The contribution of brain imaging to the understanding of psychopathy

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ABSTRACT

Psychopathy is a personality type characterized by both callous emotional dysfunction and deviant behavior that affects society in the form of actions that harm others. Historically, researchers have been concerned with seeking data and arguments to support a neurobiological foundation of psychopathy. In the past few years, increasing research has begun to reveal brain alterations putatively underlying the enigmatic psychopathic personality. In this review, we describe the brain anatomical and functional features that characterize psychopathy from a synthesis of available neuroimaging research and discuss how such brain anomalies may account for psychopathic behavior. The results are consistent in showing anatomical alterations involving primarily a ventral system connecting the anterior temporal lobe to anterior and ventral frontal areas, and a dorsal system connecting the medial frontal lobe to the posterior cingulate cortex/precuneus complex and, in turn, to medial structures of the temporal lobe. Functional imaging data indicate that relevant emotional flow breakdown may occur in both these two brain systems and suggest specific mechanisms via which emotion is anomalously integrated into cognition in psychopathic individuals during moral challenge. Directions for future research are delineated emphasizing, for instance, the relevance of further establishing the contribution of early life stress to a learned blockage of emotional self-exposure, and the potential role of androgenic hormones on the development of cortical anomalies.

INTRODUCTION

Psychopathy refers to a personality type expressed in the form of emotional callousness, lack of empathy, a grandiose estimation of self, impulsivity and persistent antisocial behavior, among other traits (Hare, 2003). This profile notably overlaps with features defining the antisocial personality disorder (DSM-V, 2013). However, such terms are not synonymous. To meet criteria for psychopathy, an individual must exhibit emotional dysfunction (Blair, 2012). Emotional features such as callousness, lack of empathy and inflated self-appraisal are not necessary to operatively define antisocial personality disorder in the main DSM-V section, which predominantly considers antisocial deviance. However, the alternative trait-based definition section of the DSM-V includes an antisocial personality disorder variant characterized by low anxiety and a bold interpersonal style, which is closer to the traditional view of psychopathy (DSM-V, 2013; Venables *et al.* 2014). Analogously, the presence of callous-unemotional traits may be used to define a "psychopathic" variant of conduct disorders in children (Patrick, 2014). A historical account of the use of these and related terms (e.g., sociopathy and dissocial disorder) can be found in Kiehl and Hoffman (2011).

The most widely used and validated instrument for the assessment of psychopathy is the interview-based Psychopathy Checklist-Revised (PCL-R; Hare 2003), which contains distinct affective–interpersonal and impulsive–antisocial factors. Various self-report instruments also exist for assessing psychopathy, as well as instruments adapted for children and adolescents (Patrick, 2014). Some inventories are inspired by the PCL-R, while others represent new developments, for instance, the Psychopathic Personality Inventory (Lilienfeld and Andrews 1996) and the Triarchic Psychopathy Measure (Patrick *et al*. 2009).

Current brain imaging tools offer a unique window to explore the structural and functional bases of normal and deviant behavior. Historically, researchers have been concerned with seeking arguments to

support a neurobiological foundation of psychopathy, as one of the most enigmatic personality disorders. In the last few years, increasingly abundant data have been provided. Nevertheless, further effort is necessary to integrate the new information. In this review, we describe the anatomical and functional features that characterize the brain of psychopathic individuals from a synthesis of neuroimaging research and discuss how such brain anomalies may account for psychopathic behavior. The available neuroimaging literature on psychopathy, defined in accordance with Hare's concept (Hare, 2003), is analyzed and the review is complemented by a secondary consideration of selected neuroimaging studies assessing young people showing antisocial behavior and callous emotional dysfunction.

BRAIN ANATOMY

Global brain assessment

The brain of primary psychopathic individuals (as opposed to patients with psychopathic-like behavior secondary to focal brain damage) does not show any gross anatomical anomalies upon visual inspection. The whole brain volume is similar to the general population in most studies that have provided the measurement (Dolan *et al.* 2002; Yang *et al*, 2005; Narayan *et al.* 2007; Tiihonen *et al.* 2008; Contreras *et al.* 2015). Significant brain volume reductions have only rarely been reported (Barkataki *et al.* 2006). When volumes have been measured for specific lobes using conventional anatomical limits, significant volume reduction was solely observed in the temporal lobe and only a minimal effect was appreciated in the prefrontal lobe (Dolan *et al.* 2002). psychopathic-like behavior

Within samples of high socioeconomic risk, an association has been reported between the persistence of the cavum septum pellucidum - a fluid-filled space between the two leaflets of the septum - and higher scores of psychopathy (Raine *et al.* 2010). However, the cavum is similarly prevalent in disruptive behavior disorders in the absence of psychopathy (Raine *et al*. 2010; Toivonen *et al.* 2013;

White *et al*. 2013,), suggesting that it is mainly a non-specific neuroradiological finding (Saba *et al.* 2013).

Changes in the content of gray matter

A large number of studies have focused on measuring the regional content of gray matter. These studies were based on trace delineation of gray/white matter boundaries, voxel-based morphometry and automated measurements of cortical thickness. To a large extent, there is general agreement regarding psychopaths' showing regional cortical reductions in relative gray matter content.

Earlier imaging studies predicted gray matter reductions in the prefrontal lobe of psychopaths (Raine *et al*. 2000; Yang *et al*. 2005). Subsequent research has both largely confirmed such a prediction and demonstrated that tissue alteration extends to other brain locations (Laakso *et al*. 2001; Laakso *et al.* 2002; Narayan *et al*. 2007; de Oliveira-Souza *et al.* 2008; Müller *et al.* 2008; Tiihonen *et al*. 2008; Yang *et al.* 2009*a, b*, 2010; Boccardi *et al*. 2011; Raine *et al.* 2011; Sato *et al*. 2011; Ermer *et al*. 2012; Gregory *et al*. 2012; Ly *et al.* 2012; Bertsch *et al*. 2013; Boccardi *et al*. 2013; Kolla *et al.* 2014; Kumari *et al*. 2014; Contreras-Rodríguez *et al*. 2015; Walters *et al*. 2015; Jiang *et al.* 2016), as summarized in Table 1. Although the number of reported brain areas indicates a tendency for changes to affect the cortex globally, gray matter volume reduction is particularly consistent across studies in (i) the rostral temporal lobe and the rostral and ventral frontal lobe including the ventral-medial and orbitofrontal cortex; (ii) the dorsal aspect of the brain medial wall involving a dorsal/medial frontal area extending to the anterior cingulate cortex and the posterior cingulate cortex/precuneus; (iii) the posterior parahippocampal gyri/medial visual cortex; and (iv) the sensorimotor cortex. Figure 1 provides an overall depiction of this consistent pattern of gray matter volume reduction in psychopaths.

The set of cortical regions shown in Figure 1 represent a combination of neocortical and paralimbic areas. Although the involvement of other (limbic) elements has frequently been emphasized in

psychopathy, only a few studies have actually detected significant volume reduction in structures such as the amygdala, hippocampus and insula, as indicated in Table 1. Moreover, some analyses specifically targeting the individual limbic structures using manual tracing failed to find the predicted volume reduction in the amygdala (Barkataki *et al.* 2006; Boccardi *et al*. 2011), hippocampus (Barkataki *et al.* 2006; Boccardi *et al.* 2010; Raine *et al*. 2004) and anterior cingulate cortex (Glenn *et al.* 2010*a*). However, the limbic/paralimbic system as a whole (integrated using latent-variable modeling) does appear to be a major contributor to psychopathy (Baskin-Sommers *et al.* 2016).

A number of meta-analyses have been conducted in attempt to summarize common findings across studies of regional brain volumes. However, it is relevant to note that none have focused specifically on psychopathy. Existing meta-analyses have instead broadly pooled finding from studies of antisocial behavior (Aoki *et al.* 2014; Yang and Raine, 2009), interpersonal violence (Lamsma *et al*. 2017), oppositional defiant disorder (Noordermeer *et al*. 2016) and conduct problems (Rogers *et al.* 2016). Although these analyses have mapped regional volume reductions consistent with the emphasis of our review (Figure 1), the frequency and extent of such alterations has notably been more discrete. It has been argued that the phenomenological and etiological heterogeneity of antisocial behavior, in particular, as well as methodological differences between studies, may explain the limited results of current meta-analytic studies (Lamsma *et al.* 2017).

In children and adolescents with psychopathic traits, research has demonstrated gray matter changes distributed in regions notably reminiscent of adult psychopathic patterns (De Brito *et al*. 2009; Ermer *et al.* 2013; Fairchild *et al.* 2013; Cope *et al*. 2014). However, such studies have produced mixed findings as to the direction of the alteration. Interestingly, young individuals (mean age of 12 years) show a gray matter volume increase (De Brito *et al*. 2009) associated with psychopathic traits, whereas in older individuals (mean age of 17 years), psychopathic traits are instead associated with a gray matter volume decrease in both males (Ermer *et al.* 2013) and females (Cope *et al*. 2014).). One study in female adolescents showed a mixed brain pattern of positive and negative correlations

(Fairchild *et al.* 2013). Taking both young and adult studies together, alterations in gray matter volume in psychopathy may be hypothesized to evolve dynamically throughout life from a relative gray matter increase to a relative decrease.

In support of a developmental dynamic basis of brain tissue alterations in psychopathy, one study reported a significant association of childhood physical abuse with gray matter volume reduction in the temporal pole of adult psychopaths (Kolla *et al.* 2014). Child abuse was also associated with reduced fronto-temporal cortical thickness predicting antisocial behavior in adolescents (Busso *et al.* 2017). In another study, the combination of relatively lower cortical volumes and higher volumes in subcortical regions was found to partially mediate the relation between adverse life events and antisocial behavior in a sample of 1,741 adolescents (Mackey *et al.* 2017). At age 25 years, a voxel-based morphometry analysis demonstrated the association of early life poverty with gray matter volume reduction precisely in the ventral-medial frontal cortex (Holz *et al.* 2015). Symptoms related to early-onset cumulative adversity have similarly been associated with reduced gray matter volumes in persistent delinquent youths (Raine *et al.* 2003).

Changes in the content of white matter

Despite consistency across studies, the extent to which reductions of gray matter volumes in adult psychopaths described above express true gray matter loss (i.e., atrophy) is not obvious. Indeed, results from white matter analyses suggest that white matter increases may contribute to relative reductions of gray matter measurements in the absence of relevant brain volume changes.

When results have been provided, white matter volume changes have generally paralleled the findings of gray matter changes in the opposite direction, with volume increases in global, prefrontal and corpus callosum white matter correlating with psychopathy scores (Raine *et al.* 2003; Yang *et al.* 2005). Larger volumes have also been demonstrated for basal ganglia elements with a very high content of white matter (Barkataki *et al.* 2006; Glenn et al. 2010*b*; Pujara *et al.* 2014).

A similar tendency has also been observed in disorders overlapping with psychopathy. In persistently violent offenders with antisocial personality disorder significantly larger white matter volumes were observed in broadly distributed brain regions grossly coinciding with areas of gray matter volume reduction (Tiihonen *et al.* 2008). In young males with psychopathic traits, a mixed pattern of changes has been reported combining both increases and decreases in regional white matter volume (De Brito *et al.* 2011).

It has been argued that the relative increase of white matter in psychopaths may be related to non-optimal brain remodeling (deficient axonal pruning), resulting in excessive anatomical connections (Raine *et al.* 2003). However, alternatively, we suggest here that larger white matter volumes in psychopathy may also relate to significantly accelerated myelination. It is important to note that white matter segments in conventional (T1-weighted) anatomical MRI scans correspond to myelinated white matter (Paus *et al.* 2001). Myelination is an active process throughout life (Yakovlev & LeCours, 1967; Pujol *et al.* 1993; Narayan *et al.* 2007), which is physiologically accelerated in early postnatal years and during adolescence (Paus *et al.* 2001; Pujol *et al.* 2006), and enhanced by repetitive use or skill learning (McKenzie *et al*. 2014; Pujol *et al.* 2016). Pathological acceleration of myelination has been suggested, for example, in melancholic depression (Soriano-Mas *et al.* 2011), childhood obesity (Ou *et al.* 2015), heavy cannabis use (Matochik *et al.* 2005) and pathological lying (Yang *et al.* 2005).

To summarize, measurable changes in gray and white matter regional tissue content can be detected in the brain of psychopaths in the absence of changes of total brain volume. This overall pattern of findings argues against gray matter atrophy as a sole explanation for gray matter volume reductions in psychopaths. We propose that accelerated myelination may be one contributing factor, in that it affects image tissue segmentation by displacing the boundary between white and gray matter.

Changes in the structure of white matter pathways

Potential alterations in the structure of white matter pathways have been investigated using diffusion tensor imaging (DTI). The common measurement across all studies is fractional anisotropy (FA), which quantifies the degree of structural maturation of white matter by estimating water diffusivity along tracts (Lebel *et al.* 2012). DTI studies of psychopathic populations coincide in showing FA reductions mostly involving frontal lobe connections (Craig *et al.* 2009; Motzkin *et al.* 2011; Sundram *et al.* 2012; Hoppenbrouwers *et al.* 2013; Sethi *et al.* 2015; Wolf *et al.* 2015; Jiang *et al.* 2017b).

Alterations in the ventral connections between the frontal lobe and the temporal lobe would appear to be a solid finding, which mostly implicate the uncinate fasciculus (Craig *et al.* 2009; Motzkin *et al.* 2011; Sundram *et al.* 2012; Hoppenbrouwers *et al.* 2013; Wolf *et al.* 2015; Jiang *et al.* 2017b). Significant FA reductions have also been identified in dorsal pathways connecting the frontal lobe with the parietal lobe (Sundram *et al.* 2012; Sethi *et al.* 2015; Jiang *et al.* 2017b). Interestingly, the cingulum is altered both ventrally and dorsally, with FA reductions detected in the segment connecting the posterior cingulate cortex with the medial temporal lobe and the segment connecting the posterior cingulate cortex with the frontal lobe (Sethi *et al.* 2015). Frontal lobe structural connectivity alterations in psychopaths therefore seem to implicate dorsal and ventral bundles that connect brain areas that broadly demonstrate gray matter volume reductions (summarized in Figure 1). However, frontal lobe connectivity changes are not limited to the anterior-posterior direction, as reduced FA has also been demonstrated in the genu of corpus callosum (transverse connections) (Sundram *et al.* 2012) and in frontal-basal ganglia connections (Sundram *et al.* 2012; Hoppenbrouwers *et al.* 2013).

Reductions in FA can be interpreted as expressing a maturation delay in late maturing bundles (Sethi *et al.* 2015). Nevertheless, accelerated, as opposed to delayed, maturation may better account for the majority of pathway alterations in psychopaths. Indeed, the increase in FA from normal childhood to adulthood reaches a peak between 20 and 40 years of age, and subsequently decreases (Lebel *et al.* 2012). Accordingly, from early adulthood, the normal physiological evolution of FA is one of progressive reduction, presumably reflecting increased white matter structural complexity

accompanying brain maturation (Douaud *et al*. 2011; Jones e*t al.* 2013). In DTI studies of psychopathy, the mean age of adult samples has broadly coincided with the FA peak, or with the beginning of FA decreases (age range across studies, 30 to 40 years), with the sole exception of one study (Jiang *et al.* 2017b). Thus, within this age range, reduced FA is better explained by accelerated maturation, or psychopaths reaching FA maturity earlier than what is normally observed. Interestingly, in the DTI study featuring the youngest population (mean age 23 years), a combination of FA decreases (predominant) and increases was reported (Jiang *et al.* 2017b).

DTI analyses in younger populations with callous-unemotional traits have provided mixed results, with different studies reporting higher, lower or no differences in FA versus healthy controls for diverse white-matter tracts (see Waller *et al.* (217) for a review). These findings offer further support for the proposal that abnormally accelerated white matter maturation contributes to the nature of anatomical changes in psychopathy and callousness. FA increase will be identified in youths, compared with typically developing controls, at ages prior to the FA age-related peak (the ascending part of the curve) for a given bundle, and FA reduction in older individuals closer to the age at which FA begins to decrease (Waller *et al.* 217). Here too, early life stress could play a significant role. In one study, adults with life-time exposure to parental abuse showed FA reduction in the hippocampal extension of the cingulum bundle, the fornix and the arcuate fasciculus (Choi *et al.* 2009).

BRAIN FUCTION

Functional connectivity

Functional connectivity is considered a measurement of activity synchrony between brain regions sharing functional properties (Biswal *et al.* 1995). In antisocial offenders, the assessment of functional connectivity changes using whole-brain measures has provided evidence of both reduced functional integration and segregation in the organization of large-scale brain networks (Jiang *et al.* 2016a). In global terms, such findings may be interpreted as reflecting deficient brain functional maturation (Fair

et al. 2009; Pujol *et al.* 2016). The integration and segregation of large-scale brain networks is a life-time process that is especially active during adolescence (Sherman *et al.* 2014). Thus, the hypothetical acceleration of white matter maturation does not seem to imply a more efficient coupling among late maturing networks in the case of psychopaths (i.e., maturation may be faster but deficient).

As in the case of other imaging alterations, global brain changes in functional connectivity have been observed in association with changes that are particularly prominent in specific brain systems. Once again, the frontal cortex is the structure that shows the most relevant connectivity alterations in psychopaths. Some evidence indicates reduced functional connectivity between ventral frontal areas and the anterior temporal lobe and amygdala at rest (Motzkin *et al.* 2011) and during emotional stimulation (Decety *et al.* 2013*a*; Yoder *et al.* 2015; Volman *et al.* 2016). Other studies have demonstrated reduced functional connectivity of the dorsal frontal cortex (and anterior cingulate cortex) with several limbic-paralimbic structures (Ly *et al.* 2012; Pujol *et al.* 2012; Contreras *et al.* 2015; Philippi *et al.* 2015) and, particularly, with the posterior cingulate cortex/precuneus complex (Pujol *et al.* 2012; Contreras *et al.* 2015; Philippi *et al.* 2015).

In addition to long-distance connectivity reduction, psychopaths appear to display higher functional connectivity within the dorsal aspect of the frontal lobes at rest (Contreras *et al.* 2015), and between dorsal frontal areas and the striatum during reward expectancy (Geurts *et al.* 2016). Higher frontal cortex connectivity was associated with more severe lifestyle/antisocial traits (Hare Factor 2) in the study carried out by Philippi *et al.* (2015). In general agreement with such functional connectivity findings, studies of structural connectivity (structural covariance) estimated from cortical thickness measurements, also implicates the superior frontal cortex as a relevant connectivity hub in psychopaths (Yang *et al.* 2012). Reduced functional connectivity also seems to combine with increased connectivity in antisocial personality disorder (Tang *et al.* 2016).

Brain activation

Brain response to emotional stimuli

A number of studies have examined how psychopaths respond to emotionally provocative stimuli, including emotional faces (Deeley *et al.* 2006; Decety *et al.* 2013*b*, 2014; Contreras *et al.* 2014; Hyde *et al.* 2014; Mier *et al.* 2014; Pera-Guardiola *et al.* 2016; Volman *et al.* 2016), unpleasant pictures (Müller *et al.* 2003; Decety *et al.* 2013*b;* Harenski *et al.* 2014; Sitaram *et al.* 2014), emotion-laden scenes (Decety *et al.* 2013*b*, 2015; Meffert 2013) and emotional words (Contreras *et al.* 2014). Collectively, these studies indicate that the neural processing of emotional stimuli is altered in psychopaths. However, depending on the nature of the experiment, studies have reported either attenuated (Deeley *et al.* 2006; Harenski *et al.* 2014; Hyde *et al.* 2014; Mier *et al.* 2014; Volman *et al.* 2016) or enhanced (Intratot *et al.* 1997; Contreras *et al.* 2014) or indeed a combination of response changes (Decety *et al.* 2013*a, b*, 2014, 2015) in different elements of the "emotion processing" network. Relevantly, enhanced brain response has been reported for visual sensory areas (Contreras *et al.* 2014), association sensory cortex (Decety *et al.* 2013*b;* Contreras *et al.* 2014), insula (Decety *et al.* 2013*b*, 2014), anterior cingulate cortex (Decety *et al.* 2013*b*), basal ganglia (Decety *et al.* 2013a, *b*) and frontal (predominantly dorsal) areas (Contreras *et al.* 2014; Decety *et al.* 2013*b*). Thus, the psychopath's brain is not necessarily "unemotional" in terms of its response to emotional stimulation, which may be enhanced at some processing stages. Nevertheless, a disruption of the emotional flow occurs, perhaps in the transition of processing from temporal lobe structures to the ventral prefrontal cortex. Indeed, the amygdala (Decety *et al.* 2013*a*, 2014; Contreras *et al.* 2014; Harenski *et al.* 2014; Hyde *et al.* 2014; Mier *et al.* 2014) and the ventral prefrontal cortex (Decety *et al.* 2013*b*, 2014) both show only a modest or attenuated response to emotional stimuli in psychopaths, and the normal functional coupling between both elements appear to be reduced during task performance (Decety *et al.* 2013*a*; Contreras *et al.* 2014; Volman *et al.* 2016).

Brain response to aversively conditioned stimuli (e.g., with pain) has also been tested in psychopaths. Once again, the results have been divergent, with evidence for both attenuated (Veit *et al.* 2002;

Larson *et al.* 2013; Decety *et al.* 2014) and enhanced (Schneider *et al.* 2000; Schultz *et al.* 2016) brain activations, which further suggests that the experimental context is critical in determining the magnitude and direction of the response. Attention seems to be a relevant factor that may explain some apparent discrepancies. For example, compared with control subjects, psychopaths showed lower right amygdala and higher left frontal response to a short (200 ms) exposure to a pain-conditioned stimulus when attention was engaged in a neutral task (Larson *et al.* 2013). By contrast, long exposure (8 s) to a pain-conditioned complex image generated a greater response, in this case in the *left* amygdala and in areas processing visual stimuli features (Schultz *et al.* 2016).

There is also evidence relating psychopathy to altered responses to incentive stimulation. Specifically, psychopathy has been associated with lower basal ganglia activation related to monetary loss (Pujara *et al.* 2014), lower medial frontal activation during reward anticipation (Veroude *et al.* 2016) and lower anterior cingulate cortex activation in response to reward uncertainty (Prehn *et al.* 2013), while increased activation has been observed in the posterior cingulate cortex and anterior insula during the task reversal phase (Gregory *et al.* 2015). Also, higher psychopathy scores have been associated with reduced response to drug abuse-related pictures in the basal ganglia and connected brain structures (Cope *et al.* 2014).

Brain activity during moral challenge

Neuroimaging research has demonstrated the involvement of a well-defined brain network in the mediation of moral judgment in the normal population. This network overlaps with the so-called default mode network connecting the medial frontal cortex, the posterior cingulate cortex and the angular gyri (Greene *et al.* 2001), but also medial structures of the temporal lobe and upper brainstem (Harrison *et al.* 2008; Pujol *et al.* 2012). In functional MRI studies, psychopaths required to make a judgment in a moral dilemma situation (Figure 2) have consistently shown deficient activation in the medial frontal and posterior cingulate cortex (Glenn *et al.* 2009; Harenski *et al.* 2010; Veit *et al.* 2010; Pujol *et al.* 2012; Yoder *et al.* 2015) and, remarkably, in the hippocampus and parahippocampal gyrus

extending to the periaqueductal gray (Pujol *et al.* 2012) and amygdala (Glenn *et al.* 2009; Pujol *et al.* 2012; Marsh *et al.* 2014; Yoder *et al.* 2015). Such experiments may therefore show the inappropriate use of a network that both mediates attention to self as an agent and has access to autobiographical storage (Moll *et al.* 2007; Bado *et al.* 2014; Leech *et al.* 2014). Consistent with this view, criminal psychopaths precisely showed lower activity in the posterior (and anterior) cingulate cortex, parahippocampal gyrus, hippocampus and amygdala during the performance of an affective memory task (Kiehl *et al.* 2001).

A functional "breakdown" in the brain network subserving moral judgment may also extend to neutral situations unrelated to the moral context. Functional MRI signal reduction or deactivation typically observed in the default mode network during conventional cognitive tasks is deficient in psychopaths (Pujol *et al.* 2012; Juárez *et al.* 2013; Freeman *et al.* 2015). Moreover, the anterior and posterior elements of the default mode network appeared to be significantly uncoupled during the resting state in functional connectivity analyses (Pujol *et al.* 2012). Therefore, the network abnormally responding during moral challenge would also seem to be primarily altered. This idea is consistent with the proposal that attentional deficits in psychopaths are not limited to situations of moral conflict, but extend more generally to other attentional domains (Newman *et al.* 2010, 2016; Aharoni *et al.* 2013; Rodman *et al.* 2016).

The arousal generated by a moral challenge in psychopaths appears to depend on how the self is taken as a reference. While watching morally-laden scenes, psychopaths showed higher frontal activation when identifying the emotional state of the victim and lower frontal activation when identifying the emotional state of the predator (Decety *et al.* 2015). However, other data suggest that if the psychopath is forced to feel like the predator - as opposed to simply having to identify the predator's emotional state- such a response attenuation may be less evident (Sommer *et al.* 2010; Decety *et al.* 2013; Meffert *et al.* 2013), further suggesting an attentional selection bias (Newman *et al.* 2010, 2016).

In brief, while psychopaths are reactive to different forms of emotional stimulation, emotional processing may be incomplete with poor temporal lobe transmission of emotional flow to the ventral frontal system. Also, moral challenge experiments have revealed the inappropriate use of a dorsal network mediating attention to our inner emotional world.

In addition to functional imaging of evoked brain activation, other studies have assessed brain function based on a variety of metabolic parameters. Regional glucose metabolism and cerebral blood flow have generally been reported to be lower in psychopaths, particularly in frontal and temporal areas (Volkow *et al.* 1995; Raine *et al.* 1997; Soderstrom *et al.* 2002). One study reported lower levels of monoamine oxidase-A, an enzyme that regulates neurotransmitters, in the orbitofrontal cortex and ventral striatum in offenders with high psychopathic traits (Kolla *et al.* 2015). Other authors have reported a positive correlation between striatal serotonin 1B receptor binding and the level of psychopathy (da Cunha-Bang *et al.* 2016).

GENERAL IMPLICATIONS

In this review, we provide a synthesis of available neuroimaging research directly concerning to psychopathy. A variety of imaging methods has been used to date to provide distinct perspectives of brain structure and function. There are notable differences across the findings of existing studies, which is likely to reflect important differences in study methodology, but may also reflect the underlying biological heterogeneity of psychopathy. Nevertheless, most studies coincide in suggesting that the brain of psychopaths differs notably from the typical brain in terms of both anatomy and function. There is a tendency for changes to affect the brain globally, but variations from the normal pattern are particularly evident in a number of functionally related brain structures. One system includes the rostral aspect of both frontal and temporal lobes, which subcortically report to the ventral striatum and anterior hippocampus/amygdala, respectively. Although this system is involved in a vast

variety of processes, in the context of psychopathy, we emphasize its role in conveying emotional input to motivated actions (Simpson & Balsam, 2016). The second system combines the medial frontal (and anterior cingulate) cortex with the posterior cingulate cortex/precuneus, core elements of the default mode network, which are critical in focusing attention on self and accessing autobiographical storage (Bado *et al.* 2014; Leech *et al.* 2014). This dorsal system is connected to caudal temporal lobe structures also altered in psychopathy. Relevant changes have been identified in the parahippocampus/posterior hippocampus and visual areas involved in the processing of sensory stimulation in general, but also relevant for the storage of significant autobiographical events (Jeong *et al.* 2015). In addition, alterations have also been reported involving the sensorimotor cortex, which is the primary representation of our bodies.

Functional data suggest that emotionally evocative stimuli are indeed capable of activating the brain and even generating excessive responses in some (mostly dorsal) emotion-relevant brain areas in psychopaths. However, the emotional processing flow may appear to be disrupted in the transition from the temporal lobe to ventral frontal areas, with the consequent failure to integrate emotion into cognition and subsequent decisions, as often proposed (Kiehl *et al.* 2001; Raine *et al.* 2006; Blair *et al.* 2007, 2016; Moll *et al.* 2008; Contreras *et al.* 2014). The alteration in emotional processing resulting from such ventral temporal-frontal blockage may be sufficient to account for psychopathic behavior if taken to the extreme. Indeed, in frontotemporal dementia and after focal damage of rostral fronto-temporal areas, the presence of psychopathic-like behavior is not exceptional (Anderson *et al.* 1999; Brower *et al.* 2001; Koenigs *et al.* 2007; Moll *et al.* 2007; Diehl-Schmid *et al.* 2013; Birkhoff *et al.* 2016; Darby *et al*. 2018).

Nevertheless, imaging data indicate that emotional processing blockage may also occur as a result of the abnormal functioning of a dorsal brain system. Probably the most consistent finding in functional imaging research in the context of adult psychopathy is the alteration of the network involved in the mediation of moral judgment overlapping with the default mode network. The normal activation of

this network serves to focus attention on the self as an agent and thus (as we propose) exposing the individual to be aroused (or "touched") from emotional (positive or negative) memories stored in temporal lobe medial structures. Activation of the default mode network during moral conflict is certainly abnormal in psychopaths (Glenn *et al.* 2009; Harenski *et al.* 2010; Veit *et al.* 2010; Pujol *et al.* 2012; Yoder *et al.* 2015), which concurs with a similarly poor activation of key memory structures such as the parahippocampal gyrus, hippocampus and amygdala (Glenn *et al.* 2009; Pujol *et al.* 2012; Marsh *et al.* 2014; Yoder *et al.* 2015).

All in all, a failure to integrate emotion into cognition would appear to result from at least two complementary breakdowns; bottom-up disruption of the emotional flow in the ventral fronto-temporal system and a top-down blockage of emotional self-exposure in the dorsal network mediating moral judgment.

FUTURE DIRECTIONS

In the present review, we have focused on how current neuroimaging research may contribute to a better understanding of pathophysiological mechanisms leading to psychopathic behavior. Nevertheless, another question is whether neuroimaging can provide clues as to its etiology? We would emphasize three potential causal factors deserving future research, in addition to genetic predisposition, which always plays a significant role in complex behavioral disorders.

As discussed earlier, one of the factors that potentially contributes to the development of brain pathology in psychopaths is life-time stress, which may well accelerate brain maturation. Life-time stress could indeed contribute to regional gray matter volume reduction through excessive neural activity leading to subsequent atrophy (a "burnout" effect) or by increasing myelinated white matter with an apparent reduction of the gray matter tissue segment, or both. Future analyses may specifically focus on determining the life-time evolution of cortical white matter content. Additionally, it may be

valuable in this context to test the hypothesis of accelerated brain maturation from a functional perspective, by assessing both brain activity and functional network connectivity in children and adolescents with psychopathic traits.

Androgens have a relevant effect on brain shaping. Critical periods include the prenatal androgenization of the brain and androgen activation during adolescence (Arnold *et al.*1984; Sato *et al.* 2008). The male and female brain differs, in part, due to androgen effects (Heany *et al.* 2016) and antisocial behavior is substantially more frequent in males (Yildirim *et al.* 2012). Thus, anomalies in developmental androgenic brain modelling may increase the predisposition to psychopathy (Yildirim *et al.* 2012). Relevantly, the effects of prolonged high-dose administration of androgenic steroids on brain anatomy are largely reminiscent of gray matter alteration patterns in psychopaths showing reduced cortical thickness in rostral frontotemporal areas, the medial frontal cortex, the posterior cingulate cortex/precuneus and visual areas (Figure 3) (Bjørnebekk *et al.* 2017).

Finally, the results from some analyses suggest that the described brain alterations could show distinct and opposite patterns of association with both affective disturbances and antisocial behavior. Indeed, some brain alterations are reported to be associated with more affective disturbances (Hare Factor 1) and less antisocial behavior (Hare Factor 2), including reductions in gray matter volume (Contreras *et al.* 2015), altered functional connectivity in large-scale cortical networks (Philippi *et al.* 2015) and amygdala reactivity (Hyde *at al.* 2014). A recent study further indicates that the severity of antisocial behavior is associated with larger prefrontal and striatal subregion volumes and higher functional connectivity between several areas of the prefrontal cortex (Korponay *et al.* 2017*a, b*). Future research on this issue is therefore of great interest to ascertain whether the described alterations in brain structure and function in psychopaths necessarily predispose them to crime. Interestingly, there are behavioral data indicating that antisocial behavior, as measured in Hare Factor 2, is better explained by poorer cognitive functioning (Baskin-Sommers *et al.* 2015).

CONCLUSIONS

This review has sought to provide a consolidated perspective on the contribution of brain imaging to understanding of psychopathy. The brain of psychopaths differs from the typical brain in terms of both anatomy and function. Anatomical alterations involve primarily a ventral system connecting the anterior temporal lobe to anterior and ventral frontal areas, and a dorsal system connecting the medial frontal lobe to the posterior cingulate cortex/precuneus complex and, in turn, to medial structures of the temporal lobe. Functional imaging data indicate that a significant disruption or 'breakdown' in the flow of emotional information processing may occur in both these two brain systems and suggest specific mechanisms via which emotion is anomalously integrated into cognition in psychopathic individuals during moral challenge. To this end, broader reviews are of interest comparing the results from different fields including, for instance, EEG, genetics, neurochemistry and neuropsychology.

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Conflicts of interest

None.

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Figures

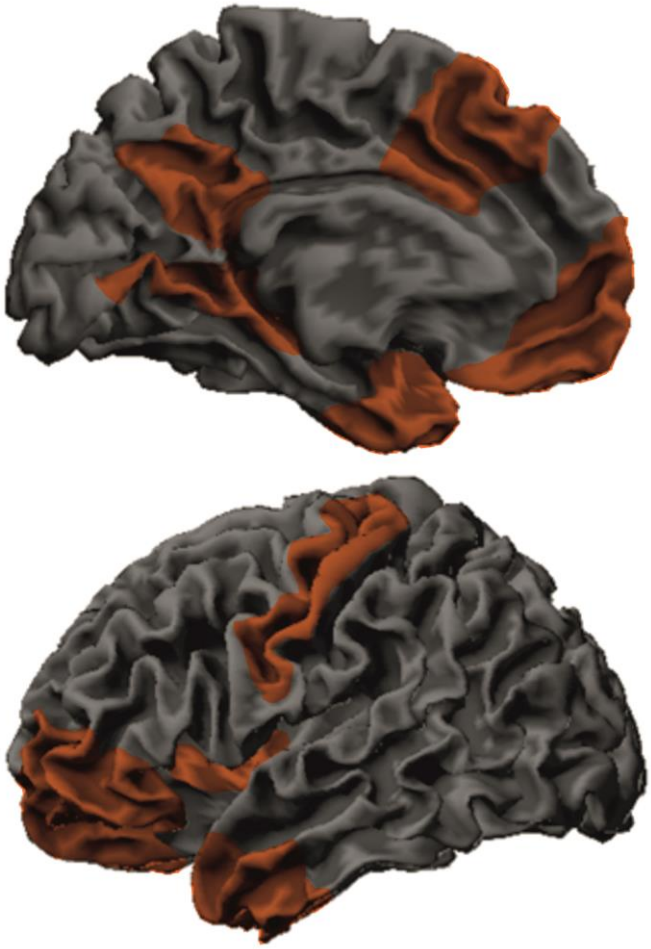

Figure 1. Schematic representation of brain regions showing the most consistent gray matter volume reduction in primary psychopathy according to the literature.

On board is an injured man that will probably not survive. If you throw this man overboard he will certainly die, but the boat will stay afloat and the others may survive. If you do not do so, the boat will probably sink and all of them will die.

Would you throw the injured man overboard?

Figure 2. Representation of a typical moral dilemma used in functional MRI experiments in psychopaths. Adapted, with permission, from Pujol *et al.* (2012).

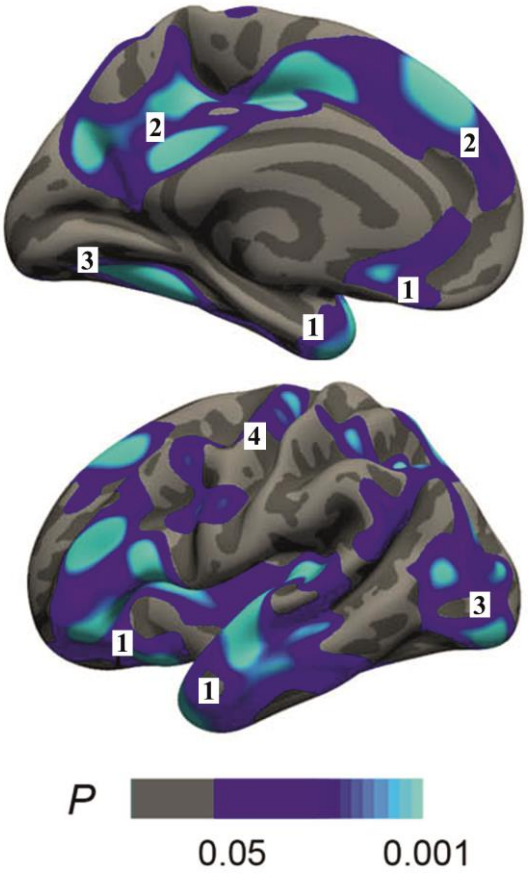

Figure 3. Regions showing reduced cortical thickness in users exceeding 10 years of anabolic-androgenic steroid exposure compared with control subjects. Adapted, with permission, from Bjørnebekk *et al.* (2017). Note the notable regional coincidence with the areas showing the most consistent volume reduction in psychopaths illustrated in Figure 1. The largest coincidences are present in the ventral temporal-frontal system (1) and the dorsal-medial system (2), but cortical reductions are also present in visual (3) and motor cortices (4).

Table 1. Gray matter reduction in psychopathy

Dorsal/lateral frontal cortex (7,8,16,17,18,19,21,23,25,26, 27,28,33)
Medial frontal cortex (6,7, 8,16,18,22,23,25,26, 27,28,33)
Orbitofrontal cortex (6,7,16,17,19,21,22,23,27,28,32,33)
Temporal pole/anterior temporal cortex (17,18,19,21,25,26,27,30,32)
Hippocampus (8,15,27,32)
Amygdala (8*,20, 21,27*,32)
Lateral temporal cortex (8,17,24,26,33)
Anterior cingulate cortex (8,18,22,26,31,33)
Posterior cingulate cortex-precuneus (8,19,21,22,24,27,28,33)
Visual cortex (7,19,21,22,24,26,28),
Parahippocampal/fusiform gyri (8,19,21,22,26,27,28,32)
Somatosensory cortex (6,7, 22,25,26,28)
Parietal cortex (7,28)
Insula (8,17,25,26)
Cerebellum (28,30)
Nucleus accumbens (29)

Significant gray matter volume reduction across reported studies distributed in gross brain parcellations. Literature references between parentheses. *marginally involved.

6:Narayan *et al*. 2007; 7:Tiihonen *et al.* 2008; 8:Contreras-Rodríguez *et al*. 2015; 15:Laakso *et al.* 2001; 16:Laakso *et al*. 2002; 17:de Oliveira-Souza *et al.* 2008; 18:Müller *et al*. 2008; 19:Yang *et al*. 2009a; 20:Yang *et al*. 2009b; 21:Yang *et al.* 2010; 22:Boccardi *et al*. 2011; 23:Raine *at al.* 2011; 24:Sato *et al.* 2011; 25:Gregory *et al.* 2012; 26:Lu *et al*. 2012; 27:Ermer *et al.* 2012; 28:Bertsch *et al.* 2013; 29:Boccardi *et al.* 2013; 30:Kolla *et al*. 2014; 31:Kumari *et al.* 2014; 32:Walters *et al.* 2015; 33:Jiang *et al.* 2016.