

## NEUROBIOLOGICAL MECHANISMS UNDERLYING ABNORMAL PROCESSING OF GUILT, DISGUST AND INTENTIONALITY IN OBSESSIVE-COMPULSIVE DISORDER: A CRITICAL REVIEW

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### Abstract

Many different and innovative neuroimaging techniques have been developed in the last decades. Functional neuroimaging allows detecting what is happening in our brain at rest or while performing a specific cognitive or emotional task, while structural methods are concerned with the physical organization of the brain, considering both micro- and macro-structural aspects. Starting from these recent developments, neuroimaging techniques have been applied to healthy individuals, as well as to clinical populations. Functional and quantitative imaging research has also focused on what is going in the brain of patients suffering from Obsessive-Compulsive Disorder (OCD). There is consistent clinical and experimental evidence showing that patients suffering from OCD are particularly sensitive to guilt and disgust emotions, with both contributing to the disorder's onset and maintenance. Further, OCD patients also show impairment in the ability to consciously control, or inhibit, specific behaviors, resulting in compulsive acting. In this review we want to provide some neurobiological evidence on the cerebral mechanisms underlying guilt and disgust processing in OCD, also considering the neural aspects of motor intentionality. Overall, neuroimaging studies suggest that the Fronto-Parieto-sub-Cortical circuit, including both cortical and sub-cortical regions, as well as their inter-connecting fibers, is involved in OCD. Overall, findings show more frontal regions, extending to the insular cortices, to be involved, in action monitoring, error detection, decision making, and in guilt and disgust processing, while the midbrain, including basal ganglia and extending to more parietal areas, is involved in movement selection, correction and inhibition, in intentionality and social cognition. We think these data might contribute in explaining the neurobiological substrate underlying some core aspects of OCD clinical manifestation, which does not necessarily rely upon a dysfunction of the central nervous system. We suggest here, that eventual OCD patients' psychological processes may affect neuronal responses, contributing to the peculiarities observed.

**Key words:** obsessive-compulsive disorder, neuroimaging, guilt, disgust, intentionality, emotion processing

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### Introduction

OCD is the fourth-most-common mental disorder worldwide with a lifetime prevalence ranging from 1 to 4 per cent (Abramowitz et al. 2009), being characterized by the presence of obsessions and/or compulsions (APA 2000). An obsession is an unwanted intrusive thought, doubt or image that repeatedly enters the mind, while compulsions are repetitive behaviors or mental acts that a person feels obliged to perform in response to an obsession. The person usually regards the intrusions as unreasonable or excessive and tries to resist them. A compulsion can take the form of either

an overt action (i.e., checking that the gas is locked) or a covert mental act (i.e., repeating specific formulas in the mind to prevent something bad to happen). There are no differences related to OCD prevalence between males and females, though women show more frequently compulsive washing, and men more sexual obsessions, magical numbers or obsessional slowness (Veale & Roberts 2014). The mean age of onset is late adolescence for men and the early 20s for women (Kessler et al. 2005). The prevalence of OCD among children and adolescents is in the range of 1% to 3% (Flament et al. 1988, Delorme et al. 2006), with a similar presentation to adults. However, OCD can also

present in older people, either after a long history of the condition hitherto undiagnosed or with symptoms that are more recent in onset (Veale & Roberts 2014).

According to the age of the subject, OCD symptoms might apparently overlap with other psychiatric conditions, such as, in childhood, Tic disorder, Tourette Syndrome (TS), a disorder characterized by multiple motor and vocal tics, or Paediatric Autoimmune Neuropsychiatric Disorder associated with streptococcal infections (PANDAS), being characterized by tics, obsessivity and emotional instability or impulsivity, and, in older ages, Fronto-temporal Dementia (FTD), which includes (especially in its behavioral variant) executive dysfunction, language impairments and affective and behavioral disturbances (Lima et al. 2013). TS, PANDAS and FTD have been often associated with OCD (Pichichero 2009, Martino et al. 2009), sometimes leading to a wrong diagnosis and, as a consequence, to an inadequate treatment management.

In contrast to neurodevelopmental and neurodegenerative disorders, OCD is characterized by peculiar cognitive and emotional features, which are driven by specific goals (Abramovitch et al. 2012). These aspects, related to intentionality, are evidently not present in the above-mentioned medical conditions. A great amount of literature (Salkovskis 1985, Rachman 2002, Shapiro & Stewart 2011, for a review), in fact, shows that patients with OCD display specific sensitivity to emotions of guilt, especially to a deontological type (Mancini & Gangemi 2011, Basile et al. 2013, D'Olimpio & Mancini 2014), and disgust (Berle & Philips, 2006, for a review), and show selective cognitive dysfunctions (involving planning, decision making, mental set-shifting, information updating and monitoring, action inhibition and control) (Greisberg & McKay 2003, Bannon et al. 2006, de Geus et al. 2007, Chamberlain et al. 2006, Abramovitch et al. 2012). The recent advances of neuroimaging methodologies might play a significant role in a better characterization of the neural mechanisms underlying the core emotional and cognitive aspects involved in OCD symptomatology. Within the last decades, many neuroimaging studies investigated neural substrate of emotional and cognitive processing, in many psychiatric conditions (Edwards et al. 2002), including OCD.

In line with these findings, and together with early mentioned clinical evidences on the core aspects of OCD, the aim of this article is to provide some neurobiological evidence of the cerebral mechanisms underlying guilt and disgust processing in OCD, also considering the role of intentionality, behavioral inhibition and action control, which might explain the compulsive aspects of the disorder. Different imaging techniques will be considered, investigating both functional and structural brain tissue organization in patients with OCD. We suggest that the neuronal mechanisms underlying OCD symptomatology can be specifically associated to the core aspects of the disorder.

## Neuroimaging techniques

Brain imaging can be grossly divided into two separate categories: functional and structural imaging. Functional imaging techniques include positron emission tomography (PET), single-photon emission computer tomography (SPECT), magnetic resonance spectroscopy (MRS), functional Magnetic Resonance Imaging (fMRI), whereas structural imaging relies on methods such as Computed Tomography (CT) and MRI, as Voxel Based Morphometry (VBM) and Diffusion

Tensor Imaging tractography (DTI). In the following sections we will briefly describe the main functional and anatomical findings on the neurobiological mechanisms underlying guilt and disgust processing and executive dysfunctions in OCD.

## Functional imaging findings in OCD

Functional neuroimaging allows detecting what is happening in our brain *in vivo* during emotional cognitive task performance, or at rest. We will here discuss the main findings of task-related imaging studies, which have focused on the neural correlates of disgust and guilt processing, and dysfunctions related to abnormal action inhibition/control and intentionality, in patients with OCD (for a recent review on overall fMRI findings in OCD see, Del Casale et al. 2014). In the last part of this paragraph, we will also consider recent findings investigating functional connectivity during rest (RS-fMRI).

Disgust processing in normal individuals, mostly investigated through disgusting stimuli administration, commonly involves increases in neural activity within the insula, the basal ganglia (BG) and parietal cortices (Philips et al. 1997, Schienle et al. 2005, Wright et al. 2004, von dem Hagen et al. 2009). When studying the neurobiological mechanisms underlying disgust processing in OCD, results revealed an exaggerated behavioral reaction and an abnormal neuronal response in patients (versus healthy subjects). More in detail, significant differences in neuronal responses were observed within the bilateral insula, the right orbito-frontal cortex (OFC,) the parahippocampal region, the caudate nucleus (as part of the BG), and in the ventrolateral prefrontal cortex (vlPFC) (Stein et al. 2006, Shapira et al. 2003, Lawrence et al. 2006).

Another emotion that plays a significant role in OCD onset and maintenance is guilt, and, more in detail, a deontological kind of guilt, generally deriving from the transgression of moral norms, D'Olimpio & Mancini 2014, Mancini 2008, Mancini & Gangemi 2011). Previous PET and fMRI studies on healthy volunteers (Shin et al. 2000, Takahashi et al. 2004, Moll et al. 2007, Kédia et al. 2008, Basile et al. 2011), showed a direct involvement of the anterior and posterior cingulate cortices (ACC, PCC), the insular cortex, the medial PFC (medPFC) and the superior temporal sulcus (STS), in the experience of guilt. However, recent evidence (Basile & Mancini 2011, Basile et al. 2011) suggests that different types of guilt, namely deontological and altruistic guilt, can be identified on a basis of their specific goals and emotional halo, and on the involvement of different underlying neuronal circuits. Beyond the common activation of the ACC and the PCC, deontological guilt, in isolation, seems to involve the insula, while altruistic guilt processing requires a selective activation of the PFC. Further, different authors (Miller 1997, Rozin et al. 2000, Phillips et al. 2003) suggest that guilt emotion, especially in its moral/deontological acceptance, shares some common features with disgust, despite the predominant physical manifestations of this emotion. One recent fMRI study (Basile et al. 2013) investigated guilt processing in a sample of OCD patients, showing that during deontological - but not altruistic - guilt experience, patients (vs controls) showed significant decreased activation in the ACC, in the anterior insulae and in the left precuneus. This result supports evidence derived from previous clinical studies (Gangemi & Mancini 2011, Franklin et al. 2009, Sica et al. 2002, Abramowitz et al. 2004) indicating a specific sensitivity

of OCD patients to deontological guilt, and, more in general, to morality-related issues.

Cognitive impairment, involving planning, decision making, mental set-shifting, information updating and monitoring, action inhibition and control, plays a significant role in OCD maintenance, and is strongly associated to compulsive behaviors (Rapoport 1991, Rauch et al. 1994). However, neuropsychological and neuroimaging studies (Kuelz 2004) did not always converge in their findings. Lack of significant differences between patients' and healthy subjects' behavioral performances or neural responses was observed during planning (as assessed through the Tower of London test), decision making (evaluated through the Iowa gambling task), set-shifting (assessed through the Wisconsin Card Sorting task), and response inhibition (in go/no-go or Stroop tasks). Commonly, when considering healthy individuals, fronto-parieto-cerebellar circuits are involved during executive functioning (for a complete review, see Nowrangi et al. 2014). Within OCD populations, overall, hyperactivity has been observed in regions such as the ACC, the dorso-lateral PFC and the OFC, with additional abnormal neural responses within the parietal lobes, the BG and the cerebellum (Van den Heuvel et al. 2005, Menzies et al. 2008, Sachdev & Malhi 2005). More in detail, the ACC, especially in its dorsal portion, is involved in the cognitive aspects of response inhibition and response selection tasks (Bush 2000), while the BG (including the striatum, the caudate nucleus, the putamen and the globus pallidus), together with the parietal lobes, are involved in the motor and motivational aspects of OCD symptomatology. Finally, the PFC and the OFC are involved, respectively, in the emotional aspects of intentionality and set-shifting, and in the emotional features of decision-making.

According to these evidences, Graybiel & Rauch (2000) suggest that the cortico-parietal-basal ganglia circuit is more involved in the motor and cognitive aspects of OCD, while the OFC (extending to the ACC) might have a major role in representation of reward and punishment, and in overall emotional aspects involved in information processing and inhibitory control. However, as suggested by Menzies et al. (2008), the desire to understand the abnormalities in OCD cognitive functioning, must take into account that combining all studies using many different paradigms is an oversimplification that might be misleading, resulting in an over-simplistic explanation of the pathophysiological mechanisms underlying the compulsive aspects of the disorder.

Within the last decade, Resting State (RS) methodology has been applied to clinical and normal populations. RS-fMRI allows to identify specific brain networks of functionally linked cortical regions reflecting precise functions, at rest. Several studies (Fitzgerald et al. 2011, Harrison et al. 2012, Jang et al. 2010, Anticevic et al. 2004) applying this method to OCD patients showed abnormal connectivity in different networks, involving OFC, the ACC, the insular cortex and the BG, and in particular the caudate nucleus. One study (Harrison et al. 2012) found a positive association between functional connectivity in the caudate nucleus and the insular cortex, and severity of sexual/religious symptoms (assessed through the Yale-Brown Obsessive Compulsive Scale).

Overall, functional imaging findings highlight the role of the Fronto-Parieto-sub-Cortical (FPsC) circuit in explaining the neurobiological substrate of specific emotional and cognitive aspects of OCD pathology.

## Structural imaging findings in OCD

Additional data supporting the role of the FPsC network in OCD derives from the application of structural imaging techniques. Such methods are concerned with the physical organization of the brain, considering both micro- and macro-structural aspects within the grey (GM) and the white matter (WM). Voxel Based Morphometry (VBM) allows to get information about levels of GM atrophy, while more advanced techniques, such as Diffusion Tensor Imaging (DTI), give information about changes in diffusion of water molecules within the WM, thus allowing to get information about the micro-structure of the fibers and bundles within the brain.

Many VBM studies investigated GM volumes within the brain of OCD patients, further confirming the involvement of the FPsC circuit in this disorder. Data revealed reduced GM volumes in frontal areas (i.e., OFC and medial PFC), extending to the ACC, and increases of GM volumes in the lenticular nucleus, the caudate nucleus (both part of the BG) and the superior parietal lobe (for a review see, Peng et al. 2012, Radua & Mataix-Cols 2009, Kim et al. 2001, Pujol et al. 2004, Valente et al. 2005). Further, a positive association was found between OCD symptoms' severity and increased GM volumes within the BG (Radua & Mataix-Cols 2009). Also, selective differences in levels of GM atrophy have been observed in OCD, when compared against patients with other anxiety disorders (Radua et al. 2010).

Studies applying DTI techniques revealed WM abnormalities within several bundles and fibers of the brain of OCD patients. Reduced or increased structural connectivity was found in the cingulate bundle (CB), the major median associative WM fasciculus (including, short fibers, connecting various areas of the cingulate cortex, and long fibers, reciprocally connecting frontal, temporal and parietal regions, thus allowing for communication between components of the limbic system), in the corpus callosum (CC, connecting the two hemispheres), in the anterior limb of the internal capsule (ALIC, connecting the frontal cortex to the thalamus), and in the uncinate fasciculus (UF, connecting anterior temporal cortex/amygdala to the frontal area) (for a review, see Koch et al. 2014, Piras et al. 2013).

Overall, these results are consistent with current OCD FPsC model (Huey et al. 2008), confirming the presence of micro-structural alterations in this pathway, targeting the OFC and the ACC, and of a hyper-connectivity in the ALIC, which further supports the notion that hyperactivity in the orbitofronto-striatal loop serves a key role in OCD. Compared to volumetric measurements, DTI is potentially more sensitive in detecting subtle and early changes in the micro-structure of the brain, and in WM organization, allowing a better characterization of the extent of micro-structural alterations.

## Neurobiological evidence of treatment outcome in OCD

Neuroimaging techniques have been used to detect and characterize changes in brain functioning, as a consequence of pharmacological or psychological interventions in several diseases. The application of such methodologies to psychopathological conditions might play a role in a better understanding of brain

tissue re-organization after efficacious treatment.

Most of the studies applying neuroimaging techniques to efficaciously treated OCD patients focused on the neuronal effects of medication (for a review, see Shin et al. 2013), although it is well established that psychological interventions, such as Cognitive-Behavioral Therapy (CBT), might be equally, or even more, effective than pharmacological treatment alone (Foa et al. 2005). A couple of PET studies (Baxter et al. 1992, Schwartz et al. 1996) showed that, after treatment with medication alone, or associated to CBT, showing a reduction of neuronal activity in the caudate nucleus, which was initially enhanced. Similar results were observed in a more recent fMRI study (Nakao et al. 2005), where authors found a decreased activation in the OFC, the ACC, the insula, the putamen and some temporo-occipital regions, during a symptoms' provocation task, after successful pharmacological (i.e., fluvoxamine) or CBT intervention. Finally, in one study applying DTI technique, Yoo et al. (2007) found that drug-naïve OCD patients showed significant increases in fractional anisotropy (an index of the degree of water diffusion) in the corpus callosum, the internal capsule and in the right caudate nucleus. Such increases were no longer detectable after 12 weeks of medication (i.e., citalopram).

Further, the identification of treatment response predictors might play an important role in acknowledging the target treatment for specific kinds of patients. In one study, Brody et al. (1998) showed that OCD patients with particular patterns of brain metabolism responded preferentially to a particular type of treatment. Authors found that the best responders to CBT showed a higher metabolism at the left OFC, before the treatment, while a lower metabolic activity in the left OFC was associated with better response to fluoxetine treatment. Studies of neuroimaging predictors of treatment response might contribute to future clinical decision making in individual patients, by identifying impaired neural circuits that could become targets of more directed (or adjunctive) treatments.

Overall, these results show that CBT, mostly when coupled to pharmacotherapy, might play a role in modifying abnormal neural activity in OCD (Porto et al. 2009). These findings support the hypothesis of cerebral tissue re-organization in OCD patients, after successful treatment, showing a recover to healthy-like neuronal responses, specifically within some areas of the FPsC.

## Conclusions

The aim of this article was to collect some evidence of the neurobiological mechanisms underlying the core emotional and cognitive aspects involved in OC pathology. Overall, these studies support the hypotheses that functional and anatomical brain peculiarities underlie specific OC features (i.e., disgust and guilt sensitivity and cognitive dysfunctions), involving a well-known FPsC network. Nevertheless, atypical functioning within areas of this circuit might also be found in healthy individuals, to which obsessive-like symptoms are experimentally induced. Studies investigating the neural substrate of OCD-like psychological processes (i.e., obsessional thinking) in healthy populations further help in understanding neuronal mechanisms in OCD. In one study, Cottraux and colleagues (1996) compared PET scans of patients with OCD with checking rituals, while obsessing, to healthy volunteers, thinking about "normal obsessions". Findings indicated

that both groups showed increased activity in the OFC, when actively involved in obsessional thinking. More recently, Mataix-Cols and colleagues (2003) found that the brain systems implicated in the mediation of anxiety in healthy subjects were similar to those identified in OCD patients involved in a symptom provocation task, where patients were confronted with washing-, checking- or hoarding-relevant pictures. These data suggest a relatively good overlap between the neuronal circuit recruited by healthy individuals, to which OCD-related emotions and obsessive thinking are induced, and patients' neuronal response (Cottraux et al. 1996). Finally, data reported here, also show that functional and structural changes observed within the FPsC of OCD patients, return to normal, after successful symptoms' recover.

Taken together, all these findings might lead to different considerations. The first one refers to the nature of the differences observed in the brain of OCD patients, as compared towards those of healthy individuals. Are these modifications a consequence of patients' dysfunctional psychological processes, or do these neuronal differences precede patients' clinical manifestations? We strongly suggest that patients' exaggerated psychological responses might lead to the neuronal changes observed in OCD patients' brain. In fact, it is self-evident, that every single mental state is accompanied by peculiar cerebral patterns (see, Mataix-Cols et al. 2003, Cottraux et al. 1996), and that the persistence of specific psychological conditions might, somehow, affect both functional, as well as structural, brain characteristics. A clear example derives from a couple of studies (Bengtsson et al. 2005, Schmithorst & Wilke, 2002) investigating cerebral abnormalities in expert pianists, as compared to non-experts. These studies show that long-term practicing/training might induce regional-specific plasticity. Authors suggest that these changes might be due to the cognitive and motor effects of training and expertise, on the brain. Similarly, another study (Bremner et al. 1997) found that early exposure to traumatic events might contribute to GM volume reduction within the hippocampus, a brain area that is notoriously involved in memory processes. It seems, thus, that external events (i.e., traumatic experiences) or specific training or repetitions (i.e., as playing piano) might influence and modify brain anatomy. Further, structural neuroimaging data do not answer the question whether changes in GM and WM precede the onset of OCD symptoms or if, instead, which seems more plausible, they represent the neural consequence of emotional, cognitive and behavioral changes occurring in OCD. To date, without any longitudinal studies, it is almost impossible to understand whether these micro-structural abnormalities represent a vulnerability factor for the development of OCD or, whether they represent the consequence of an abnormal psychological condition. Evidence deriving from neuroimaging studies investigating neuronal re-organization after OCD symptoms' reduction (through medication and/or CBT) further supports our hypothesis. Many findings, in fact, detect a reduction, or annulment, of functional and structural differences in efficaciously-treated OCD patients, with cerebral parameters returning to "normal", after symptoms' reduction. We strongly suggest that anomalous neuronal responses observed in OCD might reflect patients' expertise in specific psychological processes (i.e., obsessional thinking, rumination, etc.), that might be triggered by early socio-environmental factors, such as traumatic experiences or obsessive-like behaviors observed in caregivers. OCD etiology and maintenance is further

characterized by specific goals (i.e., fear of feeling responsible and guilty for something, compulsive behaviors' inhibition, etc.), which, over time, also contribute to the neuronal changes observed in the brain of OC patients. Conversely, cerebral alterations detected in other psychiatric or neurodegenerative conditions (i.e., FTD) do not reflect the consequence of specifically goal-oriented behaviors, but might be caused by medical condition. These findings support the hypothesis that OCD does not rely upon an organic condition, but, rather, that peculiar functional and structural brain alterations observed in OCD might be the neural substrate or the consequence of excessive training/exercise of specific emotional and cognitive processes, driven by precise goals. Another relevant issue refers to the limitations of current imaging techniques. It is still unknown if, up-to-day technology, fully detects and measures all brain's mechanisms. There might still be some other neuronal, and yet unidentified, biological processes that present techniques and devices are still not able to detect. Another concern to take into account in the interpretation of neuro-imaging findings, rely on the different methodologies used across studies. Experimental paradigms are not always well controlled, missing, for instance, of a (or an adequate) control condition. As well, findings from different studies might be difficult to compare the one another, as, for instance, some of them do not involve an active-task, as happens in script-driven paradigms. The absence of any behavioral recording does not allow controlling what subjects are actually doing within the scanner, which might, further, contribute to unreliable results. Another methodological caveat refers to the experimenter' events' timing onset, which might lead to arbitrary focus on different phenomena occurring within the brain, driving towards misleading findings. Further, experimental paradigms are designed to investigate one specific process, although the selected task does not necessarily investigate the targeted function. Finally, group analyses' contributes to level patients' characteristics, annulling individuals' OC-specific peculiarities. This also refers to those studies where hoarding patients have been included, even if, as already acknowledged by DSM-5, this sub-type is not subsumed by current conceptualizations of OCD. The inclusion of patients with such specific and diverse symptoms might further compromise findings.

To conclude, despite the fundamental contribution of neuroimaging literature to understand the neurobiological substrate of OCD core aspects, one must bear in mind that each patient has its own peculiarities and that, as we strongly suggested here, differences in neural responses do not necessarily rely upon a cerebral dysfunction. In fact, the neuronal differences observed in the brain of OCD patients may not necessarily involve a dysfunction of the central nervous system, but might, instead, reflect patients' hyper-functioning in one specific psychological process, which, in turn, causes patients' neuronal modifications.

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