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## Review article

## Core, social and moral disgust are bounded: A review on behavioral and neural bases of repugnance in clinical disorders

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## ABSTRACT

Disgust is a multifaceted experience that might affect several aspects of life. Here, we reviewed research on neurological and psychiatric disorders that are characterized by abnormal disgust processing to test the hypothesis of a shared neurocognitive architecture in the representation of three disgust domains: i) personal experience of ‘core disgust’; ii) social disgust, i.e., sensitivity to others’ expressions of disgust; iii) moral disgust, i.e., sensitivity to ethical violations. Our review provides some support to the shared neurocognitive hypothesis and suggests that the insula might be the “hub” structure linking the three domains of disgust sensitivity, while other brain regions may subserve specific facets of the multidimensional experience. Our review also suggests a role of serotonin core and moral disgust, supporting “neo-sentimentalist” theories of morality, which posit a causal role of affect in moral judgment.

## 1. Introduction

If we were asked to describe an autobiographical experience of disgust, we would probably talk about some unpleasant, poorly prepared food consumed in a bad restaurant. The link between disgust and food is probably the easiest to recall, given the relevance of feeding to our own survival and the extensive evidence that taste aversion learning is rapid across species (Gelperin, 1975; Darnauillac et al., 2004). But disgust is more than a mere gustatory matter: perceptions and judgments about disgust impact all aspects of life: disgust influences how we select our friends and our sexual partners, which social group we adhere to, the clothing we wear, the music we listen to and, probably, our concept of morality.

Although more than 140 years have elapsed since Charles Darwin published his influential work on emotions entitled *The Expression of the Emotions in Man and Animals* (Darwin, 1872), our understanding of the neural basis of disgust has progressed rapidly only in the last decades. We have acquired a framework for understanding the neural correlates of disgust, including an appreciation of the role of the insula and its interconnected circuits (Murphy et al., 2003; Wickers et al., 2003; Schäfer et al., 2005; Fusar-Poli et al., 2009; Kirby and Robinsons, 2015). Moreover, we are aware of the role played by genes in explaining inter-individual differences in experiencing disgust or aversion

to specific flavors and smells (e.g., Reed et al., 2006; Reed and Knaapila, 2010). Finally, we have a better understanding of neuro-functional relationships in different disgust-related experiences (Vicario et al., 2017), including the moral dimension of disgust (Chapman et al., 2009), and the importance of socio-cultural and educational factors in shaping aversion to certain sensorial and social outcomes (Curtis, 2011; Davey, 2011).

From a theoretical point of view, the *body-to-soul preadaptation* theory suggests that “disgust, an originally food-related emotion, expanded, both in biological and in cultural evolution, to become a guardian of the body, the social order, and the soul” (Rozin and Fallon, 1987; Rozin et al., 2008). From this perspective, disgust has evolved from the antecedent distaste response by a preadaptation process that allows a structure or system that originally evolved for one purpose to be reused in a new context. Accordingly, this theory conceives moral disgust as a phenomenon of preadaptation – the disgust response being expanded to serve functions for which it did not originally evolve. On the other hand, the *adaptationist* theory of Tybur et al. (2009, 2013) suggests that “disgust evolved to motivate behavioral solutions to multiple distinct adaptive problems such as the avoidance of substances associated with disease-causing agents in ancestral environments; the avoidance of sexual partners and behaviors that would reduce one’s long-term reproductive success; the avoidance of individuals who inflict social costs on oneself or members of

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one's social network" (Tybur et al., 2013). From this perspective, disgust has its roots in a phenomenon of adaptation that helps to avoid potential pathogens, but can be co-opted to support condemnation in the moral domain.

Both the above-mentioned theories conceive disgust as a defensive mechanism that has evolved to protect against illness, disease and contamination by promoting withdrawal from and avoidance of spoiled foods or other contaminants. Thus, disgust is an emotion critical not only for regulating one's own ingestive behavior, but also for social interactions. Moreover, both these theories provide an account of how disgust might be linked to moral judgment. This reveals the *neo-sentimentalist* or *intuitionist*<sup>1</sup> nature (Haidt, 2001) of these theories, as they argue for a causal role of affect in moral judgment. By contrast, there are other theories (e.g., Royzman et al., 2011; Royzman et al., 2009) that have placed particular emphasis on *rationalist* (or, more broadly, cognitive) inputs to moral judgment. From their perspective, disgust and morality are separate although some theorists (e.g., Kohlberg, 1971) did not deny the role of affect in moral judgment.

Overall, although the existing literature provides a framework for understanding how the brain processes certain aspects of disgust, the general picture is still fragmented. This might be due to the complex nature of disgust as an object of study, as it is a multifaceted emotion that is potentially influenced by a wide range of factors.

At least three lines of research addressing different aspects of disgust can be identified in neuroscience and psychology research. The first line of research has focused on *core disgust* – a very basic subjective experience of aversion that is triggered by potentially toxic visual, gustatory or olfactory stimuli (i.e., rotten foods, excrement) that could contaminate the body, as well as other unpleasant experiences not related to ingestion, but to mutilation, sex, and pathogens (Rozin et al., 2008, 2000; Toronchuk and Ellis, 2007). Another line of research has focused on the ability to recognize disgust in others (Frith, 2009; Wicker et al., 2003). Current theoretical models of disgust fail to consider this socio-emotional ability as a constituent of the disgust experience (Rozin and Fallon, 1987; Rozin et al., 2008; Tybur et al., 2009, 2013). However, one research tradition has shown that observing others' motor and vocal emotional expressions activate mechanisms that are responsible for the generation of the same emotion in oneself (Goldman and Sripada, 2005; Gallese et al., 2004; Niedenthal, 2007; Keysers and Gazzola, 2009; Paracampo et al., 2016; Vicario et al., 2017; Vicario et al., in press). This idea has found support in seminal studies addressing the first-person experience of disgust and the recognition of disgust in others (e.g., Calder et al., 2000; Wicker et al., 2003). Considering this line of research, we refer to *social disgust* as a relevant aspect of the disgust experience with important socio-communicative implications. Finally, the third line of research has focused on *moral disgust*, that is, the subjective sensitivity to, and negative evaluations of, moral transgressions and socially inappropriate people and behaviors, some of which involve an inappropriate use of the body (e.g., cannibalism, pedophilia, torture), while others do not (e.g., hypocrisy, fawning, betrayal; Chapman et al., 2009; Rozin et al., 2000; Haidt et al., 1997; Jones, 2007).

Whether and how these three domains of disgust are linked at behavioral and neural levels is still a matter of debate and controversy. From the neural point of view, some research suggests the existence of a shared representation of different disgust components. For instance, Wicker et al. (2003) have shown that the personal experience of smelling unpleasant scents (core disgust) and the observation of faces expressing disgust (social disgust) activate the same sites in the anterior insula (AI) and the anterior cingulate cortex (ACC). Similar results have been reported by Jabbi et al. (2008), who found corresponding regions of activation in the AI when experiencing disgust (i.e., bad tastants), when viewing someone else experiencing disgust and when imagining

the experience of gustatory disgust. This suggests that one's own experience of disgust and perception of disgust in others may tap into similar neural resources (Calder et al., 2000; Keysers and Gazzola, 2009; Rizzolatti and Sinigaglia, 2016). However, it should be noted that the study of Jabbi et al. (2008) also showed distinct patterns of insular connectivity while observing, imagining and experiencing disgust, indicating that partially different functional networks are recruited in the three tasks. Interestingly, insular and cingulate regions are also active when experiencing moral disgust related to an unfair monetary offer in the ultimatum game (Sanfey et al., 2003) and to social norm violations (Spitzer et al., 2007; Hutcherson et al., 2015; see also Vicario, 2016 for a discussion). Other brain regions, such as the medial prefrontal cortex (mPFC), might also take part in moral cognition (see Sevinc and Spreng, 2014; for a systematic review), possibly because of their involvement in decision-making and processing others mental states.

While the above evidence supports the view of shared disgust representations in the brain, it should be noted that insular and cingulate cortices are also active in a wide variety of tasks involving subjective awareness of both positive and negative feelings (Menon and Uddin, 2010; Ibañez et al., 2010; Cauda et al., 2012; Tamietto et al., 2015), and are believed to play a domain-general role in identifying the most salient among several internal and extrapersonal stimuli in order to guide behavior. Therefore, insular and cingulate involvement in the different dimensions of disgust may reflect the emotional and homeostatic salience of disgust stimuli, rather than a disgust-specific mechanism. On the other hand, direct stimulation of the insula in awake monkeys and human neurosurgery patients can elicit core disgust sensations (e.g., nausea, unpleasant tastes and sensations in the mouth and stomach) and related vegetative and oral motor responses (Ostrowsky et al., 2000; Penfield and Faulk, 1955; Selimbeyoglu and Parvizi, 2010; Caruana et al., 2011). Remarkably, a recent study also demonstrated that electrical stimulation of the AI induces a selective impairment in social disgust sensitivity (Papagno et al., 2016), thus providing causal evidence for a critical role of the AI in both core disgust and social disgust.

Behavioral investigations in healthy individuals also provide support for the hypothesis of a common system for processing core and moral disgust. A seminal study showed that similar facial reactions are evoked by core disgust – elicited by gustatory distaste or the observation of contaminants – and moral disgust – elicited by unfair treatment in an economic game (Chapman et al., 2009). Additionally, studies have reported interactions between core disgust and moral disgust. For example, a personal experience of disgust evoked by consumption of bitter liquids increased moral disapproval ratings of ethical violations (Eskine et al., 2011). Conversely, thinking about moral transgressions or virtues, relative to neutral control events, led participants to perceive a neutral-tasting beverage as disgusting or delicious, respectively (Eskine et al., 2012). Evoking core disgust experimentally renders moral judgments and behaviors more severe (Moretti and di Pellegrino, 2010; Chapman and Anderson, 2013). Moreover, disgust sensitivity predicts conservative attitudes toward abortion and gay marriage (Inbar et al., 2009). By contrast, a recent analysis by Landy and Goodwin (2015) challenges this link between core and moral disgust by showing that the modest effect of disgust on moral judgment found in the literature might be due to publication bias (but see Schnall et al., 2015 for different conclusions).

Despite evidence that the experience of disgust can be altered in several neurological and psychiatric diseases, clinical disorders have been mostly neglected by theories of disgust. Thus, the main goal of this review is to establish the behavioral and neural bases of core, social and moral disgust through an analysis of clinical disorders characterized by abnormal disgust processing in at least one of the three examined domains. Studies addressing clinical disorders are extremely important for understanding the mechanisms of disgust, and present two main advantages. First, instead of providing correlational information about the brain regions that are active when processing core, social or moral

<sup>1</sup> In his review, Haidt uses the terms "intuition" and "emotion" interchangeably.

disgust, an analysis of clinical disorders can highlight the neuroanatomical and neurochemical bases of abnormal disgust processing in the three domains. This can provide information about which brain regions and neurochemical pathways contribute to the three disgust domains. Second, studies of clinical disorders allow one to test the boundaries between the three different domains based on an established alteration in disgust sensitivity, rather than through incidental sensory manipulations (i.e., by studying the link between disgust and morality via exposure to incidental disgust), and can thus provide important insights into the current debate between the *neo-sentimentalist* and the *rationalist* views discussed above (see Landy and Goodwin, 2015 for an overview and meta-analysis). In the following paragraphs, we review evidence addressing disgust processing in neurological (i.e., Huntington's disease, Parkinson's disease, and other neurological conditions) and psychiatric disorders (i.e., obsessive compulsive disorder, schizophrenia, depressive syndrome and eating disorders). We also consider personality disorders associated with altered disgust processing. Further, to address previous suggestions that dopamine (DA), serotonin (5-HT; see Vicario, 2013a; Lövheim, 2012 for a review) and glutamate (Glu; Richard and Berridge, 2011) modulate the experience of disgust and aversion, we evaluate the relationships between behavioral responses to disgust and the neurochemical profiles associated with the selected clinical disorders.

The field of emotion research makes key distinctions between processes related to acquisition and evaluation of sensory information (e.g., visual processing of a disgust elicitor such as excrement), physiological activation (e.g., modulation of brain activity and autonomic and neuroendocrine systems), emotion expression (e.g., wrinkling the nose), action tendencies (e.g., preparing behavioral avoidance) and the subjective feeling of the emotion (e.g., the unpleasant feeling of repugnance) (Bradley and Lang, 2000). Core, social and moral disgust have been addressed using a variety of methods in healthy humans, although single studies typically fail to consider all the components. This is particularly true for studies of patients, which have mainly focused on the feeling of disgust and its physiological components.

## 2. Disgust processing in neurological disorders

The research on disgust processing in neurological disorders has mainly focused on patients with neurodegenerative diseases, such as Huntington's disease (HD) and Parkinson's disease (PD), which are addressed in the first two parts of this section. Comparatively less research has been conducted on other neurodegenerative diseases and brain damaged patients, which are discussed together in a third subsection.

### 2.1. Huntington's disease

Huntington's disease (HD) is an autosomal dominant neurodegenerative disease caused by an extended repetition of the CAG triplet in the *IT15* gene (Huntingtin gene) on chromosome 4 (Craufurd et al., 2015; Dayalu and Albin, 2015) and characterized by movement disorders involving coordination (mainly chorea, dystonia and parkinsonism), cognitive deterioration and behavioral changes (i.e., psychiatric symptoms; Martino et al., 2013). HD atrophies the striatum at an early stage (Vonsattel et al., 1985; Douaud et al., 2006), but other structures, including insular and frontal cortices, have been reported to be affected, too (e.g., Thieben et al., 2002; Rosas et al., 2008).

Research investigating core disgust sensitivity in HD is rather limited. Interesting insights were provided by Mitchell et al. (2005) and by Hayes and et al. (2007), who reported that HD patients, despite showing intact sensory discrimination of odors, rate disgusting odors as significantly less unpleasant, relative to the ratings of control participants. Moreover, evidence suggests reduced disgust expression in HD patients, with lower disgust-like facial reactions to disgusting odors (Hayes et al., 2009). A reduction in core disgust has also been reported

in HD patients using gustatory stimuli (Mitchell et al., 2005; Hayes et al., 2007). The latter study (Hayes et al., 2007) also showed that declarative semantic knowledge of disgust elicitors and classification of disgusting pictures can be affected in HD, although this altered evaluation of emotional pictures might be not limited to disgust (Ille et al., 2011).

The literature on social disgust sensitivity in HD is more extensive. An early investigation in a small sample of HD patients suggested a general impairment in emotion recognition (Jacobs et al., 1996). Sprengelmeyer et al. (1996) first documented a particularly severe impairment in the recognition of disgust expressions, although in that study, as well as in subsequent studies, recognition of fear and anger was also affected during both visual presentation of facial expressions and auditory presentation of vocal expressions (for a recent systematic review, see Bora et al., 2016). Social disgust sensitivity also appears to be affected in HD gene carriers who have not yet manifested clinical signs of HD. Gray et al. (1997) found a selective deficit in the recognition of disgust in such a pre-clinical sample. Face processing abilities were investigated using various tests, including identification of familiar (famous) faces, unfamiliar face matching, recognition memory for faces, and recognition of facial expressions of emotion. When the six basic emotions were examined separately, only disgust recognition was found to be impaired. Other studies indicated that emotion recognition deficits occur in HD patients only when they process isolated facial expressions, whereas they show preserved processing of the same facial configurations when the faces are embedded in a context (Aviezer et al., 2009; Baez et al., 2015). Moreover, recent meta-analyses including both pre-clinical and clinical HD samples, and the study by Johnson et al. (2007) on 475 pre-clinical HD gene carriers, suggest a general deficit in recognizing emotionally negative facial expressions, rather than a specific deficit in recognizing disgust (Henley et al., 2012; Bora et al., 2016). Importantly, these impairments are unlikely to be due to basic perceptual deficits (van Asselen et al., 2012).

The lower perceptual sensitivity to several negative emotions in HD is also associated with reduced spontaneous and posed imitations of the observed expressions (Hayes et al., 2009; Trinkler et al., 2013). Using the (decontextualized) emotional morphing task, Baez et al. (2015) recently reported impairments in negative expression recognition in patients with manifest HD and more selective disgust deficits in their relatives (descendants or siblings).

Early studies have pointed to the insula as the key region underlying HD impairments in social disgust (e.g., Sprengelmeyer et al., 2006; Hennenlotter et al., 2004). For instance, Hennenlotter et al. (2004) found that pre-clinical HD gene carriers showed reduced activations within the left AI during perception of disgusted facial expressions. There were no differences in AI activations between pre-clinical HD gene carriers and the control group while processing a different emotion (surprise). However, further studies suggested that a more extensive network is affected in both pre-clinical and symptomatic HD, with atrophy and reduced activity in several emotion-relevant areas such as the striatum, amygdala, insula and orbitofrontal (OFC) regions, and correlations of such anatomical and functional changes with impairments in the recognition of several negative emotions (Henley et al., 2008; Ille et al., 2011; Trinkler et al., 2013; Dogan et al., 2014a, 2014b). Other studies, however, suggest a specific relationship between the insula and the impairment in social disgust observed in pre-clinical HD (Kipps et al., 2007). Finally, Eddy and Rickards (2012) provided preliminary insights into the moral disgust domain by showing that HD patients tend to rate immoral behaviors as less severe, compared to controls (see also Eddy et al., 2011). However, this trend did not reach statistical significance, possibly because of the small sample size and heterogeneity of HD patients, or because of other methodological factors, including the method for measuring participants' ratings (see Eddy et al., 2011). Subtle impairments in recognizing an intention to harm and changes in the desire to punish were also reported by Baez et al. (2016) when HD patients observed scenes depicting accidental harm,

although it is possible that such impairments might reflect a general impairment in theory of mind (Bora et al., 2016).

Overall, the literature on HD suggests a deficit in the recognition of disgust and other negative emotional expressions, although there is evidence for reduced sensitivity to core and moral disgust, as well. One should consider that HD can also be associated with neuropsychiatric symptoms such as apathy or depression (Kordsachia et al., 2017). However, the associations of such symptoms with core, social or moral disgust have not been systematically assessed. Thus, it is not clear whether abnormal disgust (and emotion) processing in HD reflects the cooccurrence of neuropsychiatric symptoms such as apathy and depression, which affect emotional functioning broadly (see next paragraph).

Patients affected by HD are also characterized by hypoactive dopaminergic and hyperactive serotonergic systems (e.g., Bédard et al., 2011; Kish et al., 1987), in association with regional atrophy in emotion-relevant areas such as the striatum, the insula and the OFC and in memory-relevant areas such as the dorsolateral PFC and the hippocampus (Ille et al., 2011). In addition, the literature provides evidence for decreased Glu uptake in the striatal neurons of HD transgenic mice (Liévens et al., 2001). This trend has also been seen in patients (Bender et al., 2005).

## 2.2. Parkinson's disease

Parkinson's disease (PD) is a neurodegenerative syndrome – a synucleinopathy – characterized by bradykinesia, rigidity and resting tremor (Davie, 2008), and classically associated with a loss of dopaminergic innervation to the ventral striatum, the subthalamic nucleus, and other basal ganglia structures; nigral dopaminergic cell loss is typically associated with the core motor features of this condition. However, neurodegeneration is not restricted to the nigrostriatal pathway and can affect neocortical and limbic structures. Several non-motor symptoms, including emotional and cognitive deficits, may arise from the disease process or may result from pharmacologic or surgical treatment (Cooney and Stacy 2016; Santangelo et al., 2017).

With respect to core disgust sensitivity, Bowers et al. (2006) found that patients in the early stages of PD exhibit blunted reactivity and reduced arousal, as measured by the startle eyeblink response during exposure to negative/aversive pictures. Moreover, a recent study by Ille et al. (2015) documented a selective reduction in disgust proneness toward olfactory stimuli associated with spoilage and decay (e.g., smelling sour milk, rotten meat) in PD. Interestingly, ratings of disgust proneness for spoiled food items were positively correlated with OFC volume. In contrast, a recent case report study (Gopalan et al., 2013) documented enhanced disgust sensitivity for urine in a PD patient treated with the DA agonist pramipexole. This different pattern of results (i.e., higher disgust sensitivity) might be due to the acute effect of the pharmacological treatment.

Regarding social disgust, studies indicate reduced sensitivity in PD patients (Sprenkelmeyer et al., 2003; Suzuki et al., 2006). Sprenkelmeyer et al. (2003) found that the deficit in recognizing disgust was more consistently noted in un-medicated compared to medicated PD patients. However, the literature as a whole offers mixed results. A meta-analysis conducted by Gray and Tickle-Degnen (2010) revealed that PD patients might be affected by a generalized deficit in recognizing negative emotions (i.e., anger, disgust, fear, and sadness). Such a deficit was not moderated by patients' depression levels or visual impairments. Gray and Tickle-Degnen (2010) noted the importance of considering which neural structures are primarily compromised in the examined PD population, in order to predict the emotional recognition deficit. Of particular relevance to PD patients, studies have found associations between deficits in anger recognition and abnormal dopaminergic activity within the ventral striatum (Calder et al., 2004; Lawrence et al., 2007a, 2007b), between deficits in disgust recognition and abnormal activity in the basal ganglia (in particular, the putamen;

see Sprenkelmeyer et al., 2003) and the insula (for a review, see Suzuki et al., 2006), and between deficits in fear recognition and abnormal activity in the amygdala (Adolphs et al., 1999; Bouchard et al., 2008; Harding et al., 2002; Vytal and Hamann, 2010). However, recent studies do not support such associations between emotion-specific recognition deficits and abnormal activity in particular brain regions (Bora et al., 2016). In summary, the literature suggests that the emotion recognition deficit in PD is not selective for disgust, but might affect recognition of other negative emotions (anger, disgust, fear, and sadness), as well (e.g., Gray and Tickle-Degnen, 2010; Péron et al., 2012).

In contrast to the abundant literature on social disgust in PD, moral disgust remains poorly investigated, although a few studies have documented altered moral decision-making in PD (Rosen et al., 2013, 2015). In a recent study, moral decision-making was assessed with a close-to-everyday moral dilemma paradigm that opposes socially oriented “altruistic” choices with self-beneficial “egoistic” choices in short moral dilemma stories. PD patients made more egoistic moral decisions, compared to healthy controls (Rosen et al., 2015). Moreover, while theory of mind (Rosen et al., 2013), reasoning, planning and empathic abilities (Rosen et al., 2015) were correlated with moral decision making in controls, no similar relationships were found in the PD patients, further suggesting altered decision-making processes.

Overall, the literature suggests that PD is associated with deficits in core disgust, the recognition of disgust in others, and the experience of moral disgust. However, the emotion recognition deficit might include other emotions rather than being selective for disgust. Also in the case of PD, as was suggested for HD (Bora et al., 2016), the general emotion recognition deficit might be linked to a poor theory of mind (e.g., Wagenbreth et al., 2016). Moreover, more research is needed to explore deficits in the sensory disgust domain in PD.

A reduction in DA availability in the striatum (i.e., the caudate and putamen) is considered a hallmark of PD (e.g., Politis and Loane, 2011). Moreover, a growing line of research suggests that PD is a diffuse pathology, also involving the 5-HT system (Houle et al., 2000; Bédard et al., 2011). For instance, in vivo positron emission tomography (PET) has shown a reduction in 5-HT binding in striatal, brainstem, and cortical regions (Politis et al., 2010). This has been interpreted as reflecting a widespread decrease of presynaptic serotonergic terminal function in PD. However, this dysfunction follows neither the extent nor the linearity of the degeneration observed in the dopaminergic system (Politis and Loane, 2011; see also Huot et al., 2011 for a complete review). There is also evidence of striatal 5-HT augmentation in PD, which might indicate a compensatory mechanism (Bédard et al., 2011), but the recent review by Politis and Niccolini (2015) supports the non-linear progressive degeneration of 5-HT terminals in PD. Moreover, changes in the cholinergic system have been reported (e.g., Bohnen and Albin, 2011) that presumably reflect a compensatory process. Finally, abnormal Glu activity (i.e., higher Glu release) has been shown in basal ganglia circuits (Blandini et al., 2000), and is generally considered a secondary consequence of decreased DA levels (Stayte and Vissel, 2014). This implies that the disruption of multiple circuits might account for the various observed deficits in this clinical population.

## 2.3. Other neurological conditions

This subsection comprises a discussion of both patients with brain injuries (i.e., stroke or surgical resection) and patients with neurodegenerative diseases other than HD and PD.

An early study by Calder et al. (2000) investigated disgust experiences in a brain injured patient with a left hemispheric infarction involving the insula, putamen, internal capsule and globus pallidus. The patient showed significant and selective impairments in both core disgust (via disgust-provoking scenarios) and social disgust (i.e., the ability to recognize facial expressions of disgust). Similar findings were reported by Adolphs et al. (2003), who described a patient with bilateral damage to the insula that extended to temporal and frontal areas

including the ACC and ventromedial prefrontal regions, and by Borg et al. (2013), who reported altered social disgust in a rare case of ischemic lesion restricted to the posterior insula. The involvement of the insula in core disgust is also supported by a recent investigation of 84 patients with neurodegenerative diseases other than HD and PD (i.e., frontotemporal dementia, corticobasal syndrome, progressive supranuclear palsy or Alzheimer's disease; see Verstaen et al., 2016). That study reported that insular atrophy was associated with reduced disgust responding, but not sadness reactivity, according to self-report and physiological reactivity measures. Disgust reactivity was not predicted by putamen, pallidum, or caudate volumes. On the other hand, lower self-reported disgust was associated with smaller amygdala volumes (Verstaen et al., 2016), in line with the notion that core disgust involves an extended cortico-subcortical network of brain regions.

Other studies have suggested that the insula is involved in negative emotion recognition generally, rather than being specifically involved in social disgust. The three patients with insula damage reported by Terasawa et al. (2015) showed attenuated sensitivity to others' negative emotions, which was not restricted to disgust. Adolphs et al. (2000) and Dal Monte et al. (2013) examined the recognition of six basic emotions in over 100 patients with lesions and identified several regions where damage led to a decline in emotion recognition performance; these included the medial prefrontal cortex, cingulate cortex, supramarginal gyrus, and insular cortex. Patients with insular lesions were less able to discriminate between negative emotions, rather than showing a specific deficit for disgust recognition. There have also been cases in which insular damage did not alter social disgust sensitivity (Straube et al., 2010; Boucher et al., 2015; Garcia et al., 2016). Couto et al. (2013) documented deficits in all three domains of disgust examined in our review (including moral judgments related to the correctness of actions). Interestingly, those authors reported this pattern of results only for a stroke patient with compromised connections between the insular cortex and frontotemporal areas. On the other hand, no impairments were reported in a patient with an ischemic lesion limited to the insular cortex. This result, in line with previous null results (Straube et al., 2010; Boucher et al., 2015; Garcia et al., 2016), suggests that disgust processing is not specifically limited to the insular cortex as was previously suggested; rather, it might reflect the activity of a fronto-insular-temporal network (Couto et al., 2013). The functions of this network might include the processing of others' emotions. For example, anterior cingulotomy was found to disrupt social disgust but also the recognition of fearful and angry facial expressions (Tolomeo et al., 2016). Further research is needed to characterize the functions of different sectors of this network (see also Young and Koenings, 2007; Ciaramelli et al., 2007, 2012; Baez et al., 2014, 2016).

Overall, the literature examined above suggests that deficits in the perception of core, social and moral disgust can be detected in a heterogeneous population of patients with brain damage or neurodegeneration affecting an extended network of cortico-subcortical regions.

### 3. Disgust processing in psychiatric disorders

The literature on psychiatric disorders provides a large case series of disorders associated with abnormal processing in at least one of the three domains of disgust sensitivity. In the following paragraphs, we will address neural and behavioral correlates of disgust in *obsessive compulsive disorder* (OCD), *schizophrenia*, *depressive syndrome* (DS) and *eating disorders* (ED). However, as argued by Phillipset al. (1998), the list of psychiatric illnesses related to abnormal disgust processing is incomplete; it might include several other diseases, such as *dysmorphophobia*, *coprophagia* and anxiety disorders such as *social phobia*. In this section, we will also address research on personality disorders affected by abnormal disgust processing, such as *borderline personality disorder* (BPD) and *psychopathic personality* (PP).

#### 3.1. Obsessive compulsive disorder

Obsessive compulsive disorder (OCD) is characterized by unwanted and uncontrollable thoughts (obsessions), and repetitive, irresistible and often ritualized acts (compulsions) to avoid anxiety or to neutralize the obsessions (American Psychiatric Association, 2013).

The experience of disgust in OCD is paradigmatic. These patients are particularly obsessed with a fear of contaminants. (For instance, see Brady et al., 2010 for a review.) Indeed, enhanced sensitivity to core disgust has been consistently documented as a common feature of OCD, through the use of behavioral avoidance tasks (Tsao and McKay, 2004). There is also evidence that enhanced sensitivity to core disgust, in response to disgust-inducing visual stimulation (i.e., food contaminants and body products), is associated with greater activation of the right (Shapira et al., 2003) and left (Stein et al., 2006) insula, caudate, putamen and OFC.

There is also evidence of performance deficits in social disgust recognition (Sprengelmeyer et al., 1997), although this deficit has been replicated only in severe forms of OCD (Parker et al., 2004; Corcoran et al., 2007). Some reports have extended the deficit to anger recognition (Daros et al., 2014), while other studies did not detect any emotion recognition deficits in OCD patients (e.g., Bozikas et al., 2009). At a neural level, Lawrence et al. (2007a, 2007b) found enhanced activity in the left PFC, insula and putamen in response to faces expressing disgust.

Finally, there is evidence for enhanced sensitivity to ethical violations (Harrison et al., 2012; see also Vicario, 2013b for a discussion) and increased severity of moral judgments in OCD (Whitton et al., 2014), which extend the association between OCD and altered disgust processing into the domain of moral disgust. Interestingly, activations of the insula, OFC, PFC (medial and dorsolateral portions), ACC, posterior cingulate cortex, caudate and amygdala are enhanced in OCD patients while they are experiencing moral disgust (i.e., when they are exposed to stories describing moral transgressions; Harrison et al., 2012). Overall, the literature reviewed here suggests that core, social and moral disgust are equally affected in OCD. However, emotion recognition deficits in OCD do not appear to be limited to the recognition of disgust.

From a neurochemical point of view, several molecular imaging studies (e.g., Denys et al., 2004; Denys et al., 2013) have found an association between OCD and higher DA levels in fronto-striatal circuits, compared to healthy controls. For example, a PET study by Denys et al. (2013) documented decreased striatal D2/3 receptor availability in OCD, which presumably reflects higher endogenous dopamine levels in this disorder, according to the authors' interpretation (Denys et al., 2004). Moreover, Denys et al. (2004) found lower DA D<sub>2</sub> binding in the left caudate nucleus of OCD patients compared to control participants. Early studies suggested that cerebro-spinal fluid (CSF) 5-HT levels are increased in OCD (e.g., Flament et al., 1987; Zohar and Insel, 1987). On the other hand, a PET study by Matsumoto et al. (2010) reported significant reductions in 5-HT transporter binding in the right posterior and left AI of OCD patients. This might suggest a reduction in serotonin availability, as proposed by other reports (e.g., Hasselbalch et al., 2007). Finally, there is evidence for high CSF Glu levels in patients with OCD (Chakrabarty et al., 2005).

#### 3.2. Schizophrenia

Schizophrenia is a psychiatric syndrome characterized by delusions, hallucinations, disorganized speech and behavior, and other symptoms that cause social or occupational dysfunction (American Psychiatric Association, 2013).

Studies of patients affected by schizophrenia provide important insights into the current debate on the neural and behavioral correlates of disgust processing. Among the negative symptoms of schizophrenia is an overall enhanced proneness to core disgust compared to healthy

**Table 1**

The table provides an overview about the neurochemical profile and the disgust sensitivity patterns associated with the examined clinical conditions. *Symbols and labels:* \* Preliminary results; \*\* The recognition deficit includes other emotions; CSF: cerebro-spinal fluid; MR: Mixed results; NA: data not available. MR<sup>1</sup>: high serotonin in the CSF; low at central level (McDonough and Kennedy, 2002). MR<sup>2</sup>: decreased 5-HIAA (5-Hydroxyindoleacetic acid, the main metabolite of serotonin) levels in cortical regions including the cingulate and frontal cortices; increased 5-HT and 5-HIAA levels in subcortical areas such as the putamen, nucleus accumbens, and globus pallidus (Lieberman et al., 1998). MR<sup>3</sup>: decreased DA concentration in the ventral striatum, involved in negative symptoms; DA hyper-transmission at mesolimbic level (Brisch et al., 2014). MR<sup>4</sup>: Higher in the striatum and low in the thalamus (Stone et al., 2009). MR<sup>5</sup>: The results are controversial (see paragraph on hyperphagia for details). ♦: In the striatum.

	Neurochemical profile			Disgust sensitivity		
	Serotonin	Dopamine	Glutamate	Core disgust	Social disgust	Moral disgust
<b>NEUROLOGICAL DISORDERS</b>						
<i>Huntington's disease</i>	High	Low	Low	Low	Low**	Low*
<i>Parkinson's disease</i>	Low	Low	High	Low	Low**	Low
<b>PSYCHIATRIC DISORDERS</b>						
<i>Obsessive Compulsive Disorder</i>	MR <sup>1</sup>	High	High (CSF)	High	Low**	High
<i>Schizophrenia</i>	MR <sup>2</sup>	MR <sup>3</sup>	MR <sup>4</sup>	High	Low**	Low
<i>Depression</i>	Low	Low	High	High	Low**	Normal
<i>Anorexia Nervosa</i>	High	Low♦	High	High	Low**	NA
<i>Hyperphagia</i>	Low	MR <sup>5</sup>	NA	Low	Low**	NA
<b>PERSONALITY DISORDERS</b>						
<i>Borderline</i>	Low	High*	High	High	High**	Low
<i>Psychopathy</i>	Low	High	NA	NA	Low**	Low

individuals, especially for food stimuli (Ille et al., 2010).

Moreover, there is evidence of impaired social disgust recognition when schizophrenic patients are presented with faces expressing disgust (Kohler et al., 2003; Lindner et al., 2014), although deficits have also been reported in the recognition of other emotions (Kohler et al., 2003). Interestingly, Linder et al. (2014) recently reported a reduced insula activation in schizophrenic patients in response to covert (i.e., very brief) facial expressions of disgust. By contrast, no significant insula activation was found in response to covert expressions of happiness.

Finally, patients with schizophrenia are also less sensitive to detecting unfairness, to their own disadvantage (Wischniewski and Brüne, 2011; see also McGuire et al., 2014 for a review), which suggests reduced sensitivity to the experience of moral disgust. McGuire et al. (2015) documented lower Moral Judgment Interview scores in schizophrenia patients. However, they noted that this result might be due to theory of mind deficits, rather than being genuine evidence of amoral behavior, as assessed by an evaluation of psychopathic traits.

No neuroimaging investigations of core and moral disgust have been conducted in schizophrenic populations, so far, although these deficits could be explained in relation to structural abnormalities of the insula (Kim et al., 2003).

The literature reviewed above documents abnormal core and social disgust in schizophrenia, although the emotion recognition deficit extends to other emotions. The experience of moral disgust appears to be intact, in agreement with the suggestion of a deficit in the theory of mind. However, further investigation is needed to draw strong conclusions.

Schizophrenic patients are also characterized by neurochemical alterations involving the PFC (Weinberger et al., 1986) and mesolimbic (Kegeles et al., 2010) neural circuits, which might relate to their disgust processing deficits. In particular, it has been suggested that positive symptoms of schizophrenia are due to hyperactive dopaminergic transmission (Seeman and Lee, 1975). On the other hand, a deficit in dopaminergic transmission involving D1-type receptors in the PFC has been associated with negative symptoms of schizophrenia (Weinberger, 1987; see Laruelle, 2014 for a recent review). In addition, a decrease in dopaminergic activity was documented in the ventral striatum, and was correlated with the severity of negative symptoms (such as pronounced disgust proneness) in untreated schizophrenics (Kegeles et al., 2010). Schizophrenic patients are also characterized by an abnormal serotonergic profile. For example, DeLisi et al. (1981) found a significantly

higher 5-HT concentration in the blood of chronic schizophrenic patients, compared to controls. This has been confirmed by subsequent investigations (e.g., Lerer et al., 1988). Interestingly, negative symptoms, which might be linked to the activity of the caudate nucleus (O'Donnell and Grace, 1998), improve when the treatment of schizophrenia includes drugs that diminish serotonergic activity (see Carpenter, 1995 for a review). Moreover, evidence of 5-HT<sub>1A</sub> receptor density elevation has been reported in the frontal cortex of schizophrenics (Burnet et al., 1997; Gurevich and Joyce, 1997). More details about the 5-HT profile complexity are reported in the Table 1. Finally, schizophrenia is affected by glutamatergic alterations. For example, de la Fuente-Sandoval et al. (2011) reported increased glutamatergic activity in the dorsal caudate of antipsychotic-naïve subjects with prodromal symptoms of schizophrenia. Moreover, there is evidence of lower thalamic glutamatergic levels in individuals with prodromal signs of schizophrenia. The authors also found that the level of thalamic glutamate was directly correlated with gray matter volume in the medial temporal cortex and insula (Stone et al., 2009).

### 3.3. Depressive syndrome

Depressive syndrome (DS) (i.e., major depressive disorder) is a psychiatric condition characterized by persistent feelings of sadness and loss of interest in previously enjoyed activities (American Psychiatric Association, 2013). Abnormal self-oriented disgust processing is considered the hallmark of the DS profile, although depression might not involve an elevated propensity to experience externally-oriented disgust (Powell et al., 2014).

Research on DS provides extensive behavioral and neuroimaging support for abnormal disgust processing. Overton et al. (2008) documented increased self-disgust sensitivity in DS (measured by the Self-Disgust Scale). This pattern of results was corroborated by subsequent investigations (e.g., Powell et al., 2013). There is also evidence of pronounced disgust sensitivity related to death in DS patients (Ille et al., 2010).

Deficits have also been documented in the social disgust domain. For example, Douglas and Porter (2010) found a selective deficit in recognizing facial expressions of disgust in DS patients, compared to controls. However, a recent meta-analysis (Dalili et al., 2015) reported emotion recognition impairment across all basic emotions, except sadness.

A neuroimaging study by [Surguladze et al. \(2010\)](#) indicated a neural basis for the disgust deficit in depression by demonstrating greater activation in the left insula, the left OFC, the putamen, the ACC and the left and right middle/inferior temporal gyrus in response to expressions of strong disgust. This pattern of activation demonstrated an emotion processing bias in DS involving greater activity in brain regions relevant to disgust processing.

Finally, recent research on alcoholics ([Khemiri et al., 2012](#)) documented a trend toward more utilitarian responses to ethical violations (i.e., lower moral disgust sensitivity) in mildly depressed participants, compared to alcohol-addicted participants without depression. This suggests that depressed people might be less sensitive to ethical violations. By contrast, [Kornreich et al. \(2013\)](#) reported that depressed people without other clinical conditions did not show significant differences in moral judgments compared with control participants. Thus, DS is characterized by increased core disgust and reduced social disgust sensitivity, but no differences in moral disgust, relative to people without depression. However, further research is needed to draw firmer conclusions and explore the relationships between the three different disgust domains in DS. Moreover, no studies have yet explored the brain activity of DS patients experiencing core and moral disgust. Overall, the literature on DS documents altered core and social disgust, while moral disgust appears to be intact. As with other clinical conditions examined in this review, the emotion recognition deficit in DS is not specific to disgust.

[Belujon and Grace \(2014\)](#) recently provided evidence for altered dopaminergic activity in DS. They reported that an injection of ketamine improved DS by acting on D1-type receptors to restore normal patterns of dopaminergic neurotransmission, which appeared to be abnormally attenuated within the hippocampus-accumbens pathway. DS is also characterized by altered serotonergic activity. For instance, [Hahn et al. \(2014\)](#) recently showed reduced 5-HT transporter association between the dorsal raphe and the striatum in major depression. This evidence complements earlier studies showing changes in 5-HT receptors in the OFC and insular cortices of DS patients ([Biver et al., 1997](#)). These results might be interpreted as evidence of lower 5-HT concentrations in depression ([Delgado et al., 1991](#)). Finally, there is evidence of abnormal glutamatergic transmission in DS ([Hashimoto et al., 2007](#); [Witkin et al., 2007](#)). For instance, [Hashimoto et al. \(2007\)](#) found an increased level of Glu in the frontal cortex of patients affected by major DS.

### 3.4. Eating disorders

An eating disorder (ED) is a psychiatric condition characterized by abnormal eating habits that may involve either insufficient (i.e., anorexia nervosa – AN) or excessive (hyperphagia) feeding caused by deranged mechanisms for food intake control.

#### 3.4.1. Anorexia nervosa

AN is characterized by high disgust sensitivity for food, self-disgust and disgust for human body products (e.g., [Troop et al., 2000](#); [Vicario and Crescentini, 2012](#); [Vicario, 2013c](#); [Hildebrandt et al., 2015](#); [Vicario, 2015](#)). This eating disorder is associated with increased disgust in domains related to eating and weight management, suggesting that disgust-related emotional responses may be a defensive mechanism to avoid high caloric intake ([Vicario, 2013c](#)). The altered insular activity in AN patients (e.g., [Wagner et al., 2008](#); [Nunn et al., 2011](#)) may underlie their abnormal disgust processing, in line with previous neuroimaging research (e.g., [Wicker et al., 2003](#); [Schäfer et al., 2005](#)), and with the clinical literature examined in previous sections. There is also evidence of altered striatal activation (caudate and putamen, [Wagner et al., 2008](#)), which has been linked to the experience of disgusting smells ([Heining et al., 2003](#)). Interestingly, [Cowdrey et al. \(2011\)](#) reported increased neural responses to aversive tastes in the insula and putamen of recovered AN patients, compared to controls.

With respect to the social domain, AN patients show a deficit in recognition of disgust expressions, but also other negative facial expressions, compared to positive expressions ([Kucharska-Pietura et al., 2004](#)). Subsequent studies corroborated this generalized deficit in negative emotion recognition (e.g., [Cserjési et al., 2011](#)). Finally, no investigations into the experience of moral disgust in AN have been reported so far, although lower levels of empathy in acute AN have been reported ([Morris et al., 2014](#)). Overall, the literature on AN suggests an altered experience of disgust at the sensory-perceptual and social levels, although people with AN show impaired recognition of all negative emotional expressions.

From a neurochemical point of view, it has been suggested that dopaminergic dysfunction, particularly in striatal circuits, might contribute to abnormal reward processing and decreased food ingestion in subjects with AN ([Kaye et al., 2009](#)). For example, reduced CSF levels of dopamine metabolites have been documented in both affected individuals and individuals who fully recovered from AN ([Kaye et al., 1999](#)). Moreover, a PET study ([Frank et al., 2005](#)) found that subjects who recovered from AN had increased DA (i.e., D2/D3) receptor (DRD3) binding in the ventral striatum, a region that modulates responses to reward stimuli ([Montague et al., 2004](#)) and is linked to the experience of core disgust ([Heining et al., 2003](#)). This is in line with the suggestion of decreased intrasynaptic DA in this circuit ([Frank et al., 2005](#)). See also [Kontis and Theochari, 2012](#) for a systematic review). Finally, there is evidence for a stronger dopamine model reward-learning signal in the anteroventral striatum, insula, and PFC in AN ([Frank et al., 2010](#)). AN is also characterized by increased 5-HT neurotransmission ([Steiger, 2004](#)), although it has been suggested that this pattern might result masked during active illness by malnutrition-induced reductions in 5-HT activity ([Steiger, 2006](#)). Finally, the work by [Ohrmann et al. \(2004\)](#) has shown an association between executive functioning, depressive symptomatology and Glu levels in the ACC of AN patients.

#### 3.4.2. Hyperphagia

Abnormal disgust processing has also been reported in hyperphagia, such as in cases of obesity associated with episodes of binge eating. Core disgust might be reduced in these patients, explaining, at least partly, their increased appetite ([Houben and Havermans, 2010](#)). In support of this suggestion, [Houben and Havermans \(2010\)](#) reported that women with a high body mass index (BMI) showed decreased core disgust. Thus, they appear to have a higher threshold for rejecting food products, which may explain their predisposition to overeat. A recent fMRI study ([Watkins et al., 2016](#)) investigated the neuro-functional correlates of proneness to disgust in obesity. In particular, this research revealed a lower activation in the right insula of the obese group compared to the lean group when viewing contaminated food images. Moreover, it documented a negative association between disgust sensitivity scores and BOLD activation in the left anterior insula within the obese group.

With respect to the social disgust domain, a recent study showed that obese people have a reduced capacity to process facial expressions of disgust, but also other negative expressions ([Cserjési et al., 2011](#)). Finally, we recently documented ([Vicario and Rafal, 2017](#)) a negative relationship between BMI and moral disapproval ratings for ethical violations, suggesting that overweight people may be less sensitive to ethical violations, compared to healthy controls. Overall, the literature suggests altered core disgust processing in hyperphagia. There is less evidence for altered social or moral disgust processing, although evidence from healthy humans has linked high BMI to lower moral sensitivity ([Vicario and Rafal, 2017](#)). No expression recognition deficit specific to disgust has been reported in people with hyperphagia or high BMI.

Obesity is also characterized by an altered neurochemical profile. In particular, there is evidence of DA alterations in the striatum and frontostriatal regions in obese participants compared to normal-weight

individuals (Michaelides et al., 2012). For example, decreased DA type 2 receptor (D2R) availability was reported in sub-regions of the striatum, including the nucleus accumbens, which may predispose obese individuals to compulsive-like binge-eating behavior (Wang et al., 2001; Stice et al., 2008). A reduction of D2 receptor availability in obese subjects could reflect low receptor levels or increases in DA release (Volkow et al., 2008). However, a recent study (Kessler et al., 2014) reported decreased DA release with BMIs above 40. This is in line with the decreased reward circuit DA neurotransmission hypothesized by some authors (Geiger et al., 2008). Therefore, a precise idea about the DA availability in this clinical condition remains unclear. Moreover, low 5-HT metabolite levels have been reported in the CSF of bulimic patients affected by frequent binge-eating episodes (Jimerson et al., 1992). This was confirmed in subsequent studies (e.g., Kuikka et al., 2001). In particular, obese binge-eating women showed significantly decreased 5-HT transporter binding in the midbrain compared with obese controls. This result has been interpreted as evidence of a diminished serotonergic activity in this clinical condition (Kuikka et al., 2001). Finally, it has been speculated that Glu might play a role in obesity (Volkow et al., 2011), although there is no experimental evidence to support this suggestion.

### 3.5. Personality disorders

The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) classifies personality disorders as impairments in self (self-identity or self-direction) and interpersonal (empathy or intimacy) functioning (American Psychiatric Association, 2013). In the context of disgust processing, this section will focus on *borderline personality disorder* (BPD) and *psychopathy as a personality trait* (PP).

#### 3.5.1. Borderline personality disorder

BPD is a complex clinical condition characterized by impulsivity, instability in regulating affect, dysfunctional interpersonal relationships and a distorted self-image (Lieb et al., 2004). Altered sensitivity to disgust-related experiences is another distinctive trait of BPD (Rüsch et al., 2011; Schienle et al., 2003, 2013). For example, Schienle et al. (2013) investigated 30 female patients with BPD and 30 healthy women. BPD patients provided higher ratings of core disgust dispositions (i.e., the tendency to experience disgust for food and body fluids). Moreover, Arrondo et al. (2015) recently reported that BPD patients gave higher disgust ratings to disgusting tastes such as quinine, and those ratings were related to their scores in the self-disgust domain.

With respect to the social disgust domain, results are mixed. Levine et al. (1997) reported impairment in the recognition of negative emotional expressions in BPD, especially for facial expressions of anger, fear and disgust. Bland et al. (2004) documented deficits in recognizing expressions of anger, fear and sadness. Guitart-Masip et al. (2009) documented deficits for disgust and fear. Overall, this research suggests that BPD is characterized by a generalized deficit in negative emotion recognition. However, Unoka et al. (2011) reported an over-attribution of disgust and surprise to perceived emotional expressions. Moreover, Schienle et al. (2013) showed that women with BPD rated facial expressions of disgust as more intense than did healthy women. Taken together, the latter two studies indicate a bias toward social disgust in BPD, although this clinical population also has a general deficit in emotion recognition.

Finally, Standish et al. (2014) reported that moral disgust sensitivity predicts BPD. Specifically, the authors showed that lower moral disgust sensitivity, measured by the Three-Domain Disgust Scale (TDDS; Tybur et al., 2009), predicts higher prevalence of BPD features. In contrast, high prevalence of BPD features was associated with high pathogenic disgust sensitivity. Dysfunctional insular activity has been reported in BPD in the context of cooperation and social norm violation (King-Casas et al., 2007). In particular, participants with BPD showed lower insular activity, compared with controls, in response to unfair monetary offers,

which might reflect a deficit in recognizing norm violations. No neuroimaging investigations of core and social disgust in BPD have been conducted so far, but the reported pattern of abnormal disgust processing could relate to abnormal fronto-limbic activity, as suggested by some studies (e.g., King-Casas et al., 2008; Irle et al., 2007). For example, Silbersweig et al. (2007) found decreased ventromedial PFC activity (including medial OFC and subgenual ACC) in BPD patients compared to controls. Overall, the literature suggests altered core and moral disgust in BPD. Moreover, there is evidence that people with BPD are biased toward perceiving disgust in emotional facial expressions. However, they also show a general deficit in recognizing emotions from facial expressions.

Friedel (2004) hypothesized that BPD is characterized by dysfunctional dopaminergic transmission, based on evidence that a mutation of the dopamine transporter *DAT1* 9-repeat allele is a genetic risk factor for BPD (Joyce et al., 2006, 2014). This DA transporter protein is responsible for rapid re-uptake of DA from the synaptic cleft into the pre-synaptic terminals, and thus acts as a key component in regulating dopaminergic neurotransmission (Kelsoe et al., 1996). Due to abnormal functioning of the *DAT1* gene, people with BPD might have elevated dopamine levels. There is also evidence of abnormal serotonergic mechanisms in BPD (Coccaro et al., 1989; Soloff et al., 2000). In particular, Soloff et al. (2000) showed that patients with BPD have diminished responses to 5-HT stimulation in areas of the PFC associated with regulation of impulsive behavior. Finally, BPD is also characterized by glutamatergic alterations (see Dell'Osso et al., 2010 for a review). For example, Rusch et al. (2008) found significantly higher glutamatergic concentrations in the ACC of women with BPD and comorbid attention deficit hyperactivity disorder compared to healthy women.

#### 3.5.2. Psychopathic personality

Abnormal disgust processing has also been reported in people with *psychopathic personality* (PP). PP is characterized by reduced empathy, shallow affect and behaviors that cause their victims distress, like threats, bullying and violence (Marsh and Cardinale, 2012).

Although no research on core disgust processing has been conducted so far in this population, Kosson et al. (2002) documented a selective deficit in detecting expressions of disgust (i.e., social disgust) in criminal psychopaths. However, other experiments have shown ageneralized recognition deficit for both positive and negative emotions (see Dawel et al., 2012 for a meta-analysis). Neuroimaging studies have shown no differences in the brain activity of people with psychopathy traits, compared to control participants, in response to stimuli evoking core disgust (Marsh and Cardinale, 2012) or to faces expressing disgust (Dolan and Fullam, 2009).

With respect to moral disgust, people with PP are characterized by a severe empathy impairment, which might affect sensitivity to ethical violations (Marsh and Cardinale, 2014). There is also evidence that participants who indicated greater endorsement of utilitarian solutions for moral dilemmas had higher scores on measures of psychopathy (Bartels and Pizarro, 2011). Moreover, the affective deficit typical of psychopathy might be associated with insensitivity to unfairness (Osumi and Ohira, 2010). Overall, the literature on PP suggests a deficit in the experience of moral disgust. No selective deficit in processing expressions of disgust has been reported. The link between PP and core disgust has not yet been investigated.

From a neural point of view, *psychopathy* has been associated with reduced gray matter volume in several limbic and paralimbic brain regions (see Aoki et al., 2014 for a review). Interestingly, neuroimaging studies have shown reduced engagement of limbic and paralimbic regions, such as the mPFC, the amygdala, the ACC and a posterior sector of the cingulate cortex, in adult male psychopaths engaged in moral judgments (e.g., Gleen et al., 2009; Harenski et al., 2010; Pujol et al., 2012; Harenski et al., 2014). Moreover, relative to control participants, psychopathic participants exhibited significantly less activation in the ventromedial PFC, lateral OFC and cingulate cortex, but greater

activation in the insula, in response to the pain and distress of others (Decety et al., 2013).

Altered dopaminergic and serotonergic mechanisms have also been documented in psychopathic participants (Buckholtz et al., 2010). In particular, hyper-reactivity of the dopaminergic reward system, corresponding to the nucleus accumbens, may underlie impulsive-antisocial behavior and substance abuse in psychopathy. Studies have also shown a lower 5-HT concentration in the CSF of aggressive participants compared to controls (Lidberg et al., 1985; Stanley et al., 2000). Moreover, a 5-HT transporter (5-HTTLPR) genotype was associated with the impulsivity dimension of psychopathy (Sadeh et al., 2010). See also Vicario, 2014 for a review) in line with research documenting serotonin deficiencies among individuals with antisocial, aggressive, and impulsive behavior (Carver and Miller, 2006). No evidence is currently available concerning the role of Glu in psychopathy, although there is a relation between the Glu transporter EAAT2 gene and antisocial personality (Sander et al., 2000).

#### 4. General discussion

In this review, we have outlined anatomo-functional and neurochemical correlates associated with clinical populations (i.e., neurological and psychiatric) affected by abnormal disgust processing, to uncover the brain structures involved in core, social and moral disgust, and to investigate common and distinct neural mechanisms involved in disgust sensitivity.

The behavioral data from most of the clinical populations we examined in our review revealed deficits in all three disgust domains, although not every disgust domain has been investigated in each of the selected clinical populations (i.e., patients with eating disorders, PP). The results also indicate that disgust recognition is not a selective deficit, as it often co-occurs with difficulties in recognizing other emotional expressions. This might depend on the stage of the disease (i.e., in neural degeneration disorders) and its severity, but this suggestion remains to be explored (Table 1).

##### 4.1. Disgust processing and neuroimaging results in clinical populations

Our review of neuroimaging results helps to identify the key neural structures that may be responsible for altered disgust sensitivity in neurological and psychiatric disorders. Insula atrophy or injury has been consistently associated with reduced *core disgust* sensitivity in several neurological conditions (Verstaen et al., 2016); however, several other brain regions also have a role in core disgust. Neuroimaging research (i.e., Shapira et al., 2003; Stein et al., 2006) in OCD patients links higher core disgust sensitivity to abnormal activity in the insula, putamen and ACC, and damage to these regions is associated with altered core disgust (e.g., see Adolph et al., 2003). Interestingly, the roles of these regions in core disgust have been confirmed by neuroimaging studies in healthy humans (e.g., Heining et al., 2003; Wicker et al., 2003; Fusar-Poli et al., 2009). A study in OCD patients (Ille et al., 2015) also reported abnormal activity in the OFC. Ille et al. (2015) also suggested that the OFC is involved in core disgust (i.e., olfactory disgust sensitivity). Finally, a recent study by Watkins et al. (2016) documented reduced insula activity in participants with obesity, which is characterized by low core disgust sensitivity (see also Houben and Havermans, 2010). However, that study did not report changes in the activity of any other neural regions considered relevant to disgust processing (i.e., the ACC, OFC and basal ganglia).

Altered *social disgust* processing is associated with abnormal functional activity in the insula and/or putamen (see the cases of HD, PD, OCD, schizophrenia, and DS) and insular lesions can impair social disgust sensitivity (Calder et al., 2000; Adolphs et al., 1999, 2003; Dal Monte et al., 2013; Terasawa et al., 2015; but see Boucher et al., 2015). These results corroborate data from direct brain stimulation studies (Papagno et al., 2016; Caruana et al., 2011), although the neural regions critical for recognizing

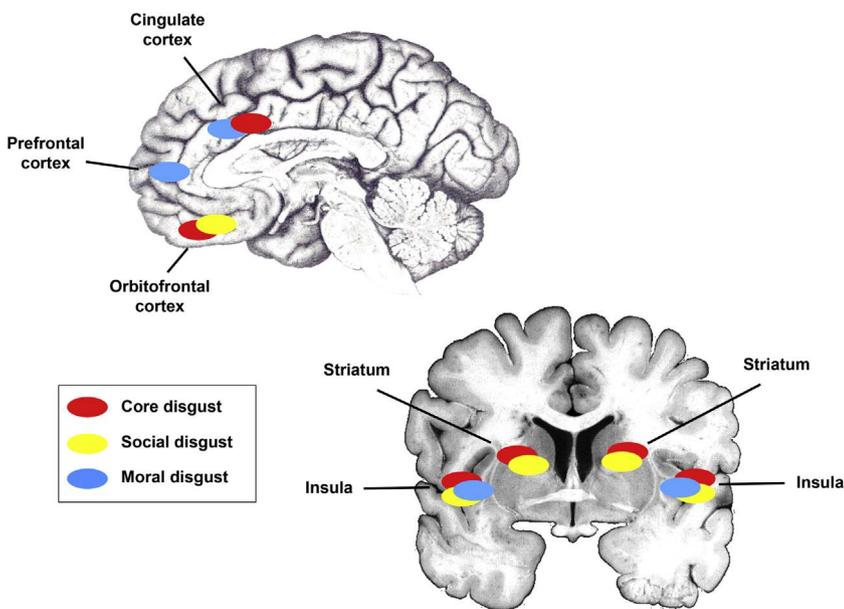
disgust are not limited to the insula and appear to be involved in recognizing other negative emotional expressions, as well (e.g., Adolphs et al., 2003). Research on HD, PD and DS has demonstrated the involvement of the OFC in social disgust (but see Lawrence et al., 2007a, 2007b; Lindner et al., 2014) and research on stroke patients points to a larger network also involving medial prefrontal, cingulate, parietal and temporal areas (e.g. Adolphs et al., 2003; Dal Monte et al., 2013). Overall, studies implicate a large cortico-subcortical neural network in processing social disgust, as well as other emotional expressions (D'Agata et al., 2011; Tamiotto et al., 2015; Diano et al., 2017).

Altered *moral disgust* processing in OCD, BPD and psychopathy has been associated with abnormal insula activation (i.e., higher in OCD and PP, and lower in BPD). Moreover, moral disgust increases the activity of the PFC and the ACC in OCD. These findings are in line with research on neurodegenerative and brain injury patients that reports a consistent association between damage to the ventromedial prefrontal cortex and changes in moral sensitivity (e.g. Ciaramelli et al., 2007; Moretto et al., 2010; Baez et al., 2014, 2016). Although Decety et al. (2013) reported greater insula activation in PP, this area was not implicated in moral disgust by other investigations (i.e., Gleen et al., 2009; Harenski et al., 2010; Pujol et al., 2012; Harenski et al., 2014). Like Decety et al. (2013), those studies documented reduced activity in PFC, amygdala and ACC activity in response to moral disgust in psychopathic patients, relative to healthy controls. Interestingly, activity in these regions is higher in OCD patients (Harrison et al., 2012), who are more sensitive to ethical violations. This suggests that the degree of activation in these areas predicts moral sensitivity. Finally, a study by Couto et al. (2013) showed altered moral judgments in a patient with a subcortical lesion (i.e., right putamen and claustrum) affecting connections between the insula and frontotemporal areas.

Two quantitative functional imaging meta-analyses pointed to the insula as the key neural structure underlying disgust processing (Murphy et al., 2003; Fusar-Poli et al., 2009) and this result finds support in our review of neurodegenerative diseases and psychiatric conditions. However, it should be noted that a more recent and comprehensive meta-analysis (Kirby and Robinson, 2015) failed to find support for disgust being centralized to the insula, and instead found disgust-related activations distributed along prefrontal and postcentral regions, as well as subcortical structures, i.e., the putamen, mammillary body and thalamic nuclei (see also the study by Couto et al., 2013). The insula appears to be involved in several other emotions, suggesting a domain-general role of the insula in emotion processing (Menon and Uddin, 2010; Cauda et al., 2012).

How can we reconcile the results of studies on disgust processing in clinical disorders, which point to the insula as the key structure in disgust, with recent metanalytic imaging evidence in healthy humans that challenges this idea? A number of factors might account for the apparent discrepancy. As outlined by several scholars (e.g., Rozin et al., 2008; Haidt, 2001), disgust is a complex and multifaceted experience with at least 9 different targets, namely, food, body products, animals, sexual behaviors, contact with death, violations of the exterior envelope of the body, poor hygiene, interpersonal contamination and certain moral offenses. Some disgust-related experiences might involve other emotions. Occasionally, these emotions can be experienced as more intensive than disgust itself in the paradigms used to elicit disgust. This was the case with anger, contempt, irritation, envy, sadness and jealousy while playing an “ultimatum game” task (see Bosman et al., 2001), and with fear while watching insects (e.g., Gerdes et al., 2008). Feeling a mix of emotions, depending on the experimental manipulation and the individual's disgust sensitivity as a personality trait, might explain, at least in part, inconsistencies reported in the literature.

Apart from this possibility, one should consider that the literature examined by Kirby and Robinson (2015) focused on neural activations associated with disgust in healthy humans. This is another crucial aspect to keep in mind because there are differences between studies conducted in healthy humans and studies conducted in clinical



**Fig. 1.** A schematic diagram of neural regions involved in processing core, social and moral disgust, based on evidence from the selected clinical populations. The figure shows that the insula mediates disgust processing in all three domains. It also shows that the orbitofrontal cortex and striatum mediate *core* and *social* disgust. The prefrontal cortex (medial) appears to be selectively involved in the experience of moral disgust. Finally, the cingulate cortex is implicated in *core* (ACC) and *moral* disgust.

populations. In fact, altered disgust sensitivity is a common feature of the clinical populations examined in our review. Accordingly, as we have reported in our review, the insula might be particularly (although not exclusively) relevant to disgust in the presence of abnormal (i.e., higher or lower than average) disgust sensitivity patterns. This would be in keeping with evidence that perturbing insula activity via brain stimulation results in a genuine subjective experience of disgust and disgust-related behaviors, as well as impaired recognition of disgust in others (Ostrowsky et al., 2000; Penfield and Faulk, 1955; Selimbeyoglu and Parvizi, 2010; Caruana et al., 2011; Papagno et al., 2016). Thus, although it is very likely that the insula plays a general role in processing salient emotional features of a stimulus or an event, as suggested by neuroimaging data in healthy participants (Menon and Uddin, 2010; Majdandžić et al., 2012; Lamm and Majdandžić, 2015), its dysfunction might reveal disgust-specific mechanisms.

In summary, the literature suggests that the insula might work as a hub structure for the experience of disgust, with the role of receiving, decoding and sorting inputs from relevant nodes localized along the prefrontal, postcentral and subcortical pathways (i.e., OFC, medial PFC, striatum, and ACC), which likely process specific and unique facets of the multidimensional disgust experience. Fig. 1 provides an overview of the key regions involved in the experience of core, social and moral disgust, as suggested by the reviewed literature.

The shared neurofunctional basis of the different forms of disgust is in keeping with both the *adaptationist* theory of Tybur and the *neo-sentimentalist* theory of Haidt (2001), both of which suggest that morality may have evolved from core disgust (Tybur et al., 2009, 2013; Haidt et al., 1997; Haidt, 2001; Rozin et al., 2008). However, it is also consistent with embodied simulation theories of emotion perception, which suggest that understanding another person's emotional state (i.e., social disgust) relies on activation of the same brain circuits involved in the personal experience of the same emotion (Wicker et al., 2003; Gallese et al., 2004; Avenanti et al., 2005, 2013; Gallese and Sinigaglia, 2011; Urgesi et al., 2014).

#### 4.2. Disgust processing and neurochemistry in clinical populations

We also provided evidence of shared, as well as distinct, neurochemical mechanisms for the three forms of disgust in neurological and psychiatric patients. Our review examined Lövhelm's (2012) proposal of an involvement of 5-HT, DA and Glu in the experience of disgust. We tested this suggestion by evaluating possible matches between the 5-HT, DA and Glu neurochemical profiles in the selected clinical

populations and the behavioral profiles of these patients with respect to the three examined disgust domains. The results of our review link 5-HT to *core disgust* sensitivity. In particular, low levels of this monoamine might be associated with enhanced core disgust sensitivity, as suggested by the evidence on DS, BPD and OCD (but also schizophrenia when considering the 5-HT pattern in the cingulate cortex; see Fig. 1 and Lieberman et al., 1998 for a review). In line with this pattern, high levels of 5-HT might be associated with low core disgust, as suggested by the evidence on HD. However, these results are in contrast with the evidence on ED (i.e., high 5-HT with high core disgust in AN and low 5-HT with low core disgust in obesity/hyperphagia) and PD (see Table 1). While these data suggest a relationship between serotonergic levels and core disgust sensitivity across a number of neurological and psychiatric conditions, further investigations are needed to directly and systematically investigate this relationship. The picture appears less consistent if we consider the predictive role of DA. In this case, low DA is associated with low core disgust sensitivity in neurological disorders (HD and PD), but with high core disgust sensitivity in schizophrenia (if we consider the results on DA levels in the ventral striatum; see Table 1 for details), DS and AN. On the other hand, high DA is associated with high core disgust sensitivity in OCD and BPD. The inconsistent literature about the DA profile of hyperphagia does not allow to make conclusive evaluations about the role of this monoamine in the processing of core disgust in this clinical population. In sum, core disgust sensitivity appears to be mainly related to levels of serotonin rather than dopamine across clinical populations.

The serotonergic profile even has predictive potential for *moral disgust* sensitivity, as suggested by research on BPD, psychopathy, schizophrenia (if we consider the 5-HT pattern in the frontal and cingulate cortices), and PD. In particular, serotonergic hypoactivity is associated with low moral disgust sensitivity. It should be noted, however, that not all the examined clinical disorders fit these results (e.g., HD, OCD and DS; see Table 1 for details). Thus, serotonergic mechanisms appear to play a role in both core and moral disgust, supporting the hypothesis of a shared neurochemical basis for these two experiences. However, this monoamine has opposite effects on these two disgust domains (i.e., low 5-HT reduces moral disgust sensitivity but increases core disgust sensitivity). Therefore, the serotonergic system might still represent a shared basis for core and moral disgust, but its influence on these two disgust domains might involve different mechanisms. Similar to core disgust, the predictive role of DA in moral disgust is unclear. Research on neurological populations indicates that low DA is associated with low moral disgust sensitivity. This is also

suggested by the research on schizophrenia (if we consider dopaminergic activity in the striatum). Moreover, research on OCD shows that high DA is associated with high moral disgust sensitivity. However, the research on *BPD and psychopathy* challenges these results, as high DA is associated with low moral disgust sensitivity in these cases. Thus, our review of patient populations supports the notion of a shared neurochemical basis for core and moral disgust, and points to a greater role of serotonin than dopamine in these disgust experiences. These data also imply that a mere discussion of the patients' neurochemical patterns, in absence of information about the neuroanatomical localization of such patterns, can be reductive, as patients may show mixed neurochemical profiles across different brain regions (e.g., see schizophrenia).

With regard to the role of 5-HT in social disgust, the results are mixed without any clear direction. On the other hand, the majority of patient populations reviewed here support the hypothesis of a relation between dopamine levels and social disgust sensitivity (HD, PD, DS, AN, BDP and schizophrenia – when considering DA concentration in the striatum). However, OCD, hyperphagia and psychopathy speak against a predictive role of DA in social disgust. Moreover, current evidence is also compatible with the general proposal that any neurotransmitter alteration in the considered patient populations can affect social disgust sensitivity. Finally, altered emotion recognition is not specific to disgust expressions (see Table 1). Thus, altered social disgust sensitivity might reflect a more general impairment in emotion processing

No relevant associations have been found between glutamatergic profiles and the three domains of disgust.

## 5. Methodological considerations

In this review we identified (where available) neuroanatomical, neurofunctional and neurochemical bases of the three domains of disgust (i.e., core, social and moral disgust) and the intensity of these disgust experiences. While our review suggests associations between the three domains of disgust across neurological and psychiatric conditions, it is based on studies that, with few exceptions, have addressed only a single domain of disgust. This reflects an isolationist perspective that does not capture the dimensional synergies that could emerge from a consideration of all three domains. This calls for an approach that examines different domains of disgust within a single design to provide conclusive evidence for associations or dissociations between such domains. Novel insights might come from integrative approaches combining behavioral, subjective and physiological assessments of disgust sensitivity in the three domains, as well as neuroanatomical, neurofunctional and neurochemical evaluations within the same patient population.

While existing research on the neural bases of disgust has mainly used structural and functional brain imaging, important insights might originate from the addition of methods with high-temporal resolution (e.g., intracranial recording, electro/magnetoencephalography, and transcranial magnetic stimulation) to explore brain dynamics in emotion processing (e.g., Kawasaki et al., 2001, 2005; Costa et al., 2014; Borgomaneri et al., 2015; Hesse et al., 2016) and other brain stimulation techniques (e.g. transcranial magnetic or electrical stimulation, Balconi and Canavesio, 2013; Peters et al., 2016; Avenanti et al., 2013, 2017), to up- and down-regulate neural functioning in key brain areas, and test their critical roles in patients' behavior. Thus, future research should adopt methodologies that address the temporal dimension and provide causal evidence for the involvement of brain regions (e.g. Croft et al., 2014; Turetsky et al., 2007; Izurieta Hidalgo et al., 2016) in the three domains of disgust.

A final methodological consideration pertains to the heterogeneity of behavioral paradigms and methods used to assess disgust. This is especially relevant to core and moral disgust, as there are several (not necessarily comparable) ways to explore such domains. For example, to study moral disgust, a researcher could either test harm avoidance or altruism, two aspects of moral behavior influenced by monoamines (see Crockett et al., 2015).

## 6. Conclusions

The evidence of a partially shared neural basis (i.e., the insula) for the three domains of disgust, together with the evidence that deficits in different disgust domains might coexist in the same disorder, suggests that there is a general process of analysis and extraction of common features for the experience of disgust, similar to what has been documented for other mental processes (i.e., magnitude processing; Speed, 2010; Vicario and Martino, 2010; Walsh, 2003; Vicario et al., 2011a,b; Vicario, 2011). Thus, in agreement with other authors (e.g., Rozin and Haidt, 2013), our results support the suggestion that social and moral disgust share a neural basis and/or cognitive mechanism that initially evolved to process core disgust (e.g., potentially harmful biological contaminants). This is in line with theories of neural reuse (e.g., Gallese and Lakoff 2005; Dehaene, 2009; Pessoa, 2008; Anderson, 2010), which state that neural circuits can continue to acquire new uses after an initial or original function is established; it is also consistent with theories of and evidence for embodied simulation of emotional, cognitive and physiological states (Hurley, 2008; Gallese et al., 2014; Gallese and Sinigaglia 2011; Jacquet and Avenanti, 2015; Borgomaneri et al., 2012, 2015; Vicario et al., 2013; Vicario and Newman, 2013; Vicario et al., 2014, 2015; Wood et al., 2016), which suggest that the very same brain circuits involved in a personal experience also participate in the perception of that experience in others.

It is intriguing to note that our findings suggest the neural bases of disgust and emotion processing largely overlap with those underpinning interoception i.e., the sense of internal bodily signals, including visceral sensations (e.g., Craig, 2003; Caruana et al., 2011; Ibanez and Manes, 2012). The emotion of disgust, by definition, is a visceral experience, and a recent meta-analysis supports the existence of a network of insular-frontotemporal regions integrating interoception, emotion, and social cognition (Adolfi et al., 2017). Importantly, most of the clinical populations we assessed in our review are affected by deficits in interoception as well as disgust. This is true for PD (Ricciardi et al., 2016) and other neurodegenerative conditions (García-Cordero et al., 2016), OCD (Yoris et al., 2017); schizophrenia (Ardizzi et al., 2016), BPD (Müller et al., 2015), depression (Simmons et al., 2016), and eating disorders (Kerr et al., 2016; Ambroseccchia et al., in press).

However, it should be noted that the analysis of neurochemical profiles in patient populations provides only partial support for theories of neural reuse or embodied simulation. Indeed, it appears that serotonergic activity might be involved in both core and moral disgust, whereas no consistent evidence for a common basis of social disgust and the other two types of disgust emerged from our analysis of the literature. This supports the notion of shared, as well as specific, mechanisms in the three disgust domains. Sensitivity to others' expressions of disgust appears to be at least partially supported by a dopaminergic neurochemical mechanism, as the majority of patient populations reviewed here show a relation between dopamine levels and disgust sensitivity. However, there are inconsistencies in the literature, and current evidence is also compatible with the general proposal that any neurotransmitter alteration in the considered patient populations alters disgust sensitivity. Such an alteration is not specific to disgust expressions and likely reflects a more general disturbance in processing one's own and others' emotions.

With respect to the common aspects of core and moral disgust, our review points to a shared neuroanatomical basis and closely related, but distinct, neurochemical mechanisms involved in affect (e.g., 5-HT). This is consistent with *neo-sentimentalist* theories (or the *social intuitionist model*; Haidt, 2001) of morality, which suggest a role of the personal experience of an emotion in moral judgments. However, current evidence provides only partial support for these theories, as we found no consistent behavioral association between the three domains and no exhaustive evidence of a common neurochemical basis across patient populations. Thus, the present review speaks in favor of a possible shared neural basis, while the specific mechanisms underlying altered core, social and moral disgust in neurological and psychiatric

populations might be at least partially independent.

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