have led to a reduction in conditioned fear associated with refraining from performing the compulsive behavior. Similarly, the vicarious desensitization intervention (the contamination condition) may have provoked disgust-related anxiety that diminished over the course of the treatment. Such repeated and systematic exposure could have caused participants to become

increasingly desensitized to real-life stimuli that would normally trigger contamination concerns (e.g., when shaking hands), and in turn compulsive-like behaviors.

Anxiety is a crucial component of the cognitive architecture of OCD (Gillan et al., 2014; Gillan & Robbins, 2014). It is believed to bias cognitive systems towards habitual and rigid thinking, leading to impairments in attentional control, including inhibition and shifting (Eysenck et al., 2007). According to one hypothesis, over-reliance on "habit systems" underlies symptoms of compulsivity in OCD (Gillan et al., 2011). In the present study, the interventions ostensibly did not reduce overall state anxiety levels and mood. Instead, the data indicate that the interventions had a more direct and specific effect on OCD-like tendencies (and perhaps anxiety and stress specific to such propensities). This in turn might have helped participants employ more effective cognitive strategies, allowing them to think in a more flexible (less rigid) manner.

Central limitations of traditional therapies for OCD, such as ERP, include costs, inconvenience of delivery (e.g., participant travel), and intolerability of the treatment procedures, resulting in considerable dropout rates (Abramowitz, 2006; Whittal et al., 2005). In the present study, participants showed high levels of adherence to the smartphone interventions: all participants completed the entire one-week intervention; and although participants had to complete as many as four sessions a day within fixed time periods, very few sessions were missed. Likewise, participants were generally attentive to the video footage on the application. These findings demonstrate the practical utility of the interventions and suggest that they could potentially overcome some of the challenges associated with traditional OCD therapies.

In summary, we introduce two smartphone interventions and show that they improve OCD symptoms and cognitive function after only one week in individuals with contamination fears. These interventions could potentially have significant public health and societal impact. They are forms of "technology-based personalized medicine" that are not only inexpensive and accessible but can be tailored for individual patients. They also have the

potential for widespread implementation and could potentially reach communities that do not have access to adequate mental health care.

6. Study 3: Effects of smartphone interventions on exploratory measures

6.1 Study aims

In Study 3, we further investigated the effects of the two novel smartphone interventions on a number of exploratory measures. These included: health anxiety and disgust sensitivity self-report questionnaires and a battery of neuropsychological tests (assessing visuospatial memory, response inhibition, and goal-directed versus habitual control); and a newly developed task indexing cleansing urges and behaviour. Measures also included ratings of anxiety, disgust and handwashing urges immediately before and after watching the smartphone video recording on the application, over the course of the 7-day intervention.

6.2 Methods

(For details on participant selection, procedure and the smartphone application see Section 5.3.)

6.2.1 Anxiety, disgust and handwashing urges pre and post app

Immediately before and after watching the video on the smartphone application, participants rated their levels of anxiety, disgust, and handwashing urges using the application rated on a VAS, ranging from 0-100 percent (Figure 5.1.2).

6.2.2 OCD symptomatology and mood assessment

Before and after the intervention, participants completed the following validated self-report questionnaires related to disgust sensitivity, and health anxiety.

The Short Health Anxiety Inventory (SHAI)

The SHAI (Salkovskis, Rimes, Warwick, & Clark, 2002) is a self-report scale that assesses health anxiety independently of physical health. It consists of 18 items, measuring concerns about health, awareness of bodily sensations and fears of falling ill, over the past 6 months. The items consist of four statements using a multiple-choice format. Each item is weighted 0-3, and scores are generated by adding the item scores; the possible range of scores is 0-54.

The Disgust Scale-Revised (DS-R)

The DS-R (Olatunji et al., 2007) is a self-report scale assessing disgust sensitivity across three domains (core disgust, animal reminder disgust, and contamination-based disgust). It consists of 25 items, of which 13 are statements rated as true or false (weighted 0-1), and 12 statements rated on a 3-point Likert scale (not = 0, slightly = 0.5, very = 1). The scores are generated by adding the item scores; the possible range of scores is 0-25.

6.2.3 Neurocognitive assessment

Before and after the intervention, the following neuropsychological measures were administered from the CANTAB battery (Sahakian & Owen, 1992) and presented on a touch-sensitive screen or Apple iPad tablet.

Paired Associates Learning task

The PAL (Sahakian et al., 1988) is a task assessing (non-verbal) visual episodic memory and learning. Participants see white boxes appearing on the screen in a random order, each displaying a different geometric pattern. After the final box has disclosed its content, participants see one pattern at a time in the center of the screen and must indicate in which box the pattern was previously displayed. Feedback is provided when participants have indicated the location of each pattern. In case of an error, they are given another chance to locate the patterns. Participants have 10 attempts to correctly locate the patterns before the test terminates. When the participants have correctly located all the patterns they can proceed to the next stage. In the current study, we used a version of the CANTAB PAL that includes 3, 6, 8, 10, and 12 pattern/location associations (Müller et al., 2013). The key measure on the PAL is the total errors made across all stages.

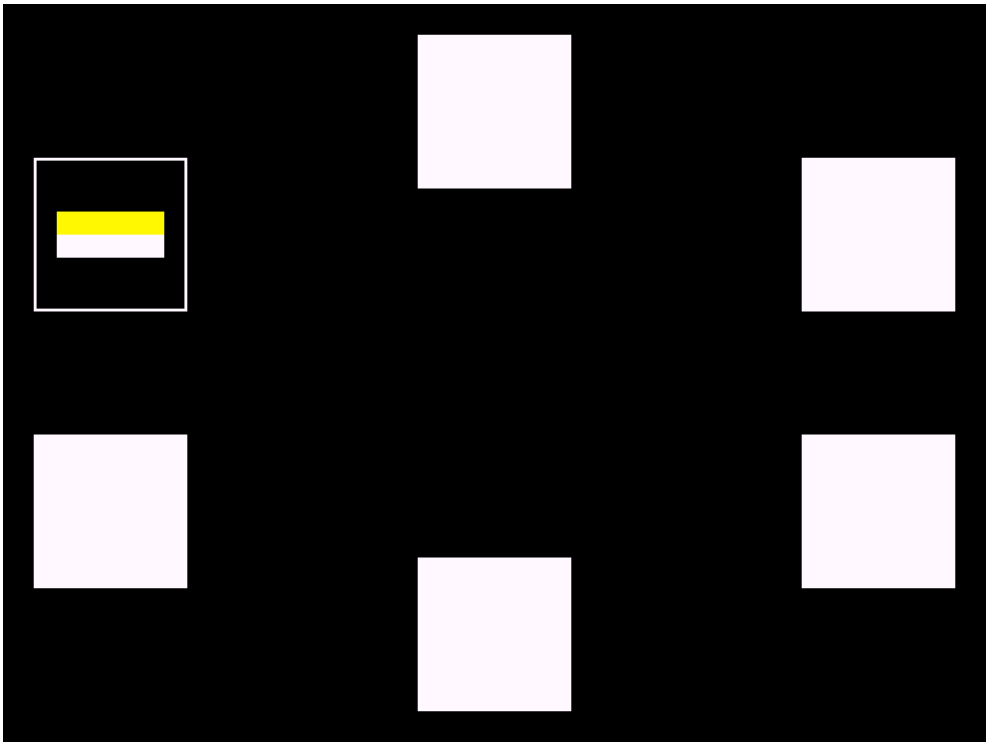

Figure 6.1.1 Illustration of the Paired Associates Learning Task

Stop Signal Task

The SST (Aron et al., 2003) is a measure of response inhibition or impulse control. The participants are presented with an arrow stimulus on the screen and must press a left key if the arrow points to the left or a right key if the arrow points to the right. When an auditory stimulus is heard, the participants should refrain from responding to the arrow stimulus; that is, inhibit their response. Participants initially complete 16 practice "go-trials" without the presence of the auditory stimulus in order to get acquainted with the task. Next the participants are told to continue to press the left and right keys depending on the direction of the arrow, and withhold any responding when they hear "a beep" sound (i.e. "no-go trials"). The task relies on a staircase design. That is, it ensures that the delay between the arrows stimulus and the presentation of the auditory stimulus is such that participants have a 50 percent success rate in inhibiting their responses. The time it takes to inhibit a response on no-go trials is called the Stop Signal Reaction Time (SSRT). The SSRT is a key outcome measure on this task, with shorter reaction times signalling superior impulse control.

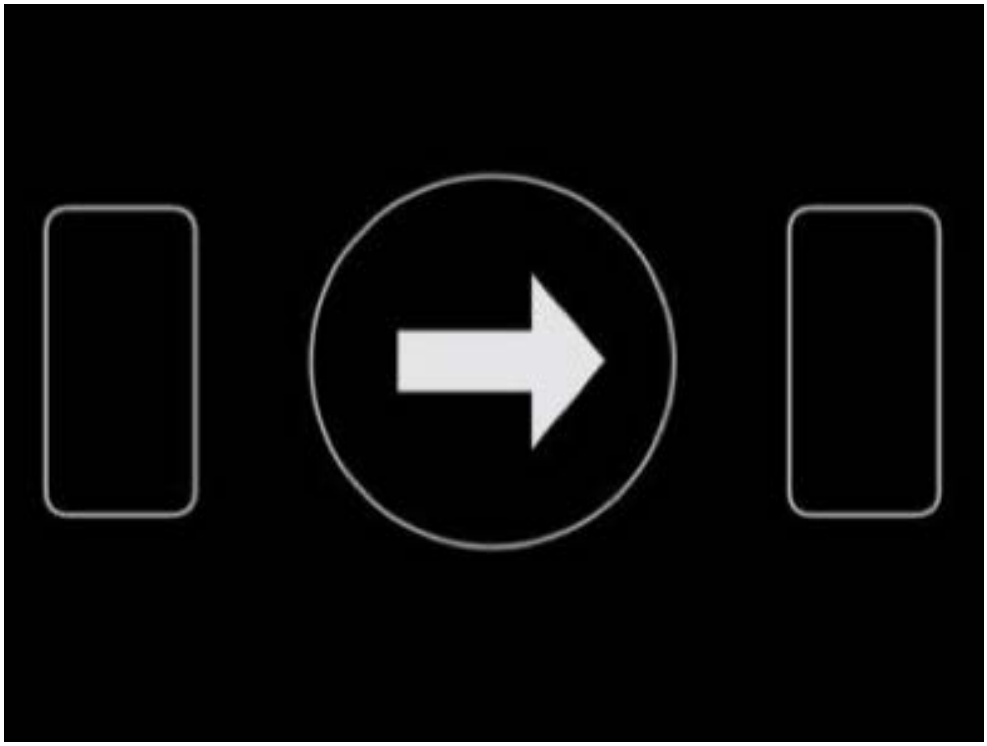

Figure 6.1.2 Illustration of the Stop Signal Task

6.2.4 Assessment of goal-directed versus habitual control

Before and after the intervention, the following measures were administered to assess the balance between goal-directed and habitual behavioral control.

Fabulous Fruit Game task

The Fabulous Fruit Game task (de Wit, Niry, Wariyar, Aitken, & Dickinson, 2007; Worbe, Savulich, de Wit, Fernandez-Egea, & Robbins, 2015), includes an (1) instrumental learning stage, (2) outcome-devaluation stage, (3) slips-of-action test, and (4) a baseline test of motor inhibition capacity (response disinhibition).

Instrumental learning stage: during this stage participants see on the screen pictures of fruits on the front of boxes (discriminative stimuli). Participants learn by trial and error which responses (left "Z" or right "M" key presses) open up the box to reveal a different fruit inside it. They have to learn which key to press for a total of 6 fruit stimuli presented on the front of the boxes, and

are told to pay attention to the fruit outcome pictures shown inside the box. Participants are presented with a total of 6 such stimuli-outcome associations. Correct key presses always lead to seeing fruit pictures inside the boxes and are rewarded with points added to their total score. In contrast, incorrect key presses open up an empty box and produce no reward. Faster responses earn more points (between 1 and 5). Participants are asked to earn as many points as possible. The instrumental stage is composed of 8 blocks, consisting of 12 trials each, and 96 trials total. The stage lasts approx. 5-6 minutes. The key outcome measures of this stage are the percentage of correct responses made and reaction times.

Outcome-devaluation stage: this stage tests knowledge of response-outcome associations learned during the instrumental learning stage. Participants are presented with two fruit pictures (outcomes) each inside a different box. One of these two fruits was previously an outcome produced by a left key press and the other a right key press. However, one of the two fruits is now devalued (i.e., no longer earns points). This outcome devaluation is signaled by a superimposed cross. Participants are told to press the key that yields the still valuable (non-crossed out) fruit outcome. The entire stage is comprised of 36 trials, and six possible combinations of fruit outcomes are presented 6 times total. Participants are rewarded with points for pressing the correct key. The task lasts approx. 2 minutes. Key outcome measures on this task include accurate responses made and reaction times.

Slips-of-action test: this test assesses the balance between goal-directed and habitual behavior across 6 blocks. During each block participants see the 6 fruit outcomes that had previously been presented to them during the instrumental learning and outcome-devaluation stage. Two of the 6 fruits are crossed out which signals that they are devalued and that collecting these leads to subtraction of points from their total score. This presentation of 6 fruit outcomes lasts for 10 seconds. Next, a series of boxes with fruit pictures on the outside are shown in quick succession (1 second per presentation). Participants are told to press the key (left or right) to open up the box and collect the valuable fruit outcome. By pressing the correct key on these “go trails” points are won. Pressing the incorrect key or failing to press anything for the still valued outcomes results in participants neither gaining nor loosing points. In contrast, participants have to refrain from pressing any key when shown a fruit picture on the front of the box that leads to a devalued fruit outcome on the inside. Pressing a key on these no-go trials results in the subtraction of points from their total score. The 6 fruit outcomes are devalued 3 times each across the 9 blocks and

presented 2 times per block. Each of the 9 blocks consists of 12 go and no-go trials, and the entire test of 108 trials. Goal-directed behavior manifests as selective responding to the still valuable outcome during go-trails as opposed to the devalued outcomes during no-go trials. By contrast, habitual behavior manifests as a tendency to respond (i.e., commit “slips-of-action”) to devalued fruit outcomes on the no-go trials. This stage lasts approx. 6 minutes. The key outcome measure on this task is the percentage of responses made on go and no-go trials.

Baseline test of response disinhibition: this baseline test assesses impairments in general motor inhibition capacity (response disinhibition) and working memory, and is randomly performed either before or after the slips-of-action test. During each of the 6 blocks of trials, participants see 6 discriminative fruit stimuli on the front of boxes. Two of the stimuli are superimposed with a cross. The cross signals that the fruit is devalued and that collecting this fruit outcome leads to subtraction of points from their total score. Next, participants see these closed boxes in quick succession and are told to respond correctly to go trials and refrain from responding to no-go trials. The test is comprised of the same number of trials and blocks as the slips-of-action test and is identical in all other respects as well, except that the discriminative fruit stimuli are devalued as opposed to the outcomes. Participants therefore rely on their knowledge of the fruit stimuli, as directly presented to them during this test, to either respond or withhold responding during trials. The baseline test is thus a suitable control for global impairments in response inhibition or working memory. Any cognitive or motor deficits should be equally reflected on both the baseline and slips-of-action test. Similar to the slips-of-action test, the key outcome measure on this test is the percentage of responses made on go and no-go trials.

There are two different versions of the slips-of-action and baseline task (namely A and B). The difference between version A and B is that the stimuli and outcome pictures are reversed. Participants are randomly assigned to complete either version A or B, and complete a different version of the task during experimental session 1 versus session 2. Moreover, the outcome pictures (i.e., stimuli and response-outcome assignment) are automatically permutated across every 6 subjects. An overview of the stages of the Fabulous Fruit Game task is shown in Figure 6.1.3.

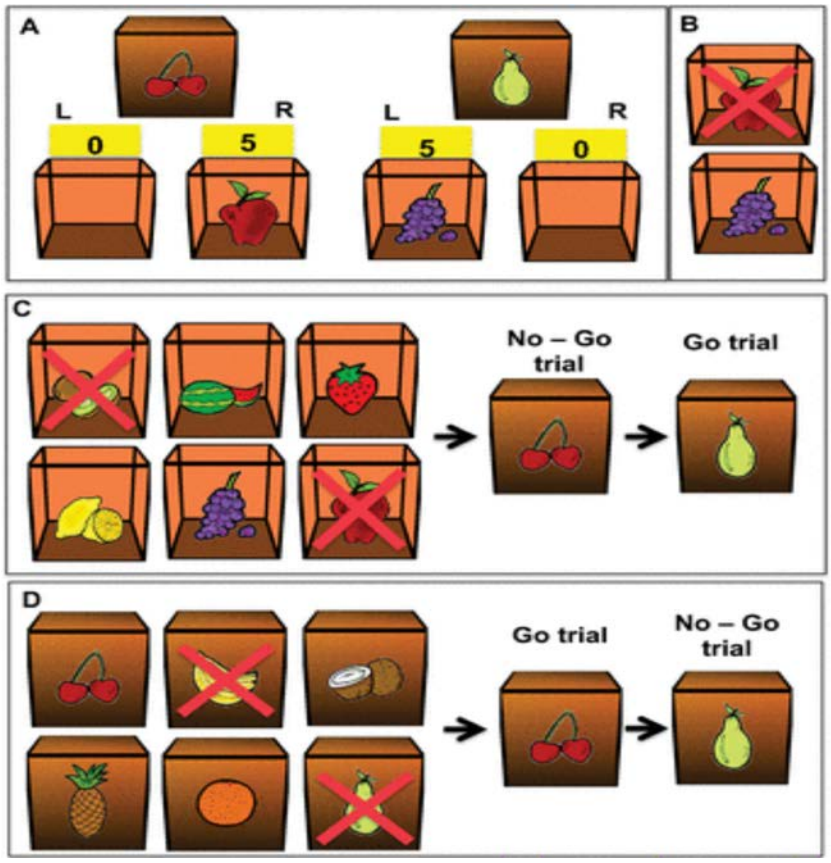

Figure 6.1.3 Overview of the Stages of the Fabulous Fruit Game[a]

[a](Figure credit: Worbe et al., 2015.) (A) Illustration of the instrumental training stage: if participants see the cherry, they have to press the right key, and left key if they see the pear. (B) Illustration of the outcome devaluation test: in this example, the apple is devalued and participants have to press the left key to collect the valuable fruit (grapes). (C) Illustration of the slips-of-action test: participants have to withhold responding during no-go trials (cherry) and respond (left or right key press) during go trials (pear). (D) Illustration of the baseline test: participants have to withhold responding during no-go trials (pear) and respond during go trials (cherry).

Aversive Stimulus Snack task

The Aversive Stimulus Snack task (Morris et al., 2015) includes: (1) an instrumental learning stage, (2) a devaluation video, and (3) a devaluation responding stage.

In this task participants initially rate their desirability of two different snack foods, namely "M&Ms" and "BBQ Mini Crackers" (snack A and B; e.g., "How much do you like

M&Ms?"), on a 7-point Likert scale. Next, they provide hunger ratings on the same scale (i.e., "How hungry are you right now?").

Instrumental learning stage: participants are then trained to liberate the snacks from a virtual vending machine (Figure 6.1.4). During this stage, pressing the left ("C") or right ("M") key is reinforced on a random-ratio 5 schedule. This means that on average one in every five key presses ("C" or "M") earns a snack outcome (snack A or B). Each time a snack is liberated from the virtual vending machine, participants are awarded the actual snack in real life. The snack is placed on a food plate in front of the participants, and they are told that they can eat it once the experiment is over. Upon earning three snacks, participants' knowledge of the instrumental contingencies is tested. As such, they are presented with the following question, "Which direction did you tilt to get [either M&Ms or BBQ Mini Crackers]" ("left" or "right"; i.e., in order to win that particular snack). The instrumental learning stage ends when participants answer six questions correctly in a row.

Devaluation video: next, participants watch a four minutes video showing one of the snacks (A or B) infested with cockroaches. (An illustration of the instrumental learning stage and snack devaluation movie are shown in Figure 6.1.4.)

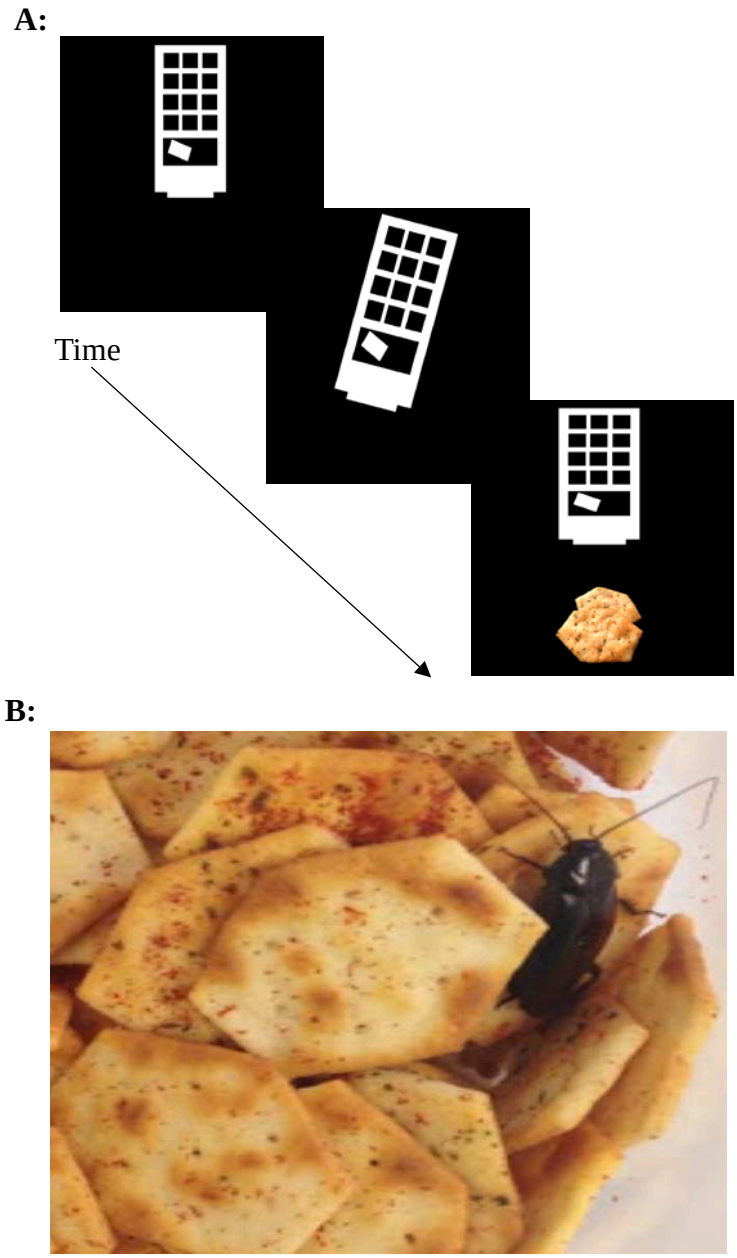

Figure 6.1.4 Aversive Stimulus Snack Task's Instrumental Learning Stage and Devaluation Movie[a]

[a](A) Illustration of the instrumental learning stage. (B) Illustration of the snack devaluation movie.

Devaluation responding stage: next participants complete the devaluation responding stage. During this stage similar to the instrumental learning stage, participants tilt the virtual vending machine left or right to win snacks, except that the snacks are not shown on the

screen and no questions are posed about instrumental contingencies. The devaluation responding stage lasts 4 minutes.

Upon completion of this stage, participants once again rate their desirability of the two snacks and provide hunger ratings. Participants are then shown the number of snacks they earned during the devaluation responding stage (similar to the instrumental learning stage, on average one in every five key presses earned a snack). Finally, they are allowed to eat the snacks earned during the experiment. Figure 6.1.5 provides an overview of the task and Table 6.1 shows the written instructions during each stage.

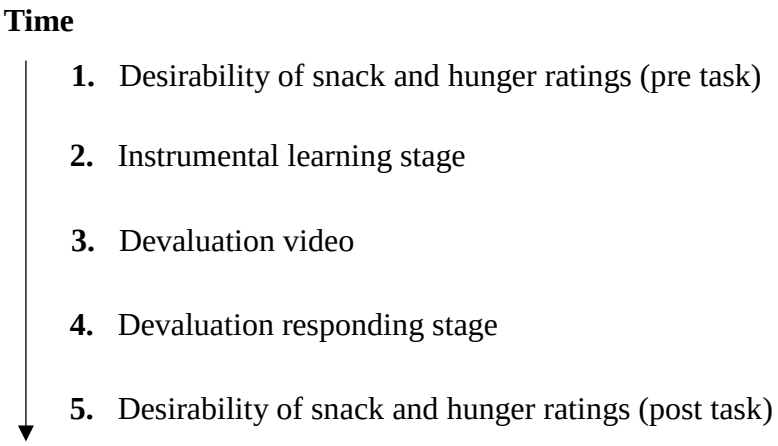

Figure 6.1.5 Overview of the Aversive Stimulus Snack Task and Pre/Post Task Ratings

Table 6.1 Verbal Instructions in the Aversive Stimulus Snack Task

Stage	**†Verbal Instructions**
Instrumental learning	"Someone has said you can get free snacks from our vending machine. Use the "C" and "M" keys to tilt the machine to the left and right, and learn how to steal different snacks!"
Devaluation video	"Something has happened to one of the snacks! Watch now to see what has happened."
Devaluation responding stage	"Now as before, you can tilt the machine for different snacks but you won't be shown any snacks on the screen. The amount earned will be recorded. Try to get as many snacks as you want as this will determine what you will eat afterwards!"

(†) At the beginning of each stage participants read the following instructions.

Counterbalancing: the snack that is devalued (in the devaluation video) and the associated left or right responses are counterbalanced. Participants are thus randomly assigned to complete one of four versions of the task (Table 6.2). Moreover, the presentation of the devalued snack outcomes is counterbalanced between sessions; such that participants either (1) has a different snack devalued at session 1 versus session 2, or (2) has the same snack devalued during both sessions (associated left and right presses, however, are not rotated from session 1 to 2).

Table 6.2 Versions of the Aversive Stimulus Snack Task Used for Counterbalancing

Version	**Left Outcome**	**Right Outcome**	**Devalued Outcome**
A	M&Ms	BBQ Mini Crackers	M&Ms
B	BBQ Mini Crackers	M&Ms	M&Ms
C	M&Ms	BBQ Mini Crackers	BBQ Mini Crackers
D	BBQ Mini Crackers	M&Ms	BBQ Mini Crackers

A "devalued responses" variable was computed (see Section 5.3.8), assessing the preference for devalued responses. This constituted the key outcome measure of goal-directed versus

habitual behaviour on this task. Other outcome measures were the snack desirability and hunger ratings at pre and post task, assessing the degree to which the snack devaluation video affected snack desirability and hunger.

6.2.5 Cleansing urges and behavior assessment

Before and after the intervention, participants completed a newly developed "Sanitizer task" assessing cleansing urges and behaviour.

Sanitizer task

Once the participants had completed the computerized (touch-screen based) tasks, the experimenter placed a hand sanitizer on the desk in front of them (i.e., just next to the testing-device). The experimenter then pointed to the hand sanitizer and asked, "How much do you feel like using the sanitizer right now?" Participants provided their answer on a visual analogue scale (VAS), ranging from 0 = not at all to 10 = extremely so. The participants were then instructed to use the sanitizer. The experimenter recorded the amount of time the participants spent cleansing their hands. VAS scores (urge or desire to use the hand sanitizer) and the amount of time spent cleansing hands constituted the outcome measures of the task.

6.2.6 Statistical analyses

Pre/post app ratings, and the SHAI, DS-R, PAL, SST, Sanitizer task before/after intervention analyses, were done via ANCOVA (for details see Section 5.3.7). Pre/post app ratings across the 7-day intervention (assessment of habituation effects) and dependent variables of the Fabulous Fruit Game task and Aversive Stimulus Snack task were analyzed via mixed MANOVA and ANOVA. The significance of the MANOVA was confirmed using Pillai's Trace and followed up by simple effect analyses with Bonferroni correction for multiple comparisons.

The distribution of residuals was checked and data transformed when necessary (see Section 5.3.7). In a few cases, residuals deviated substantially from a normal distribution and were not improved by a $\log_{10}(x + 1)$ transformation or a square-root transformation, in which case non-parametric tests were used. For ANOVA analyses with repeated measures, when the

assumption of sphericity was violated, degrees of freedom were corrected using the Greenhouse-Geisser estimates of sphericity. For one-way ANOVAs, a Welch test was used to correct for the violation of the assumption of homogeneity of variances.

On occasion, some subjects missed one question (3 subjects during session 1; 3 subjects during session 2) or two questions (1 subject during session 1) on the SHAI. To make all scores comparable, these subjects had their overall score rescaled to the maximum possible total (i.e., adjusted score = full scale maximum × subject's score ÷ subject's possible maximum).

In the Aversive Stimulus Snack task, the number of responses made during the instrumental learning stage and the devaluation responding stage were on different timescales (the duration of the former was based on learning the instrumental contingencies while the latter lasted precisely 4 minutes). Therefore, directly comparing the responses made during these stages was not possible. A preference for devalued responses variable was thus calculated at both stages (in the case of the instrumental learning stage "devalued responses" refer to responses made to the to-be devalued outcome); i.e., the proportion of devalued responses was calculated as total (i.e., $\text{devalued responses} = \frac{\text{devalued}}{(\text{devalued}+\text{nondevalued})}$) responses made for both the instrumental learning and devaluation stages. This allowed for an examination of the effect of devaluation, using an intervention (washing, contamination, control) × session (1, 2) × time (pre-devaluation, post-devaluation) ANOVA on devalued responses made.

The length of the VAS paper sheet of the Sanitizer task differed slightly for some participants (ranging from 20.3 cm to 21.6 cm). Therefore, adjusted scores were computed for all participants (i.e., $\text{adjusted VAS score} = \frac{\text{raw VAS score}}{\text{length of the VAS [cm]} \times 100}$). One participant's raw VAS score was known, but their original VAS paper sheet had been lost. The margin of error for this participant's score was small (29.17 to 31.03). As such, the VAS data were analyzed twice including either possible score; but the pattern of results remained unaltered.

(For details regarding figures pertaining to ANCOVA analyses see Section 5.3.7.) On all other figures, error bars indicate standard error of the mean, unless otherwise specified in the

text. (For details on box plots see Section 3.3.4.) The overall significance threshold for the study was set at $\alpha = 0.05$.

6.3 Results

The number of subjects who completed the exploratory measures varied between $n = 46$ and $n = 93$. The SHAI, DS-R, PAL and the Sanitizer task were completed by 93 subjects (washing condition $n = 31$, contamination $n = 31$ and control $n = 31$). The SST, Fabulous Fruit Game task and the Aversive Stimulus Snack task were completed by 46 subjects (washing $n = 16$; contamination $n = 15$; control $n = 15$). (For SHAI and DS-R baseline scores, see Table 6.3. For PAL baseline performance see Table 6.4 [IED baseline scores are shown for comparison]. For baseline performance on the SST, Fabulous Fruit Game task and the Aversive Stimulus Snack task see Table 6.5.)

Table 6.3 Health Anxiety and Disgust Sensitivity Scores for the Final Randomized Groups[a]

Condition	**Washing (*n* = 31)**		**Contamination (*n* = 31)**		**Control (*n* = 31)**		***Comparison***
	μ	**(*SD*)**	μ	**(*SD*)**	μ	**(*SD*)**	F_{df}
SHAI	15.06	(6.01)	11.78	(5.44)	14.65	(8.34)	$F_{2,90} = 2.20$, $p = 0.1166$
DS-R	15.69	(3.78)	14.66	(4.14)	16.18	(4.49)	$F_{2,90} = 1.08$, $p = 0.3438$

[a]μ, mean; *SD*, standard deviation; *n*, sample size; *F*, *F* statistic; *df*, degrees of freedom; *p*, *p* value; NS, non-significant; SHAI, Short Health Anxiety Inventory; DS-R, Disgust Scale-Revised.

Table 6.4 Baseline Performance on the IED and PAL for the Final Randomized Groups[a]

Condition	**Washing (*n* = 31)**		**Contamination (*n* = 31)**		**Control (*n* = 30)**		***Comparison***
	μ	**(*SD*)**	μ	**(*SD*)**	μ	**(*SD*)**	F_{df}
IED							
(EDS errors)	7.19	(9.62)	7.74	(9.37)	10.27	(10.77)	† $F_{2,89} < 1$, NS
(Pre-EDS errors)	5.94	(2.28)	6.00	(2.71)	6.27	(2.68)	† $F_{2,89} < 1$, NS
PAL (total errors)	17.58	(18.38)	17.33	(12.43)	22.77	(18.79)	† $F_{2,88} = 1.32$, $p = 0.2723$

[a]μ, mean; *SD*, standard deviation; *n*, sample size; *F*, *F* statistic; *df*, degrees of freedom; *p*, *p* value; NS, non-significant; IED, Intra/Extradimensional Set Shift task; EDS, Extradimensional shift; pre-EDS, pre-extradimensional shift; PAL, Paired Associates Learning task. The final sample size of the PAL was: washing, *n* = 31, contamination, *n* = 30, control, *n* = 30. (†) After applying a $\log_{10}(x + 1)$ transformation, as for the main analysis (see text).

Table 6.5 Baseline Performance on the SST, Fabulous Fruit Game Task and the Aversive Stimulus Snack Task for the Randomized Groups in the Subsample[a]

Condition	**Washing (*n* = 16)**		**Contamination (*n* = 15)**		**Control (*n* = 15)**		***Comparison***
	μ	**(*SD*)**	μ	**(*SD*)**	μ	**(*SD*)**	F_{df}
SST (SSRT)	227.22	(31.16)	222.50	(43.02)	252.96	(62.06)	† $F_{2,43} = 1.87$, $p = 0.1665$
Fabulous Fruit Game (Slips-of-Action Test, % devalued responses)	34.63	(24.91)	26.26	(27.03)	42.82	(22.70)	† $F_{2,35} = 1.78$, $p = 0.1845$
Aversive Stimulus Snack Task (devalued responses, pre/post devaluation difference)	0.08	(0.23)	0.23	(0.25)	0.08	(0.32)	$F_{2,43} = 1.67$, $p = 0.1996$

[a]μ, mean; *SD*, standard deviation; *n*, sample size; *F*, *F* statistic; *df*, degrees of freedom; *p*, *p* value; NS, non-significant; SST, Stop Signal Task; SSRT, Stop Signal Reaction Time. The final sample size for the Fabulous Fruit game task was: washing, $n = 15$, contamination, $n = 11$, control, $n = 12$. (†) After applying a $\log_{10}(x + 1)$ transformation, as for the main analysis (see text).

Additional data were missing on a small number of measures. Two participants did not complete the PAL task and were excluded. The final sample size for the PAL was: washing condition $n = 31$, contamination $n = 30$ and control $n = 30$.

Data were lost on the Fabulous Fruit Game task due to a software issue. The final sample size for the slips-of-action versus the baseline test analysis was: washing condition $n = 15$, contamination $n = 10$, control $n = 12$; for the remaining analyses: washing condition $n = 15$, contamination $n = 11$, control $n = 12$. Also, two participants completed the same version of the Fabulous Fruit Game task (either A or B) during session 1 and 2; and were excluded from the analysis examining the effect of the smartphone interventions on the slips-of-action

versus baseline test (washing n = 13, contamination n = 10, control n = 12); this analysis was also done while including them but the pattern of results remained unaltered. Finally, as noted, outcome pictures were automatically permutated across every 6 subjects if participant IDs were entered consecutively; in this study in a few cases in each condition IDs were not entered consecutively, which constitutes a limitation of the current counterbalancing approach.

Data were missing for the VAS of the Sanitizer task owing to various logistic issues (e.g., participants spontaneously using the sanitizer before completing the VAS). The final sample size for the VAS was: washing condition n = 27, contamination n = 31 and control n = 28. Two subjects had missing data for "cleansing time" of the Sanitizer task (washing condition n = 30, contamination n = 31 and control n = 30).

Correlations were checked for contamination fear and OCD symptom severity (baseline) and improvement (pre/post intervention difference scores), and pre/post app ratings (difference scores), and performance on the PAL, SST, Sanitizer task and key dependent variables of the Fabulous Fruit Game task and Aversive Stimulus Snack task (pre/post intervention difference scores), for each condition. None of the correlations reached significance upon correcting for multiple comparisons (using the Bonferroni method) and are therefore not reported.

Anxiety, disgust and handwashing urges pre and post app across intervention

To examine anxiety, disgust and handwashing urge ratings pre and post app across the 7-day intervention (i.e., assessment of habituation effects), a 7 (Day: 1-7) × 3 (Intervention: washing, contamination, control) two-way MANOVA was conducted on the anxiety, disgust and handwashing urge mean difference scores (post minus pre). The residuals of the model deviated substantially from normality and were not improved by a $\log_{10}(x + 1)$ transformation (a square-root transformation was not possible as the scores included negative values). The data were therefore analyzed using the non-parametric Friedman test. There was a significant decline in disgust ratings in the contamination condition across the 7-days ($\chi^2_6 = 46.58$, $p = 2.04 \times 10^{-7}$, Bonferroni corrected) (Figure 6.1.7); unlike the washing condition and control.

None of the remaining effects were significant (*ps* ≥ 0.074, Bonferroni corrected) (Figure 6.1.6 and Figure 6.1.8).

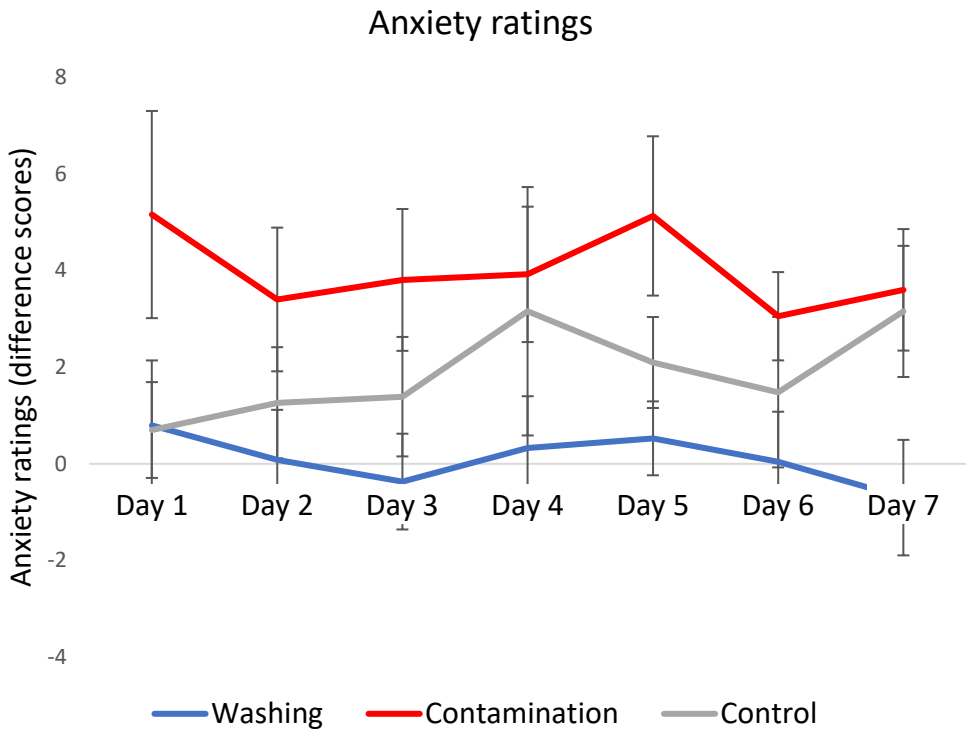

Figure 6.1.6 Pre and Post App Anxiety (Difference Scores) Across the 7 Days[a]

[a]Anxiety ratings (pre and post app) did not decline across the 7 days in the three conditions.

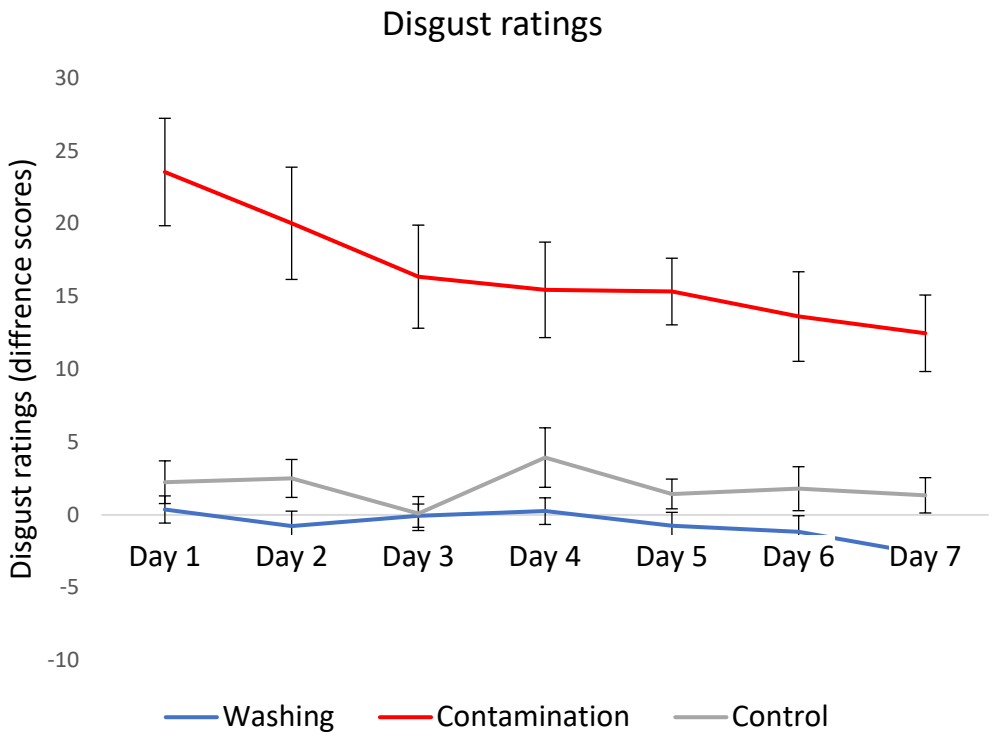

Figure 6.1.7 Pre and Post App Disgust (Difference Scores) Across the 7 Days[a]

[a]Disgust ratings (pre and post app) declined in the contamination condition across the 7 days, but not in the washing condition nor the control.

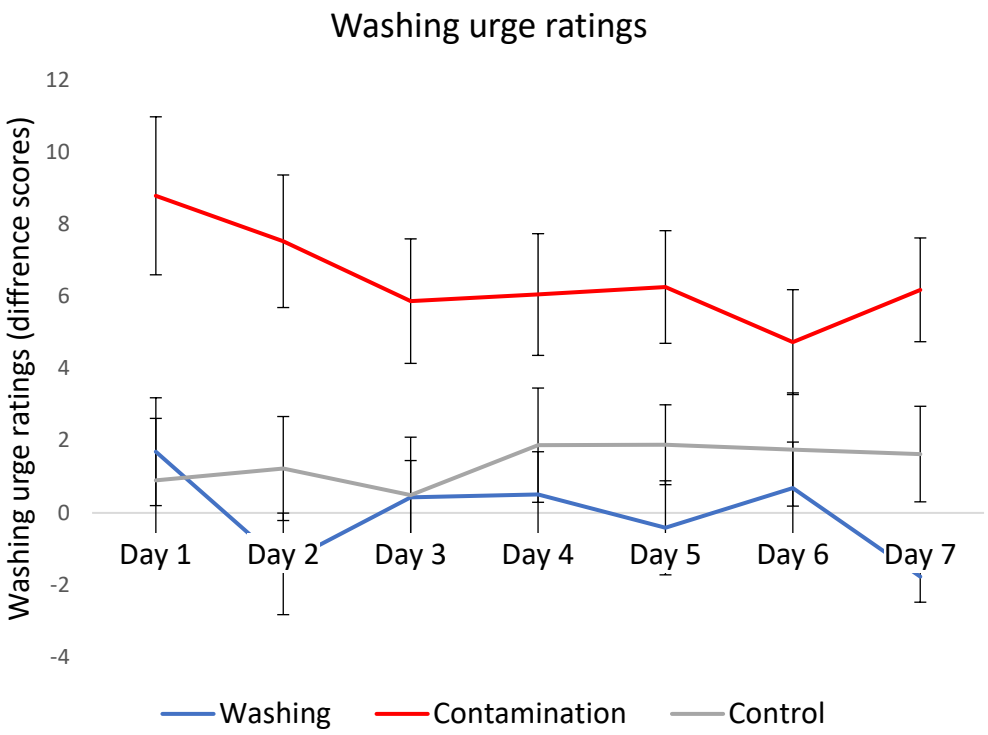

Figure 6.1.8 Pre and Post App Handwashing Urge (Difference Scores) Across the 7 Days[a]

[a]Handwashing urge ratings (pre and post app) did not decline across the 7 days in the three conditions.

Acute anxiety pre and post app

The washing intervention altered anxiety pre and post app compared to the control, unlike the contamination intervention (Figure 6.1.9). A single-slope ANCOVA model was preferred; anxiety ratings residuals deviated from normality, but were improved following a $\log_{10}(x + 1)$ transformation. Overall, there was an effect of treatment ($F_{2,88} = 9.92$, $p = 0.0001$). In pairwise ANCOVA comparisons, the washing intervention differed from the control ($F_{1,58} = 6.14$, $p = 0.0161$) but the contamination intervention did not differ from the control ($F_{1,58} = 3.60$, $p = 0.0626$).

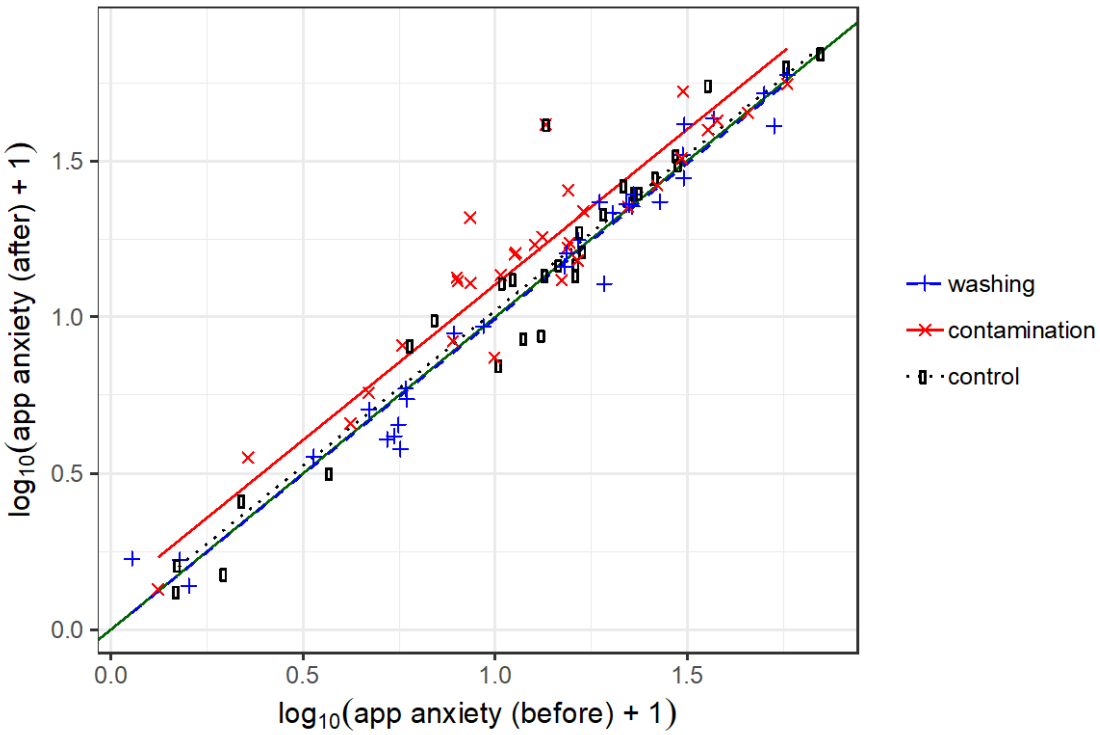

Figure 6.1.9 Anxiety Pre and Post App[a]

[a]The washing intervention altered anxiety pre and post app compared to the control, unlike the contamination intervention.

Acute disgust pre and post app

The washing intervention reduced disgust and the contamination condition increased disgust pre and post app compared to the control (Figure 6.1.10). A separate-slopes ANCOVA model was found to be preferable; residuals deviated from normality, but were improved following a $\log_{10}(x + 1)$ transformation. Overall, there was an effect of treatment ($F_{2,86} = 46.83$, $p = 1.75 \times 10^{-14}$). The ANCOVA revealed a pre-app disgust rating × intervention interaction ($F_{2,86} = 8.02$, $p = 0.0006$). Single-slope sub-ANCOVAs (not constrained to the slope from the overall ANCOVA) were performed; the washing intervention differed from the control intervention ($F_{1,58} = 13.32$, $p = 0.0006$) and the contamination intervention differed from the control ($F_{1,58} = 31.42$, $p = 6.04 \times 10^{-7}$), in the opposite direction to the washing intervention.

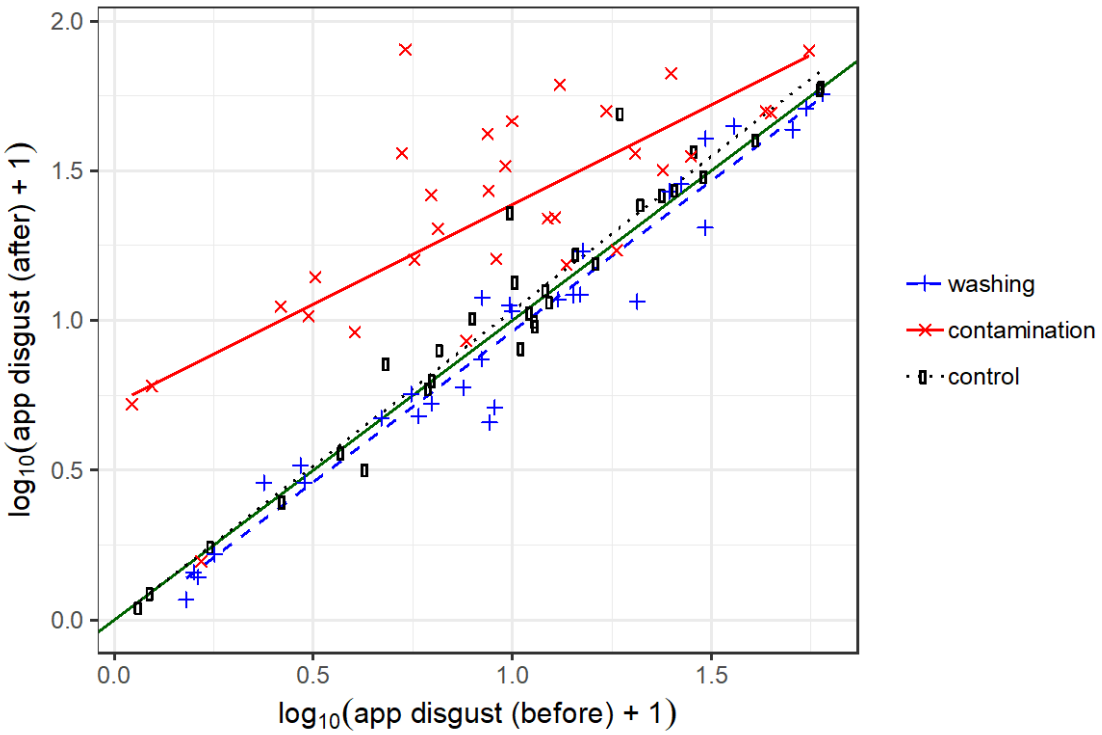

Figure 6.1.10 Disgust Pre and Post App[a]

[a]The washing intervention reduced disgust compared to the control and the contamination intervention increased disgust compared to the control in the opposite direction.

Acute handwashing urges pre and post app

Unlike the washing intervention, the contamination intervention increased handwashing urges pre and post app compared to the control (Figure 6.2.1). A single-slope ANCOVA model was preferred; ratings of handwashing urge residuals deviated from normality, but normalized following a $\log_{10}(x + 1)$ transformation. Overall, there was an effect of treatment ($F_{2,88} = 3.27$, $p = 0.0428$). In pairwise ANCOVA comparisons, the washing intervention did not differ from the control intervention ($F_{1,58} < 1$, NS), however the contamination intervention differed from the control ($F_{1,58} = 4.14$, $p = 0.0465$).

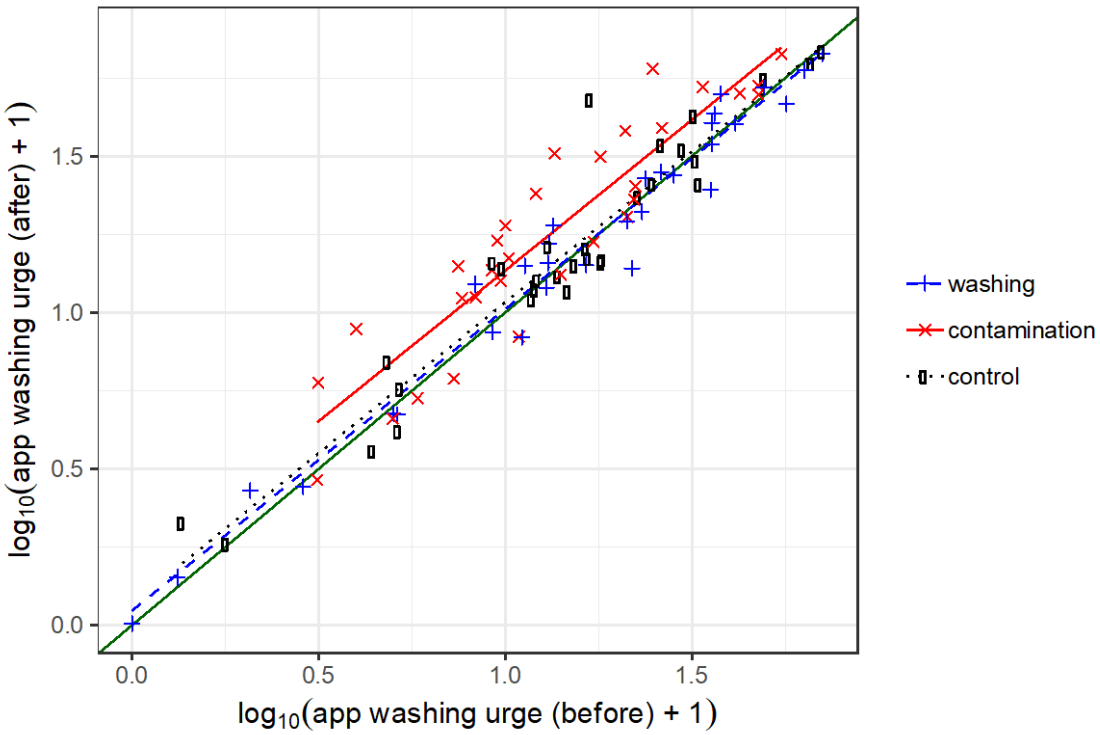

Figure 6.2.1 Handwashing Urge Pre and Post App[a]

[a]The washing intervention did not alter handwashing urges, but the contamination intervention increased handwashing urges pre and post app compared to the control.

SHAI

There was no clear-cut effect of treatment on the SHAI (Figure 6.2.2). SHAI residuals exhibited substantial non-normality; this was not materially improved by a log or square-root transformation, so with those caveats, scores were analysed untransformed. There was a main effect of treatment ($F_{2,89} = 4.29$, $p = 0.0166$) but in pairwise comparisons neither the washing intervention ($F_{1,59} = 1.42$, $p = 0.2388$), nor the contamination intervention differed from the control ($F_{1,59} = 2.56$, $p = 0.1147$).

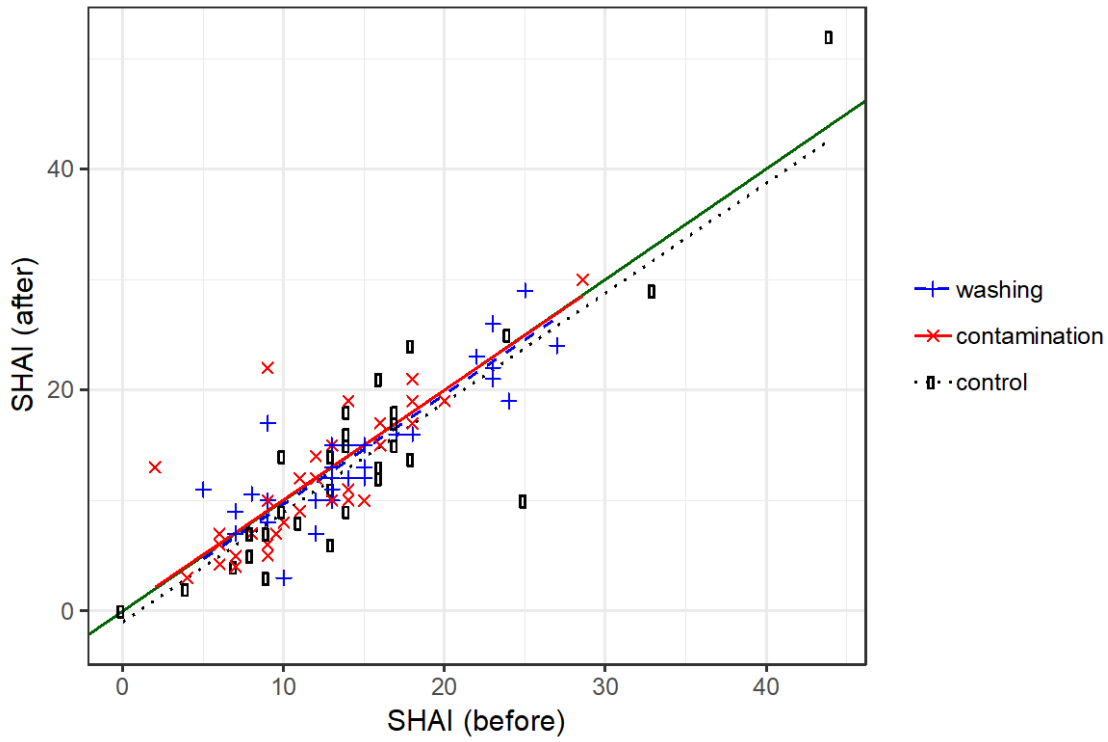

Figure 6.2.2 SHAI Scores Pre and Post Treatment[a]

[a]SHAI scores were not altered by the active interventions compared to the control.

DS-R

The washing intervention reduced, and the contamination intervention slightly increased, DS-R scores compared to the control (Figure 6.2.3). A single-slope ANCOVA model was selected; DS-R score residuals deviated from normality, but not substantially. Overall, there was an effect of treatment ($F_{1,89} = 3.57$, $p = 0.0321$). The washing intervention differed from the control ($F_{1,59} = 4.57$, $p = 0.0367$), and the contamination intervention differed from the control ($F_{1,59} = 4.89$, $p = 0.0309$), in the opposite direction.

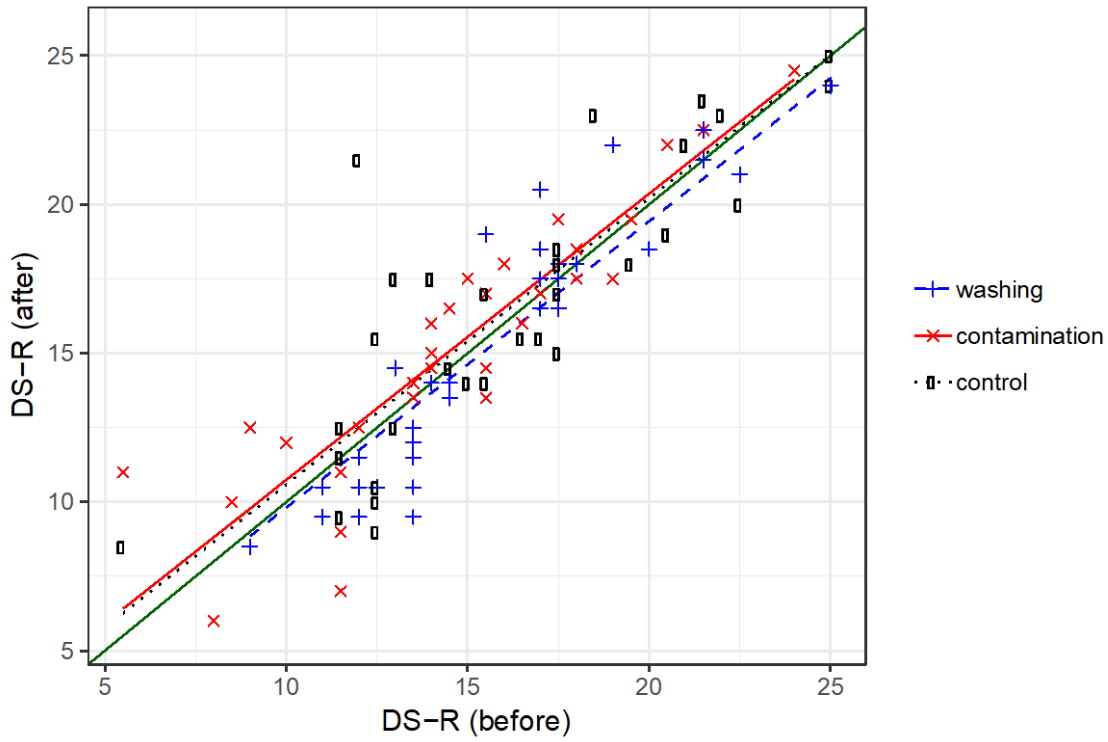

Figure 6.2.3 DS-R Scores Pre and Post Treatment[a]

[a]The washing intervention reduced DS-R scores, and the contamination intervention slightly increased DS-R scores compared to the control.

Paired Associates Learning task

PAL total errors: neither active intervention altered PAL performance compared to the control (i.e., total errors made across all stages) (Figure 6.2.4). PAL total errors residuals were not normally distributed and this was substantially improved by a $\log_{10}(x + 1)$ transformation; a single-slope ANCOVA model was then preferred. There was no effect of treatment ($F_{1,87} = 2.14$, $p = 0.1233$).

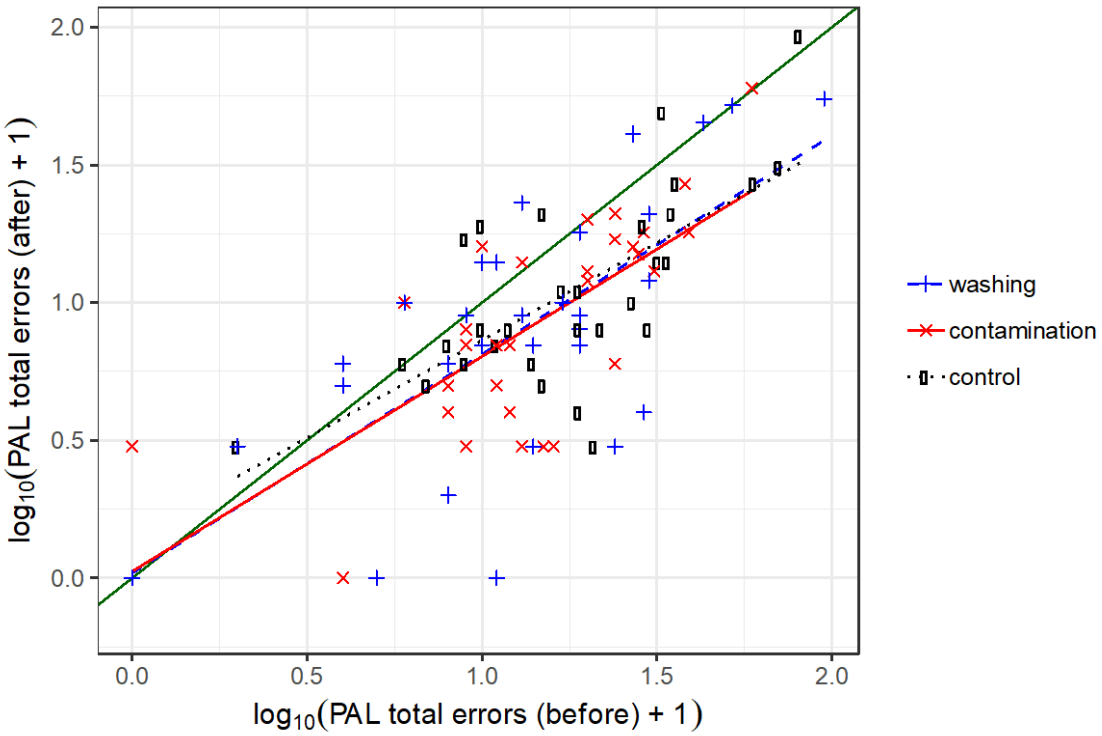

Figure 6.2.4 PAL Total Errors Pre and Post Treatment[a]

[a]PAL total errors were not altered by the active interventions compared to the control.

Stop Signal Task

SSRT: neither active intervention altered SSRT scores (Figure 6.2.5). A single-slope ANCOVA model was preferred and residuals were normally distributed. There was no effect of treatment ($F_{2,42}$ = 2.42, p = 0.1017).

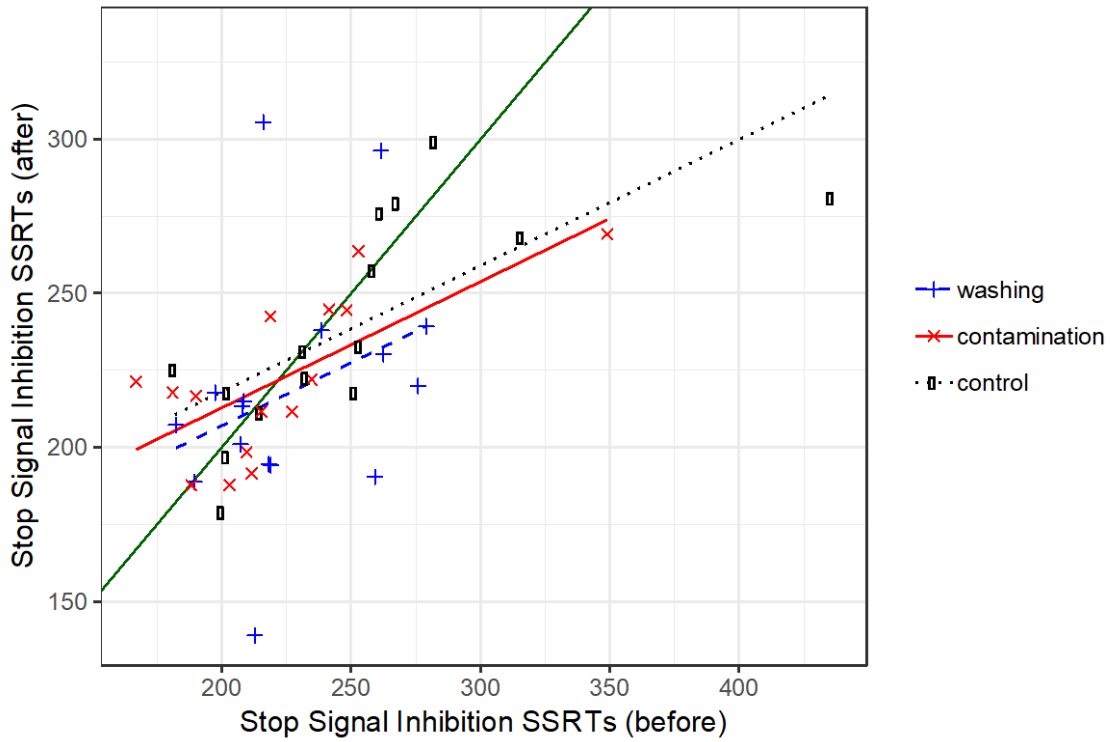

Figure 6.2.5 Stop Signal Inhibition SSRTs Pre and Post Treatment[a]

[a]SSRTs were not altered by the active interventions compared to the control.

Fabulous Fruit Game task

Counterbalancing: the version of the task (A or B) first completed by participants did not vary by intervention (washing, contamination, control), $\chi^2_2 = 4.55$, $p = 0.1025$. The order of test completion (i.e., whether the slips-of-action or baseline test was completed first) did not vary by intervention, $\chi^2_2 = 0.49$, $p = 0.7823$.

Instrumental learning stage: to examine the effects of the smartphone apps on learning rate, an 8 (Block: 1 to 8) × 2 (Session: 1, 2) × 3 (Intervention: washing, contamination, control) three-way MANOVA was conducted on the mean percentage of accurate responses and mean reaction times. The residuals of the model deviated from normality but improved by a square-root transformation (yet remained slightly non-normally distributed). The MANOVA revealed a significant main effect of Block on the overall mean percentage of accurate responses and mean reaction times ($F_{14,22} = 20.70$, $p = 1.79 \times 10^{-9}$). Follow-up ANOVAs

confirmed that participants regardless of intervention and session, significantly improved their performance over the course of the test, as the analysis revealed a main effect of Block on the mean percentage of accurate responses ($F_{3.576,35} = 74.82$, $p = 3.54 \times 10^{-30}$, Bonferroni corrected) and mean reaction times ($F_{2.762,35} = 74.87$, $p = 8.28 \times 10^{-24}$, Bonferroni corrected) (Figure 6.2.6). None of the remaining effects were significant, including the Block × Session × Intervention interaction ($ps \geq 0.107$).

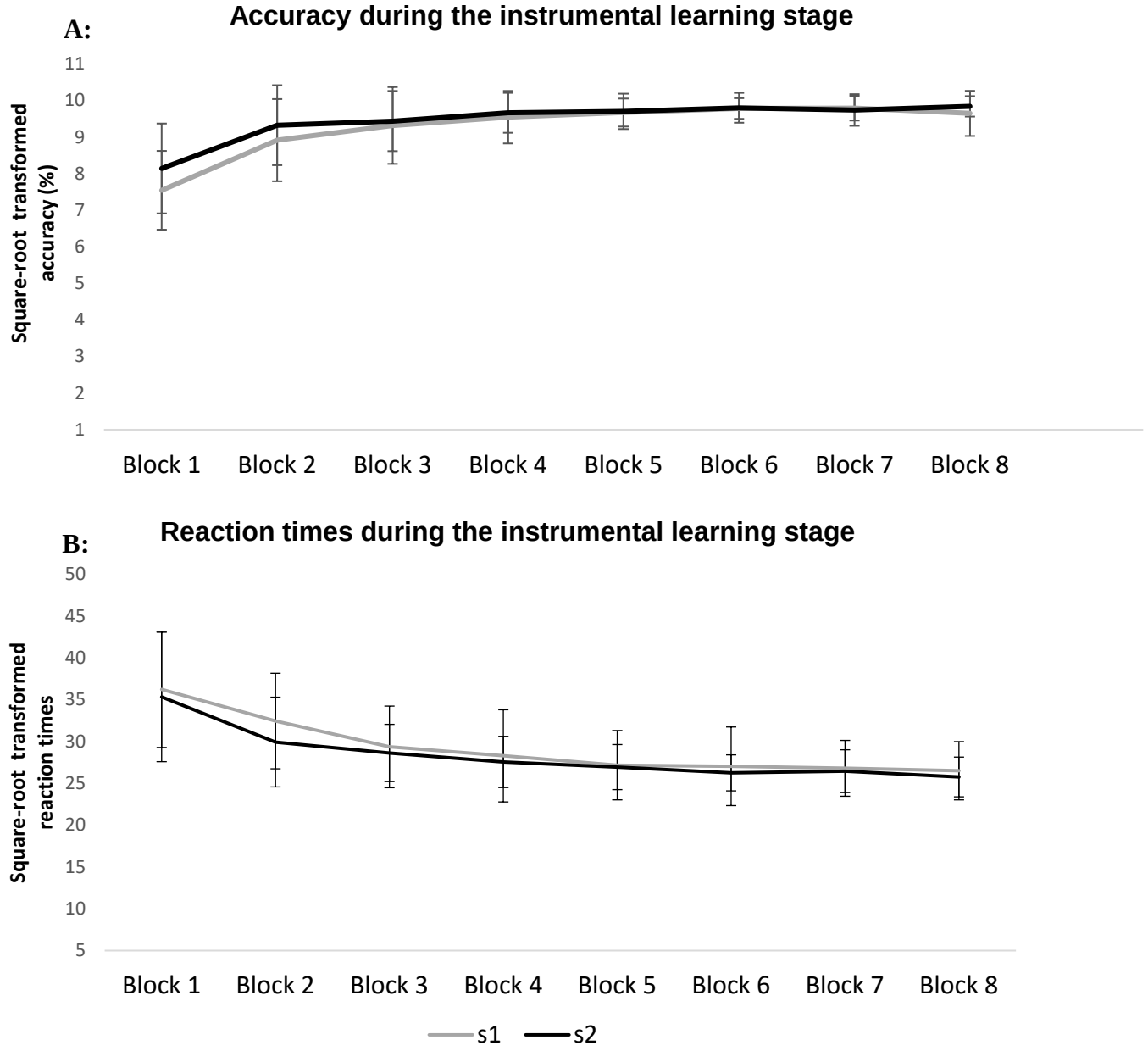

Figure 6.2.6 Accuracy and Reaction Times During the Instrumental Learning Stage of the Fabulous Fruit Game Task[a]

[a]Square-root transformed mean percentage of (A) accurate responses and (B) reaction times, over the course of the 8 blocks during sessions 1 and 2. Error bars represent standard deviations; s1, session 1; s2, session 2.

Outcome devaluation test: to examine the effects of the smartphone apps on the outcome devaluation test, a 2 (Session: 1, 2) × 3 (Intervention: washing, contamination, control) two-way MANOVA was conducted on the mean percentage of accurate responses and mean reaction times. The residuals of the model showed major deviation from normality and were not improved by a log or square-root transformation. Thus, the non-parametric Wilcoxon signed rank test with Bonferroni correction was used. Overall, regardless of intervention, the percentage of accurate responses was not improved from session 1 to session 2 (z = - 0.80, p = 0.4221, Bonferroni corrected), but reaction times became significantly shorter (z = - 2.44, p = 0.0145, Bonferroni corrected) (Figure 6.2.7). Follow-up Wilcoxon signed rank analyses showed that the interventions did not differentially impact performance on the outcome devaluation test from session 1 to session 2; i.e., vis-à-vis percentage of accurate responses ($ps \geq 0.744$) and reaction times ($ps \geq 0.151$).

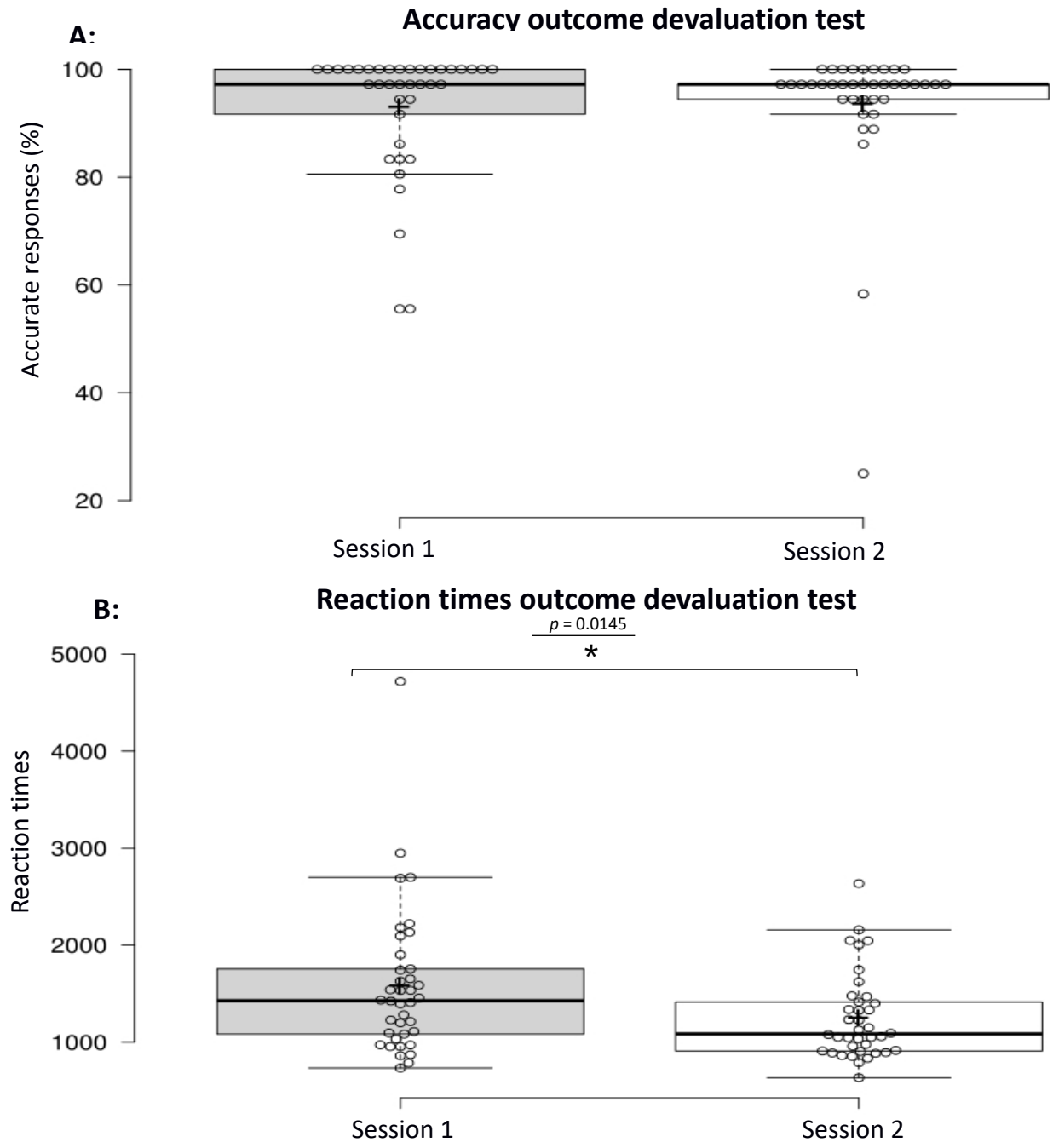

Figure 6.2.7 Accuracy and Reaction Times During the Outcome Devaluation Test of the Fabulous Fruit Game Task[a]

[a]The mean percentage of (A) accurate responses and (B) mean reaction times during the outcome devaluation test during session 1 and session 2. Error bars represent standard deviations.

Slips-of-action versus baseline test (counterbalancing): to examine the effect of task-version and order of task administration on the percentage of responses made during the two sessions, a 2 (Outcome: devalued, nondevalued) × 2 (Test-type: slips-of-action, baseline) × 2 (Session: 1, 2) × 2 (Order: slips-of-action test presented first, baseline test presented first) × 2 (Task-version: A, B) five-way ANOVA was conducted on the mean percentage of responses made. The residuals deviated slightly from normality but the overall model was improved by a square-root transformation. The data revealed a two-way Outcome × Order interaction ($F_{1,31}$ = 4.99, p = 0.0328), and a three-way Outcome × Test-type × Order interaction ($F_{1,31}$ = 6.76, p = 0.0142) on the mean percentage of responses made. Given that Order interacted with the factor of interest (i.e., Outcome) it was included in the final analysis unlike Task-version ($ps \geq 0.191$).

Slips-of-action versus baseline test (effect of interventions): to examine the effects of the interventions on the percentage of responses made, a 2 (Outcome: devalued, nondevalued) × 2 (Test-type: slips-of-action, baseline) × 2 (Session: 1, 2) × 2 (Order: slips-of-action test presented first, baseline test presented first) × 3 (Intervention: washing, contamination, control) five-way ANOVA was conducted on the mean percentage of responses made. The residuals of the model deviated slightly from normality; and the model improved by a square-root transformation. In addition to a three-way Outcome × Test-type × Order interaction ($F_{1,29}$ = 5.69, p = 0.0238), the ANOVA revealed a main effect of Outcome ($F_{1,29}$ = 284.73, p = 1.55×10^{-16}) and Test-type ($F_{1,29}$ = 7.44, p = 0.0107); and a two-way Outcome × Test-type interaction ($F_{1,29}$ = 21.49, p = 0.0001) and an Outcome × Session interaction ($F_{1,29}$ = 5.84, p = 0.0222). None of the remaining effects were significant ($ps \geq 0.107$), including the four-way Outcome × Test-type × Session × Intervention interaction ($F < 1$, NS). (The data were also analyzed without including the Order factor but the crucial four-way interaction remained non-significant [$F < 1$, NS].)

Simple effect analyses with Bonferroni correction showed that participants made more responses to the valued outcome versus the devalued outcome during both the slips-of-action test ($F_{1,29}$ = 133.87, p = 2.19×10^{-12}) and the baseline test ($F_{1,29}$ = 401.67, p = 1.55×10^{-18}). Participants regardless of test-type (slips-of-action test versus baseline test) made more

responses to the valued outcome versus the devalued outcome at both session 1 ($F_{1,29}$ = 141.09, $p = 1.16 \times 10^{-12}$) and session 2 ($F_{1,29}$ = 292.96, $p = 1.07 \times 10^{-16}$) (Figure 6.2.8).

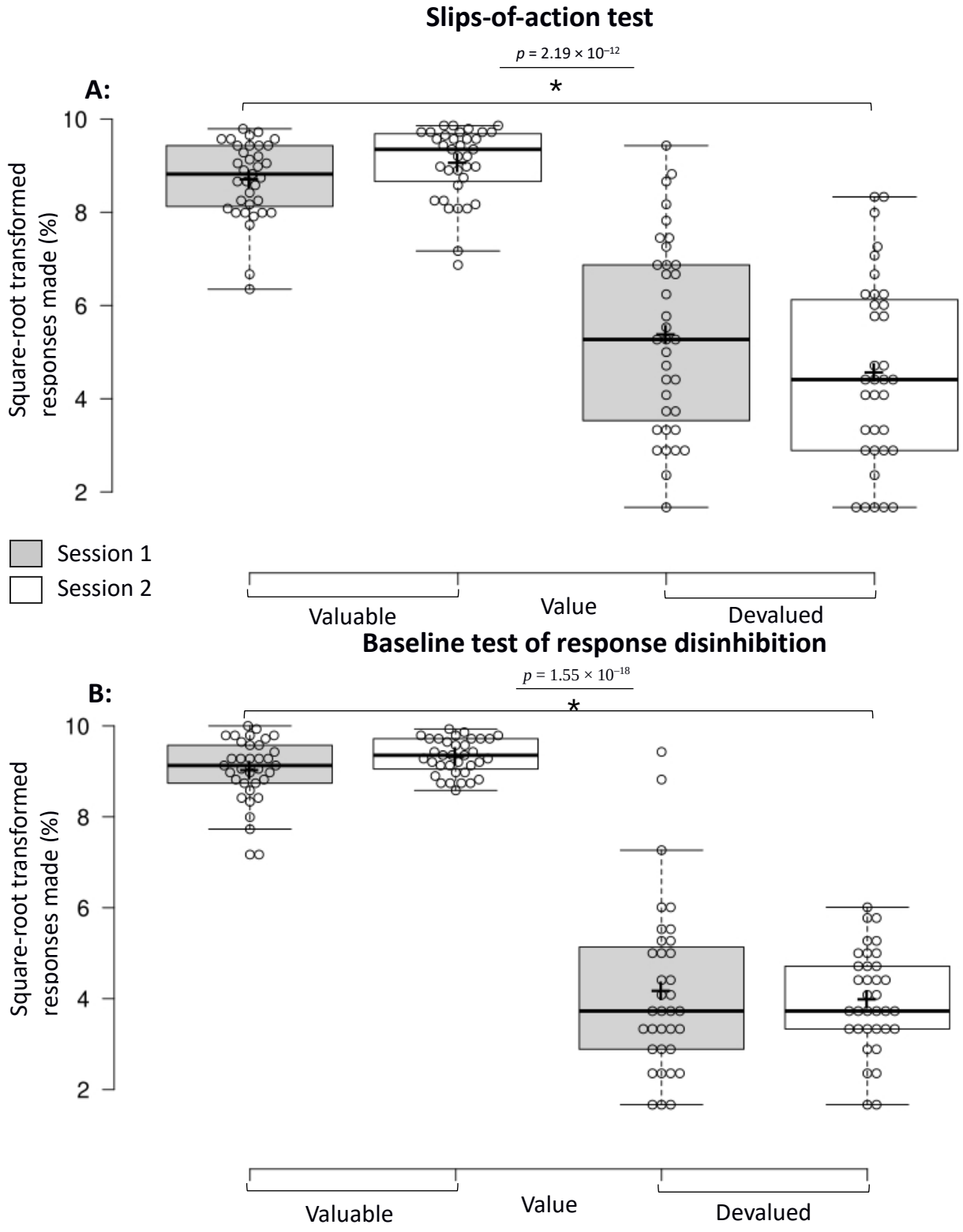

Figure 6.2.8 Responses Made During Slips-of-Action and Baseline Tests of the Fabulous Fruit Game Task[a]

[a]Square-root transformed responses made during (A) the slips-of-action test and (B) the baseline test of response disinhibition during session 1 and session 2.

Aversive Stimulus Snack task

Counterbalancing: task versions completed by participants did not vary by intervention (washing, contamination, control), $\chi^2_6 = 5.63$, $p = 0.4658$. The rate of participants who had a different snack devalued versus the same snack devalued during sessions 1 and 2, did not differ by intervention (washing, contamination, control), $\chi^2_2 = 1.94$, $p = 0.3792$.

Hunger ratings: to examine hunger ratings pre and post task, a 2 (Hunger: hunger-pre, hunger-post) × 2 (Session: 1, 2) × 3 (Intervention: washing, contamination, control) three-way ANOVA was conducted on the mean hunger ratings. Residuals of the model deviated slightly from normality and were not improved by a log or square-root transformation. None of the effects were significant ($ps \geq 0.239$).

Snack desirability (effect of interventions): to examine the effects of the smartphone apps on snack desirability ratings pre and post intervention, a 2 (Outcome: devalued, nondevalued) × 2 (Task-time: pre, post) × 2 (Session: 1, 2) × 3 (Intervention: washing, contamination, control) four-way ANOVA was conducted on the mean desirability ratings. The residuals of the model showed minor deviation from normality and were slightly improved following a $\log_{10}(x + 1)$ transformation. The analysis revealed a main effect of Task-time ($F_{1,43} = 4.90$, $p = 0.0322$) and a significant Outcome × Task-time interaction ($F_{1,43} = 23.82$, $p = 0.0000$), illustrating the basic devaluation effect (Figure 6.2.9). None of the remaining effects were significant including the four-way Outcome × Task-time × Session × Intervention interaction ($ps \geq 0.051$).

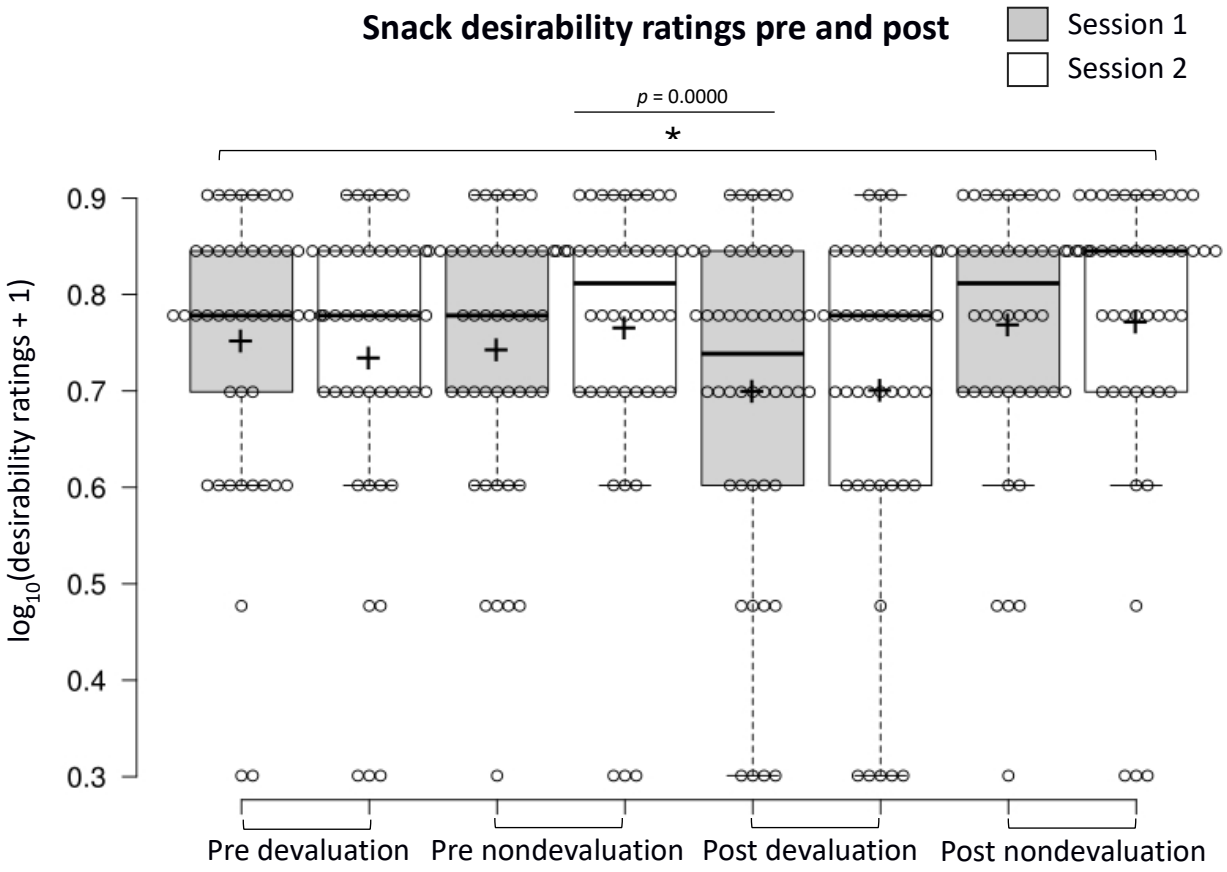

Figure 6.2.9 Snack Desirability Ratings Pre and Post Devaluation in the Aversive Stimulus Snack Task[a]

[a]$Log_{10}(x + 1)$ transformed snack desirability ratings pre and post devaluation during sessions 1 and 2.

Devalued responses (counterbalancing): to examine the effect of the task-version and order of devaluation (whether the devalued snack was the same in sessions 1 and 2 or different) on the mean devalued responses, a 2 (Task-time: pre, post) × 2 (Session: 1, 2) × 4 (Task-version: A, B, C, D) × 2 (Order: snack A, snack B) four-way ANOVA was conducted on the mean devalued responses made. The residuals of the model deviated slightly from normality and were improved by a $\log_{10}(x + 1)$ transformation. Because the factor of interest (Task-time: pre, post) did not interact with Task-version and Order at any level ($ps \geq 0.195$) they were not included as factors in the remaining analyses.

Devalued responses (effect of interventions): to investigate the effects of the smartphone apps on devalued responses made pre and post intervention, a 2 (Task-time: pre, post) × 2 (Session: 1, 2) × 3 (Intervention: washing, contamination, control) three-way ANOVA was conducted on the mean devalued responses. The residuals of the model deviated slightly from normality and were not improved by a log or square-root transformation. The data revealed a main effect of Task-time ($F_{1,43} = 10.58$, $p = 0.0022$), illustrating the basic devaluation effect (Figure 6.2.10). None of the remaining effects were significant including the crucial three-way Task-time × Session × Intervention interaction ($ps \geq 0.1330$).

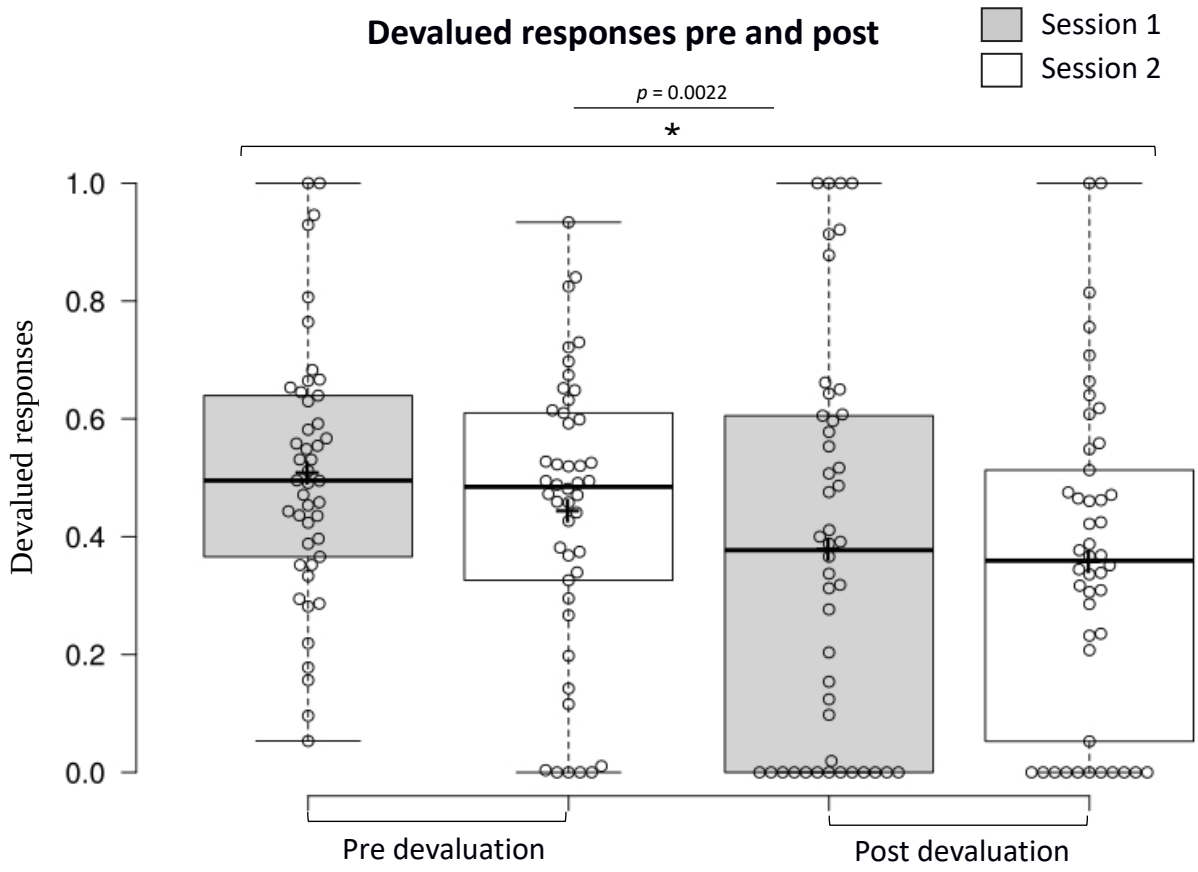

Figure 6.2.10 Devalued Responses Pre and Post Devaluation in the Aversive Stimulus Snack Task[a]

[a]Mean devalued responses pre and post devaluation during sessions 1 and 2. Note that devalued responses at pre devaluation refer to responses made to the to-be devalued outcome (as the snack devaluation had not yet occurred).

Cleansing desire/urge and behavior (Sanitizer task)

Visual analogue scale (VAS) desire to use sanitizer: neither active intervention altered the desire to use a hand sanitizer compared to the control intervention (Figure 6.3.1). A single-slope ANCOVA was found preferable and residuals were normally distributed. Given the slight group size asymmetry, type III SS was used. The effect of treatment was not significant ($F_{2,82} = 1.62$, $p = 0.2042$); the pattern was not altered if type I SS was used ($F_{2,82} < 1$, NS).

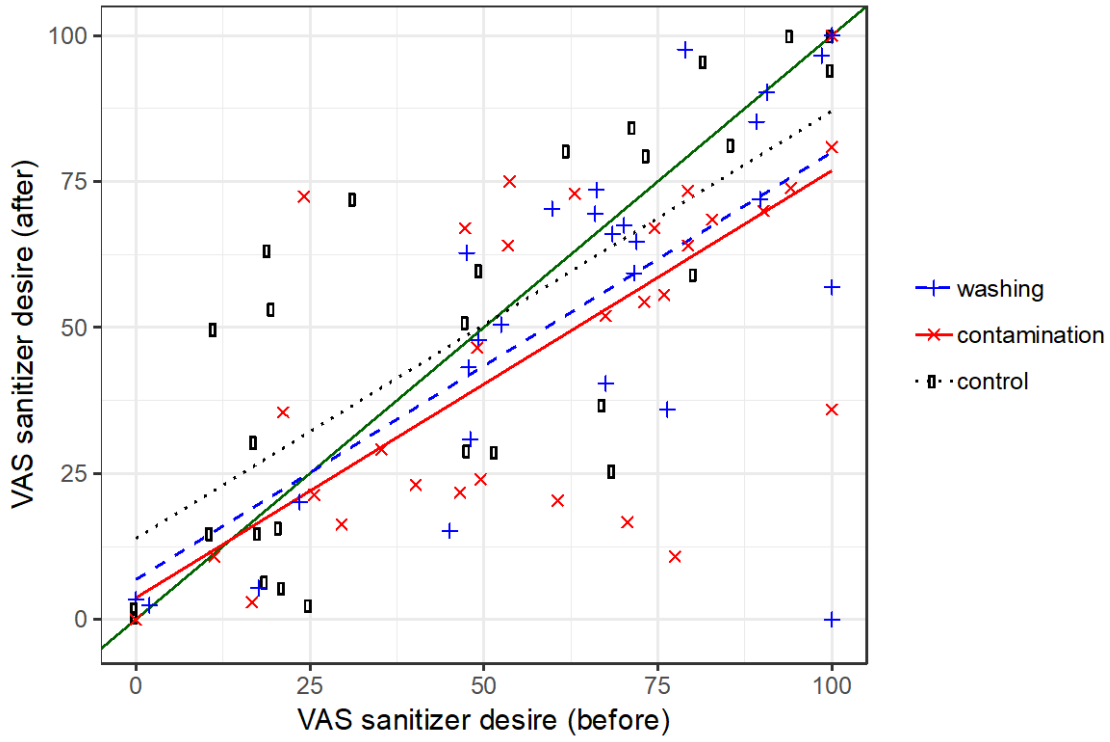

Figure 6.3.1 Desire to Use Sanitizer (VAS) Pre and Post Treatment[a]

[a]The desire/urge to use a sanitizer (VAS) was not altered by the active interventions compared to the control.

Cleansing time: neither active intervention altered time spent cleansing hands compared to the control (Figure 6.3.2). A single-slope ANCOVA model was preferred. Residuals exhibited some non-normality but were not improved substantially by a log or square-root

transformation, so the data were analysed untransformed with those caveats. There was no effect of treatment ($F_{2,87} < 1$, NS).

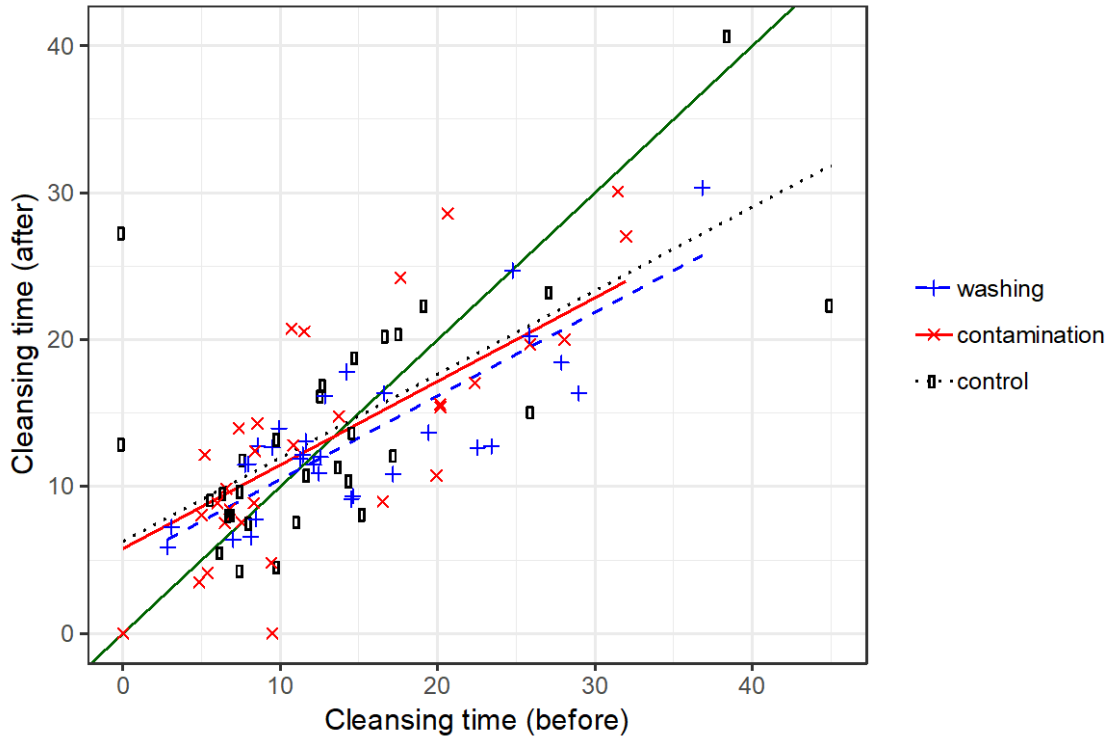

Figure 6.3.2 Cleansing Time Pre and Post Treatment[a]

[a]The time spent cleansing was not altered by the active interventions compared to the control.

6.4 Discussion

We assessed the effects of the smartphone interventions on a number of exploratory measures. Firstly, we found that ratings of disgust pre and post app declined over the course of the contamination intervention (unlike the washing and control), indicating it functions in a manner analogous to ERP (e.g., Meyer, 1966); i.e., by desensitizing participants to the video recording ("disgust stimulus"). In contrast, anxiety and handwashing urges pre and post app did not change over the course of the 7 days in any condition. It is promising that participants in the washing condition did not habituate to the video recording ("relief stimulus") during the intervention, highlighting its potential for long-term use.

In the present study, the washing intervention reduced disgust reactions pre and post app, suggesting it had a soothing overall effect. On the other hand, the contamination intervention increased disgust and handwashing urges relative to the control (as noted, such acute disgust gradually declined over the course of the intervention). We further found that the washing intervention was less anxiety provoking (i.e., calming) relative to the control (but did not impact anxiety overall pre/post app). Taken together, these findings suggest the active interventions had the most pronounced effect on disgust systems. They dovetail with research stressing the key role of disgust in driving contamination fears independent of anxiety (e.g., Olatunji et al., 2005).

These findings are consistent with the result that the washing intervention reduced disgust sensitivity pre and post treatment (i.e., had a "disgust extinguishing" effect); but not the observation that the contamination intervention slightly increased DS-R scores. One possible explanation for this might be that while participants in the contamination condition desensitized to the video recording (disgust stimulus) over the course of the 7-day intervention, it was perhaps not sufficiently long for them to fully habituate. Future research will need to disentangle this result and shed light on the role of disgust sensitivity in mediating these findings.

Health anxiety was unaltered by the active smartphone interventions. This finding is not entirely surprising in view of the fact that health anxiety is not implicated (i.e., a key driver of contamination fears) in several subtypes of contamination-related OCD (e.g., the "contact contamination", "mental pollution" and "perfectionism" variants; see Rachman, 1994; Rachman, 2004; Tallis, 1996). As such, it is plausible that participants with elevated health anxiety simply were underrepresented in our study. This result emphasizes once more that the smartphone interventions may preferentially target disgust systems rather than anxiety states.

The interventions did not impact cleansing urges and behavior as assessed on a newly developed "sanitizer task" (i.e., piloted for the purpose of this study). This measure may have been lacking ecological validity. For instance, participants would sometimes comment that

the sanitizer gel was sticky or had a strong smell. In line with this, they would spend time rubbing and blowing their hands to get rid of it. It is therefore conceivable that the sanitizer did not provide relief in some instances. Future research should include validated measures to examine the effects of the smartphone interventions on behavioral contamination symptoms.

In the current study, the interventions did not have an effect on visuospatial memory (i.e., PAL), impaired in clinical OCD (e.g., Bersani et al., 2013; Gottwald et al., 2018; Morein-Zamir et al., 2010). This mirrors research suggesting that visuospatial memory is unresponsive to treatment following non-pharmacological intervention (CBT) (e.g., Vandborg et al., 2015), unlike studies showing that visuospatial memory may improve following CBT treatment in OCD (e.g., Katrin Kuelz et al., 2006). Notably, there is evidence for a broad dissociation between the cognitive systems required for the PAL and the IED, which makes them well-suited as comparators; with the PAL assessing visuospatial memory function and the IED executive processing (Barnett et al., 2005). Indeed, although no neuropsychological test is completely domain-specific (e.g., both these tasks rely partly on working memory) the PAL relies on temporo-hippocampal load, while the EDS stage of the IED relies on greater fronto-striatal processing (e.g., Rogers et al., 2000; Wood et al., 2002). In this study the smartphone interventions selectively impacted fronto-striatal processing (cognitive flexibility), in effect, illustrating that executive function and visuospatial memory are dissociable.

The finding that the interventions did not affect response inhibition echoes research showing that such inhibition deficits in OCD remain unaltered after symptom remittance (Bannon et al., 2006). But the result stands in contrast to research illustrating that pharmacological intervention may improve response inhibition in other OCD-spectrum disorders such as ADHD (Chamberlain et al., 2007a). Compared to cognitive flexibility and visuospatial memory, response inhibition is associated with the activation of a broader neural network (primarily of the right hemisphere), including the inferior frontal, orbitofrontal and medial frontal cortices, the parietal cortices, and the basal ganglia (e.g., Aron et al., 2003; Garavan, Ross, & Stein, 1999; Horn, Dolan, Elliott, Deakin, & Woodruff, 2003; Menzies et al., 2008; Rubia, Smith, Taylor, & Brammer, 2007; see also, Aron et al., 2007).

In this study, the balance between goal-directed versus habitual behaviour was unaltered by the active interventions. As mentioned, OCD patients have been found to display an overreliance on habit systems (e.g., Gillan et al., 2011; Gillan et al., 2014). Moreover, a recent study showed that OC symptoms in a subclinical OCD group, were associated with habit bias on the Fabulous Fruit Game; and that anxiety and stress per se correlated with such biases (Snorrason, Lee, de Wit, & Woods, 2016). This is in keeping with literature suggesting that anxiety/stress promotes excessive habits (Schwabe & Wolf, 2011). Notably, it has been proposed that OCD treatments may specifically improve habitual bias and associated compulsive behaviours indirectly by reducing anxiety and stress (Gillan et al., 2016). The fact that the smartphone interventions in this study did not impact mood overall (e.g., anxiety states pre/post treatment), resonates with the finding that habitual propensities likewise were unaffected. Instead, as noted, the interventions had a more direct effect on OCD-type tendencies. Importantly, the healthy nature of the current sample might explain these findings: the strength of habit links may stem from a gradual acquisition of stimulus-response associations; eventually manifesting as clinical compulsions (Gillan et al., 2016). Habit bias in this sample was negligible (discussed below) and thus conceivably insensitive to treatment.

Finally, the results presented here raise the question of whether there are neuropsychological deficits in subclinical OCD. Our findings are consistent with research suggesting intact neurocognitive performance in this population. For example, the mean EDS error score (of the IED) at baseline (μ = 8.4, *SD* = 9.9) is lower than the average score reported in healthy control groups with low OC symptoms (μ = 16.1, *SD* = 8.3) (Johansen & Dittrich, 2013). Likewise, the mean PAL total error score at baseline in this study (μ = 19.2, *SD* = 16.5) is comparable to that of healthy volunteers who completed the same version of the PAL after being administered a placebo drug (μ = 19.5, *SD* = 14.6) (Müller et al., 2013). Participants also did not display a bias towards habitual behavior in the present study. On the Fabulous Fruit Game task, the mean percentage of devalued responses made on the slips-of-action test at baseline (μ = 34.6, *SD* = 24.9) is lower than that of healthy control subjects (μ = 49, *SD* = 25.7) and considerably lower than that of OCD patients (μ = 76, *SD* = 29.3) (Gillan et al., 2011). Similarly, unlike patients with schizophrenia (Morris et al., 2015), participants'

performance on the Aversive Stimulus Snack task was not indicative of deficits in goal-directed behaviour: changes in the value of the outcome guided their action selection in a goal-directed manner.

7. Study 3: OCD case example (smartphone washing intervention)

To get preliminary insight into the effects of the app (washing intervention) on clinical OCD symptoms, and explore its overall tolerability, one patient completed the one-week washing intervention. The patient, a female aged 49 years, was screened by an experienced psychiatrist on our research team. She met DSM-5 (American Psychiatric Association, 2013) diagnostic criteria for contamination-type OCD. Her primary obsessions and compulsions included fear of spreading germs, and excessive cleansing (e.g., household items) and ritualistic handwashing. She was currently taking 20 milligrams of Fluoxetine (an SSRI) daily. She did not suffer from any other psychiatric condition.

The patient was found to successfully complete the intervention, and missed only 1 session out of 28 app sessions total. She also appeared to watch the video footage on the application consistently: there were very few inconsistencies between the number of circles shown on the videos and subsequently reported (i.e., 3 cases of inconsistent reporting of circles out of all sessions completed). The patient's contamination fear symptoms dropped slightly from session 1 to session 2 (PI CF: from 38 to 36), and OCD symptoms dropped considerably (OCI-R: from 34 to 24; Y-BOCS: from 33 to 27) (Figure 7.1). There was no overall improvement in anxiety symptomatology from session 1 to session 2 (STAI-T: from 54 to 53; STAI-S: from 46 to 48) and depression symptoms increased moderately (BDI-II: from 25 to 32). On average across the 7 days, before and after watching the smartphone video, the patient reported reductions in ratings of anxiety (pre app [μ = 66.22, *SD* = 22.07] versus post app [μ = 53.62, *SD* = 21.00]); disgust (pre app [μ = 21.83, *SD* = 15.50] versus post app [μ =19.51, *SD* = 10.64]); and handwashing urges (pre app [μ = 37.49, *SD* = 16.64] versus post app [μ = 35.29, *SD* = 15.90]).

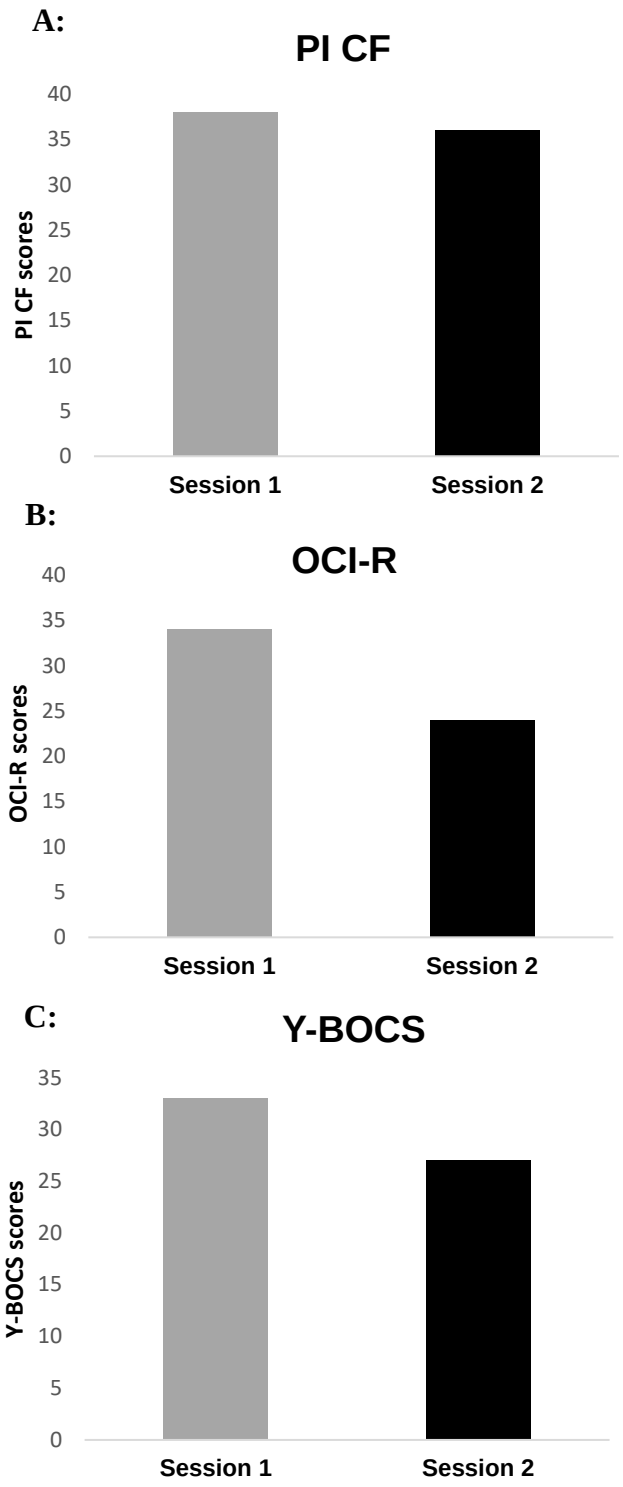

Figure 7.1 PI CF, OCI-R, and Y-BOCS Scores Pre and Post Treatment

8. Statistical and methodological considerations (caveat)

8.1 Statistical power

Statistical power is the probability that one will reject a null hypothesis (H_o) (e.g., that a particular intervention has no effect at all), when the H_o is wrong (i.e., the alternative hypothesis [H_A] is true; the intervention, in fact, has an effect) (Thomas, 1997). In hypothesis testing, statistical power should be as high as possible to increase the chances of detecting effects in the population (i.e., to decrease the probability of a Type II error or false-negative finding) (Murphy, Myors, & Wolach, 2014; Yarkoni, 2009). Other pitfalls of low powered studies include the increased probability that a statistically significant finding does not reflect a true effect and that the magnitude of any effect found is inflated (referred to as the "winner's curse") (Button et al., 2013). According to the conventional view, the statistical power of 0.80 is considered adequate; that is, yielding an 80 percent chance of detecting a real effect (Prajapati, Dunne, & Armstrong, 2010). Low statistical power results from factors such as small effect sizes, the chosen alpha level and statistical approach (e.g., whether directional and focused tests are used); and notably a low sample size (Dumas-Mallet, Button, Boraud, Gonon, & Munafò, 2017; Maxwell, 2004). As Cohen (1962) noted, "Since power is a direct monotonic function of sample size, it is recommended that investigators use larger samples than they customarily do" (p. 153).

Given the negative impact of low power, it is highly advised to perform power calculations before data collection to estimate the sample size needed to achieve adequate power (i.e., $\geq$ 0.80) (Button et al., 2013). For the current studies, we did not conduct a priori power analyses. This constitutes a limitation of our statistical approach. Therefore, to get insight into the power level at which our studies operated post hoc power calculation was conducted on key analyses. In Study 1, for the analyses comparing vicarious contamination sensations in the OCD (n = 29) and NAC group (n = 34), a power analysis indicated a high observed power of 0.98, 1.00, and 0.99 respectively (i.e., for disgust: p = 0.0002; anxiety: $p = 4.97 \times 10^{-9}$; and handwashing urges: p = 0.0002). This stood in contrast to the analysis comparing relief in the active vicarious handwashing condition (i.e., participants contaminate themselves and then watch the experimenter wash his hands) to the two control conditions in the OCD group (n = 29); indeed, a power analysis indicated an observed power of 0.47, 0.10, and 0.10

(i.e., for disgust-related relief: $p = 0.058$; anxiety-related relief: NS; and handwashing urge-related relief: NS). For the analysis comparing relief in the vicarious handwashing condition to the two control conditions in the OCD ($n = 29$) and NAC group ($n = 34$), a power calculation indicated an observed power of 0.27 (i.e., for disgust-related relief). In Study 2, for the analysis examining contamination sensations when the dummy was initially contaminated (5 min. upon initiating stroking) in the experimental ($n = 14$) and control condition ($n = 13$), a power calculation indicated an observed power of 0.17 (NS); for the analysis examining contamination sensations (i.e., habituation effects) 5 min. after the fake hand was contaminated in the two conditions, an observed power of 0.28 ($p = 0.32$); and for the analysis assessing contamination sensations in the two conditions during *in vivo* exposure, an observed power of 0.65 ($p = 0.046$). Finally, in Study 3, for key analyses testing the effects of the two smartphone interventions on OCD symptoms and cognitive flexibility (relative to the control intervention), a calculation indicated an observed power of 0.48, 0.99, 0.78, and 0.80 (i.e., for the PI CF: $p = 0.0928$; OCI-R: $p = 5.15 \times 10^{-5}$; Y-BOCS: $p = 0.0114$; and EDS errors: $p = 0.0092$).

Taken together, these post hoc power calculations suggest that in Study 1, the tests examining vicarious contamination sensations were highly powered, whereas those exploring vicarious handwashing were substantially underpowered. Likewise, overall the analyses of Study 2 were considerably underpowered. By contrast as a whole, the analyses of Study 3 were adequately powered; except for the analysis looking at the effects of the active smartphone interventions on contamination fears (i.e., the PI CF). As noted, given that power is inversely related to the likelihood of committing a Type II error, it is plausible that low power may help explain some of the null findings reported in this thesis; e.g., vis-à-vis vicarious handwashing in the OCD group (i.e., with respect to anxiety-related relief and handwashing urge-related relief) (Study 1), rubber hand contamination and habituation (Study 2), and the PI CF (Study 3).

8.2 Subjective self-report ratings and the arithmetic mean for ordinal data

In the present thesis, subjective self-report ratings (Likert scales) were used (in addition to, e.g., objective measures of disgust facial expression and neuropsychological tests).

Subjective rating scales provide arguably the most direct avenue to measure a particular construct, including discrete emotional states. For example, while heart rate is associated with anxiety, the two are not equivalent. Indeed, physiological symptoms can similarly be induced by related emotions like fear or embarrassment (Gravetter & Forzano, 2003). Likewise, self-report scales are practical, efficient (e.g., easy to administer), and cost-effective (Heppner, Wampold, & Kivlighan, 2008; Paulhus & Vazire, 2007).

However, subjective rating scales also have notable limitations. They lack precision (compared to objective measures) and can be influenced by situational factors like the presence of the experimenter. Participants may wish to project themselves in a favorable light (i.e., self-favoring bias) resulting in response bias (Gravetter & Forzano, 2003); e.g., by distorting their answers to please the experimenter, either deliberately or through self-deception (on social desirability bias, see Fisher & Katz, 2000) (Paulhus & Vazire, 2007). Additional factors influencing subjective ratings include the way questions are formulated (relying on the unique interpretation of the participant), and so-called "hypothesis guessing": participants guessing the hypothesis and then providing responses in line with or against this (Gravetter & Forzano, 2003; Heppner et al., 2008). Moreover, in clinical settings patients may conceal their symptoms (e.g., due to shame), which is often the case for OCD patients (Hauschildt, Jelinek, Randjbar, Hottenrott, & Moritz, 2010). Conversely, some patients may portray themselves as being more distressed than they are to elicit the sympathy of the experimenter; e.g., in hope that this will result in continued treatment (Heppner et al., 2008). Such confounding effects could potentially, therefore, compromise the validity of subjective ratings.

In the current studies, the arithmetic mean was used as a measure of central tendency for our self-report Likert scale data. However, there is an ongoing debate about whether calculating the mean for Likert scales is appropriate (e.g., Carifio & Perla, 2008; Jamieson, 2004; Pell, 2005). Indeed, some critics argue that treating the Likert scale (which is technically speaking ordinal; i.e., with a rank order) as if interval in nature is problematic. For instance, for ordinal scales the distance between responses (e.g., "not at all," "somewhat" and "very much") is not necessarily equidistant; i.e., responses are not evenly spaced out even though they appear to

be so numerically (Jamieson, 2004). (That is, for true interval scales the distance between numerical values is always equal [Schuster & Zuuring, 1986].) In light of this argument, ordinal scales cannot yield meaningful mean values. According to the standard statistical view, the median or mode should be used to measure the central tendency for ordinal data (i.e., analyzed nonparametrically). Furthermore, it is argued, even if one treats Likert scales as if interval in character, they tend to yield skewed scores as participants often select extreme responses (i.e., lowest and highest categories). Polarized data can give the impression that the average score centers around the middle category, which may not accurately reflect the underlying data (Jamieson, 2004; see also, Sullivan & Artino, 2013).

In contrast to this view, other experts argue it is legitimate to treat Likert scales as if they were interval in nature (an argument based largely on empiricism rather than logical reasoning). For instance, Carifio and Perla (2008) note that Likert scales should be viewed in their entirety and that individual items are not autonomous; it is the overall unified scale generating a single score that matters. Indeed, at scale level Likert scales (i.e., with multiple items) yield interval data; and, as such, single-item Likert scales should be used sparingly (Carifio & Perla, 2008). However, other researchers stress that even single-item Likert scales yield unbiased interval data (e.g., with the caveat that the lowest Likert-type response is not zero) (Vickers, 1999; for an overview see, Norman, 2010). In brief, parametric tests of central tendency (more versatile and powerful than their non-parametric counterparts) may be used for Likert scale data, if key assumptions are met (e.g., the distribution is not highly skewed) (Norman, 2010; Pell, 2005; Sullivan & Artino, 2013). Advocates on both sides of the debate encourage researchers to minimally consider reporting on whether their data violate key assumptions of parametric tests (Jamieson, 2005; Pell, 2005). In the present thesis, we have done so as much as possible.

9. General discussion

In Study 1, we demonstrated for the first time that patients with OCD can experience contamination sensations and relief merely by observing an experimenter contaminating himself and washing his own hands. Relative to healthy volunteers, OCD patients reported greater disgust, anxiety, and handwashing urges when watching the experimenter contaminating himself. But more notably, OCD patients, upon first contaminating themselves, reported significant disgust reductions (comparable to actual handwashing) by watching the experimenter washing his own hands, relative to control conditions. Finally, an exploratory analysis showed that OCD patients with moderate symptoms, unlike severe patients, reported greater reductions in disgust and handwashing urges from vicarious handwashing relative to control conditions, compared to healthy control subjects; and a tendency towards anxiety reductions during vicarious handwashing. Collectively, the results of Study 1 dovetail with our previous research illustrating that disgust and relief can be induced vicariously in college students with OCD symptoms (Jalal & Ramachandran, 2017). They are also broadly consistent with the exploratory findings of Study 3, namely: that the contamination intervention increased disgust and handwashing urges pre and post app and the washing intervention reduced disgust relative to the control.

Interestingly, the findings of Study 1 mirror verbal reports of Study 3. That is, several participants in the washing condition reported (prior to the debriefing at the end of the second session) that the intervention made them feel relaxed and had a soothing effect. As one participant noted, “[it felt as if] I had washed my hands, so I didn’t need to wash my hands anymore… my hands were clean after using the app.” Another participant reported, “I was surprised that watching myself washing hands produces relief”; and another that “if I am commuting, [e.g.,] on the bus and touch something contaminated and can’t wash my hands for the next two hours, the app would be a sufficient substitute.” Likewise, participants in the contamination condition remarked that they initially felt disgusted when watching the video footage, but that such feelings were reduced over time. One participant added, “the first half of the week, I found the video disgusting. Second half, not as disgusting…”; and another, “in real life one would not touch something as disgusting… touching something so disgusting becomes normalized” (by watching the video). One

participant noted, “my contamination and washing tendencies reduced a lot. For example, if I put the rubbish out and touch the bin, I would normally wash my hands immediately. But after I started to use the app, I felt like it would be silly to wash my hands…” and “I have become desensitized to the video and other things as well. If I normally were to wipe a kitchen worktop, I would throw the cloth away because I felt it was disgusting to clean that cloth for another time. But since using the app I now use the cloth, clean it, and use it again another time”; thus, “…it generalized to other things, so I felt like other things weren’t as disgusting as I previously thought they were.”

These reports, while anecdotal, provide valuable insights about participants’ subjective psychological state while exposed to the smartphone interventions. They are also congruous with findings that participants in the contamination condition became desensitized to the video recording (“disgust stimulus”) over the course of the intervention; i.e., suggesting it may function in a manner akin to exposure therapy (e.g., Meyer, 1966). Overall, Study 1 and Study 3 provide evidence for the first time of vicarious contamination and relief from observation of handwashing behaviours in clinical and subclinical OCD.

Consistent with these results, research points to the key role of disgust in the etiology and maintenance of contamination-related OCD (e.g., Olatunji et al., 2010). Evidence from imaging research suggests enhanced activity in brain regions mediating disgust, such as the insula in OCD (Shapira et al., 2003; for a review see, Husted et al., 2006). Interestingly, pathological disgust is amenable to non-pharmacological treatment (McKay, 2006). In fact, OCD patients are likely to experience overall symptom improvement, if treatments reduce disgust propensity (Knowles et al., 2018; see also, Athey et al., 2015) (Jalal et al., in review). Similarly, research has shown that non-clinical individuals with elevated contamination fears have difficulties disengaging from disgust-related stimuli (Cisler & Olatunji, 2010), display a propensity to interpret ambiguous situations based on disgust reactions (Charash & McKay, 2009) and exhibit heightened avoidance behaviour in disgust provoking situations compared to those with low contamination fears (Tsao & McKay, 2004). Taken together, research stresses the key role of disgust in driving contamination fears; indeed, independent of anxiety (Olatunji et al., 2005; although disgust and anxiety can interact to generate such contamination fear, see Cisler, Reardon, Williams, & Lohr, 2007).

Unlike disgust, observation of handwashing did not reduce anxiety and handwashing urges in the overall OCD sample in Study 1 and in Study 3. As noted, clinical severity may account for the findings of Study 1. Indeed, OCD participants were under intensive residential care, reserved for severe and refractory patients (e.g., Veale et al., 2016). Conceivably, it would be more difficult to disrupt firmly entrenched stimulus-response links in this population by introducing a "benign substitute compulsion" (i.e., vicarious handwashing) compared to less severe patients (e.g., regular outpatients). In contrast, lack of severity may account for the results of Study 3. Excessive anxiety and compulsive cleansing (arising from a gradual acquisition of stimulus-response habits; Gillan et al., 2016) are associated with clinical OCD not subclinical groups (Abramowitz et al., 2014). In line with this, in Study 2 patients with moderate symptoms (unlike severe patients) reported clear-cut disgust and handwashing urge reductions (and marginally so reductions in anxiety) from vicarious handwashing, relative to both control conditions and healthy volunteers (Jalal et al., in review).

In Study 3, unlike Study 1 and Jalal and Ramachandran's study (2017), participants observed themselves (not someone else) performing the disgust provoking or handwashing behaviours. Viewing oneself (versus another person) on film might be advantageous for several reasons. Self-identification with the agent performing the relief- or contamination-inducing behavior (washing hands or being contaminated) might enhance any empathetic response. Also, merely the memory of oneself performing such a salient behavior (i.e., one that eliminates or provokes contamination obsessions) is likely to help trigger an emotional reaction (on human emotion and memory see, Phelps, 2004). Moreover, compulsions in OCD, such as excessive hand-cleansing rituals, can be highly idiosyncratic, visibly differing from one person to the next (Abramowitz et al., 2009). This reality was echoed in our recent study (Jalal & Ramachandran, 2017): to maximize vicarious relief sensations felt by watching someone else washing their hands, participants would sometimes specify how the other person's cleansing ritual should be performed. Displaying video footage of participants performing their own handwashing therefore potentially ensures that this ritual is sufficiently personalized to maximize relief.

We have previously speculated that this “vicarious exposure” effect might reflect the activity of the MNS (Jalal & Ramachandran, 2017), implicated in social cognition (e.g., Gallese et al., 2004). But as noted, in Study 3 as opposed to Study 1, the relief and contamination stimuli were not presented vicariously per se, but in a vicarious-like manner. Nonetheless, it is still conceivable that an empathetic response triggered by viewing a virtual representation of oneself (via video) was mediated by the MNS; that is, underlying the understanding of another, in this case virtual, agent’s actions.

In a thematically related experiment, Study 2 explored the therapeutic potential of the RHI for OCD. Notably, results suggested sensory assimilation of contamination sensations into the body image via the illusion. Dummy contamination during synchronous stimulation resulted in elevated contamination reactions relative to asynchronous stroking. But contrary to expectations, it did so after the fake hand had been contaminated for 5 minutes; assessed via disgust facial expressions (a secondary outcome) and *in vivo* exposure (upon discontinuing the illusion). Surprisingly also, synchronous and asynchronous stroking induced an equally intense and fast arising illusion, which may explain why both conditions initially (5 minutes after initiating tactile stimulation) provoked comparable contamination reactions. This study is the first to demonstrate heightened plasticity of the bodily self in OCD. It may pave the way for a simple and tolerable (immersive yet indirect) low-cost technique for treating contamination fears (for details see Section 4.5, and below).

In Study 2, an exploratory analysis further showed that “fake hand exposure” during asynchronous stroking provoked contamination sensations to the same degree as actual real hand exposure. This finding is highly counterintuitive. It dovetails with our related studies showing that both college students with OCD symptoms (i.e., Jalal & Ramachandran, 2017) and severe OCD patients (i.e., Study 1), report indistinguishable levels of disgust when merely watching an experimenter contaminating his own hand and when their hand is contaminated. This research illustrates the cognitive impenetrability of contamination sensations (i.e., how such gut reactions can override logic and break down “self-other” barriers). Intriguingly, they also suggest that direct skin contamination may be unnecessary to gain the beneficial effects of exposure therapy. Contaminating proxy stimuli such as alien

limbs (synthetic or biological) can potentially trigger clinically relevant contamination reactions (see also, Study 3).

Finally, this "fake hand contamination" procedure may pave the way for precision medicine, by providing an objective measure of contamination fears (e.g., when paired with physiological data like heart rate or skin conductance). Such assessment is important as OCD patients often conceal their symptoms (e.g., due to shame and stigma concerns) (Hauschildt et al., 2010). Currently, few clinicians use behavioral tests to assess OCD (around 12 percent), owing possibly to time-burden and cost (Jacobson, Newman, & Goldfried, 2016). As our method is inexpensive, easy to administer and demands little time of clinicians, it may be useful as a hands-on diagnostic tool for the early detection of contamination fears and behavioural probe to track symptom improvement. This application aligns with attempts to improve nosology by moving away from relying solely on DSM categories, in favour of establishing objective classification (e.g., Gillan, Fineberg, & Robbins, 2017).

In Study 3, we found two novel smartphone interventions (i.e., based on the principle of "vicarious exposure"; see Study 1) to significantly improve OCD symptoms and cognitive flexibility (unlike the control) after only one week in subclinical individuals. The fact that cognitive flexibility improved is especially promising because impaired set shifting is thought to reflect repetitive and stereotyped symptoms of OCD (Menzies et al., 2008), like compulsive cleansing. We also found high levels of adherence to the interventions, stressing their clinical utility and overall tolerability. That is, while participants had to complete several sessions per day within fixed time periods, very few sessions were missed. Taken as a whole, the OCD case study results were in keeping with the key findings of Study 3: the patient appeared to find the washing intervention tolerable (all sessions, except one, were completed on time) and OCD symptoms (i.e., OCI-R scores) improved considerably.

The findings in Study 3 that the smartphone interventions improved cognitive flexibility but did not impact mood pre/post treatment parallel recent research on DBS in OCD. That is, one study examined the effectiveness of DBS of the ventral capsule/ventral striatal (VC/VS) or

anteromedial subthalamic nucleus (amSTN) (and also combined stimulation of both sites) (12 weeks per stimulation period) across a group of refractory OCD patients. One key aim was to specifically assess the effects of DBS on mood and cognitive flexibility. Both VC/VS and amSTN DBS improved OCD symptoms to the same degree indicating comparable efficacy. Yet, interestingly, DBS of the amSTN, unlike the VC/VS site, improved cognitive flexibility (EDS errors). VC/VS DBS, on the other hand, had a more pronounced impact on mood (Tyagi et al., 2019).

As noted earlier, while the initial CSTC account did not make any distinction between OFC sub-areas, it is now established that the lateral and medial OFC have different functions (Milad & Rauch, 2012; Robbins et al., 2019). Notably, reduced functional connectivity between the lateral OFC and dorsal caudate is linked to cognitive inflexibility (that is, greater EDS errors) in patients with OCD (Vaghi et al., 2017). In contrast, the medial OFC appears to be important for affective processing (see Tyagi et al., 2019); e.g., associated with excess activation during early fear learning (conditioning) in patients with OCD (i.e., indicative of safety learning impairments) (Apergis-Schoute et al., 2017). Likewise, reduced functional connectivity between the basolateral amygdala and medial OFC has been reported in OCD, predicting improved CBT intervention (Fullana et al., 2017).

In line with this, in the above-mentioned study (Tyagi et al., 2019), imaging (tractography) showed that DBS at each respective location linked to separate neural networks: amSTN DBS chiefly to the lateral OFC (and also the dlPFC and dorsal anterior cingulate cortex); and VC DBS the medial OFC (and regions like the thalamus and amygdala). Taken together, this suggests that separate neural systems underlie unique OCD symptomatology that may improve in response to treatment. Indeed, that our smartphone interventions improved cognitive flexibility but not mood, broadly mirrors amSTN DBS in OCD. Plausibly they targeted the same neural network ("cognitive/lateral circuitry") mediating cognitive flexibility, e.g., involving the lateral OFC linked to EDS performance in OCD (Vaghi et al., 2017). This is also in keeping with clinical observation and research showing that serotonin-boosting SSRIs robustly ameliorate both OCD symptoms and mood (Tyagi et al., 2019);

whereas serotonin systems do not impact EDS stage performance (Rogers et al., 1999; for an animal study see, Clarke et al., 2005; see too, Vaghi et al., 2017).

In this thesis, the inclusion of exploratory analyses was theoretically justified (i.e., grounded in prior work). In Study 1, it was plausible that patients with moderate symptoms would experience greater vicarious relief compared to severe patients (see "hypothesis" Section 3.2). Moreover, exploring whether vicarious relief would differ when the same or a different experimenter first contaminated himself, was based on our prior study (Jalal & Ramachandran, 2017); suggesting disgust reactions can override cognitive inferences (see Section 3.2). In Study 2, in view of previous research, we anticipated that OCD would be broadly associated with atypical multisensory processing (see Section 4.2). Similarly, in Study 2, given our research showing that direct and vicarious exposure trigger similar disgust reactions (Jalal & Ramachandran, 2017), conceivably, RHI dummy exposure (another indirect approach) would provoke comparable contamination reactions as *in vivo* exposure. In Study 3, in light of research implicating health anxiety, disgust sensitivity, compulsive urges and behavior, visuospatial memory and response inhibition deficits, and habit biases in OCD, it was possible these would improve in response to treatment; e.g., as suggested by some studies (reviewed in Section 1). Also, based on our research on vicarious disgust and relief (Jalal & Ramachandran, 2017), it was expected that the contamination intervention would increase and the washing intervention reduce contamination ratings relative to the control pre/post app. And, akin to ERP, it was anticipated that contamination ratings would decline over the course of the 7-day contamination intervention (which mirrors conventional exposure), unlike the washing and control.

Notably, it is important to clearly distinguish between primary and exploratory analyses, and the respective weight attributable to each approach. Indeed, it is crucial to outline at the outset which analyses are primary and exploratory as to differentiate their priorities. Primary (confirmatory) analyses provide evidence for well-defined a priori hypotheses. They allow for conclusions to be made as to whether major hypotheses are supported (permit final decisions) (Bender & Lange, 2001). In contrast, for exploratory analyses (e.g., post hoc tests), although there may be an overall goal in mind, the aim is not to produce clear-cut

evidence in support of a priori hypotheses. Exploratory tests allow instead for a more open-ended inquiry that can reveal patterns, which is why a flexible data analysis methodology can be applied (e.g., as noted, multiplicity adjustment is unnecessary). However, it is important to stress that any significant finding from an exploratory test per se is preliminary (constitutes lower grade evidence providing a rough guide), and should be subject to future confirmatory investigation to arrive at explicit conclusions (Bender & Lange, 2001; Palmer, n.d.; see too, Moyé, 2015).

There are several intricate steps involved in the translation of preclinical findings into "empirically supported psychological treatments" applicable in clinical settings (e.g., Tolin, McKay, Forman, Klonsky, & Thombs, 2015). These are relevant to highlight here in view of the aims of this thesis. In this respect, the American Psychological Association (APA) Division 12 Task Force and other work groups have outlined criteria for establishing the validity of treatments (e.g., Chambless & Ollendick, 2001; Task Force on Promotion and Dissemination of Psychological Procedures, 1993; see too, Kramer, Bernstein, & Phares, 2009; Tolin et al., 2015).

"Well-established" treatments are corroborated, minimally, by two randomized controlled trials (rigorously designed) where the intervention is: (1) superior to placebos or an established intervention (Kramer et al., 2009; Tolin et al., 2015); or (2) equally efficacious as an established intervention (shown in light of sufficient statistical power; around $N = 30$ per group) (Tolin et al., 2015). Alternatively, (3) an extended series of meticulously controlled single-case experiments should show the intervention to be efficacious relative to another intervention. Such clinical studies must be done (i.e., efficacy shown) by two separate research groups/investigators (Kramer et al., 2009; Tolin et al., 2015). "Probably efficacious" treatments, for example, have been corroborated by (1) one meticulously designed randomized controlled trial where the intervention is superior to placebos or an established intervention (Kramer et al., 2009); or (2) a limited series of meticulously designed controlled single-case experiments showing efficacy relative to another treatment (Tolin et al., 2015). Finally, "promising" interventions are determined by less stringent criteria; e.g., require support from a rigorously controlled experiment and minimally also

another not as rigorously controlled experiment (Chambless & Ollendick, 2001; Kramer et al., 2009) (for detailed criteria see Chambless & Ollendick, 2001; Task Force on Promotion and Dissemination of Psychological Procedures, 1993; Tolin et al., 2015).

Other key aspects have been stressed in the literature that must be considered as well when translating preclinical findings into clinical practice. In addition to symptom reduction, it is critical, for instance, to establish whether treatments improve overall functioning (e.g., vis-à-vis work-related and social activities) and quality of life (Tolin et al., 2015). Moreover, besides showing "efficacy" (i.e., beneficial effects in a controlled research environment), studies should demonstrate that treatments are "effective." That is, they must show applicability and acceptability in real-world clinical environments that are representative and generalizable (Kramer et al., 2009); e.g., when implemented by clinicians (not researchers) in heterogeneous patients with co-occurring conditions (Tolin et al., 2015). There should similarly be an evaluation of the long-term efficacy of interventions; e.g., do symptoms return after treatment is ceased and how durable are treatment effects over time? Furthermore, research should aim to disentangle and shed light on particular treatment elements underlying any beneficial effects (versus emphasizing treatment packages). Critically, it should also be assessed whether a treatment is cost-effective (Kramer et al., 2009; Tolin et al., 2015). Treatments should be weighted according to their relative clinical and economic burden. In the case of two equally efficacious interventions, the one less costly to patients and society, and less time-consuming overall (e.g., fewer and shorter treatment sessions) should be prioritized. Finally, the adverse side effects of interventions should be considered as well (Kramer et al., 2009; Tolin et al., 2015). In brief, these steps involved in translating laboratory research into the clinic must be addressed in future work to translate the present findings into empirically supported treatments for OCD.

9.1 Future research and concluding remarks

Future research should extend these experiments in several ways. For example, in Study 1 and Study 2 key hypotheses relied on subjective self-report ratings (Likert scales). As discussed, such scales have notable limitations (see Section 8.2). Future experiments should additionally use objective measures to examine vicarious contamination and relief, and RHI

contamination and habituation; e.g., indexes of autonomic function such as heart rate or skin conductance. These would provide more stable and reliable measures of contamination fears. Moreover, disgust facial expression should ideally be assessed by using video recording (e.g., captured via head-mounted camera). Alternatively, experimenters rating disgust facial expressions should be blinded to the experimental and control group.

In Study 1, the baseline assessment (i.e., viewing the contaminant for 30 seconds) was not counterbalanced. Although this task did not entail active confrontation, it can still be considered a form of exposure. Future research should take such potential exposure carryover effects into account; e.g., obtain baseline ratings on a separate occasion.

In Study 2, we provided evidence from our previous research in healthy volunteers concerning the time course of the RHI (how soon it is reliably induced) and at which timepoint fake hand contamination differentiates the RHI procedure and control (vis-à-vis contamination sensations) (Jalal et al., 2015); i.e., serving as a comparison to the present study. Nonetheless that we did not include a healthy control group for direct comparison (e.g., relevant for RHI habituation and *in vivo* exposure assessment) constitutes a limitation. Critically, this should be addressed in future work. Also, in Study 2 we did not capture any habituation effects possibly due to the brevity of the experiment. Thus, future research should rely on a longer duration. It might be (like ERP) that up to 30-45 minutes of RHI exposure is needed for habituation to occur (see Jalal et al., in press).

Future research should control for the impact of comorbid psychiatric conditions (e.g., major depressive disorder). Furthermore, such studies should ideally use an outpatient sample; i.e., more typical of OCD patients, for instance, less severe and thus possibly more likely to experience vicarious handwashing relief (Jalal et al., in press). Importantly, future research should rely on a large (adequately powered) sample. Indeed, based on our retrospective power analysis, Study 1 (specifically vicarious handwashing assessment) and Study 2 were underpowered, which may explain some of the null findings. For future studies, a priori power analyses should be conducted.

Future work, in OCD patients, should explore the efficacy and feasibility of these novel treatments. Double-blind placebo-controlled trials should compare our "rubber hand contamination" procedure to ERP (Jalal et al., in press). Future research should include a study of the novel smartphone interventions in patients with a clinical diagnosis of OCD. Ideally, this study would be conducted over a longer period of time, for example, 4 months, which might make it possible to quantify the efficacy of the interventions and improvement of the participants' symptoms within their everyday life. This future experiment could also examine the neural correlates of symptom and cognitive flexibility improvement. Future studies should also directly compare our smartphone interventions to remotely delivered forms of CBT (cCBT and iCBT) and available smartphone interventions for OCD like "LiveOCDFree" (an app-guided ERP treatment; Boisseau et al., 2017).

The findings regarding "vicarious exposure" presented in this PhD thesis may have implications for other psychiatric disorders which have components of compulsivity and cognitive inflexibility, for example: non-suicidal self-injury, binge-drinking, and trichotillomania. Future research could explore these additional groups.

In closing, in three programmatic studies this thesis explored innovative approaches for treating OCD. In Study 1, we demonstrated for the first time vicarious activation of contamination sensations and relief in OCD with possible implications for therapy. In Study 2, we introduced an indirect yet immersive multisensory technique for treating OCD using the RHI with potential to trigger clinically relevant contamination reactions. Finally, in Study 3 we presented two smartphone interventions and showed they can significantly improve OCD symptoms and cognitive function after only one week in individuals with contamination fears.

These novel interventions may overcome challenges of conventional therapies for OCD, including intolerability of treatment procedures, inconvenience of delivery (e.g., participant travel), and socio-medical costs. Indeed, unlike ERP they do not require patients to touch highly disgust-provoking "contaminants." It is therefore plausible that patients who are too anxious to engage in ERP (i.e., fear direct confrontation with contaminants) would be

more accepting of these approaches (Jalal et al., in press). As noted, 25 percent of patients refuse exposure therapy at the outset mainly due to intolerability issues (Maltby & Tolin, 2005). Widespread treatment fears may help explain why patients on average begin effective therapies 17 years after the onset of OCD (Hollander et al., 1997). Accordingly, our proposed interventions might reduce this long onset-to-treatment gap; i.e., provide an avenue for targeting compulsions in the early stages of the disorder before they worsen and become difficult to treat. In short, such timely initiation of therapy may ultimately shorten the chronicity of OCD (Skoog & Skoog, 1999), improve treatment outcomes (Dell'Osso et al., 2010), and alleviate unnecessary suffering.

Furthermore, the cost-effective, accessible and transportable nature of our interventions make them eminently suitable for poorly resourced and emergency settings, including low-income and developing countries with minimal access to health care and high-tech solutions like virtual reality. Importantly also, these treatments lend themselves to "technology-based personalized medicine" (see, Jalal et al., 2018). Such smartphone solutions can be tailored for individual patients, allowing for targeted therapies that encourage patients to actively partake in their recovery process and promote the learning of cognitive strategies to eradicate compulsive urges. They are well-suited for modern societies where people, across social status and age group, are becoming increasingly reliant on smartphone technology (Pew Research Center, 2018). Notably, in the year 2016, there were 3.9 billion smartphone subscribers worldwide, a number expected to rise dramatically by 2022 (Barboutov et al., 2017). All in all, these simple and low-cost solutions for treating OCD might result in higher treatment uptake, lower drop-out and facilitate early intervention—in effect reducing the global disease burden of OCD. Indeed, as this cruel condition afflicts up to 2-3 percent of the general population (Robins et al., 1984; Ruscio et al., 2010) with economic costs estimated at 10.6 billion dollars per year in the United States alone (Eaton et al., 2008), they may have significant public health and societal impact.

"All the perfumes of Arabia" were insufficient to "sweeten" Lady Macbeth's little hands—but perhaps watching a simple smartphone recording of herself washing them might eventually have done the trick.

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