NEURAL NETWORKS CONNECTING EMOTION AND COGNITION ASSESSED IN PSYCHOPATHS, COCAINE USERS AND OBSESSIVE-COMPULSIVE DISORDER USING MRI.

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Summary

Emotional processing is fundamental for normal socialization, interpersonal interactions, successful decision-making and overall to self-regulate behavior according to each context. Adequate emotional processing relies in the satisfactory and balance function within certain brain networks of coactivated emotional, cognitive and perceptual regions that respond and integrate the emotional information to successfully guide behavior. Magnetic resonance techniques provide a method to directly non-invasively challenge whole-brain processes underlying diverse emotional processes as well as brain functional activity during rest. The present thesis aims at identifying functional alterations within the brain networks processing emotion and connecting emotion with cognition in psychopathic individuals, along with two clinical populations showing common or opposite behavioral features such as cocaine dependence and obsessive-compulsive disorder. Overall, the five studies presented herein constitute a step forward in the characterization of how the brain responds to emotional situations and how changes in this response pattern may compromise flexible and advantageous behaviors across pathologies.

Key words: emotion brain processing, magnetic resonance imaging, psychopathy, cocaine use, obsessive-compulsive disorder.

Resum

El processament de les emocions és fonamental per una correcta socialització, unes bones relacions interpersonals, una pressa de decisions competent i en general, per una bona regulació de la conducta en funció del context específic. Un processament emocional adequat depèn del funcionament satisfactori i equilibrat de xarxes cerebrals formades per regions emocionals, cognitives i perceptives que responen i integren informació emocional per tal de guiar la conducta amb èxit. Les tècniques de ressonància magnètica funcional permeten obtenir mesures directes, de forma no invasiva, dels mecanismes cerebrals que sustenten els processos emocionals, així com també del funcionament del cervell en repòs. Aquesta tesi té per a objectiu identificar alteracions funcionals dins les xarxes cerebrals que processen les emocions i les connecten amb processos cognitius en psicòpates i en dues condicions clíniques, consumidors de cocaïna i trastorn obsessiu compulsiu, amb les que mostra trets conductuals comuns i diferencials. A grans trets, els cinc estudis que es presenten constitueixen un pas endavant en la caracterització de la resposta cerebral a les diferents situacions emocionals i com canvis en aquests patrons de resposta poden comprometre conductes flexibles i adaptatives en diferents patologies.

Paraules clau: processament cerebral emocional, ressonància magnètica funcional, psicopatia, consum de cocaïna, trastorn obsessiu- compulsiu

Preface

Emotional processing is fundamental to promote normal socialization, interpersonal interactions, successful decision-making and overall to self-regulate behavior according to each context. Adequate emotional processing relies in the satisfactory and balance function within certain brain networks of coactivated emotional, cognitive and perceptual regions that respond and integrate the emotional information to successfully guide behavior.

Magnetic resonance techniques provide a method to directly non-invasively challenge whole-brain processes underlying diverse emotional processes as well as brain functional activity during rest. Notably, these techniques have contributed to the characterization of the neural substrates underlying emotional processing in some social contexts, such as moral judgment and emotional face processing (Greene and Haidt, 2002; Greene, Sommerville, Nystrom, Darley, and Cohen, 2001; Haxby, Hoffman, and Gobbini, 2000; Moll, Zahn, de Oliveira-Souza, Krueger, and Grafman, 2005), thus providing insights into its function in healthy and clinical samples (Cardoner et al., 2009; Harrison et al., 2008; Pujol et al., 2009).

Some populations present problems in both processing emotional information and behavior self-regulation. One interesting personality condition to investigate such dysfunctions may be psychopathy. Psychopathic individuals are characterized by pronounced problems in emotional processing, such as a lack in emotional empathy and a sense of guilt, which is thought to be directly related to disruptions in the socialization processes (Blair 2003a, 2003b). Although most psychopaths have preserved cognitive capacities to know and distinguish what is conventionally considered to be morally right or wrong, they show a failure to conform commonly accepted mores of society that often ultimately results in antisocial and inflexible forms of behavior. Psychopathic offenders commit a greater number of crimes, more types of crimes, more violent crimes, and recidivate at higher rates than non-psychopathic offenders (Hare, 2003).

Some particular clinical conditions such as cocaine dependence and obsessive-compulsive disorders may also present emotional processing and self-regulation disturbances. Specifically, cocaine dependence and psychopathy to some extent present a similar behavioral phenotype. It is, therefore, of great interest to characterize both specific and

common features of the neural substrate underlying these conditions, which may have important implications for a differentiated management. Obsessive-compulsive disorder, in turn, presents a heightened moral sensitivity that contrasts with the apparent moral callousness in the psychopathic individual, thus suggesting opposite neural functioning within the neural networks underlying emotional processing.

The present thesis aims at identifying functional alterations within the brain networks processing emotion and connecting emotion with cognition in psychopathic individuals, and in two clinical populations showing common or opposite behavioral features such as cocaine dependence and obsessive-compulsive disorder. Brain function was assessed in the three populations during a situation of moral dilemma using a task specifically developed for the purpose of this study. Psychopaths were additionally assessed using an emotional face processing task and during a state of rest with no stimulation. Anatomical sequences were obtained to explore a possible association between functional and structural alterations. Finally, we also explored for associations between imaging results and behavioral and clinical variables.

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1. INTRODUCTION

1.1. Emotion brain processing

1.1.1 Concept and relevance of the study of emotions

Emotion consists in multifaceted whole-body phenomena that involve loosely coupled changes in the domains of subjective experience, behavior and central and peripheral physiology (Kandle, Schwartz, and Jessell, 2000; Plutchik, 2001). This heterogeneous pattern of expression, the high variability in the subjective experience of emotion and the wide variety of emotions, ranging from basic emotions (i.e. fear and anger) to social and moral emotions (i.e. guilt and compassion) have generated confusion and debate about what constitutes an emotion (Ekman, 1973; Moll, de Oliveira-Souza, and Eslinger, 2003; for revision of main theories of emotion see Strongman, 2003). While some investigators view emotions simply as the value we consciously (or unconsciously) assign to stimuli surrounding us, others go further incorporating concepts such as 'drive' and 'motivation' to define the term emotion (Damasio, 1994; Rolls, 2005). This latter conceptualization considers emotion as a state elicited by rewards and punishments that have a later impact in guiding behavior. For instance, the happiness produced by being given a reward such as a hug would encourage that we work to approach such a situation, whereas a punishment like the fear expression on someone's face would result in the opposite behavior.

However, if we momentarily put aside the exact definition of emotion, we probably all agree that emotions play an important role in determining the quality and range of everyday human experience. In fact, evolutionary perspectives suggest that environmental emotional events are susceptible to be preferentially and perceptually processed due to the need to form rapid and appropriate behavioral responses to survival (Darwin, 1872/1965). Under these views, emotional information does posses an imperative quality, being able to interrupt what we are doing and coming into our awareness rapidly and automatically by enhancing attention even without conscious awareness (Critchley and Harrison, 2013; Dolan, 2002; LaBar and Cabeza, 2006; Tamietto and Gelder, 2010). This privileged perceptual processing leads emotion to have a key role in the formation of our memories, interpersonal relationships, decisions to approach or avoid certain situations and to do right

or to avoid to do wrong. Subsequently, solving the question of how emotional stimuli are processed is fundamental to understand human behavior.

Moral decision-making is one situation where appropriate emotional processing is crucial. While traditional rationalist approaches to moral cognition emphasized the role of conscious reasoning from explicit principles (Kohlberg, 1981), modern emotion-based accounts have proposed the important role of intuitive emotional processes in human decision-making (Damasio, 1994; Haidt, 2001). Emotion-based accounts draw support from both behavioral studies that demonstrate that manipulations of the affective state can alter moral judgment and studies of clinical populations that reveal an association between emotional processing deficits and disturbances in moral behavior (Anderson, Bechara, Damasio, Tranel, and Damasio, 1999; Eslinger, Grattan, and Damasio, 1992; Jones and Fitness, 2008; Mendez, Anderson, and Shapira, 2005). Moreover, neuroimaging studies have repeatedly showed activation in brain areas known to process emotions during moral judgment tasks (Greene, Nystrom, Engell, Darley, and Cohen, 2004; Greene et al., 2001; for a review see Moll et al., 2003). Accordingly, present theoretical perspectives suggest that predictive judgments are made by the linkage between emotional physiological states (i.e. skin conductance reactivity, startle response) evoked according to the contemplation of the possible scenarios that constitute options for action (Damasio, 1994). More specifically to moral situations, it has been proposed that what makes acceptable one moral situation but not another is the tendency to engage people's emotions, that is, the perceptual emotional salience of the moral situation at hand (Greene et al., 2001). The complex interplay between emotional-cognitive brain elements when individuals weigh their actions within a moral context will be further discussed in later sections.

During our interpersonal relationships an appropriate emotional processing is also essential. In these social situations, the adequate processing of the other emotional face expression contributes to normal socialization processes and successful social interactions (Blair, 2003a). In fact, there is evidence that deficits in emotional face recognition contributes to mediate the individuals' propensity to prosocial or antisocial behavioral (Gibbs, 1987; Staubs, 1978). For instance, the display of sad expressions has been linked to the inhibition of aggression and the elicitation of prosocial behavior (Blair, 1995; Blair, 1999; Blair and Frith, 2000; Eisenberg and Mussen, 1989) and anger is displayed to curtail the behavior of others in situations where they have broken the social rules or expectations

(Averill, 1982). Accordingly, Blair and Coles (2000) found an inverse relationship between children's ability to recognize emotions of sadness and fearfulness and their level of behavioral problems.

Once emphasized the importance of emotion in guiding behavior and its specific contribution to moral decision-making, normal socialization and social interactions, next section will summarize the neuroimaging literature on the brain networks underling emotion processing. After that, a brief introduction to the brain networks challenged by our moral dilemma and emotional face recognition tasks (section 2.1) will be provided.

1.1.2. Neural correlates of emotion processing

This section aims to provide an integrative description of the neural basis underling emotion processing to understand how complex behaviors benefit from rich, dynamic and close interaction between the different brain units. To reach such a comprehensive view of the brain, both the specific role given to the main brain structures traditionally linked to emotional processing, together with their relationship within larger functional brain networks will be discussed.

The concept of functional localization has shaped the understanding of brain function since at least Broca (1863). In attempting to localize specific emotional processing functions in the brain, an appealing approach has been to separate the 'emotional' from the 'cognitive' brain. However this categorization is problematic for various reasons. First, brain regions conceptualized as 'emotional' are also involved in cognitive processes (Harrison et al., 2011; Holland and Gallagher, 1999) and brain regions viewed as 'cognitive' are also involved in emotional processes (Haxby et al., 2000; Nauta, 1971). Second, this phenomenological distinction does not seem to be respected in the brain, where the two systems continuously and reciprocally interact, making their dissociation sometimes difficult (Pessoa, 2008).

Current non-modular views of brain organization support the notion that the neural elements underling emotion and cognition continuously interact, being totally integrated and jointly contributing to complex behaviors like learning, memory and decision-making (Kastner and Ungerleider, 2000; Pessoa, 2008). In this line, emotion processes can be only understood by examining the interactions between the brain units that constitute a certain

brain network. Aptly, functional connectivity approaches in functional magnetic resonance imaging, which correlate spatially remote neurophysiologic brain temporal signals, allow the assessment of these inseparable relationships thus providing relevant information regarding the equilibrium between the brain processing emotional units in a certain brain network.

Throughout centuries, science has attempted to elucidate the neural systems underlying human emotions. It was not until the proposal by Papez (1937) that a brain network theory for emotion was advanced. Subsequently, the so-called Papez circuit was further elaborated by MacLean (1949), who proposed the concept of the 'limbic system', which considered the amygdala and parts of the frontal cortex as key brain structures in emotion processing (Figure 1). McLean's limbic system concept survives as the dominant conceptualization of the 'emotional brain' and neuro-scientific view of emotion. Nowadays it is established that subcortical areas such as the amygdala-hippocampus complex, ventral striatum, insula and basal forebrain areas, including the hypothalamus and prefrontal and cingulate cortices are involved in the integration of the external world and inner body emotional information under particular contexts (i.e. emotional face, picture and vocal processing, moral dilemma situations, fear conditioning, expectations of reward and punishment, craving states, induction of positive and negative mood states, pain, empathy) (Critchley, 2005; Dalgleish,

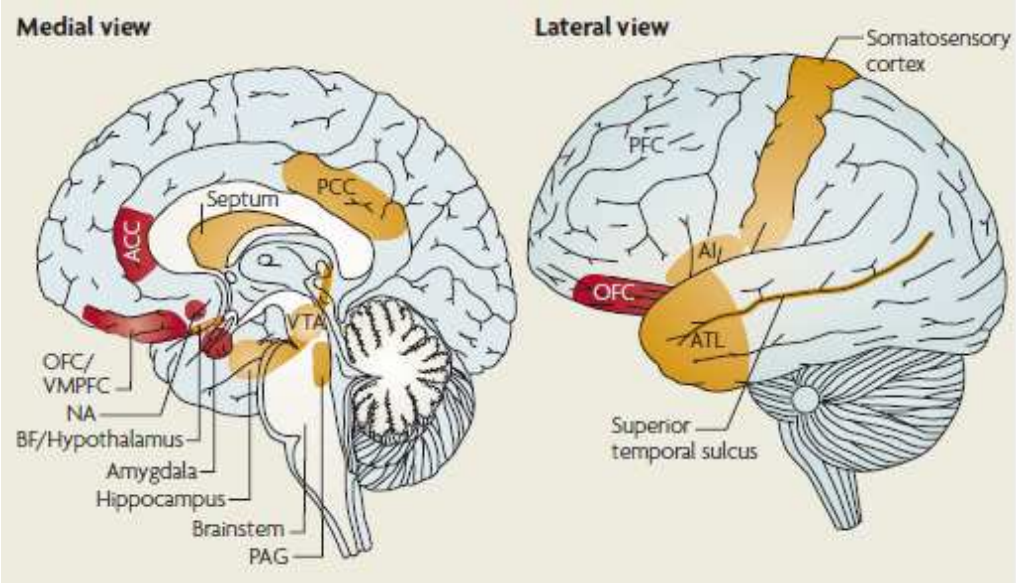

Figure 1. Key brain areas subserving emotional processing. The core emotional regions (dark red) include, subcortically, the amygdala, the nucleus accumbens and the hypothalamus, and cortically, the orbitofrontal cortex, the anterior cingulate cortex and the ventromedial prefrontal cortex. Extended regions (brown) include, subcortically, the brainstem, the ventral tegmental area (and associated mesolimbic dopamine system), the hippocampus, the periaquaeductal grey, the septum and the basal forebrain (including the nucleus basalis of Meynert), and cortically, the anterior insula, the prefrontal cortex, the anterior temporal lobe, the posterior cingulate cortex, superior temporal sulcus, and somatosensory cortex (adapted from Pessoa 2008).

2004; Kober et al., 2008; Murphy, Nimmo-Smith, and Lawrence, 2003; Vignemont and Singer, 2006).

Within the neural network that processes emotion, neuroimaging research has emphasized the crucial role of the amygdala (Kluver and Bucy, 1937; LeDoux, 1998). This brain region has been suggested to relevantly contribute to the processing, detection and conditioning of fear (Adolphs, 2002, 2008; Bechara, Tranel, Damasio, and Adolphs, 1995; LeDoux, 2000) although current views support a much broader role of this brain structure based on its activation to facial expressions other than fear and to social and reward cues (Adolphs, 2008, 2010; Davidson, 2000; Sergerie, Chochol, and Armony, 2008). Overall, the amygdala may participate in determining the biological significance of the emotional stimulus through many routes. At a basic level, the amygdala influences arousal levels through its projections with cholinergic, noradrenergic and serotonergic systems, each of which innervates widespread areas of the cortex, and in conjunction with the hypothalamus and the periaqueductal gray, the amygdala takes part in the elaboration of adequate freeze-flight-fight responses when environmental threats are detected (Aston-Jones, Rajkowski, and Cohen, 2000; Gallagher, 1999; Holland and Davidson, 2000; Liddell et al., 2005). Finally, in conjunction with ventromedial prefrontal cortices and striatum regions, the amygdala participates in reinforcement stimuli processes (Carmichael and Price, 1995; Berridge and Robinson, 2003; Montague and Berns, 2002).

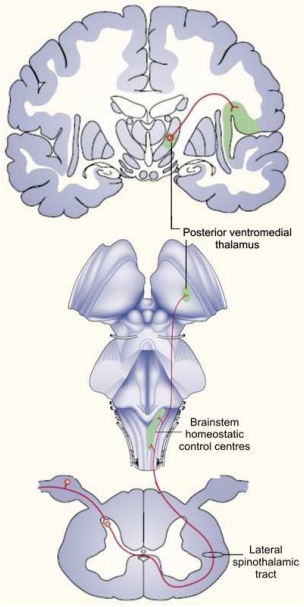

Figure 2. Lamina 1 Spinothalamocortical Pathway. Small diameter primary afferents project homeostatic and viscerosensory information to the nucleus of the solitary tract and directly to the thalamus. Projection fields within the dorsal posterior insula cortex present a cortical image of the bodies' physiology (adapted from Gray 2007)

For the emotional experience to be completed, however, our brain needs to integrate the interoceptive state of the body; for instance physiological, thermal, muscular and visceral sensations. James-Lange suggested that the evaluation of the state of the body in response to pertinent stimulus constitutes the basis for emotion (Cannon, 1987). Extended work by Damasio and colleagues (1994) with the 'Somatic Marker

Hypothesis' proposes that interoceptive bodily reactions (somatic markers) provide self-emotional awareness and serve to guide decision-making. Within the primate brain, interoceptive information relays via thalamus to insula cortex where sequential representations permit associative integration with other processing streams (Craig, 2002, 2009; Critchley, Elliott, Mathias, and Dolan 2000; Critchley et al., 2003; Rainville, 2002) (Figure 2). The integration of the interoceptive feedback from the state of the body with prefrontal regions is crucial for this information to influence behavior (Bush, Luu, and Posner, 2000; Damasio, 1994; Nauta 1971; Ochsner and Gross, 2005). For instance, Naqvi, Rudrauf, Damasio, and Bechara (2007) showed that smokers with insula damage quit smoking easily, but also damage to insular related brain regions, such as orbitofrontal or anterior cingulate cortices, can attenuate autonomic responses to motivational cues leading to changes in behavior (Bechara, 2004).

As previously advanced in previous paragraphs while describing the joint function of the amygdala and insula regions with other brain regions, neuroimaging studies have routinely observed activation in the prefrontal cortex, including the anterior cingulate cortex, during diverse emotional tasks (Harrison et al., 2008; Ishai, Ungerleider, and Haxby, 2000; López-Solà et al. 2010; Moll et al., 2005). The prefrontal cortex has generally been conceptualized in terms of continuum from ventromedial 'affective' and dorsal 'cognitive' subdivision (Bush, Luu, and Posner, 2000; Margulies et al., 2007). The affective subdivision is suggested to have special relevance during emotional evaluation of self-related material, the monitoring of somatic states and the emotional value representation of stimuli and actions (Craig, 2003; Rolls and Grabenhorst, 2008; Rudebeck, Bannerman, and Rushworth, 2008). The cognitive subdivision in turn, has been more related to attentional and higher order executive functions such as the monitoring, detection and signaling of conflicts and errors during information processing, including emotion processing (Botvinick, Cohen, and Carter, 2004; Carter et al., 2002; Koski and Paus, 2000).

Finally, it is worth noting potential implications of posteromedial regions in emotional processing, including the posterior cingulate and the precuneus cortices. These regions present dense structural connections to many emotional processing brain regions, such as the hippocampus (Margulies et al., 2009), and show activity during self-awareness processing and during res (Harrison et al., 2008; Pujol et al., 2002). As this area is also part

of the so-called 'default mode network', larger discussion of the role of this area will be provided in later sections.

1.1.3. Attentional influences on emotion processing

For adequate emotional processing, a balanced perception and use of the emotional information is required. Neuroimaging studies have hypothesized that the dorsal and ventral attentional brain networks can likely contribute to this equilibrium (Corbetta and Shulman, 2002). These brain networks carry different attentional functions to the demands in complex contexts. The dorsal attentional system includes superior frontal and intraparietal cortices and facilitates goal-directed attention (i.e. top-down) and associated behavioral (motor) responses. Conversely, a right hemisphere-dominant ventral attentional network includes temporoparietal and inferior frontal cortices and notices stimuli in the environment that may be salient or behaviorally important.

Both attentional systems reciprocally interact during emotional processing. For instance, the ventral attentional system would work as a 'circuit breaker' for the dorsal attentional system thus directing attention to salient events (i.e. to threat), whereas this latest modulates the saliency of emotion-laden stimuli, placing the focus of attention in alternative stimuli. This latest has been supported by Pessoa, McKenna, Gutierrez, and Ungerleider (2002) showing that the amygdala do not respond differentially to emotional faces when attentional resources were recruited elsewhere, indicating that emotional processing in the amygdala is susceptible to top–down control. As a matter of curiosity, it has been suggested that attentional processes may mediate emotional processing deficits in psychopathy (Lorenz and Newman, 2002; Newman and Baskin-Sommers, 2011). This point will be further discussed in section 1.3.

Finally, emotion processing and saliency attribution can be also determined by the modulation exerted on sensory processing. Neuroimaging studies support a role of the amygdala in this kind of modulation by showing visual cortex activation to be dependent from feedback from this brain structure during implicit emotional processing. In this line, Morris et al. (1998) showed that amygdala responses predict specific neural activity in extrastriate cortex, effect attenuated in patients with amygdala damage (Vuilleumier and Driver 2007; Vuilleumier, Richardson, Armony, Driver, and Dolan, 2004) (Figure 3).

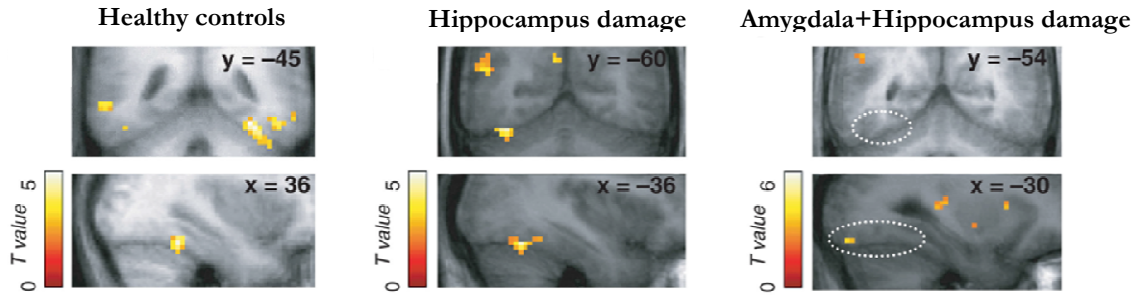

Figure 3. Main effect of emotion (fearful>neutral faces). Activation of posterior visual areas was found in healthy controls and patients with hippocampal damage only but not in patients with hippocampal and amygdala damage (adapted from Vuilleumier 2007).

Overall, for a complete emotional experience, both external and internal emotional signals should be jointly processed with prefrontal and sensory cortices in the brain. Therefore, the influence emotion exerts on behavior is not the direct consequence of the quality and intensity of the emotional laden stimuli but holds a high degree of inter-subject variability.

- Moral judgment brain network

In recent years, neuroscience has shown a growing interest in human morality advancing the understanding of the cognitive and emotional processes involved in moral decisions and their anatomical substrates. The brain regions underlying moral judgment include medial and lateral frontal regions, limbic and paralimbic regions and temporal cortices (Moll, Zahn, de Oliveira-Souza, Krueger, and Grafman, 2005) (Figure 4).

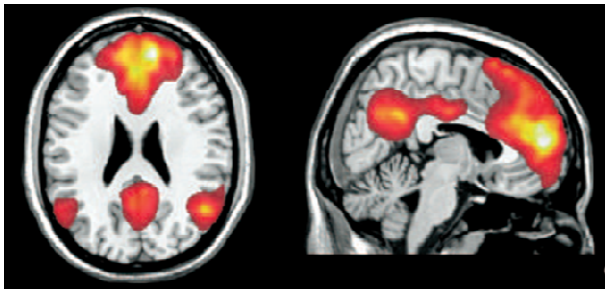

Figure 4. Brain network underlying moral judgment in healthy subjects (adapted from Harrison 2008).

Initial evidence of the crucial implication of prefrontal areas in moral processes was provided by early accounts of frontal lobe damage and neurosurgical reports of war wounds (Anderson et al., 1999; Grafman et al., 1996; Koenigs et al., 2007; Macmillan, 2000). Eslinger and Damasio (1985) described moral behavioral deficits in a patient with damage to the ventromedial PFC acquired in adulthood, who was remarkably unimpaired in specific moral reasoning tasks. Moreover, ventromedial PFC lesions acquired at an early age led to

impairments in both moral reasoning and behavior, indicating that moral development can be arrested by early PFC damage (Anderson et al., 1999).

Neuroimaging data in healthy subjects suggest that the role of different frontal areas probably differs during moral decision processing. Some have proposed that whereas the orbital and ventromedial prefrontal cortices emotionally drive moral decisions (Damasio, 1994; Heekeren, Wartenburger, Schmidt, Schwintowski, and Villringer, 2003; Greene et al., 2001; Moll et al., 2003; Rolls, 2000), the dorsolateral prefrontal cortex acts mainly as a rational 'filter', being involved in problem-solving and cognitive control processes suppressing prepotent emotional reactions in ventromedial prefrontal cortices(Greene et al., 2004; Kim and Hamann, 2007; Ochsner, Bunge, Gross, and Gabrieli, 2002, Ochsner et al., 2004). This dual opposite processing between ventromedial and the dorsolateral prefrontal cortex seems to be mediated by the anterior cingulate cortex (Greene et al., 2001; Greene et al., 2004; Harenski, Antonenko, Shane, and Kiehl, 2008), while the posterior cingulate cortex may be more closely related to social ability skills (Greene et al., 2001; Greene et al., 2004).

Limbic and paralimbic brain regions, such as the amygdala and the insula, have also a key role in moral judgment processes. The amygdala shows activation to moral emotions (Moll et al., 2005), evaluation of moral judgment (Greene et al., 2004) and violation of severity ratings for moral pictures (Harenski et al., 2008). Insular activation is also found during various morals tasks, specifically in relation to disgust and uncertainty processing (Cooper, Kreps, Wiebe, Pirkl, and Knutson, 2010; Greene et al., 2004; Moll et al., 2005). These brain structures are crucial in the assignment of the emotional and motivational significance to the specific moral situation thus exerting a powerful influence over final decisions by its integration through cortico-limbic networks (Amaral and Insausti, 1992; Carmichael and Price, 1995). In other words, cortical representations allow a realization that someone is hurt, but when information from emotion-related brain centers is integrated, the same situation elicits anxiety and attachment, which encourage helping the suffering person.

Another important brain structure for moral behavior is the temporal lobe. Neuroimaging studies found activation in the superior temporal sulcus, anterior and middle temporal gyrus, temporo-parietal and angular gyrus under diverse moral situation tasks (Greene et al., 2004; Heekeren et al., 2003, Harenski and Hamann, 2006; Moll et al., 2005; Sommer et al.,

2010). Social perceptual features such as facial expressions, gaze, prosody, body posture and gestures are stored in superior temporal sulcus (Allison, Puce, and McCarthy, 2000; Hein and Knight, 2008). However, the link of the social perceptual features with semantic knowledge is performed by anterior temporal cortex (Patterson, Nestor, and Rogers, 2007). A further temporal region activated during moral dilemma evaluation is the angular gyrus which has been involved in evaluating moral agency and responsibility (Borg, Hynes, Van Horn, Grafton, and Sinnott-Armstrong, 2006). Finally, the temporo-parietal junction is associated with the spontaneous, unsolicited attention directed towards cues that have potential moral salience, in agreement with belonging to the ventral attentional systems discussed prior (Corbetta and Shulman, 2002).

It is of important for the present work to briefly introduce some of the most relevant neurobiological models in moral judgment. The dual-process model of moral behavior (Greene and Haidt, 2002; Grenne et al., 2004; Greene et al., 2001) posits mutually competitive roles of cognition and emotion during resolution of moral conflict. In this line, a study shows how personal dilemmas are more likely to engage brain regions underlying socio-emotional processes (i.e. amygdala, medial cortex, posterior cingulate/precuneus), whereas impersonal and utilitarian moral judgments tend to engage brain areas associated with abstract reasoning and problem solving such as lateral fronto-parietal regions (Greene et al., 2004). Contrarily, the event-feature-emotion complex framework of Moll et al. (2005) proposes that morality emerges from the integration, not the competition, of the different cognitive and emotional brain regions implicated.

- Emotion face processing brain network

The existence of a specialized neural system for face perception was first suggested by the observation that patients with prosopagnosia, a syndrome characterized by selectively impaired ability to recognize faces from known individuals, was associated with focal brain damage in ventral occipitotemporal cortex (Damasio, Damasio, and Van Hoesen, 1982; McNeil and Warrington, 1993). Further evidence came from single-unit recording studies in macaques that identified neurons in the temporal cortex that respond selectively to faces (Desimone, 1991; Perrett, Rolls, and Caan, 1982). Following these initial evidences, functional imaging techniques have characterized the neural network underlying face perception in humans (Haxby et al., 2000; Ishai, Ungerleider, and Haxby, 2000).

Overall, processing the emotional significance from faces of other individuals requires the participation of two routes: (i) a cortical pathway from visual cortex via temporal cortex and onto limbic areas (retinogeniculostriate-extrastriate-fusiform) and (ii) a subcortical pathway (retinocollicular-pulvinar-amygdalar) (Adolphs, 2002; de Gelder, Vroomen, Pourtois, and Weiskrantz, 1999; Morris et al., 1999). The cortical route is thought to allow more precise stimulus encoding, while the subcortical route is thought to provide coarse stimulus processing (Armony and LeDoux, 1997; LeDoux, 2000) (Figure 5).

Cumulating neuroimaging studies report consistent activity in the fusiform gyrus, occipital-visual cortices and posterior superior temporal sulcus during perception of faces (Haxby et al., 2000; Ishai et al., 2000). The so-called term 'fusiform face area' derived from repeated observations of greater fusiform gyrus activity to emotional faces than to neutral faces and non-face objects (Ishai et al., 2000; Vuilleumier, Armony, Driver, and Dolan, 2001). Specifically, its function has been mostly related to the perception of invariant aspects of faces, such as recognition of identity, while activation of the posterior superior temporal sulcus has been related to the perception of biological movement, including movement of the eyes and mouth (Haxby et al., 2000; Ishai et al., 2000).

Within the emotion brain elements, the perception of emotional expressions has been found to evoke activity in the amygdala and insula regions. Consistent amygdala activation is found in response to positive and negative emotional expressions (Baird et al., 1999; Blair, 1999; Breiter et al., 1996), although most consistent activation has been reported for fearful face expressions (Morris et

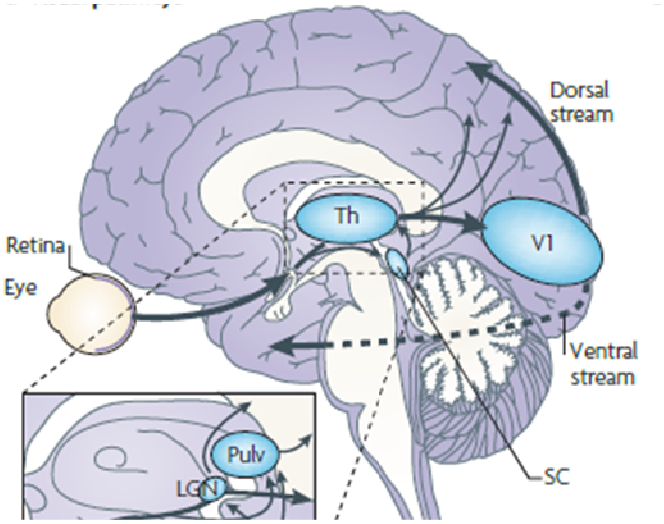

Figure 5. The primary visual pathway (thick arrow) originates from the retina and projects to the primary visual cortex (V1) in the occipital lobe via an intermediate station in the thalamus (Th). From V1, visual information reaches the extrastriate cortex along the ventral (occipitotemporal, cortical route) and the dorsal (occipitoparietal) streams. However, a minority of fibres from the retina takes a secondary route (thin arrow) and reaches both the superior colliculus (SC) and the pulvinar (Pulv) (subcortical route).

al., 1996; Whalen et al., 1998). In agreement, amygdala damage is associated with deficits in recognizing 'basic' emotional expressions, again most reliably for fear (Adolphs et al., 1999; Calder et al., 1996) and with alterations to infer more complex "social" emotions, such as guilt (Adolphs, 2002). The perception of disgust in turn, more likely evokes response in both insula and basal ganglia as supported by the impaired recognition of disgust in patients with Huntington disease that initially affects the basal ganglia (Gray, Young, Barker, Curtis, and Gibson, 1997; Phillips et al., 1997; Sprengelmeyer et al., 1996).

The activity in the elements of the network underlying emotional face recognition is modulated via their well-established reciprocal connections (Fairhall and Ishai, 2007; Pessoa et al., 2002; Pujol et al., 2009). For instance, the amygdala maintains feedback projections with visual occipito-temporal cortex and the fusiform gyrus (Amaral and Insausti, 1992; Fairhall and Ishai, 2007; Haxby et al., 2000). Considering the above-mentioned attentional effects through cortical activity modulation, these projections allow the amygdala to influence the level of activation of sensory cortices, thus enhancing the advantage of emotional face information in social relationships (Damaraju, Huang, Barrett, and Pessoa, 2009; Morris et al., 1998). Moreover, the relationship between the amygdala and the fusiform face area is modulated by anxiety-related personality traits and emotional abilities in general (Japee, Crocker, Carver, Pessoa, and Ungerleider, 2009; Pujol et al., 2009).

Finally, although not specific to the neural substrate for emotional face processing, prefrontal cortices also act in concert with the face-responsive occipito-temporal regions to allow emotional face expressions to access consciousness, determining its emotional significance and modulating final behavior (Corbetta and Shulman, 2002; Haxby et al., 2000; Ishai et al., 2000).

1.2. Spontaneous fluctuations

1.2.1. The concept of spontaneous brain activity

Neuroimaging research has provided an abundance of useful data in characterizing the function of the neural networks underlying emotional processing and how the brain balances the demands in complex attentional contexts. This previous knowledge fits well with the view of the brain as driven by momentary environmental demands. However, a significant amount of brain activity and metabolic requirements persist in the absence of external challenges during rest, sleep and anesthesia states (Raichle and Mintun, 2006). This implies that intrinsic activity at rest may be at least as important as evoked activity in understanding overall brain function.

First imaging insights into the intrinsic activity of the brain during rest states come from the studies conducted by David Ingvar (Ingvar, 1974, 1979), whose work established that '*the brain is not idle when left undirected but persists in the absence of external stimulation and that increased activity during rest is localized to specific brain regions*'. Decades later, the study of resting brain activity was again embraced when methods for brain imaging gained prominence. By the mid-1990s resting-state brain activity were often acquired in PET studies for a control comparison, and researchers began to repeatedly notice brain regions were more active in passive control conditions than to the active target tasks (Baker et al., 1996; Ghatan et al., 1995). A further step to the study of the resting brain activity was provided by the study of Andreasen et al. (1995) when, confronted with the difficulty of defining a baseline state for autobiographical memory task, they hypothesized that such tasks inherently involved internally directed cognition, like the spontaneous cognition that occur during resting-states. However, a series of publications by Raichle, Gusnard et al. (Gusnard, Akbudak, Shulman, and Raichle, 2001; Gusnard and Raichle, 2001; Raichle et al., 2001) constitute the initial point for considering the baseline state of the brain as an area of study itself. They provided evidence regarding its specific deactivation from other forms of deactivations and compiled information about its particular anatomy and function.

At all levels of the nervous system, from individual neurons (Tsodyks, Kneet, Grinvald, and Arieli, 1999) and cortical columns (Arieli, Shoham, Hildesheim, and Grinvald, 1995) to whole brain systems (Biswal, Yetkin, Haughton, and Hyde, 1995; De Luca, Beckmann, De Stefano, Matthews, and Smith, 2006), there is spontaneous activity that is related to the functional and anatomic organization of the brain (Greicius, Supekar, Menon, and Dougherty, 2009; Vincent et al., 2007). Based on studies showing an association between cortical electrical activity and the BOLD signal (Goldman, Stern, Engel, and Cohen, 2002;

Martinez-Montes, Valdes-Sosa, Miwakeichi, Goldman, and Cohen, 2004) and the observation of changes in baseline in brain function following neurological disease (Greicius, Srivastava, Reiss, and Menon, 2004), a considerable fraction of the variance in the BOLD signal in low-frequency (below 0.1 Hz) has been suggested to reflect the neuronal baseline activity of the brain. These spontaneous fluctuations in neuronal activity exhibit striking patterns of temporal coherence and are correlated across the brain during resting-states, allowing the characterization of the intrinsic architecture of large-scale brain systems (Damoiseaux et al., 2006; De Luca et al., 2006; Beckmann, DeLuca, Devlin, and Smith, 2005), an approach often referred to as resting-state functional connectivity (Biswal et al., 1995, Fox and Raichle, 2007; Haughton and Biswal, 1998).

The functional role of these spontaneous fluctuations across brain networks remains speculative. A putative proposal has been that the intrinsic function of the brain subserves the temporal binding of information, particularly related to the coordination and neuronal organization of brain activity between regions that frequently work in combination while other suggest a function in the maintenance of information for interpreting, responding to and even predicting environmental demands (Engel, Fries, and Singer, 2001; Fox and Raichle, 2007; Fransson, 2005).

1.2.2.Neuroimaging outline of spontaneous function

Neuroimaging studies have shown highly organized and coherent patterns of fluctuations during resting-states within known brain networks spontaneously increasing and decreasing its activity together in a correlated manner in the absence of observable behaviors associated with those systems during resting-states (De Luca et al., 2006; Greicius, Krasnow, Reiss, and Menon, 2003; Greicius et al., 2004). These fluctuating patterns of coherence are remarkably consistent among individuals as well as across subject groups (Beckmann et al., 2005; Damoiseaux et al., 2006; De Luca et al., 2006; Fox et al., 2005). Although the default mode network has been the most studied spontaneous network, several resting state networks have been identified, including dorsal attentional, executive control, salience, sensorimotor, visual and auditory brain networks (Beckmann et al., 2005; Damoiseaux et al., 2006; De Luca et al., 2006) (Figure 6).

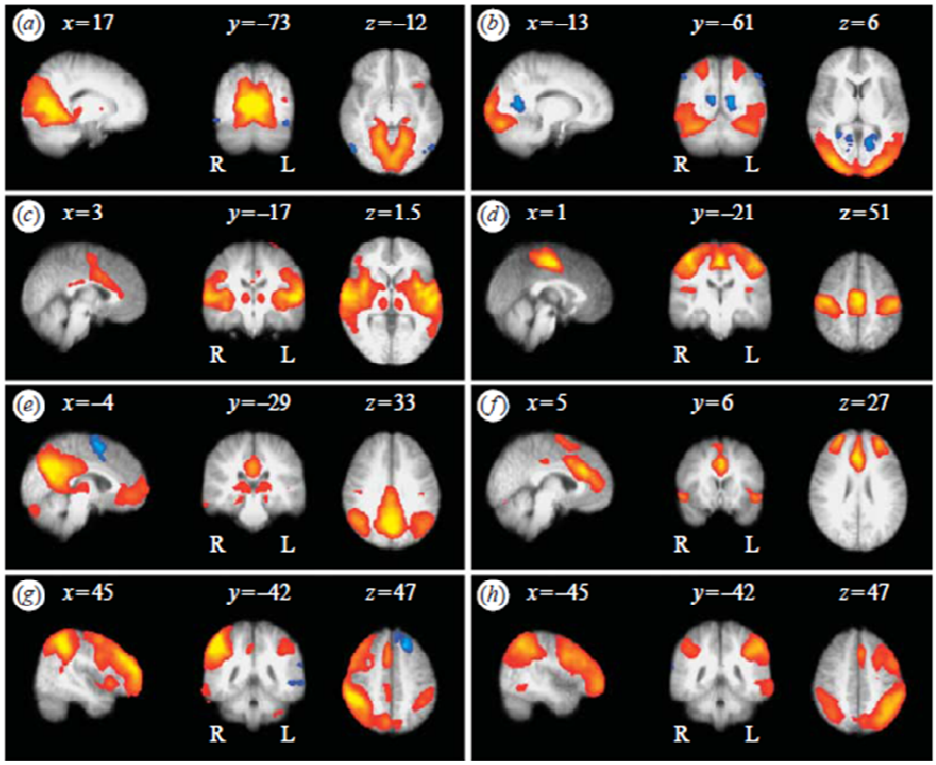

Figure 6. Low-frequency resting patterns: Medial visual areas (a); Lateral visual areas (b); Auditory system (c);Sensory-motor system (d); Visuo-spatial system (e); Executive control system (f); Dorsal attentional system (g, h) (adapted from Beckmann 2005).

The default mode network (Raichle, 2001), included medial frontal and posteromedial parietal cortices, including posterior cingulate and adjacent precuneus cortices, and bilateral angular gyri. Although less consistently reported, this network can also include the hippocampus and adjacent temporal cortices associated with episodic memory function (Greicius et al., 2004). This set of brain regions shows both a highly active metabolism and synchronized activity fluctuations during wakeful rest states. Nevertheless, this brain network also activates during tasks involving self-relevant experiences, including moral judgment tasks (Buckner and Carroll, 2007; Greene et al., 2001; Harrison et al., 2008; Pujol et al., 2008). Nevertheless, the default mode network strongly deactivates when the attentional focus is driven to external targets (Grecius et al., 2003; Gusnard and Raichle, 2001; Fox et al., 2005; Harrison et al., 2008; Raichle et al., 2001). This is because the default network operates in opposition to other brain systems that are used for focused external attention and sensory processing (Greicius et al., 2003; Fox et al., 2005; Uddin, Kelly, Biswal, Castellanos, and Milham, 2009). When the default network is most active, external attentional systems are attenuated and vice versa (Harrison et al., 2008).

Although the activity within the default mode network appears to be a relatively enduring phenomenon (Vincent et al., 2007), the function of the default mode network is modulated by cognitive and emotional states. For instance, the degree of deactivation during tasks that require an external attentional focus depends on task-difficulty; as more cognitively demanding the task, a stronger deactivation is observed (Harrison et al., 2011; McKiernan, D'Angelo, Kaufman, and Binder, 2006; Singh and Fawcett, 2008). In addition, relevant changes in the default mode network function emerge associated with emotional states. Harrison et al. (2008) found both decrease functional connectivity in midline regions of the default mode network but increase functional connectivity in the interoceptive awareness paralimbic related resting-state network, when comparing the recalling of sad experiences with a neutral condition. Finally, personality traits have been reported to have an influence on the default mode function, contributing to understand the role of this network in behavior (Deckersbach et al., 2006; Kim, Hwang, Park, and Kim, 2008; Kunisato et al., 2011). As a matter of interest at this point, psychopathic traits in healthy samples have been inversely related to the activation of the default brain network during a moral dilemma task (Reniers et al., 2012).

1.3. Approach to the study populations

This sections aims to provide an overview of the clinical profiles and the most relevant brain changes reported by the neuroimaging scientific literature in psychopathic individuals, cocaine dependence and obsessive-compulsive disorder patients.

1.3.1. Psychopathy

- Clinical features

Few psychological concepts evoke simultaneously as much fascination and misunderstanding as psychopathy. Pioneer clinical descriptions of psychopathy were provided in the book 'The Mask of Sanity', written by Hervey Cleckley and first published in 1941 (Cleckley, 1976). This seminal work provided the most influential clinical description of psychopathy in the 20th century which is still relevant today. The term 'mask of sanity' derived from Checkley observes that, unlike people with major mental disorders, a psychopath can appear normal despite their emotional and behavioral disturbances.

The psychopathic diagnosis, as defined by the Hare's Psychopathy Checklist-Revised (PCL-R; Hare, 2003), includes both affective-unemotional and interpersonal features as well as antisocial behaviors. Core affective and interpersonal features refer to shallow affect, lack of guilt and remorse, glib superficial charm, grandiose sense of self-worth, pathological lying and coning and manipulative features. In the behavioral domain, psychopaths show parasitic lifestyle, poor behavioral control, need for stimulation or proneness to boredom, lack of realistic long-term goals, impulsivity and irresponsibility, juvenile delinquency and criminal versatility (Hare, 2003). These traits characterizing the psychopathic individual are present at very early age (Frick, 1995; Frick, Bodin, and Barry, 2000; Frick, O'Brien, Wootton, and McBurnett, 1994). Finally, although no epidemiological studies have been conducted examining the prevalence of adult psychopaths in the community, the prevalence in forensic samples has been estimated to be 25% of those with a diagnosis of antisocial personality disorder (Hare, 1996). Based on this calculation previous and the 3% community incidence rate of antisocial personality disorder suggested by the DSM-IV, the incidence of adult psychopaths has been estimated to be up to 0.75% in the community.

Although the PCL-R has been found to correlate with antisocial personality disorder (Leistico, Salekin, de Coster, and Roger, 2008), it is important to note that psychopathy constitutes a different condition. Criteria for the diagnosis of antisocial personality disorder are based on behavioral traits and fail to capture the affective core deficits in psychopathy (First, Gibbon, Spitzer, Williams, and Smith Benjamin, 1997). Thus, differences between conditions fall upon the fact that while psychopaths are cold-hearted, grandiose, manipulative, display shallow affect, are unable to form long-lasting bonds, lack emotional empathy, remorse and guilt, individuals diagnosed with antisocial personality disorder typically demonstrate behaviors that go against social norms, but they may not demonstrate the personality traits common to psychopathic individuals listed earlier.

Cumulating scientific evidence indicates blunted processing of emotional information in psychopathic individuals. Although initial suggestions that the emotional processing deficit may be restricted to negative information, especially fear-related cues (Lykken, 1957); psychopaths have demonstrated similar impairments when using positive valence information (Cleckley, 1976; Eisenbarth, Alpers, Segrè, Calogero, and Angrilli, 2008; Herpertz et al., 2001; Levenston, Patrick, Bradley, and Lang, 2000). Overall, psychopaths benefit less from emotional content in memory tasks (Christianson et al., 1996; Glass and Newman, 2009; although see Kiehl et al., 2001), have problems to discriminate the

subtleties between affective and neutral words (Williamson, Harpur, and Hare, 1991), show impairment in aversive conditioning, passive avoidance learning and response reversal (Flor, Birbaumer, Hermann, Ziegler, and Patrick, 2002; Lykken, 1957; Mitchell, Colledge, Leonard, and Blair, 2002; Newman and Kosson, 1986; Newman, Patterson, and Kosson, 1987) and present deficits when processing both emotional voice speech and emotional face expressions (Bagley, Abramowitz, and Kosson, 2009; Blair and Coles, 2000; Blair, Colledge, Murray, and Mitchell, 2001; Blair et al., 2002). Moreover, psychopaths show reduced skin conductance responses and startle blink inhibition while visualizing emotional stimuli (Blair, Jones, Clark, and Smith, 1997; Herpertz, 2001; Levenston et al., 2000; Lykken, 1957; Newman, Curtin, Bertsch, and Baskin-Sommers, 2010; Pastor, Moltó, Vila, and Lang, 2003; Patrick, Bradley, and Lang, 1993; Patrick, Cuthbert, and Lang, 1994; Sutton, Vitale, and Newman, 2002) and during aversive conditioning tasks (Aniskiewicz, 1979; Birbaumer et al., 2005).

Traditional emotional-based perspectives have hypothesized that the emotional impairment found in individuals with psychopathy interferes with the socialization processes, such that the individual does not learn to avoid antisocial behavior (Blair, 2003b; Blair and Mitchell, 2009). In other words, behavior will be compromised by the fact that the deficient processing of emotional cues will compromise abilities that require empathizing with others, forming stable relationships, learning from mistakes and making adaptive decisions, especially in moral circumstances. Nevertheless, others have suggested that altered attentional processes may mediate emotional processing deficits in psychopaths because a deficit in shifting attention from effortful organization and implementation of goal-directed behavior to its evaluation (Lorenz and Newman, 2002). Consistent with this previous model, psychopathic individuals and non-psychopathic offenders display comparable behavioral and psychophysiological responses under emotion-focused conditions, but not during alternative-focus conditions, or when an extended intertrial interval is provided (Arnett, Howland, Smith, and Newman, 1993; Arnett, Smith, and Newman, 1997; Glass and Newman, 2009; Hiatt, Schmitt, and Newman, 2004; Newman et al., 2010; Newman and Kosson, 1986; Newman et al., 1987). Moreover, psychopaths are less interfered by emotional but also neutral cues suggesting that alterations may involve impairment in larger brain networks (Blair, 2006; Dvorak-Bertsch, Sadeh, Glass, Thornton, and Newman, 2007; Hiatt et al., 2004; Lykken, 1957; Newman, Schmitt, and Voss, 1997; Vitale, Brinkley, Hiatt, and Newman, 2007; Zeier, Maxwell, and Newman, 2009).

- Contributions of neuroimaging research on psychopathy

The neurobiological basis of psychopathy has been traditionally linked to certain dysfunctions in a circuit comprising the amygdala and ventromedial prefrontal cortex (Blair, 2004, 2006, 2007). Abnormalities within this brain network have been related to the psychopaths' deficient reinforcement learning, such as fear conditioning-associations (Davis and Whalen, 2001), (mis)representations of the value of behavioral outcomes (Blair, 2007), and deficits in extinction and reversal learning (Birbaumer et al., 2005; Veit et al., 2002). Most repeated finding in neuroimaging studies point towards amygdala reduced activations both during the processing of emotional information (Deeley et al., 2006; Jones, Laurens, Herba, Barker, and Viding, 2009; Kiehl et al., 2001; Marsh et al., 2008) as well as in socio-moral contexts (Glenn, Raine, and Schug, 2009; Osumi et al., 2012; Marsh et al., 2011), and there are some reports of amygdala volume reductions (Tiihonen et al., 2000; Yang, Raine, Narr, Colletti, and Toga, 2009; Yang, Raine, Narr, Lencz,, and Toga, 2006). Alterations in ventromedial prefrontal cortex have also been reported (de Oliveira-Souza et al., 2008; Veit et al., 2002; Yang, Raine, Colletti, Toga, and Narr, 2010). Additionally, many recent studies have reported the existence of connectivity alterations between the amygdala and ventromedial prefrontal cortices using both functional and structural connectivity measures (Craig, 2009; Marsh et al., 2011; Marsh et al., 2008; Motzkin, Newman, Kiehl, and Koenigs, 2011).

Despite the emphasis on amygdala-ventromedial prefrontal cortex alterations, others researchers have proposed that a broader paralimbic dysfunction may also contribute to the deficits observed in psychopathic individuals (Kiehl, 2006). In agreement, psychopaths show reduced activation during emotional processing tasks (Birbaumer et al., 2005; Kiehl et al., 2001; Müller et al., 2003; Veit et al., 2002;), reduced functional connectivity at rest (Ly et al., 2012), and structural alterations (de Oliveira-Souza et al., 2008; Ly et al., 2012; Yang et al., 2009) involving the insula, the cingulate and temporal cortices. Moreover, in line with models suggesting a putative contribution of the attentional mechanisms to explain the psychopathic affective-interpersonal and self-regulatory deficits, it has been hypothesized that psychopaths may possess alterations within dorsal fronto-cingulate networks (MacCoon, Wallace, and Newman, 2004; Newman and Baskin-Sommers, 2011). None the less, the neuroimaging data supporting this previous dysfunction in psychopaths remains

inconsistent and few studies have directly assessed its function (White et al., 2012a, 2012b). In general, psychopaths showed reduced dorsal anterior cingulate cortex activation (Birbaumer et al., 2005; Kielh et al., 2001; Veit et al., 2002;), but also concomitant activation of lateral frontal (arguably) compensatory mechanisms (Glenn et al., 2009; Intrator et al., 1997; Kiehl et al., 2001) during emotional tasks. Regarding the anatomical integrity of the executive brain networks in psychopaths, some studies report volumetric changes (Müller et al., 2008; Yang et al., 2009) while others do not (Glenn, Raine, and Colletti, 2010; Yang et al., 2010) and there are a number of studies showing decreased cortical thickness (Ly et al., 2012; Yang et al., 2010; Yang et al., 2009). Relevantly, a recent study shows the frontal network as an information flow control hub in psychopaths using anatomical connectivity measures (Yang et al., 2012).

In conclusion, psychopaths present with neural changes in certain emotional and cognitive regions during emotional processing tasks (Birbaumer et al., 2005; Glenn et al., 2009; Kiehl et al., 2001; Marsh et al., 2008), although some preliminary evidences do report the presence of changes also affecting the spontaneous function of the brain (Ly et al., 2012; Motzkin et al., 2011). However, there is a need of integrative studies assessing the function within large-scale brain networks that integrate emotional and cognitive neural processes both during emotional tasks and during resting states to better clarify brain disturbances in psychopathic individuals.

1.3.2. Cocaine users

- Clinical features

Drug addiction is a chronically relapsing disorder characterized by a compulsion to seek and take the drug, loss of control in limiting intake, and emergence of a negative emotional state (i.e. dysphoria, anxiety, irritability) reflecting a motivational withdrawal when the drug is prevented (First et al., 1997). Compulsion to take the drug seems to be dissociated to the known severe adverse consequences in negative health and in personal and social domains in the addicted subject (Volkow and Li, 2005).

Cocaine is the second most commonly used and trafficked illicit drug in the world after cannabis. Based on the latest reports from the US Department of Health and Human

Services, there were 1.5 million current cocaine users aged 12 or older in 2010, comprising 0.6% of the population (Samhsa, 2007). Somatic, psychological, psychiatric, socio-economic and judicial complications have been associated to cocaine addiction. This substance is a powerful central nervous system stimulant which increases alertness, feelings of well-being and euphoria, energy and motor activity, feelings of competence and sexuality.

Studies assessing emotional processing deficits in cocaine users point towards an exaggerated valuation during the perception and anticipation of drug-related stimuli, while a decreased response to other relevant emotional and social cues is observed (Garavan et al. 2000; Goldstein and Volkow 2002; Volkow et al., 2011), especially during protracted abstinence (Verdejo-García, Rivas-Pérez, Vilar-López, and Pérez-García, 2007). For instance, Garavan et al. (2000) found that cocaine users liked a film depicting two men engaged in a drug-specific dialogue while smoking 'crack cocaine' more than comparison subjects, although this study did not find between-group differences regarding the preference to other non-related drug films, including sex films. In this line, other studies report blunted affective responses to emotional facial expressions (Aguilar de Arcos, Verdejo-García, Peralta-Ramírez, Sánchez-Barrera, and Pérez-García, 2005; Fernández-Serrano, Lozano, Pérez-García, and Verdejo-García, 2010; Kemmis, Kingston, and Morgan, 2007) and to the subjective sensitivity to increasing amount of money (Goldstein et al., 2007), although exaggerated autonomic responses to monetary rewards has been also observed, probably because of an association with buying drugs.

This displacement of the emotional focus to the processing of drug-related cues would posit drug seeking and taking as a main motivational drive (Verdejo-García and Bechara, 2009; Verdejo-García, Pérez-García, and Bechara, 2006). At the behavioral level this previous would manifest in the impulsive and maladaptive behaviors shown by this population, the tendency to choose the immediate reward at the expense of negative future consequences and the failure to learn from repeated mistakes (Bechara, 2001; Bechara and Damasio, 2002; Bechara, Dolan, and Hindes, 2002; Grant, Contoreggi, and London, 2000) overall compromising decision-making processes. In other words, non-related drug positive emotional elements associated to motivationally relevant aspects in normal population are not 'strong' enough to balance those associated with drug use and to guide decision-making toward adaptive objectives, instead of toward drug use, in substance dependent subjects. In this line, Bechara and Damasio (2002) showed impaired anticipatory skin conductance

response in a subgroup of substance dependent individuals during the performance of the Iowa Gambling Task (IGT; Bechara, Damasio, Damasio, and, Anderson, 1994), suggesting an altered processing of non- related drug information that would impair behavioral selection.

The Somatic Marker model (Damasio, 1994) attributes the drug users' difficulty in making advantageous decisions in real-life to a defect in the neural circuitry responsible for the generation and integration of emotional signals or somatic markers (Verdejo-García and Bechara, 2009; Verdejo-García et al., 2006). The term 'somatic' refers to the collection of responses generated both in the body and in the brain that are hallmarks of emotional responses, which connected by learning to anticipated futures outcomes serve to anticipate and flexibly modulate behavior in different contexts. As previously discussed for the moral dilemma situations, when a negative somatic marker is juxtaposed to a particular future outcome the combination functions as an alarm bell but when a positive somatic marker is juxtaposed instead, it becomes a beacon of incentive. Neural systems thought to be affected under this model will be discussed in the next section.

- Contributions of neuroimaging research on cocaine users

Initial research assessing the brain network altered under drug dependence focused on the acute rewarding effects of drug intake in midbrain and in basal ganglia areas, where the nucleus accumbens in located. Nevertheless, current neuroimaging studies focus on larger brain networks including ventromedial frontal, cingulate cortices and further limbic regions. This set of brain regions is engaged during drug-related processes, such as coding for saliency attribution, the awareness and interoception of pleasant and unpleasant feelings and also subserve decision-making processes (Goldstein and Volkow, 2011).

As previously introduced, the Somatic Marker Hypothesis provides an integrative neural model linking decision-making deficits in substance users with emotional processing impairment (Damasio, 1994). Specifically, this model hypothesized that the drug users' difficulty in making advantageous decision in complex real-life is due to a defect in the neural cortico-limbic circuitry that subserves the triggering and integration of the emotional signals (somatic markers) (Verdejo-García and Bechara, 2009). Within this model, the limbic regions would detect and recognize environmental features that are potential sources of immediate pleasure or satisfaction of homeostatic needs (i.e. such as withdrawal relief),

triggering responses in other brain areas that may become translated into feelings of desire, anticipation, and urge to take the drug. Following this, ventromedial frontal regions would serve a role in coupling two sets of neural systems. The first system involves the dorsolateral prefrontal cortex which subserves working memory and executive processes (inhibition, planning, cognitive flexibility). The second system, mainly governed by emotional processing brain regions such as the insula, amygdala and posterior cingulate cortices, is responsible for processing emotions, including awareness of interoceptive signals (Critchley et al., 2003). The Somatic Marker Hypothesis proposes that an imbalance function within these two brain systems may contribute to the maladaptive decision-making in drug users.

Neuroimaging studies support the plausibility of the above model showing alterations in cortico-limbic circuits in cocaine users (Bolla et al., 2003; Tanabe et al., 2009). Particularly, these brain circuits are repeatedly stimulated by the continuous cocaine abuse (Breiter et al., 1997; Goldstein et al., 2009; Kufahl et al., 2008; Kufahl et al., 2005) and show an enhanced activation to drug-related stimuli (Childress et al., 2008; Childress et al., 1999; Goldstein et al., 2009; Goldstein and Volkow, 2002; Maas et al., 1998; Wilcox, Teshiba, Merideth, Ling, and Mayer, 2011), even when cocaine cues are presented without awareness (Childress et al., 2008). However, a reduced response within the same cortico-limbic circuits to non-related drug stimuli has been observed (Asensio et al., 2010; Garavan et al., 2000; Goldstein and Volkow, 2011; Wexler et al., 2001; Wilcox et al., 2011). This contradictory function of the cortico-limbic circuitry to the cocaine-related and non-related cues may contribute to the maladaptive decision-making in cocaine users. Nevertheless, no study to our knowledge has directly assessed brain activation during complex decision-making tasks. Moreover, despite preliminary reports of spontaneous functional connectivity changes during rest in active cocaine users (Camchong, et al., 2011; Gu et al., 2010; Wilcox et al., 2011), no study has been conducted in cocaine users during controlled abstinence.

In conclusion, cocaine-dependent subjects present an imbalance neural processing to related and non-related cocaine cues (Childress et al., 2008). However, although this previous has been suggested to impair adaptive decision-making processes in cocaine-dependent subjects (Verdejo-García and Bechara, 2009), no study has assessed brain activity under a complex decision-making task such as the moral dilemma task employed in the present thesis. Furthermore, based on the existent neuroimaging scientific literature suggesting impaired functional connectivity in active cocaine users (Camchong et al., 2011;

Gu et al., 2010; Tomasi et al., 2010; Wilcox et al., 2011; Worhunsky et al., 2012), there is a need to investigate whether such changes do exist even during protracted cocaine abstinence.

1.3.3. Obsessive-compulsive disorder

- Clinical features

Obsessive-compulsive disorder is a chronically debilitating disorder characterized by two sets of symptoms: obsessions and compulsions (First et al., 1997). Obsessions are unwanted, intrusive, recurrent thoughts or impulses that are often concerned with themes of contamination and 'germs', checking household items in case of fire or burglary, order and symmetry of objects, or fears of harming oneself. The anxiety generated by these obsessions push these individuals to ritualistic and repetitive compulsions, which can be manifested both at the behavioral and mental contexts i.e., washing, household safety checks, counting, rearrangement of objects in symmetrical array or constant checking of oneself and others to ensure no harm has occurred. These symptoms are time-consuming and cause marked distress and impairment. The lifetime prevalence of obsessive-compulsive disorder is estimated to be of 2–3% (Robins et al., 1984; Weissman et al., 1994).

Although it has been suggested that obsessive-compulsive disorder is associated with an enhanced processing of threatening information and reduced levels of cognitive inhibition (for a review see Summerfeldt and Endler, 1998), the experimental demonstration for such impairments has been less consistent and robust relative to other anxiety disorders (Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, and van IJzendoorn, 2007; Bishop, 2008; Cisler, Olantunji, Feldner, and Forsyth, 2010). The studies published so far have provided conflicting results. Although several studies have found such a bias (Foa, Ilai, McCarthy, Shoyer, and Murdock, 1993; Lavy, van Oppen, and van den Hout, 1994; McNeil, Tucker, Miranda, Lewin, and Nordgren, 1999; Novara and Sanavio, 2001), others failed to find processing differences for emotional material in obsessive-compulsive disorder (Kyrios and Iob, 1998; McNally, 1999; Moritz et al., 2008; Moritz et al., 2004). It has been suggested that these contradictory results may reflect difficulties in identifying standardized threat

stimuli for obsessive-compulsive subjects, due to the circumscribed and peculiar preoccupations in these individuals.

Cognitive behavioral models posit that obsessive-compulsive disorder emerges as a function of inflated responsibility composed of beliefs including the threat of a negative outcome, including moral threats, the prevention of a negative outcome as the primary goal and the belief in one's personal power to prevent the negative outcome (Salkovskis, 1985; Salkovskis and Forrester, 2002). Theoretical and empirical extensions of this model argue that the appraisals of responsibility, which were characteristic of obsessive-compulsive disorder, are mediated by fear of behaving badly and associated feelings of guilt (Mancini and Gangemi, 2004). To this regard, a better understanding of the components underlying attentional biases in obsessive-compulsive disorder may be informed by using stimuli that directly evoke fear of behaving badly and associated guilt feelings which seem to constitute unique attentional biases in these individuals. In this line, one study using erotica stimuli, which can evoke feeling of guilt because of their taboo nature and moral/religious concerns, found impaired target detection when these erotic stimuli were previously presented, indicating difficulty with attentional disengagement (Olatunji, Ciesielski, and Zald, 2011).

- Contributions of neuroimaging research on obsessive-compulsive disorder

A currently dominant model in obsessive-compulsive disorder focuses on abnormalities in cortico-frontal circuitry, with particular emphasis on the orbitofrontal-striatal circuits (Alexander, DeLong, and Strick, 1986; Menzies et al., 2008; Saxen, Brody, Schwartz, and Baxter, 1998). On the basis of functional neuroimaging studies, enhancement to symptom provocation tasks (Breiter et al., 1996; Mataix-Cols et al., 2004; Schienle, Schäfer, Stark, Walter, and Vaitl, 2005; Shapira et al., 2003), but a reduction to cognitive tasks within these fronto-subcortical circuits, have been reported in obsessive-compulsive disorder (Chamberlain et al., 2008; Gu et al., 2008; van den Heuvel et al., 2005). Moreover, it has been well established that the orbitofrontal cortex activity is increased even during resting-state conditions in patients with a diagnosis of obsessive-compulsive disorder (Harrison et al., 2009) while anatomical alterations have also been reported in this brain region (Kim et al., 2001; Pujol et al., 2004; Soriano-Mas et al., 2007; Valente et al., 2005).

Nevertheless, despite cumulating evidence supporting alterations within orbitofrontal-striatal circuits in obsessive-compulsive disorder, there is also consistent data showing activation abnormalities in lateral frontal, anterior cingulate, occipital and parietal cortices and the cerebellum, suggesting that more distributed large-scale brain systems disturbances may be involved. In fact, a number of neuroimaging studies employing cognitive tasks have reported abnormalities in regions of the lateral prefrontal cortex and parietal cortex (Maltby, Tolin, Worhunsky, O'Keefe, and Kiehl, 2005; Pujol et al., 1999; Remijnse et al., 2006; van den Heuvel et al., 2005; Viard et al., 2005).

Finally, even though there is some neuroimaging data reporting enhanced brain responses to specific disorder-related stimulation in obsessive-compulsive patients (Mataix-Cols et al., 2004; Schienle et al., 2005; van den Heuvel et al., 2005), it is less clear to what extent these brain regions also overactivate to basic, social relevant but disease-unrelated emotional cues in line with hypothesis suggesting enhanced emotional processing mechanisms in these individuals similar to anxiety disorders. The few neuroimaging studies that have used disease-unrelated but relevant salient emotional stimuli to assess the neurobiological mechanisms in obsessive-compulsive patients report inconclusive data. For instance, obsessive-compulsive patients showed brain hyperactivation to emotional face expressions in some neuroimaging studies (Cardoner te al., 2011; Via et al., 2013), disorder-irrelevant aversive pictures (Schienle 2005), while in others did not (Britton et al., 2010; Cannistraro et al., 2004; Lawrence et al., 2007).

In conclusion, cumulating evidence demonstrates that obsessive-compulsive disorder presents alterations in cortico-frontal circuits and in other brain regions (Harrison et al., 2009; Menzies et al., 2008; Pujol et al., 1999; Remijnse et al., 2006; Saxena et al., 1998). However it remains uncertain whether enhanced brain responses are restricted to the processing of disorder-relevant stimuli, involve other disease-unrelated emotional information in line with the bias processing that characterize anxiety disorders (Bishop, 2008) or are otherwise only overactive to stimuli that evoke feelings of guilt and responsibility which seem to constitute unique attentional biases in obsessive-compulsive individuals (Salkovskis, 1985; Salkovskis and Forrester, 2002).

2. METHODOLOGY

2.1. Experimental contexts

Moral Dilemma task: This paradigm was selected both to challenge activation in frontolimbic and default mode networks (Studies 1, 2 and 3). This approach involves 24 non-moral control story vignettes and 24 dilemma vignettes fully described in the supplementary material of the Study 1. On the day of the experiment, all dilemma and non-dilemma vignettes were accompanied by an artist-sketched illustration that depicted the core theme and a voice-prompted. For the control non-dilemma vignettes, subjects were told to simply indicate the outcome of each event when voice prompted for 'yes/no' answer. For the moral dilemma conditions, subjects were instructed to provide their own moral judgment on the different dilemma vignettes by raising either their index finger (yes) or index and middle fingers (no). Further details on the moral dilemma task are provided in Study 1, 2 and 3 of the present thesis.

Stroop task: This paradigm was used to assess the deactivation of the default mode network in psychopathic individuals (Study 1). Briefly, the task consisted in a self-paced computerized version of the Stroop color-word interference task. This paradigm involved three interleaved conditions; resting visual-fixation (R), congruent color-word stimulus blocks (C) and incongruent color-word stimulus blocks (I). During congruent trials, the stimulus 'XXXX' was centered on a black screen in one of three colors: red, green or blue. Correct responses were mapped to the following target stimuli; 'RED', 'GREEN' or 'BLUE', located below the cue stimulus and displayed in congruent ink color. During incongruent trials, the same stimulus configuration was presented, but, instead, the cue stimulus was one of the same three words presented in incongruent ink color. Subjects were instructed to match the color of the cue stimulus with the corresponding target word stimulus as quickly and accurately as possible, while mentally vocalizing their response (color naming). Subjects' task responses were registered using a right and left hand response device. Further details on the moral dilemma task are provided in Study 1 of the present thesis.

Emotional face processing task: This paradigm aimed to assess brain activation and functional connectivity responses in criminal psychopaths (Study 4). Specifically, we used a

modified version of the emotional face-matching task originally reported by Hariri, Bookheimer, and Mazziotta (2000). In brief, subjects were presented with a target face (center top; happy or fearful) and two probe faces (bottom left and right; happy, fearful and angry) and were instructed to match the probe expressing the same emotion to the target by pressing a button in either their left or right hand. As a control condition, subjects were presented with five-second trials of ovals or circles in an analogous configuration and were instructed to match the shape of the probe to the target. Subjects' task responses were registered using a right and a left hand MRI-compatible response device. Further details on the face emotional processing task are provided in Study 4 of the present thesis.

Resting-state sequence: This approach involves the study of the baseline temporal organization (i.e. functional connectivity or activity synchrony between distinct brain regions) of major emotional networks during a resting state. In the present thesis, this measure was used to explore the possible existence of an abnormal baseline organization of brain network subserving emotional processing (Studies 1, 2 and 5). Subjects were instructed to relax, stay awake and to lie still with their eyes closed.

2.2. Functional and anatomical MRI statistical analyses

Model-driven activation analysis: The majority of fMRI studies to date have adopted a conventional voxel-based mapping approach based on extensions of the general linear model for time-series analysis (Friston, Ashburner, Kiebel, Nichols, and Penny, 2007; Huettel, Song, and McCarthy, 2004). The basic premise behind such approaches is that the observed fMRI data may be accounted for by a combination of several experimental (or model) parameters (factors) and uncorrelated (or independently distributed) noise. Given the high number of statistical tests performed (one for each voxel) some correction factors for multiple comparisons will generally be applied, leading to the generation of statistically threshold 'activation' maps related to the experiment at hand.

Psychophysiological interaction analysis: This approach allows the assessment of the influence of a certain task (the "psychological factor") on the strength of functional coupling ("functional connectivity") between the time course of each region of interest (ROI) and the voxels activated during the task (Friston et al., 1997). Task-induced functional connectivity maps where the fMRI signal is predicted by the cross-product (PPI

interaction term) of the "physiological" (deconvolved time course of the given ROI) and the "psychological" factors (regressor representing the experimental paradigm) are obtained for each subject. In addition to the PPI interaction term, both the physiological and the psychological factors were included in the final SPM model as confound variables.

Seed-based functional connectivity analysis: This is a useful approach for the assessment of resting-state functional connectivity, that is, the temporal co-oscillation of BOLD signal between separate brain regions representing brain patterns of synchronized neural activity (Harrison et al., 2009). In this approach, the time course of a priori selected region of interest ("*seed*") is used as a regressor to be correlated with the time course of all the voxels throughout the brain. In addition to the signal of interest ("*seed*"), estimates of white matter, CSF, and global brain signal fluctuations are derived, to be included as non-interest nuisance variables in the linear regression analyses. These nuisance signals are typically adjusted for resting-state functional connectivity studies as they reflect global signal fluctuations of non-neuronal origin (e.g., physiological artifacts associated with variables such as cardiac and respiratory cycles, CSF motion, and scanner drift; Fox and Raichle, 2007). Criteria selection for each region of interest ("*seed*") is described in the pertinent study where the method was used (studies 1, 2, 5).

Global functional connectivity degree: This approach challenges entire brain functional connectivity by providing a quantitative measure of the extent each voxel is connected to every voxel in the brain. As in the seed-based functional connectivity analyses, estimates of white matter, CSF, and global brain signal fluctuations were all separately regressed out from every voxel's time course in order to account for uninteresting correlations. For every subject a connection matrix was computed and later binarized at a certain threshold ($r>0.3$) giving an unweighted connection matrix. This connection matrix makes it possible to look at the brain as a network or graph where each voxel is considered a node that may or may not be connected to the other nodes.

Anatomical analysis: Voxel-based morphometry approaches were conducted to assess both for concentration and volume changes in psychopathic individuals. Anatomical data were first preprocessed using standard steps which involve bias-correction, optimally tissue classification using non-linear deformation fields, image registration using linear and non-linear transformations. For the volumetric analysis, the normalized gray matter images were modulated with the Jacobians determinants to restore volumetric information. Both gray

matter concentration and volumetric images were smoothed with a Gaussian kernel of 8 mm full width half maximum (FWHM). Finally, for the volumetric analyses, the second-level model includes the total intracranial volume as a covariate allowing for the assessment of relative volumetric between-group differences.

3. OBJECTIVES OF THE THESIS

The general aim of this thesis is to study the brain networks processing emotion and connecting emotion with cognition in psychopathic individuals, and in cocaine use and obsessive-compulsive disorder patients. For this purpose, the specific objectives for each of the studies contained in the present thesis are the following:

Study 1)

- Based on a study showing reduced brain activation to a moral dilemma task in psychopaths (Glenn et al., 2009), the presence of structural alterations in these brain areas in these individuals (de Oliveira-Souza et al., 2008), together with preliminary data suggesting an association between psychopathic traits and altered deactivations in default network regions (Sheng, Gheytanchi, and Aziz-Zadeh, 2010), we aim to assess whether alterations within the brain network subserving moral dilemma processing are present (i) during specific challenges using a moral judgment task, (ii) in deactivation during a nonspecific (cognitive) task, and (iii) during a resting-state condition in psychopathic individuals.
- To assess whether the network alterations relate to the psychopathy severity scores.

Study 2)

- Based on the imbalance function of corticolimbic networks to related and non-related cocaine cues and preliminary reports of disrupted functional connectivity during rest in these circuits in active cocaine users (Gu et al., 2010; Verdejo-García and Bechara 2009), we aimed to assess for (i) potential brain activation disturbances within corticolimbic networks during a moral dilemma task and (ii) functional connectivity alterations within these same brain networks during rest in cocaine users during controlled abstinence.

Study 3)

- Based on inconclusive data regarding a general bias to a heightened processing of emotional information in obsessive-compulsive disorder (Foa et al., 1993; Moritz et

al., 2004) and suggestions that this bias may be only manifested to stimuli that evoke feelings of guilt and responsibility (Salkovskis, 1985; Salkovskis et al., 2002), we aim to assess for putative activation alterations within the brain networks subserving moral judgment in patients with obsessive-compulsive disorder.

- To assess whether the network alterations relate to the obsessive-compulsive severity scores.

Study 4)

- Based on reports showing isolated reduced amygdala activation (Jones et al., 2009; Marsh et al., 2008) and functional connectivity with ventromedial frontal cortices to emotional face expressions in youth with psychopathic traits (Marsh et al., 2008), we aim to assess for putative activation and functional connectivity alterations within the whole-brain network subserving emotional face processing in adult psychopaths.
- To assess whether the network alterations relate to the psychopathy severity scores.

Study 5)

- Based on preliminary reports suggesting a disrupted functional connectivity during rest (Ly et al., 2012; Motzkin et al., 2011) and preliminary studies suggesting alterations involving neocortical regions in psychopathic individuals (Yang et al., 2010; Yang et al., 2012), we aim to comprehensively explore for putative resting functional connectivity changes in relevant emotional and cognitive large-scale brain networks in psychopathic individuals using both anatomical and functional approaches.
- To assess whether the network alterations relate to the psychopathy severity scores.

4. HYPOTHESES OF THE THESIS

The specific hypotheses raised for each of the studies contained in the present thesis are the following:

Study 1)

- An inadequate use of the brain networks underlying moral judgment will not be limited to the processing of moral dilemma situations, but a primary network breakdown will exist in psychopathic individuals compared to control subjects.

Study 2)

- An inadequate use of the brain networks underlying moral judgment will not be limited to the processing of moral dilemma situations, but a primary network breakdown will exist in cocaine users compared to control subjects even during controlled protracted abstinence.

Study 3)

- The experience of moral dilemma in patients with obsessive-compulsive disorder will provoke significantly increased activation of the ventromedial prefrontal and orbitofrontal cortex and in other tasks-relevant brain regions compared with control subjects.

Study 4)

- A disruption between emotional and cognitive brain elements of the face-processing network will exist in the psychopathic individuals compared to control subjects. Specifically, we predict a combination of decreased and increased activation of limbic and neocortical areas respectively, together with a reduction in functional connectivity between the amygdala and the other network key regions.

Study 5)

- A disrupted functional connectivity at rest will be observed between emotional and cognitive brain networks, although the functional coupling within the cognitive

networks will be more preserved in the psychopathic individuals compared with control subjects.

5. RESULTS

- **Study 1:** *Breakdown in the brain network subserving moral judgment in criminal psychopathy.*

- **Study 2:** *Functional alteration in frontolimbic systems relevant to moral judgment in cocaine-dependent subjects.*

- **Study 3:** *Neural Correlates of Moral Sensitivity in Obsessive-Compulsive Disorder.*

- **Study 4:** *Disrupted neural processing of emotional faces in Psychopathy.*

- **Study 5:** *Selective functional connectivity enhancement within dorsal executive networks in psychopathy.*

Pujol, J., Batalla, I., Contreras-Rodríguez, O., Harrison, B.J., Pera, V., Hernández-Ribas, R., Real, E., Bosa, L., Soriano-Mas, C., Deus, J., López-Solà, M., Pifarré, J., Menchón, J.M., Cardoner, N. (2011). **Breakdown in the brain network subserving moral judgment in criminal psychopathy**. *Social Cognitive and Affective Neurosciences*, 7(8),917-923.

http://scan.oxfordjournals.org/content/7/8/917.long

Verdejo-García*, A., Contreras-Rodríguez*, O., Fonseca, F., Cuenca, A., Soriano-Mas, C., Rodríguez, J., Pardo-Lozano, R., Blanco-Hinojo, L., de Sola Llopis, S., Farré, M., Torrens, M., Pujol, J., de la Torre, R. **Functional alteration in frontolimbic systems relevant to moral judgment in cocaine-dependent subjects**. *Addict Biol.* 2012; 19(2): 272-281.[Epub ahead of print].

http://onlinelibrary.wiley.com/doi/10.1111/j.1369-1600.2012.00472.x/abstract;jsessionid=E32F591BE7A6804C26C541EEC1291FA9.d02t02

Harrison, B.J., Pujol, J., Soriano-Mas, C., Hernández-Ribas, R., López-Solà, M., Ortiz, H., Alonso, P., Deus, J., Menchon, J.M., Real, E., Segalàs, C., Contreras-Rodríguez, O., Blanco-Hinojo, L., Cardoner, N. (2012). **Neural Correlates of Moral Sensitivity in Obsessive-Compulsive Disorder.** *Arch Gen Psychiatry.*, 69(7), 741-749.

http://archpsyc.jamanetwork.com/article.aspx?articleid=1211981

Contreras-Rodríguez, O., Pujol, J., Batalla, I., Harrison, B.J., Bosque, J., Ibern-Regàs, I., Hernández-Ribas, R., Soriano-Mas, C., Deus, J., López-Solà, M., Pifarré, J., Menchón, J.M., Cardoner, N. **Disrupted neural processing of emotional faces in psychopathy**. *Soc Cogn Affect Neurosci. 2014; 9(4): 505-12* [Epub ahead of print].
http://scan.oxfordjournals.org/content/early/2013/04/17/scan.nst014.long

Contreras-Rodríguez, O., Pujol, J., Batalla, I., Macià, D., Harrison, B.J., Soriano-Mas, C., Deus, J., López-Solà, M., Pifarré, J., Menchón, J.M., Cardoner, N. **Selective functional connectivity enhancement within dorsal executive networks in psychopathy**. *Unpublished.*

SELECTIVE FUNCTIONAL CONNECTIVITY ENHANCEMENT WITHIN DORSAL EXECUTIVE NETWORKS IN PSYCHOPATHY

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Background: Psychopathy is characterized by a distinctive interpersonal style that includes callous-unemotional traits and antisocial features. Traditional emotional-based perspectives link the emotional impairment to alterations in amygdala-ventromedial prefrontal circuits and other paralimbic regions. However, these models alone could not explain why psychopaths can benefit from emotional information in certain contexts and why they are less interfered also by non-affective contextual cues. The present study aims to comprehensively explore for putative resting-functional connectivity changes in both emotional and cognitive large-scale brain networks in psychopathic individuals using both anatomical and functional approaches. **Methods:** Twenty-two psychopaths and 22 control subjects participated in the study. Anatomical and resting-state images were acquired to identify whole-brain anatomical and functional connectivity changes in psychopaths. Combined findings were later used to explore for functional connectivity changes using seed functional connectivity analyses. **Results:** Psychopaths showed significant gray matter anatomical decreases involving both prefrontal and limbic-paralimbic brain regions. Overlapping the anatomical findings, the psychopaths showed greater global functional connectivity degree in the dorsomedial prefrontal cortex which was associated with the psychopaths' emotional disturbances. Finally, reduced functional connectivity between limbic-paralimbic with dorsal executive brain networks although an enhanced functional connectivity within this latest brain network was observed in the psychopathic individuals. **Conclusions:** Our results suggest that combined alterations involving both a reduced functional coupling between emotional and prefrontal regions together with an increased strength of functional connectivity within the dorsal executive brain network may contribute to the inflexible and disadvantageous behavior displayed by the psychopathic individuals.

Keywords: Psychopathy, functional connectivity, dorsal executive network, amygdala, flexible self-regulation

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INTRODUCTION

Psychopathy is characterized by a distinctive interpersonal style that includes callous-unemotional traits and antisocial features (Cleckley, 1976; Hare, 2003). Traditional emotional-based perspectives link the emotional impairment in psychopathy to alterations in amygdala-ventromedial prefrontal circuits (Blair, 2005; Blair 2007; Yang, Raine, Colletti, Toga, and Narr 2010) and other paralimbic regions such as the cingulate cortex (Kiehl, 2006). Cumulating evidence of the dysfunction within these brain systems come from studies using emotional tasks such as emotional face recognition (Blair and Coles, 2000; Contreras-Rodríguez et al., 2013; Dadds et al., 2006; Marsh et al., 2008), aversive conditioning (Birbaumer et al., 2005; Flor, Birbaumer, Hermann, Ziegler, and Patrick, 2002), response modulation according to contingency change (Mitchell, Colledge, Leonard, and Blair, 2002; Newman, Patterson, and Kosson, 1987) and moral decision making (Glenn, Raine, and Schug, 2009; Pujol et al., 2011; Raine and Yang, 2006). However, emotion-based models alone cannot explain why psychopaths normally benefit from emotional information when its processing constitutes the central goal (Hiatt, Schmitt, and Newman, 2004; Newman, Curtin, Bertsch, and Baskin-Sommers, 2010; Newman and Kosson, 1986) and when an extended intertrial interval is provided reducing the psychopaths' effort to process emotional information (Arnett, Howland, Smith, and Newman, 1993; Newman, Patterson, and Kosson, 1987). However, psychopaths present with a reduced interference to both affective and neutral cues suggesting alterations in other non-emotional brain networks (Blair et al., 2006; Dvorak-Bertsch, Sadeh, Glass, Thornton, and Newman, 2007; Hiatt et al., 2004; Lykken, 1957; Newman, Schmitt, and Voss, 1997; Vitale, Brinkley, Hiatt, and Newman, 2007; Zeier, Maxwell, and Newman, 2009).

Without opposing to the abundant evidence pointing to a primary emotional processing alteration in psychopathy, the Response Modulation model further proposes a reduced ability to use and give sufficient consideration to relevant information that is peripheral to a dominant response in these individuals (Lorenz and Newman, 2002). This is supposed to occur because a deficit in shifting attention from effortful organization and implementation of goal-directed behavior to its evaluation. Although such a proposal may imply that psychopaths present with a deficient implementation of executive functions in some contexts, others suggest preserved executive skills in this population (Blair and Mitchell, 2009) in agreement with studies reporting decreased interference in executive tasks (Blair et al., 2006; Hiatt et al., 2004; Newman, Wallace, and Schmitt, 1997).

This intricate framework further complicates if one attends to the inconsistent neuroimaging data on the dorsal executive networks in psychopathic samples. Psychopaths have demonstrated reduced dorsal anterior cingulate cortex activation (Birbaumer et al., 2005; Kiehl et al., 2001; Veit et al., 2002) but the use of lateral frontal

compensatory mechanisms (Glenn, Raine, and Schug, 2009; Intrator et al., 1997; Kiehl et al., 2001) during emotional tasks. Regarding to the anatomical integrity of the executive brain networks in psychopaths, some studies report volumetric changes (Müller et al., 2008; Yang et al., 2010), while others do not (Glenn, Yang, Raine, and Colletti, 2010) and there are a number of studies showing decreased cortical thickness (Ly et al., 2012; Yang 2010; Yang, Raine, Colletti, Toga, and Narr, 2009). Relevantly, recent imaging studies show that brain disturbances in individuals with psychopathy can be better clarify attending to the presence of alterations in large-scale brain networks that integrate emotional and cognitive neural processes (Contreras-Rodríguez et al., 2013; Craig et al., 2009; Ly et al., 2012; Motzkin, Newman, Kiehl, and Koenigs, 2011; Pujol et al., 2011; Yang et al., 2012). In this line it is worth noting a recent study by Yang and colleagues (2012) showing the frontal network as information flow control hub in psychopaths using anatomical connectivity measures.

The present study aims to comprehensively explore for putative resting functional connectivity changes in relevant emotional and cognitive large-scale brain networks in psychopathic individuals using both anatomical and functional approaches. We specifically hypothesized that (i) the anatomical and functional analyses would successfully map relevant emotional and cognitive structural changes in psychopaths being useful to guide subsequent seed functional connectivity analyses, (ii) a specific breakdown in functional connectivity will be observed between emotional and cognitive brain networks in the psychopathic individuals, although (iii) functional connectivity within cognitive networks will be much preserved.

MATERIAL AND METHODS

Participants

Twenty-two psychopathic men (Hare, 2003) with a documented history of severe criminal offense were assessed and compared to 22 non-offender control subjects. Characteristics of both samples are fully described in Table 1 and in previous reports (Contreras-Rodríguez et al., 2013; Pujol et al., 2011). The psychopathic sample showed a mean Psychopathy Checklist- Revised (PCL-R) score (Hare, 2003) of 27.8 and served to select individuals having total PCL-R score greater than 20 or PCL-R Factor 1 greater than 10 for fMRI evaluation. Additional sample characteristics are fully described in Supplementary material (S1).

Table 1. Characteristics of study groups.

	Controls	Psychopaths
Age, years, mean + SD (range)	40.6 ± 9.5 (28-61)	39.8 ± 9.2 (28-64)
Gender	22 men	22 men
Vocabulary WAIS-III + SD (range)	10.3 ± 2.3 (6-14)	10.9 ± 3.0 (4-18)
Education, years, mean + SD (range)	10.5 ± 2.3 (8-16)	9.0 ± 2.7 (4-14)
Handedness (left-handers/right-handers)	2/20	1/21
PCL-R Total, mean + SD (range)	0.8 ± 1.9 (0-8.4)	*27.8 ± 4.5 (15.8-34.4)
PCL-R Factor 1, mean + SD (range)	0.4 ± 1.1 (0-5)	*12.5 ± 2.2 (8-16)
PCL-R Factor 2, mean + SD (range)	0.3 ± 0.6 (0-2)	*13.2 ± 4.7 (4.4-20)
Comorbidities:		
DSM-IV-R Axis I diagnosis#	None	None
Hamilton Depression score, mean + SD (range)	0.4 ± 1.0 (0-4)	*1.9 ± 2.1 (0-8)
Hamilton Anxiety score, mean + SD (range)	0.8 ± 1.1 (0-4)	1.8 ± 3.2 (0-10)
Y-BOCS total score, mean + SD (range)	0 ± 0 (0-0)	0.5 ± 2.2 (0-10)
Current substance abuse	None	None
DSM-IV-R Axis II diagnosis (except APD)	None	None
Barratt Impulsiveness Scale, total score	34 ± 15 (16-72)	*53 ± 23 (16-103)
Torrubia's Sensitivity to Punishment	5.8 ± 4.9 (0-17)	8.1 ± 5.5 (0-19)
Torrubia's Sensitivity to Reward	7.1 ± 4.6 (0-20)	*11.9 ± 5.5 (5-22)

* indicates p< 0.01. # except past history of substance abuse. PCL-R, Psychopathy Checklist- Revised. Y-BOCS, Yale-Brown Obsessive Compulsive Scale. APD, Antisocial Personality Disorder.

Image acquisition

A 1.5 T Signa Excite system (General Electric, Milwaukee, WI, USA) equipped with an eight-channel phased-array head coil and single-shot echoplanar imaging (EPI) software was used. Both structural and functional resting-state sequences were obtained to assess for putative anatomical and resting-state functional connectivity alterations in the psychopathic individuals. Imaging acquisition parameters for each sequence are fully described below.

Anatomical sequence. High-resolution axial T1-weighted anatomical images were acquired for each subject using a 3-dimensional fast spoiled gradient inversion-recovery prepared sequence (T1 3D fSPGR IR-prep) sequence.

Acquisition parameters were 134 contiguous slices (repetition time [TR], 11.8 ms; echo time [TE], 4.2 ms; flip angle, 15°; field of view, 30 cm; 256 x 256 pixel matrix; slice thickness, 1.2 mm).

Resting-state sequence. This functional sequence consisted of gradient recalled acquisition in the steady state ([TR], 2000 ms; [TE], 50 ms; flip angle, 90º; field of view; 24 cm; 64 x 64 pixel matrix; slice thickness, 4 mm). Twenty-two interleaved slices, parallel to the anterior-posterior commissure (AC-PC) line, were acquired to cover the whole-brain. The sequence first included four additional dummy volumes to allow the magnetization to reach equilibrium.

A four-minute continuous resting-state scan was acquired for each subject. Subjects were instructed to relax, stay awake and to lie still with their eyes closed. The scan generated 120 whole-brain EPI volumes.

Preprocessing and analysis of imaging data

Both anatomical and functional resting-state imaging data were processed using MATLAB version R2008b (The MathWorks Inc, Natick, Mass) and image preprocessing was performed in SPM8 (http://www.fil.ion.ucl.ac.uk/spm/). We excluded data from one psychopathic individual and one control from the larger original samples of 23 subjects, because of technical problems during imaging acquisition.

Anatomical analyses. For the anatomical imaging processing, we used the 'VBM8 toolbox' (http://dbm.neuro.unijena.de/vbm.html) default parameters. All images were visually checked for artifacts and intensity non-uniformity before voxel-by-voxel analyses.

We firstly obtained total intracranial (resulting from the addition of gray matter, white matter and CSF volumes) and gray matter volumes from the original non-normalized images and compared them separately between groups with independent samples t test in SPSS 15.0 (SPSS Inc., Chicago IL).

Standard preprocessing steps involved (i) bias-correction, (ii) optimally tissue classification using non-linear deformation fields to obtain tissue probability maps of gray matter based on the ICBM Tissue Probabilistic Atlas (http://www.Ioni.ucle.edu/ICBM_TissueProb.html) that best overlay the individual subjects' images (rather than assuming a stationary prior probabilities), (iii) and image registration using linear (12-parameter affine) and non-linear transformations (warping) within a unified model (Ashburner and Friston, 2005). For the volumetric analyses, the normalized gray matter images were modulated with the Jacobian determinants (derived from the spatial normalization step) to restore volumetric information (Good et al., 2001; Soriano-Mas et al., 2011). Finally, both gray matter concentration and volumetric images were smoothed with Gaussian kernel of 8 mm full width half maximum (FWHM).

The individual voxel-wise gray matter concentration and volume images were then included in a group (second-level) random-effects analysis to assess for between-group differences. In order to avoid possible edge effects between different tissue types, we excluded all voxels with values of less than 0.2 (absolute masking threshold). For the volumetric analysis, the second-level model includes the total intracranial volume as a covariate allowing for the assessment of relative volumetric between-group differences.

Global functional connectivity degree. Preprocessing steps involved motion correction, spatial normalization and smoothing using a Gaussian filter (FWHM 8 mm). Data were normalized to the standard SPM-EPI template and resliced to a 6 x 7.5 x 9 mm resolution in Montreal Neurological Institute (MNI) space.

To obtain a quantitative measure of the extent each voxel is connected to every other voxel in the brain, we used an unweighted global brain connectivity (uGBC) approach (Cole, Pathak, and Schneider, 2010). Prior to performing the analysis, the mean BOLD signal from a

CSF, white matter and a global brain signal mask were all separately regressed out from every voxel's time course in order to account global drifts and physiological uninteresting correlations. These masks were made by setting a 70% tissue probability threshold on the SPM8 a-priori template segments of gray matter, white matter and CSF, which are normalized to the same (the MNI standard) stereotactic space as the subjects' EPI volumes.

For every subject, we computed a 2938 x 2938 correlation matrix. This connection matrix was later binarized at a threshold of r>0.3 giving way to an unweighted connection matrix. The threshold sets the minimum linear correlation coefficient to be considered as significant. The connection matrix makes it possible to look at the brain as a network or graph where each voxel is considered a node that may or may not be connected to the other nodes. From the connection matrix we computed the connectivity degree for each of the 2938 voxels inside the mask for every single subject in the study. The connectivity degree for a given voxel is computed as the ratio of the sum of all its significant connections over all the possible connections. The individual connectivity maps were then included in a group (second-level) random-effects analysis to assess for between-group differences.

Seed functional connectivity analyses. Preprocessing involved the same steps used for the global functional connectivity analysis, except that the data were resliced to 2 mm isotropic resolution in Montreal Neurological Institute (MNI) space.

Resting-state functional connectivity analyses were conducted using a region of interest ("seed") based approach as detailed at length in recent studies (Harrison et al., 2009; Pujol et al., 2011). We aim to explore for putative resting functional connectivity changes using both anatomical and functional approaches. For that, the seed guiding the primary functional connectivity analysis was selected using a double criterion: (i) peak activation of those regions showing between-group differences in the anatomical analyses which (ii) anatomically overlap with the brain regions showing between-group differences in global connectivity.

The time course of each seed region was used as a regressor to be correlated with the time course of all brain voxels. Each seed was defined as 3.5-mm radial spheres (sampling approximately 25 voxels) using MarsBaR region-of-interest toolbox in Montreal Neurological Institute stereotaxic space (Brett, Valabregue, and Poline, 2003) and its signal value was calculated as the average signal of all the included voxels at each data point. Functional connectivity maps were estimated for each of the selected seed by including our signal of interest (seed) together with the same nuisance signals used in the global connectivity analysis (CSF, white matter and global brain signal) as predictors of interest or no interest respectively, in whole-brain linear regression analyses in SPM8. A high-pass filter set at 128 seconds was used to remove low-frequency drifts of less than approximately 0.008 Hz. Contrast images were generated for each subject by estimating the regression coefficient between the seed time series

and each brain voxel signal. Resulting images were then included in group (second-level) random-effects analyses to assess for within and between-group effects.

Correlation analyses Voxel-wise correlation analyses were performed in SPM8 between psychopathy severity scores (Factor 1 and Factor 2 as regressors) with the anatomical (concentration and volume), global functional connectivity and principal seed functional connectivity analyses in the psychopathic group.

Thresholding criteria Spatial extent thresholds for all statistical comparisons were determined by 1000 Monte Carlo simulations using AlphaSim (Ward, 2000) as implemented in the SPM REST toolbox (Song et al., 2011). For the within and between-group effects, the input parameters to AlphaSim included an individual voxel threshold probability of 0.005, a cluster connection radius of 5 mm, 8 mm FWHM smoothness, incorporating a whole- brain image mask volume of 256299 voxels for the anatomical and seed functional connectivity analyses and a mask volume of 2938 voxels for the global functional connectivity analysis. The minimum cluster size extent (CS) was determined to be 169 voxels and 3 voxels, respectively, in order to satisfy a family-wise error rate correction of *P*FWE< 0.05.

For the correlation analyses the same input parameters were used but considering an individual voxel threshold probability of 0.01. The minimum cluster size extent (CS) for the anatomical and seed functional connectivity analyses was determined to be 263 voxels while for the global functional connectivity analysis it was determined to be 4 voxels.

RESULTS

Anatomical analyses

Global Volumes Mean±SD was similar between psychopaths and control subjects for total intracranial volume (1396±95 and 1419±95 mL, respectively; t_{42}= -0.8; P= 0.43) and gray matter volume (642±39 and 633±43 mL, respectively; t_{42}= 0.72; P= 0.47).

Gray matter concentration In the direct between-group comparison, psychopaths showed a significant decrease in gray matter concentration in the prefrontal cortex, a large portion of the cingulate gyrus from anterior to posterior sections, also extending to the precuneus.

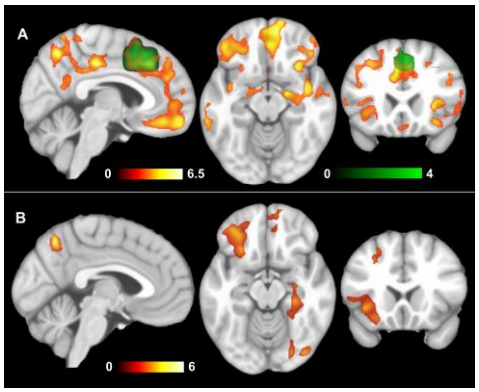

Figure 1. Top panel (A) shows concentration (orange) and global functional connectivity degree (green) changes in psychopaths. Bottom panel (B) shows volumetric changes in psychopaths.

Decreased gray matter concentration was also observed in bilateral amygdala-hippocampus and insula-operculum complexes, right fusiform gyrus and left temporal cortices (Table 2; Figure 1).

Table 2. Anatomical decreases in psychopaths

Brain Regions	x	y	z	t	CS
	Gray matter concentration				
Dorsomedial frontal	-6	23	38	4.8	34775*
Medial frontal	-1	46	10	3.5	34775*
Ventral frontal	6	57	-15	5.2	34775*
Lateral frontal	30	51	10	5.3	34775*
Anterior cingulate	-6	22	37	4.8	34775*
Posterior cingulate	3	-22	40	6	34775*
Precuneus	1	-61	49	6.2	34775*
R Amygdala-HPC	21	-9	-13	4.3	34775*
L Amygdala-HPC	-21	0	-18	3.8	271
R Insula-Operculum	40	-18	10	4.5	34775*
L Insula-Operculum	-37	-6	1	4.1	34775*
Fusiform gyrus	22	-64	-9	4.8	1155
Temporal	-60	-31	1	4.7	34775*
	Gray matter volume				
Ventral frontal	12	39	-18	3.8	298
Lateral frontal	-24	21	48	3.2	204
Precuneus	-1	-63	51	4.7	397
R Amygdala-HPC	28	-13	-15	3.2	1006
L Insula-Operculum	-45	28	3	4.5	2598
Fusiform gyrus	25	-72	-13	3	593

Coordinates (x, y, z) are given in Montreal Neurological Institute (MNI) Atlas space. HPC: Hippocampus. CS: Cluster size. R: Right, L: Left. * part of the large cluster.

Gray matter volume In contrast to the tissue concentration findings, psychopaths showed only mild gray matter volume decreases in ventral and lateral prefrontal cortices, the precuneus, right amygdala-hippocampus, left insula-operculum and the fusiform gyrus (Table 2; Figure 1).

Global functional connectivity degree In the direct between-group comparison, psychopaths showed greater global functional connectivity degree in the dorsomedial prefrontal cortex (MNI peak coordinates x, y, z: 4.2, 30.4, 40, t= 3.9; P=0.005, 11 voxels), overlapping the decreased tissue concentration in this group (Figure 1).

Seed functional connectivity

According to the criteria previously defined, the placement of the principal seed corresponded to the dorsomedial frontal cortex (MNI coordinates x, y, z: -6, 23, 38) which shows anatomical and functional changes in the psychopathic individuals. Moreover, to further explore for resting-state functional connectivity alterations in psychopaths, additional analyses were performed selecting as seeds the peak coordinates of those brain regions showing between-group differences in functional connectivity in the principal dorsomedial frontal seed analysis. Specifically, these seeds were placed in the amygdalae (right: 18, -4, -12; left: -16, -2, -20) and the lateral frontal cortex (right: 26, 14, 44; left: -30, 12, 42).

Dorsomedial frontal seed Positive functional connectivity maps included medial and lateral frontal cortices and the left anterior insula-operculum complex in both groups (Figure 2, Table S2). Control subjects additionally included the right anterior insula-operculum complex and the thalamus. In the direct between-groups comparison, psychopaths showed increased functional connectivity between the dorsomedial frontal seed with lateral frontal cortices but decreased functional connectivity with the right anterior insula-operculum complex and the thalamus (Figure 2; Table 3). The anticorrelation maps included the amygdala-hippocampus complex, ventral insulae, lingual gyri, posterior cingulate cortex and the periaqueductal gray in both groups. However, control subjects showed additional anticorrelation between the dorsomedial frontal seed with the right amygdala-hippocampus only, whereas psychopaths presented an anticorrelation with the hypothalamus

(Figure 2, Table S2). In the direct between-groups comparison, psychopaths showed a significant increased anticorrelation between the dorsomedial frontal seed with the amygdalae and the hypothalamus (Figure 2; Table 3).

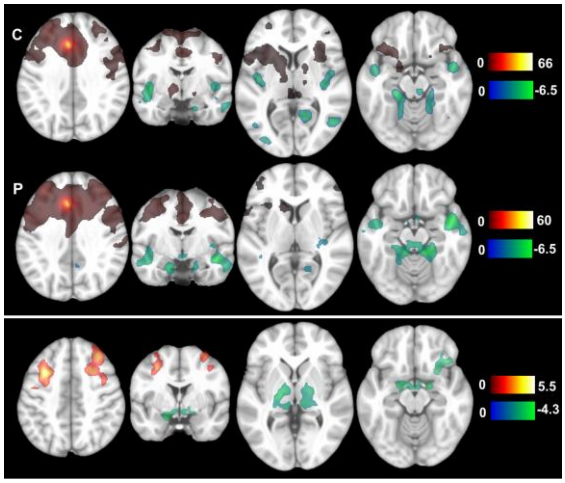

Figure 2. Functional connectivity of the dorsomedial frontal seed in controls (C) and psychopaths (P), and between-group differences (bottom panel).

Complementary seeds functional connectivity analyses

Right amygdala seed Positive functional connectivity maps included the left amygdala-hippocampus, insulae-opercula, thalamus, temporal poles and brainstem regions in both groups. Control subjects showed additional functional connectivity with dorsomedial frontal and sensorimotor cortices (Figure 3, Table S2). In the direct between-groups comparison, psychopaths showed significant decreased functional connectivity between the right amygdala with dorsomedial frontal and sensorimotor cortices (Figure 3; Table 3). The anticorrelation maps included medial and ventral frontal cortices, parietal and occipital cortices in both groups. Psychopaths showed additional anticorrelation with left lateral frontal cortex and the caudate nuclei (Figure 3, Table S2). In the direct between-groups comparison, psychopaths maintained a significant increased anticorrelation between the right amygdala with the lateral frontal cortex (Figure 3; Table 3). Psychopaths also showed a significant increase functional connectivity between the right amygdala with the fusiform gyrus. Although the fusiform did not show significant functional connectivity with the amygdala in any group, the between-group differences were driven by a tendency towards increased connectivity in the psychopaths but an opposite pattern in the control subjects between these brain areas.

Left amygdala seed Positive functional connectivity maps were highly similar for both groups and no between-group differences were observed (Table S2). Anticorrelation maps included right lateral frontal, medial parietal and temporal cortices in both groups. Psychopaths showed additional anticorrelation with the dorsomedial frontal cortex and the controls subjects with the occipital cortex (Table S2). In the direct between-groups comparison, psychopaths showed significant increased anticorrelation between the left amygdala with dorsomedial frontal areas but a decreased anticorrelation with the occipital cortex (Table 3). For a shake of brevity and due to the similar findings between both of the amygdalae seeds,

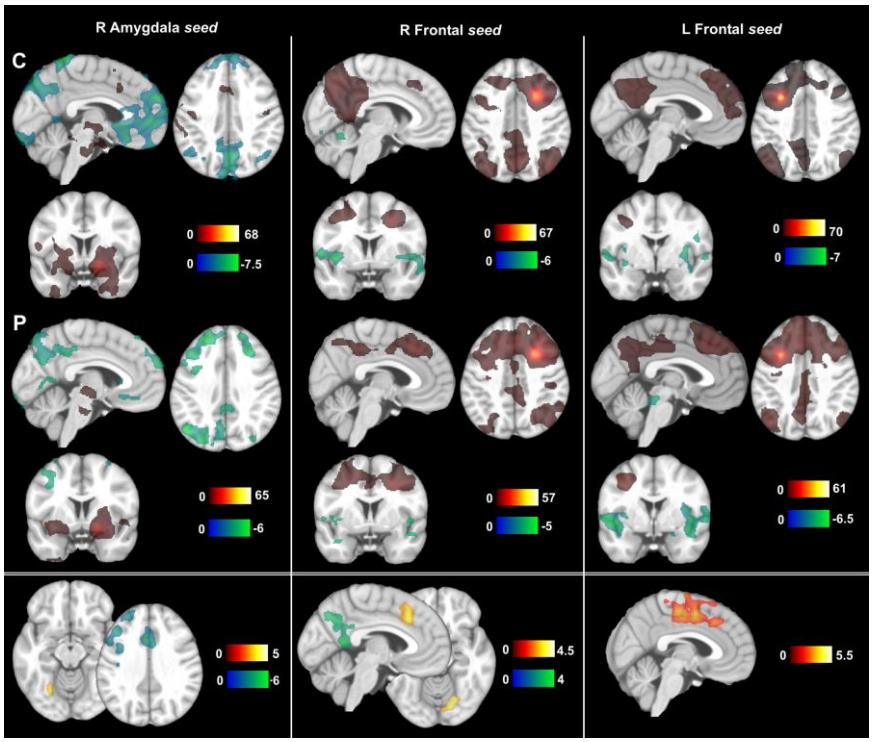

Figure 3. Functional connectivity of the right amygdala, right lateral frontal and left lateral frontal seeds in controls (C) and psychopaths (P), and between-group differences (bottom panel).

only the between-group differences for the right amygdala are displayed.

Right frontal seed Positive functional connectivity maps included medial and lateral frontal regions, as well as parietal cortices in both groups. However, the controls' functional connectivity with the posterior cingulate cortex encompassed ventral sections and largely involved the precuneus while the psychopaths showed large functional connectivity with dorsomedial frontal areas (Figure 3; Table S2). In the direct between-group comparison, the psychopaths showed a significant decreased functional connectivity between the right frontal with the ventral posterior cingulate cortex and the precuneus and an increased functional connectivity with dorsomedial frontal areas (Figure 3; Table 3). Anticorrelation maps were highly similar within groups except for the additional anticorrelation of the control subjects with the cerebellum (Figure 3; Table S2). In the direct between-group comparison, psychopaths showed a decreased anticorrelation with the cerebellum (Figure 3; Table 3).

Table 3. Between-group functional connectivity changes.

Regions	x	y	z	t	CS	Regions	x	y	z	t	CS
	Controls>Psychopaths						**Psychopaths>Controls**				
				Dorsomedial frontal *seed*							
R Amygdala	18	-4	-12	4.3	1150*	R Lateral frontal	26	14	44	3.2	308
L Amygdala	-16	-2	-20	3.9	1150*	L Lateral frontal	-30	12	42	5.1	353
Insula	40	24	-16	3.9	228						
Thalamus	-16	-10	0	3.9	1150*						
Hypothalamus	4	-8	-10	3.7	1150*						
				Right Amygdala *seed*							
Dorsomedial frontal	-8	18	40	5.6	1060*	Fusiform gyrus	-24	-66	-12	4.4	231
Lateral frontal	-34	-4	48	4	1060*						
Sensorimotor	32	-20	60	3.8	261						
				Left Amygdala *seed*							
Dorsomedial frontal	-10	20	32	4.4	274	Occipital	-10	-80	-12	4.6	171
				Right Frontal *seed*							
PCC (ventral)	6	-48	2	4	580	Dorsomedial frontal	2	20	48	4.3	551
Precuneus	4	-68	38	3.5	695	Cerebellum	16	-78	-12	4.5	323
				Left Frontal *seed*							
						Dorsomedial frontal	-6	20	40	5.4	1079

Anatomical coordinates (x, y, z) are given in Montreal Neurological Institute (MNI) Atlas space. PCC: Posterior Cingulate Cortex. CS: Cluster size (voxels). R: Right. L: Left. * part of the large cluster.

Left frontal seed As for the right frontal seed, psychopaths again showed a large pattern of positive functional connectivity with dorsomedial frontal areas (Figure 3; Table S2). This reached statistical significance in the direct between-group comparison, with psychopaths showing an increased functional connectivity between the left frontal seed with dorsomedial frontal areas (Figure 3; Table 3). Anticorrelation maps were highly similar within groups and no between-group differences were observed (Figure 3; Table S2).

Correlation analyses Psychopaths showed both PCL-R Factor 1 and 2 associated with anatomical changes (concentration and volume) although in a negative and a positive way, respectively.

Specifically, Factor 1 was associated with greater anatomical reductions in the amygdalae, the insula-operculum and the dorsomedial frontal cortex and with volume changes in lateral frontal cortices. The Factor 2 in turn was associated with lesser anatomical reductions in prefrontal, opercular and temporal regions.

An additional association was found between the global functional connectivity in the dorsomedial, lateral frontal and temporal cortices with PCL-R Factor 1 (Table 4). No significant associations were found for the principal dorsomedial frontal seed analysis.

Table 4. Correlations between the psychopathy factor scores and the imaging findings

Brain regions		x	y	z	t	CS
	GM concentration					
Factor 1						
Dorsomedial frontal	(-)	2	51	36	4.9	417
Operculum	(-)	65	5	13	7.8	1156
Insula	(-)	-42	-1	0	3.3	339
R Amygdala	(-)	15	2	-21	4.5	1436*
L Amygdala	(-)	-17	2	-18	4.9	1436*
Parietal	(-)	-45	-29	48	3.7	469
Cerebellum	(-)	-12	-51	-21	4.5	454
Factor 2						
Dorsomedial frontal	(+)	-3	15	37	4.8	316
R Lateral frontal	(+)	47	50	10	5	553
L Lateral frontal	(+)	-36	39	27	5.2	2341*
Ventral frontal	(+)	21	35	-20	4.2	336
Operculum	(+)	-48	23	-5	4.1	2341*
Postcentral gyrus	(+)	62	-12	33	6.4	723
Temporal	(+)	63	-54	15	6	289
Cerebellum	(+)	-3	-53	-8	4.7	475
	GM volume					
Factor 1						
Dorsomedial frontal	(-)	9	42	45	5.2	5361*
R Lateral frontal	(-)	45	48	12	3.8	1434^
L Lateral frontal	(-)	-33	42	31	5.1	5361*
Operculum	(-)	54	33	-2	5.4	1434^
R Amygdala	(-)	-20	-1	-14	3.3	1311
L Amygdala	(-)	24	5	-15	6.6	1640
Temporal	(-)	-48	15	-27	4.4	956
Cerebellum	(-)	-18	-64	-23	4.4	1029
Factor 2						
Dorsomedial frontal	(+)	12	51	25	4.1	2522*
Medial frontal	(+)	6	66	-5	4.2	2522*
R Lateral frontal	(+)	50	30	10	4.8	925
Operculum	(+)	-47	26	-3	6.2	1905
Cerebellum	(+)	18	-52	-32	5.5	742
Temporal	(-)	-53	-66	0	3.5	386
	Global FC					
Factor 1						
Dorsomedial frontal	(+)	-8	61	31	3.4	5
Medial frontal	(+)	4	53	12	3.2	6
R Lateral frontal	(+)	23	53	22	3	7
Temporal	(+)	-53	-46	12	2.7	4

Anatomical coordinates (x, y, z) are given in Montreal Neurological Institute (MNI) Atlas space. CS: Cluster size (voxels). GM: Gray matter. FC: Functional connectivity. R: Right. L: Left. (+) and (-) indicate to positive and negative correlations respectively. *^ part of the large cluster.

DISCUSSION

In the present study, we used anatomical and functional approaches to comprehensively explore for putative resting functional connectivity changes in relevant emotional and cognitive large-scale networks in psychopathic individuals. Psychopaths showed significant gray matter anatomical decreases involving prefrontal and limbic-paralimbic brain regions such as the amygdala, cingulate cortex and the insula. Furthermore, overlapping the gray matter concentration changes, the psychopaths showed greater global functional connectivity degree in the dorsomedial prefrontal cortex. Finally, the seed functional connectivity analyses showed a reduced functional connectivity between limbic-paralimbic with dorsal executive brain networks, although an increased pattern of functional connectivity within this latest brain network was observed in the psychopathic individuals.

The distributed pattern of anatomical alterations comprising prefrontal and limbic-paralimbic brain regions is in agreement with previous studies in adult psychopaths (Bertsch et al., 2013; de Oliveira-Souza et al., 2008; Ermer, Cope, Nyalakanti, Calhoun, and Kiehl, 2012). The discrepant concentration and volume patterns reductions in psychopaths may likely reflect morphological cortical changes in these individuals. In accordance, reports of decreased cortical thickness in psychopaths partially coincide with the brain regions showing reduced gray matter concentration herein (Ly et al., 2012; Yang et al., 2009; Yang et al., 2010). Moreover, the emotional deficits were associated with greater

anatomical changes in line with a recent study of Gregory and colleagues (Gregory et al., 2012). It is worth noting the amygdala uniquely relationship with the emotional deficits thus supporting its key contribution to the unemotional traits display by the psychopathic individuals (Blair, 2005).

Concurrent anatomical and global functional connectivity findings engaged a dorsomedial frontal area in the psychopathic group. This region participates in the integration of affectively significant signals from emotional brain regions with controls signals in the prefrontal cortex (Botvinick, Cohen, and Carter, 2004; Carter et al., 2000; Etkin, Egner, and Kalisch, 2011; Koski and Paus, 2000; Margulies et al., 2007). Although suggestions that alteration in this region and adjacent prefrontal regions in psychopaths may be associated with their affective and self-regulatory deficits (MacCoon, Wallace, and Newman, 2004; Newman and Baskin-Sommers, 2011), few functional imaging studies have directly assessed its function (White 2012a, 2012b). In the present study, the psychopaths showed the dorsomedial frontal region as a control hug. Subsequent functional connectivity analyses revealed that this effect may be driven by an increased connectivity with lateral frontal cortices since the coupling with emotional areas was reduced, thus suggesting an imbalance coupling between top-down and bottom-up mechanisms in psychopaths.

Increase functional connectivity within the dorsal frontal network fits well with reports of the psychopathic individuals normally performing on simple executive neuropsychological tasks and benefiting from emotional information during sequential tasks (Hiatt et al., 2004; Newman et al., 2010; Newman and Kosson, 1986). In fact prior functional imaging studies using focused emotional tasks showed frontal hyperactivity in psychopaths, interpreted as reflecting a compensatory neural mechanism (Glenn et al., 2009; Intrator et al., 1997; Kiehl et al., 2001; Müller et al., 2003). However, this functional hyperconnectivity may also contribute to an impaired ability to use and give sufficient consideration to the contextual information, thus contributing to the inflexible and disadvantageous behavior displayed by the psychopathic individuals (Hiatt et al., 2004; Lykken, 1957; Lorenz and Newman, 2002). Supporting that previous, affective-interpersonal traits have been related with an abnormal sensitivity to peripheral information, including emotional information (Baskin-Sommers, Curtin, and Newman, 2011; Newman et al., 2010; Sadeh and Verona, 2008;) and we found PCL-R Factor 1 to be positively associated with the global connectivity increase in the dorsomedial frontal cortex.

Furthermore, the reduced functional connectivity between dorsal executive frontal and limbic-paralimbic brain networks may probably contribute to decrease the influence of salient emotional cues in signaling conflict or contraindicate the psychopaths' goal-behavior (Seeley et al., 2007). A replicated finding in the psychopaths' scientific literature has been the decreased anatomical and functional connectivity between the amygdala and ventromedial

prefrontal cortices (Craig et al., 2009; Marsh et al., 2008; Motzkin et al., 2011). Our data may complement the disruption between emotional and cognitive brain elements in psychopathy by suggesting that the altered coupling may also exist between emotional elements with dorsal executive brain networks. In agreement, we recently found decreased functional connectivity between the amygdala and the lateral frontal cortex during an emotional face matching task (Contreras-Rodriguez et al., 2013) and the same has been observed between the insula and the dorsal cingulate cortex during rest (Ly et al., 2012).

It is worth to discuss on how our data fit with prevailing views on psychopathy. Despite of cumulating evidence regarding emotional brain alterations in psychopaths (Blair, 2005), this study represents the first to demonstrate alterations within the entire dorsal frontal network using a resting-state functional connectivity approach in psychopathic individuals. Such a finding is in agreement with the Response Modulation Hypothesis (Lorenz and Newman, 2002) which preliminarily suggest the potential dysfunction of these neural networks in psychopathy (MacCoon et al., 2004; Newman and Baskin-Sommers, 2011). Nevertheless, the present data suggest that combined alterations involving both a reduced functional coupling between emotional and prefrontal regions, together with an increased strength of functional connectivity within the dorsal executive brain network, may relevantly contribute to the psychopathic deficits (Corbetta and Shulman, 2002). Whether the emotional brain dysfunction is primary or it is rather a consequence of an enhanced suppression exerted by a hyperfunction within dorsal frontal systems remains unknown. Further studies using higher temporal resolution techniques would be of interest to investigate this relevant issue, mainly in youth with psychopathic traits.

Other minor points should be discussed. First, psychopaths showed a decreased functional connectivity between the right lateral frontal with the ventral section of the posterior cingulate cortex, part of the default mode network. Using the same sample of psychopathic individuals, we previously reported primary breakdown in the default mode network (Pujol et al., 2011). Relevantly, Glenn and colleagues (2009) showed combined alterations of the brain network subserving moral dilemma judgment, which partially overlaps the default mode network (Harrison et al., 2008), together with higher activation in the lateral prefrontal cortex. Our results draw again attention to the need to further explore the relationship between these brain networks in psychopathic samples. Finally, we observed an impaired resting functional coupling within the amygdala-visual pathway, in line with our previous study (Contreras-Rodriguez et al., 2013) and studies suggesting reduced priming of emotional representations in sensory cortices (Deeley et al., 2006; Marsh et al., 2008).

In conclusion, the functional hyperconnectivity within the dorsal executive brain networks complement the recent evidence provided by Yang et al (2012) showing that psychopaths have the frontal networks as an information control hub. Moreover it provides for the

first time evidence of the hypothesized functional dysfunction within this neural network in psychopathic individuals (MacCoon et al., 2004; Newman and Baskin-Sommers, 2011). This previous, together with a disrupted coupling between emotional and cognitive brain regions, may suppose an imbalance function between top-down and bottom-up mechanisms contributing to the inflexible and disadvantageous behavior displayed by the psychopathic individuals.

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REFERENCES

Arnett, P. A., Howland, E. W., Smith, S. S., Newman, J. P. (1993). Autonomic responsivity during passive avoidance in incarcerated psychopaths. *Personality and Individual Differences*, 14, 173-185.

Ashburner, J., Friston, K. J. (2005). Unified segmentation. *Neuroimage,* 26(3), 839-851.

Baskin-Sommers, A. R., Curtin, J. J., Newman, J. P. (2011). Specifying the attentional selection that moderates the fearlessness of psychopathic offenders. *Psychological Science*, 22(2), 226-234.

Bertsch, K., Grothe, M., Prehn, K., Vohs, K., Berger, C., Hauenstein, K., Keiper, P., Domes, G., Teipel, S., Herpertz, S. C. (2013). Brain volumes differ between diagnostic groups of violent criminal offenders. *European Archives of Psychiatry and Clinical Neuroscience*, [Epub ahead of print]

Birbaumer, N., Veit, R., Lotze, M., Erb, M., Hermann, C., Grodd, W., Flor, H. (2005). Deficient fear conditioning in psychopathy: a functional magnetic resonance imaging study. *Archives of General Psychiatry*, 62(7), 799-805.

Blair, R. J. (2005). Applying a cognitive neuroscience perspective to the disorder of psychopathy. *Development and Psychopathology*, 17(3), 865-891.

Blair, R. J. (2007). The amygdala and ventromedial prefrontal cortex in morality and psychopathy. *Trends in Cognitive Sciences*, 11(9), 387-392.

Blair, R. J. R., and Coles, M. (2000). Expression recognition and behavioural problems in early adolescence. ***Cognitive Development***, 15(4), 421-434.

Blair, R. J., Mitchell, D. G. (2009). Psychopathy, attention and emotion. *Psychological Medicine*, 39(4), 543-555.

Blair, K. S., Newman, C., Mitchell, D. G., Richell, R. A., Leonard, A., Morton, J., Blair, R. J. (2006). Differentiating among prefrontal substrates in psychopathy: neuropsychological test findings. *Neuropsychology*, 20(2), 153-165.

Botvinick, M. M., Cohen, J. D., Carter, C. S. (2004). Conflict monitoring and anterior cingulate cortex: an update. *Trends and Cognitive Sciecne*s, 8(12), 539-546.

Brett, M., Valabregue, R., Poline, J. (2003). Region of Interest analysis using an SPM toolbox. *Neuroimage,* 16 (Supplement.).

Carter, C. S., Macdonald, A. M., Botvinick, M., Ross, L. L., Stenger, V. A., Noll, D., Cohen, J. D. (2000). Parsing executive processes: strategic vs. evaluative functions of the anterior cingulate cortex. *Proceedings of National Academy of Sciences U.S.A.*, 97(4), 1944-1948.

Cleckley, H. (1976). *The Mask of Sanity*. (5th ed.). Saint Louis: CV Mosby Co.

Cole, M. W., Pathak, S., Schneider, W. (2010). Identifying the brain's most globally connected regions. *Neuroimage*, 49(4), 3132-3148.

Contreras-Rodríguez, O., Pujol, J., Batalla, I., Harrison, B.J., Bosque, J., Ibern-Regàs, I., Hernández-Ribas, R., Soriano-Mas, C., Deus, J., López-Solà, M., Pifarré, J., Menchón, J.M., Cardoner, N. (2013). Disrupted neural processing of emotional faces in psychopathy. S*ocial Cognitive and Affective Neurosciences*, [Epub ahead of print].

Corbetta, M., and Shulman, G. L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nature Reviews Neurosci*ence, 3(3), 201-215.

Craig, M. C., Catani, M., Deeley, Q., Latham, R., Daly, E., Kanaan, R., Picchioni, M., McGuire, P. K., Fahy, T., Murphy, D. G. (2009). Altered connections on the road to psychopathy. *Molecular Psychiatry*, 14, 946-953.

Dadds, M. R., Perry, Y., Hawes, D. J., Merz, S., Riddell, A. C., Haines, D. J., Solak, E., Abeygunawardane, A. I. (2006). Attention to the eyes and fear-recognition deficits in child psychopathy. British Journal of Psychiatry, 189, 280-281.

Deeley, Q., Daly, E., Surguladze, S., Tunstall, N., Mezey, G., Beer, D., Ambikapathy, A., Robertson, D., Giampietro, V., Brammer, M.J., Clarke, A., Dowsett, J., Fahy, T., Phillips, M.L., Murphy, D.G. (2006). Facial emotion processing in criminal psychopathy. Preliminary functional magnetic resonance imaging study. *British Journal of Psychiatry*, 189, 533-539.

de Oliveira-Souza, R., Hare, R.D., Bramati, I.E., Garrido, G.J., Azevedo Ignácio, F., Tovar-Moll, F., Moll, J. (2008). Psychopathy as a disorder of the moral brain: fronto-temporo-limbic grey matter reductions demonstrated by voxel-based morphometry. *Neuroimage*, 40(3), 1202-1213.

Dvorak-Bertsch, J.D., Sadeh, N., Glass, S.J., Thornton, D., Newman, J.P. (2007). Stroop tasks associated with differential activation of anterior cingulate do not differentiate psychopathic and non-psychopathic offenders. *Personality and Individual Difference*s, 42(3), 585-595.

Ermer, E., Cope, L. M., Nyalakanti, P. K., Calhoun, V. D., Kiehl, K. A. (2012). Aberrant paralimbic gray matter in criminal psychopathy. *Journal of Abnorml Psychology*., 121(3), 649-658.

Etkin, A., Egner, T., Kalisch, R. (2011). Emotional processing in anterior cingulate and medial prefrontal cortex. *Trends in Cognitive Sciences*, 15(2), 85-93.

Flor, H., Birbaumer, N., Hermann, C., Ziegler, S., Patrick, C. J. (2002). Aversive Pavlovian conditioning in psychopaths: peripheral and central correlates. *Psychophysiology*, 39(4), 505-518.

Glenn, A. L., Raine, A., Schug, R. A. (2009). The neural correlates of moral decision-making in psychopathy. *Molecular Psychiatry*, 14, 5-6.

Glenn, A. L., Yang, Y., Raine, A., Colletti, P. (2010). No volumetric differences in the anterior cingulate of psychopathic individuals. *Psychiatry Research*, 183(2), 140-143.

Good, C. D., Johnsrude, I. S., Ashburner, J., Henson, R. N., Friston, K. J., Frackowiak, R. S. (2001). A voxel-based morphometric study of ageing in 465 normal adult human brains. *Neuroimage*, 14(1 Pt 1), 21-36.

Gregory, S., ffytche, D., Simmons, A., Kumari, V., Howard, M., Hodgins, S., Blackwood, N. (2012). The antisocial brain: psychopathy matters. *Archives of General Psychiatry*, 69(9), 962-972.

Hare, R. D. (2003). *Hare Psychopathy Checklist-Revised (PCL-R).* (2th ed.). Toronto: Multi-Health Systems Inc.

Harrison, B. J., Pujol, J., López-Solà, M., Hernández-Ribas, R., Deus, J., Ortiz, H., Soriano-Mas, C., Yücel, M., Pantelis, C., Cardoner, N. (2008). Consistency and functional specialization in the default mode brain network. *Proceedings of the National Academy of Sciences U.S.A.*, 105(28), 9781-9786.

Harrison, B. J., Soriano-Mas, C., Pujol, J., Ortiz, H., López-Solà, M., Hernández-Ribas, R., Deus, J., Alonso, P., Yücel, M., Pantelis, C., Menchon, J. M., Cardoner, N. (2009) Altered corticostriatal functional connectivity in obsessive-compulsive disorder. *Archives of General Psychiatry*, 66(11), 1189-1200.

Hiatt, K. D., Schmitt, W. A., Newman, J. P. (2004). Stroop tasks reveal abnormal selective attention among psychopathic offenders. *Neuropsychology,* 18(1), 50-59.

Intrator, J., Hare, R., Stritzke, P., Brichtswein, K., Dorfman, D., Harpur, T., Bernstein, D., Handelsman, L., Schaefer, C., Keilp, J., Rosen, J., Machac, J. (1997). A brain imaging (single photon emission computerized tomography) study of semantic and affective processing in psychopaths. *Biological Psychiatry*, 42, 96-103.

Kiehl, K. A. (2006). A cognitive neuroscience perspective on psychopathy: evidence for paralimbic system dysfunction. *Psychiatry Research*, 142(2-3), 107-128.

Kiehl, K. A., Smith, A. M., Hare, R. D., Mendrek, A., Forster, B. B., Brink, J., Liddle, P. F. (2001). Limbic abnormalities in affective processing by

criminal psychopaths as revealed by functional magnetic resonance imaging. *Biological Psychiatry*, 50(9), 677-684.

Koski, L., and Paus, T. (2000). Functional connectivity of the anterior cingulate cortex within the human frontal lobe: a brain-mapping meta-analysis. *Experimental Brain Research*, 133(1), 55-65.

Lorenz, A. R., and Newman, J. P. (2002). Deficient response modulation and emotion processing in low-anxious Caucasian psychopathic offenders: results from a lexical decision task. *Emotion*, 2(2), 91-104.

Ly, M., Motzkin, J. C., Philippi, C. L., Kirk, G. R., Newman, J. P., Kiehl, K. A., Koenigs, M. (2012). Cortical thinning in psychopathy. *American Journal Psychiatry* , 169(7), 743-749.

Lykken, D. T. (1957). A study of anxiety in the sociopathic personality. *Journal of Social and Abnormal Psychology*, 55, 6-10.

MacCoon, D. G., Wallace, J. F., Newman, J. P. (2004). Self-regulation: the context-appropriate allocation of attentional capacity to dominant and non-dominant cues. In R. F. Baumeister and K. D. Vohs, (ed.), *Handbook of Self-Regulation: Research, Theory, and Applications.* (p. 422-446). New York: Guilford.

Margulies, D. S., Kelly, A. M., Uddin, L. Q., Biswal, B. B., Castellanos, F. X., Milham, M. P. (2007). Mapping the functional connectivity of anterior cingulate cortex. *Neuroimage,* 37(2), 579-588.

Marsh, A. A., Finger, E. C., Mitchell, D. G., Reid, M. E., Sims, C., Kosson, D. S., Towbin, K. E., Leibenluft, E., Pine, D. S., Blair, R. J. (2008). Reduced amygdala response to fearful expressions in children and adolescents with callous-unemotional traits and disruptive behavior disorders. *American Journal of Psychiatry*, 165, 712–720.

Mitchell, D. G., Colledge, E., Leonard, A., Blair, R. J. (2002). Risky decisions and response reversal: is there evidence of orbitofrontal cortex dysfunction in psychopathic individuals? *Neuropsychologia*, 40(12), 2013-2022.

Motzkin, J. C., Newman, J. P., Kiehl, K. A., Koenigs, M. (2011). Reduced prefrontal connectivity in psychopathy. *Journal of Neuroscience*, 31, 17348-17357.

Müller, J. L., Gänssbauer, S., Sommer, M., Döhnel, K., Weber, T., Schmidt-Wilcke, T., Hajak, G. (2008). Gray matter changes in right superior temporal gyrus in criminal psychopaths. Evidence from voxel-based morphometry. *Psychiatry Research,* 163(3), 213-222.

Müller, J. L., Sommer, M., Wagner, V., Lange, K., Taschler, H., Röder, C.H., Schuierer, G., Klein, H. E., Hajak, G. (2003). Abnormalities in emotion processing within cortical and subcortical regions in criminal psychopaths: evidence from a functional magnetic resonance imaging study using pictures with emotional content. *Biological Psychiatry*, 54, 152-162.

Newman, J. P and Baskin-Sommers, A. R. (2011). Early Selective Attention Abnormalities in Psychopathy: Implications for Self-Regulation. In M. Poser (Ed), *Cognitive Neuroscience of Attention* (p.421-440). New York: Guilford Press.

Newman, J. P., Curtin, J. J., Bertsch, J. D., Baskin-Sommers, A. R. (2010). Attention moderates the fearlessness of psychopathic offenders. *Biological Psychiatry*, 67(1), 66-70.

Newman, J. P., and Kosson, D. S. (1986). Passive avoidance learning in psychopathic and nonpsychopathic offenders. *Journal of Abnormal Psychology*, 95(3), 252-256.

Newman, J. P., Patterson, C. M., Kosson, D. S. (1987). Response perseveration in psychopaths. *Journal of Abnormal Psychology*, 96(2), 145-148.

Newman, J. P., Schmitt, W. A., Voss, W. D. (1997). The impact of motivationally neutral cues on psychopathic individuals: assessing the generality of the response modulation hypothesis. *Journal of Abnormal Psychology*, 106(4), 563-575.

Newman, J. P., Wallace, J. F., Schmitt, W. A., Arnett, P. A. (1997). Behavioral inhibition system functioning in anxious, impulsive, and psychopathic individuals. *Personality and Individual Differences, 23,* 583-592.

Pujol, J., Batalla, I., Contreras-Rodríguez, O., Harrison, B. J., Pera, V., Hernández-Ribas, R., Real, E., Bosa, L., Soriano-Mas, C., Deus, J., López-Solà, M., Pifarré, J., Menchón, J. M., Cardoner, N. (2011). Breakdown in the brain network subserving moral judgment in criminal psychopathy. S*ocial Cognitive and Affective Neurosciences*, 7(8), 917-923.

Raine, A., and Yang, Y. (2006). Neural foundations to moral reasoning and antisocial behavior. S*ocial Cognitive and Affective Neurosciences*, 1(3), 203-213.

Sadeh, N., and Verona, E. (2008). Psychopathic personality traits associated with abnormal selective attention and impaired cognitive control. *Neuropsychology*, 22(5), 669-80.

Seeley, W. W., Menon, V., Schatzberg, A. F., Keller, J., Glover, G. H., Kenna, H., Reiss, A. L., Greicius, M. D.(2007). Dissociable intrinsic connectivity networks for salience processing and executive control. *Journal of Neuroscience*, 27(9), 2349-2356.

Song, X. W., Dong, Z. Y., Long, X. Y., Li, S. F., Zuo, X. N., Zhu, C. Z., He, Y., Yan, C.G., Zang, Y.F. (2011). REST: a toolkit for resting-state functional magnetic resonance imaging data processing. *PLoS One,* 6(9), e25031.

Soriano-Mas, C., Hernández-Ribas, R., Pujol, J., Urretavizcaya, M., Deus, J., Harrison, B. J., Ortiz, H., López-Solà, M., Menchón, J. M., Cardoner, N. (2011). Cross-sectional and longitudinal assessment of structural brain alterations in melancholic depression. *Biological Psychiatry*, 69(4), 318-325.

Veit, R., Flor, H., Erb, M., Hermann, C., Lotze, M., Grodd, W., Birbaumer, N. (2002). Brain circuits involved in emotional learning in antisocial behavior and social phobia in humans. *Neuroscience Letters*, 328(3), 233-236.

Vitale, J. E., Brinkley, C. A., Hiatt, K. D., and Newman, J. P. (2007). Abnormal selective attention in psychopathic female offenders. *Neuropsychology*, 21(3), 301-312.

Ward BD. Simultaneous Inference for FMRI Data. . *http://stuff.mit.edu/afs/sipb.mit.edu/project/seven/doc/AFNI/AlphaSim.ps.* 2000.

White, S. F., Marsh, A. A., Fowler, K. A., Schechter, J. C., Adalio, C., Pope, K., Sinclair, S., Pine, D. S., Blair, R. J. (2012a). Reduced amygdala response in youths with disruptive behavior disorders and psychopathic traits: decreased emotional response versus increased top-down attention to nonemotional features. *American Journal Psychiatry*, 169(7), 750-758.

White, S. F., Williams, W. C., Brislin, S. J., Sinclair, S., Blair, K. S., Fowler, K. A., Pine, D. S., Pope, K., Blair, R. J. (2012b). Reduced activity within the dorsal endogenous orienting of attention network to fearful expressions in youth with disruptive behavior disorders and psychopathic traits. *Development and Psychopathology*, 24(3), 1105-1116.

Yang, Y., Raine, A., Colletti, P., Toga, A. W., Narr, K. L. (2009). Abnormal temporal and prefrontal cortical gray matter thinning in psychopaths. *Molecular Psychiatry*, 14(6), 561-2, 555.

Yang, Y., Raine, A., Colletti, P., Toga, A. W., Narr, K. L. (2010). Morphological alterations in the prefrontal cortex and the amygdala in unsuccessful psychopaths. *Journal of Abnorml Psychology*, 119(3), 546-554.

Yang, Y., Raine, A., Joshi, A. A., Joshi, S., Chang, Y. T., Schug, R. A., Wheland, D., Leahy, R., Narr, K. L. (2012). Frontal information flow and connectivity in psychopathy. *British Journal of Psychiatry*, 201(5), 408-409.

Zeier, J. D., Maxwell, J. S., Newman, J. P. (2009). Attention moderates the processing of inhibitory information in primary psychopathy. *Journal of Abnormal Psychology*, 118(3), 554-563.

SUPPLEMENTARY MATERIAL

S1. Additional characteristics of study groups

A total of 105 convicted subjects were initially evaluated using a comprehensive clinical protocol. The sample showed a mean Psychopathy Checklist- Revised (PCL-R) score (Hare, 2003) of 27.8 and served to select individuals for fMRI evaluation according to the following criteria (i) total PCL-R score greater than 20 or PCL-R Factor 1 greater than 10, (ii) documented severe criminal offense, (iii) absence of DSM-IV Axis I diagnosis with the exception of past history of substance abuse, (iv) absence of DSM-IV Axis II diagnosis, apart from Antisocial Personality Disorder, (v) absence of symptomatic medical and neurological illness, (vi) normal IQ according to WAIS-III-R (Wechsler, 1997) (sample total IQ, mean $\pm$ SD, 108 $\pm$ 14), and (vii) obtaining subject-specific full administrative permissions and special police custody during the fMRI assessment day, which was limited to 23 individuals (valid cases n= 22).

Psychopathy Assessment. Information for rating the PCL-R was collected by a trained senior psychiatrist from a comprehensive semi-structured interview with the inmate and a review of his institutional files and all available additional information. For the PCL-R, each of the 20 items was scored 0, 1, or 2, depending on the degree to which it was exhibited. The Spanish version of PCL-R was used (Hare, 2003). The internal consistency of the assessment was tested for the whole 105-subject sample obtaining a Cronbach's alpha coefficient of 0.79 (inter-item correlation mean, 0.36) for PCL-R total score.

Offense history. All 22 individuals were incarcerated in correctional institutions situated in Catalonia (Spain). Mean ($\pm$ SD) completed incarceration time at inclusion was 88 $\pm$ 63 months, range 12-251 months. Mean time of accumulated sentences was 243 $\pm$ 127

months; ranging 96-546 months. All were violent armed offenders. Twenty-one of the individuals had committed violent robberies. Fifteen individuals were convicted murderers. Twelve individuals had a criminal record prior to the age of 15. None of them had a sexual offense record.

Substance use/abuse and medical records. Although we sought to recruit a group of relatively "pure" psychopaths, we avoided excessive subject exclusion from associated medical factors in an attempt to maximally provide a generally representative inmate psychopath population. No subject had consumed alcohol (except for one sporadic consumer) or relevant amounts of psychoactive substances for at least two months prior to the assessment (verified using drug-urine testing). A total of 5 individuals showed a past history of alcohol abuse and 15 individuals had been sporadic consumers of alcohol. Sixteen individuals had a past history of other psychoactive substance use.

None of the subjects had suffered from any relevant symptomatic medical illness prior to the study. A total of 4 individuals showed positive testing for asymptomatic HIV, 4 additional individuals for asymptomatic hepatitis B virus and 3 for asymptomatic hepatitis C virus. None of them presented with neurological complications.

The sample of healthy non-offender subjects were recruited from the community matching the psychopathy group by age, sex and scores on the Vocabulary subscale of WAIS-III and also underwent a comprehensive medical and psychiatric assessment (see Table 1 in main Text file). All cases and control subjects gave written informed consent after receiving a complete description of the study, which was approved by local research and ethics committees (IMIM Hospital del Mar, Barcelona, and Hospital Universitari Arnau de Vilanova, Lleida). The investigation was carried out in accordance with the Declaration of Helsinki.

REFERENCES

Hare, R. D. (2003). *Hare Psychopathy Checklist- Revised (PCL-R).* (2th ed.). Toronto: Multi-Health Systems Inc.

Wechsler, D. (1997). Wechsler Adult Intelligence Scale-Third Edition (WAIS-III). San Antonio, TX: The Psychological Corporation.

Table S2. Within-group positive and negative functional connectivity maps

Regions	x	y	z	t	CS	x	y	z	t	CS
	Controls					Psychopaths				
Dorsomedial frontal *seed*										
Positive correlations										
Dorsomedial frontal	6	-6	46	6.1	18158*	2	-2	38	6.9	27934*
R Lateral frontal	34	44	26	5.2	2802	24	46	22	3.8	27934*
L Lateral frontal	-30	48	24	8.5	18158*	-28	48	24	6.8	27934*
Sensorimotor	46	-6	44	3.9	1543	50	-28	42	5.1	27934*
Insula-operculum	34	16	8	4.7	2802				ns	
Thalamus	-12	-8	0	5.9	18158*				ns	
Striatum	-16	6	8	4.6	18158*	-12	16	0	3.5	246
Negative correlations										
R Amygdala-Hippocampus	20	-4	-26	4.5	5047*	20	-4	-26	4	10119*
L Amygdala-Hippocampus				ns		-16	-8	-26	5.2	10119*
Posterior Insula	44	-6	4	4.2	1518	48	-18	0	5.1	10119*
Hypothalamus				ns		4	-8	-10	3.9	10119*
Lingual gyrus	12	-50	-8	6.5	5047*	22	-34	-16	5.7	10119*
PCC	14	-58	12	5.7	5047*	12	-58	24	4.5	10119*
Periaqueductal gray	8	-28	-12	5.2	5047*	6	-28	-14	4.4	10119*
Right Amygdala *seed*										
Positive correlations										
Dorsomedial frontal	-8	18	40	5.8	348				ns	
Sensorimotor	-44	-14	40	3.8	267				ns	
Amygdala- Hippocampus	-18	-2	-18	6.4	12816*	-26	-28	-8	5.8	9473*
Insula-operculum	30	14	-10	6.7	12816*	30	12	-10	6.3	9473*
Thalamus	-6	-20	-4	4.8	12816*	-6	-20	-4	4.3	9473*
Temporal	-34	0	-40	5	12816*	-32	-4	-44	3.4	190
Periaqueductal gray	6	-32	-22	3.9	12816*	-2	-28	-24	3.3	9473*
Pons	4	-24	-32	4.4	12816*	10	-24	-30	4.6	9473*
Negative correlations										
Medial frontal	0	62	28	7	9199*	-2	62	28	5	4763*
Lateral frontal				ns		-44	28	34	4.4	4763*
Ventral frontal	0	24	-18	5.3	9199*	-4	22	-14	3.6	1035~
Caudate				ns		8	22	4	4	1035~
Medial Parietal	8	-56	22	4.5	4724	0	-32	44	4.7	5464^
Angular gyrus	46	-64	38	3.8	744	34	-78	34	4	667
Occipital	-4	-96	-18	5	1135	6	-90	-18	4.4	5464^
Left Amygdala *seed*										
Positive correlations										
Amygdala- Hippocampus	18	2	-14	7.8	7111*	18	0	-16	6.7	1826

Hypothalamus	6	-6	-10	4.6	7111*	2	-6	-10	4.3	2843
Negative correlations										
Dorsomedial frontal				ns		8	38	38	5	4445*
R Lateral frontal	36	28	46	4.4	383	36	32	44	5.5	4445*
Medial Parietal	6	-80	46	4.8	3792	8	-68	54	5.3	2844
Temporal	46	-68	-26	4.6	2320	48	-70	-14	5.4	261
Occipital	-10	-80	-12	5.1	2320				ns	
Right Frontal *seed*										
Positive correlations										
Dorsomedial frontal	-12	28	40	4.9	15330*	4	26	42	8.1	21018*
Lateral frontal	-30	34	40	3.5	15330*	-34	34	36	4.1	21018*
PCC (ventral)	-6	-52	8	6.3	15330*				ns	
PCC (dorsal)	-2	-32	34	6.5	15330*	6	-38	42	5.4	21018*
Precuneus	6	-66	40	7.8	15330*	10	-64	48	4.5	21018*
Angular gyrus	58	-62	28	5.1	3705	46	-74	36	4.8	21018*
Negative correlations										
Insula-operculum	36	6	0	4.4	1490	46	2	0	3.9	497
Occipital	22	-68	-14	6	984	16	-92	-6	5	274
Cerebellum	-8	-68	-28	4.2	2135				ns	
Left Frontal *seed*										
Positive correlations										
Dorsomedial frontal	-6	26	48	5.9	11055*	-6	24	44	9.9	17198*
Medial frontal	-2	54	8	4.9	11055*				ns	
Lateral frontal	42	18	44	6.3	11055*	48	26	38	5.9	17198*
Ventrolateral frontal	-48	38	-12	5.6	11055*	-48	28	-10	3.8	448
Caudate				ns		-12	14	6	4.8	208
Temporal	-62	-42	-10	7	979	-64	-32	-12	3.9	199
PCC	-6	-54	22	5.6	2842	0	-56	18	4.2	17198*
Angular gyrus	50	-60	44	6.4	1321	48	-64	42	5.3	915
Negative correlations										
R Amygdala				ns		20	-2	-14	3.7	7475*
Insula-operculum	36	0	12	5.2	4693*	34	12	2	5.1	7475*
Supramarginalis gyrus	62	-24	26	6.7	4693*	52	-32	26	5.2	7475*
Superior temporal gyrus	60	-4	2	4.5	4693*	60	-22	6	4.9	7475*
Occipital	14	-76	2	5.2	2255				ns	
Periaqueductal gray				ns		4	-34	-18	4.9	7475*

Anatomical coordinates (x, y, z) are given in Montreal Neurological Institute (MNI) Atlas space. PCC: Posterior Cingulate Cortex. CS: Cluster size (voxels). R: Right. L: Left. * ~ ^part of the large cluster.

6. GENERAL DISCUSSION

The present thesis aims at identifying functional alterations within the brain networks processing emotion and connecting emotion with cognition in psychopathic individuals, and in two clinical populations showing common or opposite behavioral features such as cocaine dependence and obsessive-compulsive disorder by using both functional and anatomical magnetic resonance approaches. Emotional processing is fundamental to promote normal socialization, interpersonal interactions, successful decision-making and overall to self-regulate behavior according to each context. An adequate emotional processing relies in the adequate and balance function within certain brain networks that contain emotional, cognitive and perceptual elements that respond and integrate the emotional information to successfully guide behavior.

The use of our experimental moral dilemma task was able to generate robust brain responses thus evoking, at the group level, solid and significant activity within the cognitive and emotional brain elements subserving moral dilemma processing in the psychopathic individuals, the cocaine users and the obsessive-compulsive disorder patients. We successfully characterized the existence of different patterns of brain activation in the three study samples which were associated with the clinical severity ratings in the psychopathic and the obsessive-compulsive individuals. Furthermore, the use of a continuous resting-state fMRI paradigm allowed us to investigate whether the brain alterations in response to the moral dilemma task shown by the psychopaths and cocaine users were also present in the spontaneous brain organization as it has been previously demonstrated in obsessive-compulsive samples (Harrison et al., 2009). Moreover, our emotional face processing task also evoked consistent emotional and cognitive brain activations within the network of interest, thus allowing us to characterize relevant activation and task-induced functional connectivity changes in the psychopathic individuals. Finally, in the last study, anatomical assessments proved valid to depict both concentration and volume anatomical changes in psychopaths and, together with global functional connectivity degree measurements, they were useful to guide whole-brain functional connectivity analyses thus providing a whole picture of brain impairment in these subjects during rest.

Our first study provided relevant new data on the brain network subserving moral judgment in psychopathic individuals that largely overlap with the default mode network (Greene et al., 2001; Harrison et al., 2008; Moll et al., 2005). Previous research studies

hypothesized that rule-breaking psychopathic behavior may be associated with a disruption to this neural network (Raine and Yang, 2006). Our data confirms the previous evidence that psychopathy is associated with a reduced implication of the brain areas subserving moral judgment (Glenn et al., 2009). In fact, psychopaths presented with a negative association between parts of the brain network showing decreased activation to the moral dilemma task with the psychopathy severity scores. Nevertheless, psychopaths additionally presented with an abnormal deactivation during the Stroop task restricted to the medial frontal cortex. Finally, findings from the resting-state functional connectivity analysis showed a preserved local connectivity but an altered long-distance connectivity between frontomedial and posterior cingulate brain elements. Overall, results across the different fMRI assessments support a primary functional alteration in the brain network subserving moral judgment in psychopathic individuals.

Furthermore, it is worth discussing the implications of the psychopaths' dysfunction in ventromedial frontal cortices. As introduced before, the ventromedial frontal cortex constitutes a crucial brain region in assessing the emotional aspects in moral dilemma contexts. On the basis of the psychopathic behavior, impairment within ventromedial frontal cortices has been related to the inability to activate somatic states linked to socially-related punishment and reward (Anderson et al., 1999; Damasio, 1994; Koenigs, 2012). Finally, psychopaths additionally demonstrated a reduced activation of the hippocampus-amygdala junction, the caudal periaqueductal gray and the locus coeruleus brain regions during the moral dilemma task. These brain regions belong to the basic threat response system, key in emotional processing and subsequent behavioral selection (Davidson, 2000; Liddell et al., 2005). In psychopaths, a dysfunction within this brain system is thought to contribute to the deficient processing of fear-related stimuli thus preventing these individuals from learning to avoid actions that will harm others (Blair and Mitchell, 2009).

When specifically applied to the study of brain pathophysiology in cocaine users and obsessive-compulsive patients, the moral dilemma task was again useful to capture major abnormalities within cognitive and emotional brain elements in these study samples. Importantly, cocaine users showed largely coincident reduced brain responses paralleling the pattern of brain reductions shown by the psychopathic individuals in medial frontal cortices, involving the ACC, and in the periaqueductal gray extending to adjacent parahippocampal cortices. Nevertheless, the cocaine users showed an additional decreased activation in the left insula to the moral dilemma task. Subsequent functional connectivity

analyses at rest revealed a deficient coupling within the brain regions showing a decreased activation to the moral dilemma task. Specifically, cocaine users showed a decreased functional connectivity between the ACC with the mediodorsal thalamus and between the periaqueductal gray with the left insula and putamen regions.

Overall, the pattern of brain reductions to moral dilemmas in the cocaine users engaged the salience network, which serves a role in emotion generation, integration and awareness. Chronic cocaine use involves persistent stimulation of this brain network in anticipation of drug use (Goldstein et al., 2009), hence it's thought that these systems would become progressively sensitized to drug cues (Childress et al., 2008) but less responsive to relevant emotional cues (Volkow et al., 2011). Moreover, the dysfunction observed within the salience network in the cocaine users fits well with the neural predictions of the somatic-marker theory of addiction (Damasio, 1994; Verdejo-García and Bechara 2009) which suggests that substance dependence, including cocaine, is characterized by difficulties to generate or to integrate ascending emotional signals that normally arise to guide complex decisions.

Finally, obsessive-compulsive patients showed an opposite brain response to the moral dilemma task when compared with its reference sample of control subjects. In particular, obsessive-compulsive patients exhibited significantly more pronounced activation in some of the brain regions subserving moral dilemma processing including a large region extending from the ventromedial to the orbitofrontal and left lateral temporal cortices. Additionally, significantly greater activation in obsessive-compulsive patients was located in the left dorsolateral prefrontal cortex which may putatively be related to the disorder-relevant cognitive biases engaged during moral decision-making. These previous brain regions together with the caudate nucleus, hypothalamus and dorsal medial frontal cortex showed a positive association with the patients' DY-BOCS ratings of total symptom severity. Finally it is important to note for further discussion below that the activation in the medial and lateral frontal cortices were negatively associated with the individual tendency to endorse moral violations to the dilemma vignettes across groups.

Activation in both ventromedial and orbitofrontal cortices has been linked to the experience of guilt and shame (Koenigs et al., 2007; Krajbich, Adolphs, Tranel, Denburg, and Camerer, 2009; Mendez, 2009; Moretto, Làdavas, Mattioli, and di Pellegrino, 2010; Thomas, Croft, and Tranel, 2011). Based on this, greater engagement of these regions in

patients with OCD may enhance such a feeling thus increasing the perceived salience of the emotive dilemma stimuli or an excessive valuation of decision outcomes. Moreover, it is plausible that disorder-relevant cognitive biases engaged during moral decision making evoke heightened activation in frontotemporal regions. Overall, our findings support alteration both in conscious cognitive appraisal of emotional stimuli and those more directly associated with the subjective experience of moral emotions.

In light of the similar brain deficits shown by the psychopathic subjects and the cocaine users it may be hypothesized that the continuous use of cocaine would partially impair similar fronto-limbic brain networks hypothesized to be primarily dysfunctional in psychopathic individuals (Blair, 2003b; Goldstein et al., 2009). Dysfunction within fronto-limbic networks may well suggest that both psychopaths and cocaine users may encode less the relative value and salience of environmental stimuli that support anticipation of future outcomes, complex decision-making and thus adaptive behavior. The decrease influence of the emotional information on behavior regulation has been consistently reported in psychopathic samples (Flor et al., 2002; Lykken, 1957; Mitchell et al., 2002; Newman and Kosson, 1986; Newman et al., 1987). However, in cocaine users, this effect seems to be uniquely manifested in non-related drug cues whereas an increased fronto-limbic responses have been reported in cocaine-related stimuli (Garavan et al., 2000; Goldstein and Volkow, 2002; Volkow et al., 2011; Wilcox et al., 2011). This divergent brain response to cocaine-related and non-related stimuli may be indicative of altered motivational and reward processes in cocaine users. These may give rise to impulsive and compulsive drug-seeking and drug-using behaviors thus contributing to behavioral and decision making deficits in real life (Cunha et al., 2011; Fernández-Serrano et al., 2010; Verdejo-García et al., 2006).

In contrast to psychopaths and cocaine users, the brain-enhanced responses in obsessive-compulsive patients seems to support a primary heightened moral sense in these patients (Koenigs et al., 2007; Krajbich et al., 2009; Moretto et al., 2010; Shafran, 2005; Thomas et al., 2011). Supporting this, enhanced brain response to the moral dilemma task in obsessive-compulsive patients remains significant even after controlling for group differences in comorbid affective symptoms thus given importance to the use of experimental paradigms that directly evoke associated guilt feeling to study unique emotional biases in these individuals (Salkovskis, 1985, Salkovskis and Forrester, 2002). Overall, the disparity in brain responses between psychopaths and cocaine users with the OCD patients suggest that different function within ventromedial prefrontal cortices may

be important to account for the level of sensitivity and emotional implication we assign to complex moral decision situations. In fact, the individual tendency to endorse moral violations across OCD and reference control subjects was negatively associated with the medial prefrontal cortex, which was less activated in the psychopaths and the cocaine users. However, despite the higher brain activation, the study groups differed in their proportion of yes/no responses in only 5 of 24 vignettes, although we cannot discard effects on decision latency due to our experimental design.

Regarding the assessment of the spontaneous function of the brain, both the psychopaths and the cocaine users showed an impaired functional connectivity within the brain regions hypoactivated in the moral dilemma task. Complementing the evidence of disruption between anterior temporal and ventral frontal areas (Craig et al., 2009; Marsh et al., 2008; Motzkin et al., 2011), the altered long-distance connectivity between the frontomedial anterior and cingulate posterior brain elements suggest an additional dorsal disruption in the default mode network, which is in turn closely related to both the hippocampal-amygdala complex and the orbitofrontal cortex, in psychopathic individuals (Buckner and Carroll, 2007). In active cocaine users, preliminary reports have shown inconsistent functional connectivity alterations during rest pointing to both an increase and decrease in functional coupling between subcortical and prefrontal brain (Camchong et al., 2011; Gu et al., 2010; Wilcox et al., 2011). Our study recruited chronic cocaine users after a supervised abstinence period. In that sense, our findings may contribute to the existing literature by providing further clues regarding putative long-term neuroadaptations in brain network subserving cognitive-emotion integration and processing of the interoceptive state of the body following chronic cocaine use.

In our fourth study, we aimed to further examine brain activation and functional connectivity responses in psychopaths to another relevant emotional social stimuli such as emotional face expressions (Hariri et al., 2000). Although hypotheses generated from a large body of behavioral data commonly point towards an association between the deficit in facial affect recognition and amygdala dysfunction in antisocial individuals (Marsh et al., 2008), there is only one study with adults formally satisfying psychopathic criteria (Deeley et al., 2006). In our study, amygdala activation during the task was only significantly activated in control subjects but no significant differences were observed when the groups were directly compared. Nevertheless, psychopaths showed significantly greater activation of neocortical areas involving both visual and prefrontal cortices in comparison with the

control subjects and this cortical hyperactivation was positively associated with the unemotional-interpersonal severity scores in psychopaths. In regards to the functional connectivity changes under the task, most relevant findings revealed a decreased functional connectivity between the amygdala with prefrontal and visual cortical regions in psychopaths. Taken as a whole, the observed pattern of results suggests that differences in the neural processing of emotional faces may combine both deficient (limbic) and compensatory (neocortical) operations.

The assessment of the brain response to emotional face expression in psychopaths again strengthen the idea of a decreased salience attribution to surrounding stimuli in such individuals in line with the first study of the present thesis. Moreover, we found a reduced integration of the emotional information with cortical regions in agreement with previous studies (Craig et al., 2009; Marsh et al., 2008; Motzkin et al., 2011). However, we demonstrated for the first time an altered functional coupling between visual posterior areas with the amygdala which constitutes a relevant pathway for the detection of stimulus saliency, thought to be modulated by emotional abilities and traits (Adolphs, 2008; Japee et al., 2009; Pujol et al., 2009). Moreover, due to the greater activation of cortical areas and the positive association of the frontal cortex hyperactivity with unemotional-interpersonal traits in psychopaths, it is worthwhile to discuss the possible use of compensatory mechanisms in such a population. It is proposed that psychopaths may make an efficient use of neocortical abilities to overcome the deficient engagement of limbic systems to the emotional faces and perform the task as well as control subjects. This adds evidence to prior functional imaging studies reporting cortical hyperactivity during emotional tasks in psychopaths samples (Glenn et al., 2009; Intrator et al., 1997; Kiehl et al., 2001; Müller et al., 2003).

Our last time-related study was specifically designed to comprehensively explore for putative resting-state functional connectivity changes in relevant emotional and cognitive large-scale brain networks in psychopathic individuals using both anatomical and functional approaches. At the anatomical level, psychopaths showed significant gray matter anatomical decreases involving prefrontal and limbic-paralimbic brain regions. Moreover, overlapping the anatomical findings, the psychopaths showed greater global functional connectivity degree in the dorsomedial prefrontal cortex which was associated with the psychopaths' emotional disturbances. Finally, reduced functional connectivity between limbic-paralimbic with dorsal executive brain networks together with an enhanced

functional connectivity within the dorsal executive brain network was observed in the psychopathic individuals.

Although previous suggestions that alterations in dorsomedial frontal areas may contribute to the affective and self-regulatory deficits in psychopathic individuals (MacCoon et al., 2004; Newman and Baskin-Sommers, 2011), this study is the first to demonstrate resting-state functional connectivity alterations within the entire dorsal frontal network in psychopathic individuals. Such a finding is in agreement with the Response Modulation Hypothesis which hypothesized a reduced ability to use and give sufficient consideration to relevant information that is peripheral to a dominant response in these individuals (Lorenz and Newman, 2002). Moreover, the enhanced functional connectivity within dorsal executive brain networks may also fit with reports of the psychopathic individuals normally performing on simple executive neuropsychological tasks and benefiting from emotional information during sequential tasks (Hiatt et al., 2004; Newman et al., 2010; Newman and Kosson, 1986). In fact, it is worth noting that in our previous studies psychopaths presented comparable behavioral performance with control subjects (Contreras-Rodríguez et al., 2013; Pujol et al., 2011). Nevertheless, we again observed a reduced functional coupling between emotional with prefrontal regions in the psychopathic individuals although this deficit is presented not only when the circuit is challenge by an emotional task but also manifests in the spontaneous brain function (Contreras-Rodríguez et al., 2013).

To sum up, the studies conducted with psychopathic individuals are in agreement with a dysfunction of the brain regions primarily responding to emotional information (Blair, 2003b). However, the decreased influence of emotion to regulate behavior may also reside in the fact that these emotional brain areas are less coupled to diverse neocortical brain regions, thus compromising the emotional amplification brain mechanism. This disruption in functional connectivity was observed whole-brain including different brain networks and not limited to the well-reported disruption within amygdala-ventromedial frontal cortices (Craig et al., 2009; Marsh et al., 2008; Motzkin et al., 2011). Moreover, our data suggests that psychopaths may benefit from emotional information by the use of compensatory fronto-cingulate mechanisms in goal-directed task, although this would contribute to their inflexible behavior by encouraging the emotional-cognitive imbalance (Corbetta and Shulman, 2002; Menon and Uddin, 2010), making them less flexible in rich social-emotional environmental contexts. Finally, it is worth noting that functional connectivity disruptions in psychopaths were present both while engaged in emotional tasks and also

during rest when subjects were not required to intentionally process emotional information thus suggesting that psychopaths may possess primary neural alterations.

The present thesis has attempted to approach the study of the emotional processing in the brain using an integrative view to understand how complex behaviors result from rich, dynamic and closely related interactions between the different brain units. All in all, the five studies presented herein constitute a step forward in the characterization of how the brain responds to emotional situations and how changes in this response pattern may compromise flexible and advantageous behaviors across pathologies.

We bring this thesis to an end by facing up future work directions through the following open issues:

- Whether the emotional brain dysfunction in psychopaths is primary or it is rather a consequence of an enhanced suppression exerted by a hyperfunction within fronto-cingulate systems constitutes a relevant topic of discussion at present. Further studies should try to elucidate this probably by using higher temporal resolution techniques in youth with psychopathic traits.

- At the present, most studies assessing brain function in cocaine users have been done with active use. There is the need to investigate whether brain changes persist during long protracted abstinence and whether they are associated with relevant clinical variables useful to prevent drug relapse.

- The study of the neural pathophysiology in obsessive-compulsive disorder may benefit from tasks evoking unique feelings of guilt and responsibility to reveal the specific neural deficits in these individuals thus guiding the selection of tailored clinical treatments.

7. CONCLUSIONS

1. Results across the different fMRI assessments support a primary functional alteration in the brain network subserving moral judgment in psychopathic individuals.

2. The decreased function within the salience network in cocaine users may relate with their difficulties to generate or to integrate ascending emotional signals that normally arise to guide complex decisions.

3. The enhanced activation of the brain network subserving moral judgment in obsessive-compulsive patients may increase the perceived salience of the emotive dilemma stimuli or an excessive valuation of decision outcomes.

4. Neural processing of emotional faces in psychopaths combine both deficient (limbic) and compensatory (neocortical) operations. Furthermore, the pattern of task-related functional connectivity alterations suggests impairment within emotional amplification mechanisms.

5. The imbalance resting functional connectivity involving both a decreased (limbic) and an increased (cognitive) coupling with dorsal fronto-cingulate areas may contribute to the psychopaths' affective and self-regulatory deficits, thus contributing to an inflexible behavior.

8. BIBLIOGRAPHY

Adolphs, R. (2002). Recognizing emotion from facial expressions: Psychological and neurological mechanisms. *Behavioral and Cognitive Neuroscience Reviews*, 1, 21-61.

Adolphs, R. (2008). Fear, faces, and the human amygdala. *Current Opinion in Neurobiology, 18,* 166-172.

Adolphs, R. (2010). What does the amygdala contribute to social cognition? *Annals of the New York Academy of Sciences*, 1191(1), 42-61.

Adolphs, R., Tranel, D., Hamann, S., Young, A.W., Calder, A.J., Phelps, E.A., Anderson, A., Lee, G.P., Damasio, A.R. (1999). Recognition of facial emotion in nine individuals with bilateral amygdala damage. *Neuropsychologia*, 37(10), 1111-1117.

Aguilar de Arcos, F., Verdejo-García, A., Peralta-Ramírez, M.I., Sánchez-Barrera, M., Pérez-García, M. (2005). Experience of emotions in substance abusers exposed to images containing neutral, positive, and negative affective stimuli. *Drug Alcohol Dependence*, 78(2), 159-167.

Alexander, G., DeLong, M., Strick, P. (1986). Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annual Review of Neuroscience*, 9, 357-381.

Allison, T., Puce, A., McCarthy, G. (2000). Social perception from visual cues: role of the STS region. *Trends in Cognitive Science*, 4(7), 267-278.

Amaral, D.G., and Insausti, R. (1992). Retrograde transport of D-[3H]-aspartate injected into the monkey amygdaloid complex. *Experimental Brain Research*, 88, 375-388.

Anderson, S.W., Bechara, A., Damasio, H., Tranel, D., Damasio, A.R. (1999). Impairment of social and moral behavior related to early damage in human prefrontal cortex. *Nature Neuroscience*, 2(11), 1032-1037.

Aniskiewicz, A.S. (1979). Autonomic components of vicarious conditioning and psychopathy. *Journal of Clinical Psychology*, 35(1), 60-67.

Andreasen, N.C., O'Leary, D.S., Cizadlo, T., Arndt, S., Rezai, K., Watkins, G.L., Ponto, L.L., Hichwa, R.D. (1995). Remembering the past: two facets of episodic memory explored with positron emission tomography. *Americal Journal of Psychiatry*, 152, 1576-1585.

Arieli, A., Shoham, D., Hildesheim, R., Grinvald, A. (1995). Coherent spatiotemporal patterns of ongoing activity revealed by real-time optical imaging coupled with single-unit recording in the cat visual cortex. *Journal of Neurophysiology*, 73, 2072-2093.

Armony, J.L., and LeDoux, J.E. (1997). How the brain processes emotional information. *Annals of the New York Academy Sciences*, 821, 259-270.

Arnett, P.A., Howland, E.W., Smith, S.S., Newman, J.P. (1993). Autonomic responsivity during passive avoidance in incarcerated psychopaths. *Personality and Individual Differences*, 14, 173-185.

Arnett, P.A., Smith, S.S., Newman, J.P. (1997). Approach and avoidance motivation in psychopathic criminal offenders during passive avoidance. Psychology, 72(6), 1413-1428.

Asensio, S., Romero, M.J., Palau, C., Sanchez, A., Senabre, I., Morales, J.L., Carcelen, R., Romero, F.J. (2010). Altered neural response of the appetitive emotional system in cocaine addiction: an fMRI study. *Addiction Biolology*, 15, 504-516.

Aston-Jones, G., Rajkowski, J., Cohen, J. (2000). Locus coeruleus and regulation of behavioral flexibility and attention. *Progress in Brain Research*, 126, 165-182.

Averill, J. R. (1982). *Anger and aggression: An essay on emotion.* New York: Springer-Verlag.

Bagley, A.D., Abramowitz, C.S., Kosson, D.S. (2009). Vocal affect recognition and psychopathy: converging findings across traditional and cluster analytic approaches to assessing the construct. *Journal of Abnormal Psychology*, 118(2), 388-398.

Baker, S.C., Rogers, R.D., Owen, A.M., Frith, C.D., Dolan, R.J., Frackowiak, R.S., Robbins, T.W. (1996). Neural systems engaged by planning: a PET study of the Tower of London task. *Neuropsychologia*, 34, 515-526.

Bechara, A. (2001). Neurobiology of decision-making: risk and reward. *Seminars in Clinical Neuropsychiatry*, 6(3), 205-216.

Bechara, A. (2004). The role of emotion in decision-making: evidence from neurological patients with orbitofrontal damage. *Brain and Cognition*, 55(1), 30-40.

Bechara, A., Damasio, A.R., Damasio, H., Anderson, S.W. (1994). Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition,* 50, (1-3), 7-15.

Bechara, A., and Damasio, H. (2002). Decision-Making and Addiction (Part I): Impaired Activation of Somatic States in Substance Dependent Individuals When Pondering Decisions With Negative Future Consequences. *Neuropsychologia,* 40, 1675-1689.

Bechara, A., Dolan, S., Hindes, A. (2002). Decision-making and addiction (part II): myopia for the future or hypersensitivity to reward? *Neuropsychologia*, 40(10), 1690-1705.

Bechara, A., Tranel, D., Damasio, H., Adolphs, R. (1995). Double dissociation of conditioning and declarative knowledge relative to the amygdala and hippocampus in humans. *Science,* 269, 1115-1118.

Baird, A.A., Gruber, S.A., Fein, D.A., Maas, L.C., Steingard. R.J., Renshaw, P.F., Cohen, B.M., Yurgelun-Todd, D.A. (1999). Functional magnetic resonance imaging of facial affect recognition in children and adolescents. *Journal of American Academy of Child and Adolescent Psychiatry*, 38(2), 195-199.

Bar-Haim, Y., Lamy, D., Pergamin, L., Bakermans-Kranenburg, M.J., van IJzendoorn, M.H. (2007). Threat-related attentional bias in anxious and nonanxious individuals: a meta-analytic study. *Psychological Bulletin*, 133(1), 1-24.

Beckmann, C.F., DeLuca, M., Devlin, J.T., Smith, S.M. (2005). Investigations into resting-state connectivity using independent component analysis. *Philosophical Transactions of the Royal Society London B Biological Sciences*, 360(1457), 1001-1013.

Berridge, K.C., and Robinson, T.E. (2003). Parsing reward. *Trends in Neurosciences*, 26(9), 507-513.

Birbaumer, N., Veit, R., Lotze, M., Erb, M., Hermann, C., Grodd, W., Flor, H. (2005). Deficient fear conditioning in psychopathy: a functional magnetic resonance imaging study. *Archives of General Psychiatry*, 62(7), 799-805.

Bishop, S.J. (2008). Neural mechanisms underlying selective attention to threat. *Annals of the New York Academy of Sciences*, 1129, 141-152.

Biswal, B., Yetkin, F.Z., Haughton, V.M., Hyde, J. S. (1995). Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magnetic Resonance in Medicine*, 34, 537-541.

Blair, R.J. (1995). A cognitive developmental approach to morality: Investigating the psychopath. *Cognition,* 57*,* 1-29.

Blair, R.J.R. (1999). Responsiveness to distress cues in children with psychopathic tendencies. *Personality and Individual Differences*, 27 (1), 135-145.

Blair, R.J. (2003a). Facial expressions, their communicatory functions and neuro-cognitive substrates. *Philosophical Transactions of Royal Society of London B Biolology Science*, 358(1431), 561-572.

Blair, R.J.R. (2003b). Neurobiological basis of psychopathy. *British Journal Psychiatry*, 182, 5-7.

Blair, R.J. (2004). The roles of orbital frontal cortex in the modulation of antisocial behavior. *Brain and Cognition*, 55(1), 198-208.

Blair, R.J. (2006). The emergence of psychopathy: implications for the neuropsychological approach to developmental disorders. *Cognition*, 101(2), 414-442.

Blair, R.J. (2007). The amygdala and ventromedial prefrontal cortex in morality and psychopathy. Trends in Cognitive Science, 11(9), 387-392.

Blair, R.J.R., and Coles, M. (2000). Expression recognition and behavioural problems in early adolescence. *Cognitive Development*, 15(4), 421-434.

Blair, R.J., Colledge, E., Murray, L., Mitchell, D.G. (2001). A selective impairment in the processing of sad and fearful expressions in children with psychopathic tendencies. *Journal of Abnormal Child Psychology*, 29(6), 491-498.

Blair, R.J.R. and Frith, U. (2000). Neurocognitive explanations of the antisocial personality disorders. *Criminal Behaviour and Mental Health*, 10, S66-S82.

Blair, R.J., Jones, L., Clark, F., Smith, M. (1997). The psychopathic individual: a lack of responsiveness to distress cues? *Psychophysiology*, 34(2), 192-198.

Blair, R.J.R, and Mitchell, D.G. (2009). Psychopathy, attention and emotion. *Psychological Medicine*, 39(4), 543-555.

Blair, R.J., Mitchell, D.G., Richell, R.A., Kelly, S., Leonard, A., Newman, C., Scott, S.K. (2002). Turning a deaf ear to fear: impaired recognition of vocal affect in psychopathic individuals. *Journal of Abnormal Psychology*, 111(4), 682-686.

Blair, R.J., Morris, J.S., Frith, C.D., Perrett, D.I., Dolan, R.J. (1999). Dissociable neural responses to facial expressions of sadness and anger. *Brain*, 122(Pt 5), 883-893.

Bolla, K.I., Eldreth, D.A., London, E.D., Kiehl, K.A., Mouratidis, M., Contoreggi, C., Matochik, J.A., Kurian, V., Cadet, J.L., Kimes, A.S., Funderburk, F.R., Ernst, M. (2003). Orbitofrontal cortex dysfunction in abstinent cocaine abusers performing a decision-making task. *Neuroimage*, 19(3), 1085-1094.

Borg, J.S., Hynes, C., Van Horn, J., Grafton, S., Sinnott-Armstrong, W. (2006). Consequences, action, and intention as factors in moral judgments: an FMRI investigation. *Journal of Cognitive Neuroscience,* 18(5), 803-817.

Botvinick, M.M., Cohen, J.D., Carter, C,S. (2004). Conflict monitoring and anterior cingulate cortex: an update. *Trends and Cognitive Sciecne*s, 8(12), 539-546.

Breiter, H.C., Etcoff, N.L., Whalen, P.J., Kennedy, W.A., Rauch, S.L., Buckner, R.L., Strauss, M.M., Hyman, S.E., Rosen, B.R. (1996). Response and habituation of the human amygdala during visual processing of facial expression. *Neuron*, 17(5), 875-887.

Breiter, H.C., Gollub, R.L., Weisskoff, R.M., Kennedy, D.N., Makris, N., Berke, J.D., Goodman, J.M., Kantor, H.L., Gastfriend, D.R., Riorden, J.P., Mathew, R.T., Rosen, B.R., Hyman, S.E. (1997). Acute effects of cocaine on human brain activity and emotion. *Neuron*, 19(3), 591-611.

Breiter, H.C., and Rauch, S.L. (1996). Functional MRI and the study of OCD: from symptom provocation to cognitive-behavioral probes of cortico-striatal systems and the amygdala. *Neuroimage*, 4(3 Pt 3), S127-S138.

Britton, J.C., Stewart, S.E., Killgore, W.D., Rosso, I.M., Price, L.M., Gold, A.L., Pine, D.S., Wilhelm, S., Jenike, M.A., Rauch, S.L. (2010). Amygdala activation in response to facial expressions in pediatric obsessive-compulsive disorder. *Depression and Anxiety*, 27(7), 643-651.

Broca, P. (1863). Localisations des fonctions cérébrales. Siège de la faculté du langage articulé. *Bulletin de la Société d'Anthropologie*, 4, 200-208.

Buckner, R.L., and Carroll, D.C. (2007). Self-projection and the brain. *Trends and Cognitive Sciecnes*, 11(2), 49-57.

Bush, G., Luu, P., Posner, M.I. (2000). Cognitive and emotional influences in anterior cingulate cortex. *Trends and Cognitive Sciecnes,* 4, 215-222.

Calder, A.J., Young, A.W., Rowland, D., Perrett, D.I., Hodges, J.R., Etcoff, N.L. (1996). Facial Emotion Recognition after Bilateral Amygdala Damage: Differentially Severe Impairment of Fear. *Cognitive Neuropsychology*, 13(5), 699-745.

Camchong, J., MacDonald, A.W. 3rd., Nelson, B., Bell, C., Mueller, B.A., Specker, S., Lim, K.O. (2011). Frontal hyperconnectivity related to discounting and reversal learning in cocaine subjects. *Biological Psychiatry*, 69(11), 1117-1123.

Cannistraro, P.A., Wright, C.I., Wedig, M.M., Martis, B., Shin, L.M., Wilhelm, S., Rauch, S.L. (2004). Amygdala responses to human faces in obsessive-compulsive disorder. *Biological Psychiatry*, 56(12), 916-920.

Cannon, W.B. (1987). The James-Lange theory of emotions: a critical examination and an alternative theory. *American Journal of Psychology*, 100(3-4), 567-586.

Cardoner, N., Harrison, B.J., Pujol, J., Soriano-Mas, C., Hernández-Ribas, R., López-Solá, M., Real, E., Deus, J., Ortiz, H., Alonso, P., Menchón, J.M. (2011). Enhanced brain responsiveness during active emotional face processing in obsessive compulsive disorder. *World Journal of Biological Psychiatry*, 12(5), 349-363.

Carmichael, S.T. and Price, J.L. (1995). Limbic connections of the orbital and medial prefrontal cortex in macaque monkeys. *Journal of Comparative Neurology*, 363(4), 615-641.

Carter, C.S., Macdonald, A.M., Botvinick, M., Ross, L.L., Stenger, V.A., Noll, D., Cohen, J.D. (2000). Parsing executive processes: strategic vs. evaluative functions of the anterior cingulate cortex. *Proceedings of National Academy of Sciences U.S.A.*, 97(4), 1944-1948.

Chamberlain, S.R., Menzies, L., Hampshire, A., Suckling, J., Fineberg, N.A., del Campo, N., Aitken, M., Craig, K., Owen, A.M., Bullmore, E.T., Robbins, T.W., Sahakian, B.J. (2008). Orbitofrontal dysfunction in patients with obsessive-compulsive disorder and their unaffected relatives. *Science*, 321(5887), 421-422.

Childress, A.R., Ehrman, R.N., Wang, Z., Li, Y., Sciortino, N., Hakun, J., Jens, W., Suh, J., Listerud, J., Marquez, K., Franklin, T., Langleben, D., Detre, J., O'Brien, C.P. (2008). Prelude to passion: limbic activation by 'unseen' drug and sexual cues. *PLoS One*, 3, e1506.

Childress, A.R., Mozley, P.D., McElgin, W., Fitzgerald, J., Reivich, M., O'Brien, C.P. (1999). Limbic activation during cue-induced cocaine craving. *American Journal Psychiatry*, 156(1), 11-18.

Cisler, J.M., Olatunji, B.O., Feldner, M.T., Forsyth, J.P. (2010) Emotion Regulation and the Anxiety Disorders: An Integrative Review. *Journal of Psychopathologyand Behavioral Assessement*, 32(1), 68-82.

Cleckley, H. (1976). *The Mask of Sanity*. (5th ed.). Saint Louis: CV Mosby Co.

Contreras-Rodríguez, O., Pujol, J., Batalla, I., Harrison, B.J., Bosque, J., Ibern-Regàs, I., Hernández-Ribas, R., Soriano-Mas, C., Deus, J., López-Solà, M., Pifarré, J., Menchón, J.M.,

Cardoner, N. (2013). Disrupted neural processing of emotional faces in psychopathy. S*ocial Cognitive and Affective Neurosciences*, [Epub ahead of print].

Cooper, J.C., Kreps, T.A., Wiebe, T., Pirkl, T., Knutson, B. (2010). When giving is good: ventromedial prefrontal cortex activation for others' intentions. *Neuron*, 67(3), 511-521.

Corbetta, M., and Shulman, G.L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nature Reviews Neurosci*ence, 3(3), 201-215.

Craig, A.D. (2002). How do you feel? Interoception: the sense of the physiological condition of the body. *Nature Reviews Neurosciences,* 3, 655-666.

Craig, A.D. (2003). Interoception: the sense of the physiological condition of the body. *Current Opininion in Neurobiology*, 13, 500-505.

Craig, A.D. (2009). How do you feel--now? The anterior insula and human awareness. *Nature Reviews Neurosci*ence*,* 10(1), 59-70.

Craig, M.C., Catani, M., Deeley, Q., Latham, R., Daly, E., Kanaan, R., Picchioni, M., McGuire, P.K., Fahy, T., Murphy, D.G. (2009). Altered connections on the road to psychopathy. *Molecular Psychiatry*, 14, 946-953.

Christianson, S.A., Forth, A.E., Hare, R.D., Strachan, C., Lidberg, L., Thorell, L H. (1996). Remembering details of emotional events: A comparison between psychopathic and nonpsychopathic offenders. *Personality and Individual Differences, 20*(4), 437-446.

Critchley, H.D. (2005). Neural mechanisms of autonomic, affective, and cognitive integration. *Journal of Comparative Neurology*, 493(1), 154-166.

Critchley, H.D., Elliott, R., Mathias, C.J., Dolan, R.J. (2000). Neural activity relating to generation and representation of galvanic skin conductance responses: a functional magnetic resonance imaging study. *Journal of Neuroscience*, 20(8), 3033-3040.

Critchley, H.D., Good, C.D., Ashburner, J., Frackowiak, R.S., Mathias, C.J., Dolan, R.J. (2003). Changes in cerebral morphology consequent to peripheral autonomic denervation. *Neuroimage*, 18(4), 908-916.

Critchley, H.D., and Harrison, N.A. (2013). Visceral influences on brain and behavior. *Neuron*, 77(4), 624-638.

Cunha, P.J., Bechara, A., de Andrade, A.G., Nicastri, S. (2011), Decision-making deficits linked to real-life social dysfunction in crack cocaine-dependent individuals. *American Journal on Addictions*, 20, 78-86.

Dalgleish, T. (2004). The emotional brain. *Nature Reviews Neurosci*ence*,* 5, 583-589.

Damaraju, E., Huang, Y.M., Barrett, L.F., Pessoa, L. (2009). Affective learning enhances activity and functional connectivity in early visual cortex. *Neuropsychologia*, 47(12), 2480-2487.

Damasio, A. (1994). *Descartes' Error: Emotion, Reason and the Human Brain*. New York: Grosset/Putman.

Damasio, A.R., Damasio, H., Van Hoesen, G.W. (1982). Prosopagnosia: anatomic basis and behavioral mechanisms. *Neurolology*, 32, 331-341.

Damoiseaux, J.S., Rombouts, S.A., Barkhof, F., Scheltens, P., Stam, C.J., Smith, S.M., Beckmann, C.F. (2006). Consistent resting-state networks across healthy subjects. *Proceedings of the National Academy of Sciences U S A*., 103(37), 13848-13853.

Darwin, C. (1872/1965). *The Expression of the Emotions in Man and Animals*. Chicago: Chicago University Press.

Davidson, R.J. (2000). Affective style, psychopathology, and resilience: brain mechanisms and plasticity. *American Psychologist,* 55(11), 1196-1214.

Davis, M., and Whalen, P.J. (2001). The amygdala: vigilance and emotion. Molecular *Psychiatry*, 6, 13-34.

de Gelder, B., Vroomen, J., Pourtois, G., Weiskrantz, L. (1999). Non-conscious recognition of affect in the absence of striate cortex. *Neuroreport*, 10(18), 3759-3763.

De Luca, M., Beckmann, C.F., De Stefano, N., Matthews, P.M., Smith, S.M. (2006). fMRI resting state networks define distinct modes of long-distance interactions in the human brain. *Neuroimage*, 29, 1359-1367.

de Oliveira-Souza, R., Hare, R.D., Bramati, I.E., Garrido, G.J., Azevedo Ignácio, F., Tovar-Moll, F., Moll, J. (2008). Psychopathy as a disorder of the moral brain: fronto-temporo-limbic grey matter reductions demonstrated by voxel-based morphometry. *Neuroimage*, 40(3), 1202-1213.

Deckersbach, T., Miller, K.K., Klibanski, A., Fischman, A., Dougherty, D.D., Blais, M.A., Herzog, D.B., Rauch, S.L. (2006). Regional cerebral brain metabolism correlates of neuroticism and extraversion. *Depression and Anxiety*, 23, 133-138.

Deeley, Q., Daly, E., Surguladze, S., Tunstall, N., Mezey, G., Beer, D., Ambikapathy, A., Robertson, D., Giampietro, V., Brammer, M.J., Clarke, A., Dowsett, J., Fahy, T., Phillips, M.L., Murphy, D.G. (2006). Facial emotion processing in criminal psychopathy. Preliminary functional magnetic resonance imaging study. *British Journal of Psychiatry*, 189, 533-539.

Desimone, R. (1991). Face-selective cells in the temporal cortex of monkeys. *Journal of Cognitive Neurosciences*, 3, 1-8.

Dolan, R.J (2002). Emotion, cognition, and behavior. *Science*, 298(5596), 1191-1194.

Dvorak-Bertsch, J.D., Sadeh, N., Glass, S.J., Thornton, D., Newman, J.P. (2007). Stroop tasks associated with differential activation of anterior cingulate do not differentiate psychopathic and non-psychopathic offenders. *Personality and Individual Differences*, 42(3), 585-595.

Eisenbarth, H., Alpers, G.W., Segrè, D., Calogero, A., Angrilli, A. (2008). Categorization and evaluation of emotional faces in psychopathic women. *Psychiatry Research*, 159, 189-195.

Eisenberg, N., and Mussen, P. (1989). *The roots of prosocial behavior in children*. Cambridge: Cambridge University Press.

Ekman, P. (1973). *Darwin and Facial Expression: a Century of Research in Review Academic*. New York: Academic Press.

Engel, A.K, Fries, P., Singer, W. (2001). Dynamic predictions: oscillations and synchrony in top-down processing. *Nature Reviews Neurosci*ence, 2(10), 704-716.

Eslinger, P.J., and Damasio, A.R. (1985). Severe disturbance of higher cognition after bilateral frontal lobe ablation: patient EVR. *Neurology,* 35, 1731-1741.

Eslinger, P.J., Grattan, L.M., Damasio, A.R. (1992). Developmental consequences of childhood frontal lobe damage. *Archives of Neurology*, 49, 764-769.

Fairhall, S.L., and Ishai, A. (2007). Effective connectivity within the distributed cortical network for face perception. *Cerebral Cortex*, 17(10), 2400-2406.

Fernández-Serrano, M.J., Lozano, O., Pérez-García, M., Verdejo-García, A. (2010). Impact of severity of drug use on discrete emotions recognition in polysubstance abusers. *Drug and Alcohol Dependence*, 109(1-3), 57-64.

First, M.B., Gibbon, M., Spitzer, R.L., Williams, J.B.W., Smith Benjamin, L. (1997). *Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II)*. Washington DC: American Psychiatric Press.

Flor, H., Birbaumer, N., Hermann, C., Ziegler, S., Patrick, C.J. (2002). Aversive Pavlovian conditioning in psychopaths: peripheral and central correlates. Psychophysiology, 39(4), 505-518.

Foa, E.B., Ilai, D., McCarthy, P.R., Shoyer, B., Murdock, T. (1993). Information processing in obsessive-compulsive disorder. *Cognitive Therapy and Research*, 17, 173-189.

Fox, M.D., and Raichle, M.E. (2007). Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nature Reviews Neurosci*ence, 8(9), 700-711.

Fox, M.D., Snyder, A.Z., Vincent, J.L., Corbetta, M., Van Essen, D.C., Raichle, M.E. (2005). The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proceedings of the National Academy of Sciences U.S.A.*, 102(27), 9673-9678.

Fransson, P. (2005). Spontaneous low-frequency BOLD signal fluctuations: an fMRI investigation of the resting-state default mode of brain function hypothesis. *Human Brain Mapping*, 26(1), 15-29.

Frick, P.J. (1995). Callous-unemotional traits and conduct problems: a two-factor model of psychopathy in children. *Issues Criminological Legal Psychology*, 24, 47-51.

Frick, P.J., Bodin, S.D., Barry, C.T. (2000). Psychopathic traits and conduct problems in community and clinic-referred samples of children: further development of the psychopathy screening device. *Psycholological Assessement*, 12(4), 382-393.

Frick, P.J., O'Brien, B.S., Wootton, J.M., McBurnett, K. (1994). Psychopathy and conduct problems in children. *Journal of Abnormal Psychology*, 103(4), 700-707.

Friston, K. J., Ashburner, J., Kiebel, S. J., Nichols, T. E., Penny, W. D. (2007): *Statistical Parametric Mapping: The Analysis of Functional Brain Images*. London: Academic Press.

Friston, K.J., Buechel, C., Fink, G.R., Morris, J., Rolls, E., Dolan, R.J. (1997). Psychophysiological and modulatory interactions in neuroimaging. *NeuroImage*, 6, 218–229.

Garavan, H., Pankiewicz, J., Bloom, A., Cho, J.K., Sperry, L., Ross, T.J., Salmeron, B.J., Risinger, R., Kelley, D., Stein, E.A. (2000). Cue-induced cocaine craving: neuroanatomical specificity for drug users and drug stimuli. *American Journal Psychiatry*, 157(11), 1789-1798.

Ghatan, P.H., Hsieh, J.C., Wirsén-Meurling, A., Wredling, R., Eriksson, L., Stone-Elander, S., Levander, S., Ingvar, M. (1995). Brain activation induced by the perceptual maze test: a PET study of cognitive performance. *Neuroimage*, 2, 112-124.

Gibbs, J. C. (1987). *Social processes in delinquency: The need to facilitate empathy as well as sociomoral reasoning. In W.M. Kurtines and J.L. Gewirtz (Eds.), Moral development through social interaction*. New York: John Wiley.

Glass, S.J., and Newman, J.P. (2009). Emotion processing in the criminal psychopath: the role of attention in emotion-facilitated memory. *Journal of Abnormal Psychology*, 118(1), 229-234.

Glenn, A.L., Raine, A., Schug, R.A. (2009). The neural correlates of moral decision-making in psychopathy. *Molecular Psychiatry*, 14, 5-6.

Glenn, A.L., Yang, Y., Raine, A., Colletti, P. (2010). No volumetric differences in the anterior cingulate of psychopathic individuals. *Psychiatry Research*, 183(2), 140-143.

Goldman, R.I., Stern, J.M., Engel Jr., J., Cohen, M.S. (2002). Simultaneous EEG and fMRI of the alpha rhythm. *NeuroReport*, 13(18), 2487-2492.

Goldstein, R.Z., Alia-Klein, N., Tomasi, D., Zhang, L., Cottone, L.A., Maloney, T., Telang, F., Caparelli, E.C., Chang, L., Ernst, T., Samaras, D., Squires, N.K., Volkow, N.D. (2007). Is decreased prefrontal cortical sensitivity to monetary reward associated with impaired motivation and self-control in cocaine addiction? *American Journal Psychiatry*, 164(1), 43-51.

Goldstein, R.Z., Craig, A.D., Bechara, A., Garavan, H., Childress, A.R., Paulus, M.P., Volkow, N.D. (2009). The neurocircuitry of impaired insight in drug addiction. *Trends in Cognitives Sciences,* 13, 372-380.

Goldstein, R.Z., and Volkow, N.D. (2002). Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex. *American Journal Psychiatry*, 159(10), 1642-1652.

Goldstein, R.Z., and Volkow, N.D. (2011). Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications. *Nature Reviews Neurosci*ence, 12(11), 652-669.

Grafman J, Schwab K, Warden D, Pridgen A, Brown HR, Salazar AM. (1996). Frontal lobe injuries, violence, and aggression: a report of the Vietnam Head Injury Study. *Neurology,* 46, 1231-1238.

Grant, S., Contoreggi, C., London, E.D. (2000). Drug abusers show impaired performance in a laboratory test of decision making. *Neuropsychologia*, 38(8), 1180-1187.

Gray, J.M., Young, A.W., Barker, W.A., Curtis, A., Gibson, D. (1997). Impaired recognition of disgust in Huntington's disease gene carriers. *Brain*, 120 (Pt 11), 2029-2038.

Greicius, M.D., Krasnow, B., Reiss, A.L., Menon, V. (2003). Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. *Proceedings of the National Academy of Sciences U.S.A.*, 100(1), 253-258.

Greicius, M.D., Srivastava, G., Reiss, A.L., Menon, V. (2004). Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI. *Proceedings of the National Academy of Sciences U.S.A.*, 101, 4637-4642.

Greicius, M.D., Supekar, K., Menon, V., Dougherty, R.F. (2009). Resting-state functional connectivity reflects structural connectivity in the default mode network. *Cerebral Cortex*, 19(1), 72-78.

Greene, J., and Haidt, J. (2002). How (and where) does moral judgment work? *Trends and Cognitive Sciecnes*, 6(12), 517-523.

Greene, J.D., Nystrom, L.E., Engell, A.D., Darley, J.M., Cohen, J.D. (2004). The neural bases of cognitive conflict and control in moral judgment. *Neuron*., 44(2), 389-400.

Greene, J.D., Sommerville, R.B., Nystrom, L.E., Darley, J.M., and Cohen, J.D. (2001). An fmri investigation of emotional engagement in moral judgment. *Science*, 293, 2105-2108.

Gu, B.M., Park, J.Y., Kang, D.H., Lee, S.J., Yoo, S.Y., Jo, H.J., Choi, C.H., Lee, J.M., Kwon, J.S. (2008). Neural correlates of cognitive inflexibility during task-switching in obsessive-compulsive disorder. *Brain*, 131(Pt 1), 155-164.

Gu, H., Salmeron, B.J., Ross, T.J., Geng, X., Zhan, W., Stein, E.A., Yang, Y. (2010). Mesocorticolimbic circuits are impaired in chronic cocaine users as demonstrated by resting-state functional connectivity. *Neuroimage*, 53(2), 593-601.

Gusnard, D.A., Akbudak, E., Shulman, G.L., Raichle, M.E. (2001). Medial prefrontal cortex and self-referential mental activity: relation to a default mode of brain function. *Proceedings of the National Academy of Sciences U.S.A.*, 98, 4259-4264.

Gusnard, D.A., and Raichle, M.E. (2001). Searching for a baseline: functional imaging and the resting human brain. *Nature Review Neurosciences*, 2, 685-694.

Haidt, J. (2001). The emotional dog and its rational tail: A social intuitionist approach to moral judgment. *Psychological Review*, 108, 814-834.

Hare, R.D. (1996). Psychopathy and antisocial personality disorder: A case of diagnostic confusion. *Psychiatric Times,* 13(2), 39-40.

Hare, R. D. (2003). *Hare Psychopathy Checklist- Revised (PCL-R).* (2th ed.). Toronto: Multi-Health Systems Inc.

Harenski, C.L., Antonenko, O., Shane, M.S., Kiehl, K.A. (2008). Gender differences in neural mechanisms underlying moral sensitivity. S*ocial Cognitive and Affective Neurosciences*, 3(4), 313-321.

Harenski, C.L., and Hamann, S. (2006). Neural correlates of regulating negative emotions related to moral violations. *Neuroimage*, 30(1), 313-324.

Hariri, A.R., Bookheimer, S.Y., Mazziotta, J.C. (2000). Modulating emotional responses: effects of a neocortical network on the limbic system. *NeuroReport*, 11, 43-48.

Harrison, B.J., Pujol, J., Contreras-Rodríguez, O., Soriano-Mas, C., López-Solà, M., Deus, J., Ortiz, H., Blanco-Hinojo, L., Alonso, P., Hernández-Ribas, R., Cardoner, N., Menchón, J.M. (2011). Task-induced deactivation from rest extends beyond the default mode brain network. *PLoS One*, 6(7), e22964.

Harrison, B.J., Pujol, J., López-Solà, M., Hernández-Ribas, R., Deus, J., Ortiz, H., Soriano-Mas, C., Yücel, M., Pantelis, C., Cardoner, N. (2008). Consistency and functional specialization in the default mode brain network. *Proceedings of the National Academy of Sciences U.S.A.*, 105(28), 9781-9786.

Harrison, B.J., Pujol, J., Ortiz, H., Fornito, A., Pantelis, C., Yücel, M. (2008). Modulation of brain resting-state networks by sad mood induction. *PLoS One*, 3(3), e1794.

Harrison, B.J., Soriano-Mas, C., Pujol, J., Ortiz, H., López-Solà, M., Hernández-Ribas, R., Deus, J., Alonso, P., Yücel, M., Pantelis, C., Menchon, J.M., Cardoner, N. (2009) Altered corticostriatal functional connectivity in obsessive-compulsive disorder. *Archives of General Psychiatry*, 66(11), 1189-1200.

Haughton, V., and Biswal, B. (1998). Clinical application of basal regional cerebral blood flow fluctuation measurements by FMRI. *Advances in Experimental Medicine and Biolology*, 454, 583-590.

Haxby, J.V., Hoffman, E.A., Gobbini, M.I. (2000). The distributed human neural system for face perception. *Trends in Cognitive Sciences* 4, 223-233.

Heekeren, H.R., Wartenburger, I., Schmidt, H., Schwintowski, H.P., Villringer, A. (2003). An fMRI study of simple ethical decision-making. *Neuroreport.*, 14(9), 1215-1219.

Hein, G., and Knight, R.T. (2008). Superior temporal sulcus--It's my area: or is it? *Journal of Cognitive Neurosciences*, 20(12), 2125-2136.

Herpertz, S.C., Werth, U., Lukas, G., Qunaibi, M., Schuerkens, A., Kunert, H.J., Freese, R., Flesch, M., Mueller-Isberner, R., Osterheider, M., Sass, H. (2001). Emotion in criminal offenders with psychopathy and borderline personality disorder. *Archives of General Psychiatry*, 58, 737-745.

Hiatt, K.D., Schmitt, W.A., Newman, J.P. (2004). Stroop tasks reveal abnormal selective attention among psychopathic offenders. *Neuropsychology,* 18(1), 50-59.

Holland, P.C. and Gallagher, M. (1999). Amygdala circuitry in attentional and representational processes. *Trends in Cognitive Sciences* 3, 65-73.

Huettel, S. A., Song, A. W., McCarthy, G. (2004). *Functional magnetic resonance imaging*. Massachusetts: Sinauer Associates.

Ingvar, D. H. (1974). *Patterns of brain activity revealed by measurements of regional cerebral blood flow*. Copenhagen: Alfred Benzon Symposium VIII.

Ingvar, D. H. (1979). "Hyperfrontal" distribution of the cerebral grey matter flow in resting wakefulness: on the functional anatomy of the conscious state. *Acta Neuroolica Scand*inavica, 60, 12-25.

Intrator, J., Hare, R., Stritzke, P., Brichtswein, K., Dorfman, D., Harpur, T., Bernstein, D., Handelsman, L., Schaefer, C., Keilp, J., Rosen, J., Machac, J. (1997). A brain imaging (single photon emission computerized tomography) study of semantic and affective processing in psychopaths. *Biological Psychiatry*, 42, 96-103.

Ishai, A., Ungerleider, L.G., Haxby, J.V. (2000). Distributed neural systems for the generation of visual images. *Neuron*, 28(3), 979-990.

Japee, S., Crocker, L., Carver, F., Pessoa, L., Ungerleider, L.G. (2009). Individual differences in valence modulation of face-selective M170 response. *Emotion*, 9, 59-69.

Jones, A., and Fitness, J. (2008). Moral hypervigilance: The influence of disgust sensitivity in the moral domain. *Emotion*, 8(5), 613-627.

Jones, A.P., Laurens, K.R., Herba, C.M., Barker, G.J., Viding, E. (2009). Amygdala hypoactivity to fearful faces in boys with conduct problems and callous-unemotional traits. *American Journal of Psychiatry*, 166, 95-102.

Kandel, E. R., Schwartz, J. H., Jessell, T. M. (2000). *Principles of Neural Science* (4th ed.). New York: McGraw-Hill.

Kastner, S., and Ungerleider, L.G. (2000). Mechanisms of visual attention in the human cortex. *Annual Review of Neuroscience*, 23, 315-341.

Kemmis, L., Hall, J.K., Kingston, R., Morgan, M.J. (2007). Impaired fear recognition in regular recreational cocaine users. *Psychopharmacology (Berl)*, 194(2), 151-159.

Kiehl, K.A. (2006). A cognitive neuroscience perspective on psychopathy: evidence for paralimbic system dysfunction. *Psychiatry Research*, 142(2-3), 107-128.

Kiehl, K.A., Smith, A.M., Hare, R.D., Mendrek, A., Forster, B.B., Brink, J., Liddle, P.F. (2001). Limbic abnormalities in affective processing by criminal psychopaths as revealed by functional magnetic resonance imaging. *Biological Psychiatry*, 50(9), 677-684.

Kim, S.H., and Hamann, S. (2007). Neural correlates of positive and negative emotion regulation. *Journal of Cognitive Neuroscience*, 19(5), 776-798.

Kim, S.H., Hwang, J.H., Park, H.S., Kim, S.E. (2008). Resting brain metabolic correlates of neuroticism and extraversion in young men. *NeuroReport*, 19, 883-886.

Kim, J.J., Lee, M.C., Kim, J., Kim, I.Y., Kim, S.I., Han, M.H., Chang, K.H., Kwon, J.S. (2001).Grey matter abnormalities in obsessive-compulsive disorder: statistical parametric mapping of segmented magnetic resonance images. *British Journal of Psychiatry*, 79, 330-334.

Kluver, H., and Bucy, P. C. (1937). Psychic blindness' and other symptoms following bilateral temporal lobectomy. *American Journal of Physiology,* 119, 254-284.

Kober, H., Barrett, L.F., Joseph, J., Bliss-Moreau, E., Lindquist, K., Wager, T.D. (2008). Functional grouping and cortical–subcortical interactions in emotion: A meta-analysis of neuroimaging studies. *Neuroimage*, 42(2), 998-1031.

Koenigs, M. (2012). The role of prefrontal cortex in psychopathy. *Review Neuroscience*, 23(3), 253-262.

Koski, L., and Paus, T. (2000). Functional connectivity of the anterior cingulate cortex within the human frontal lobe: a brain-mapping meta-analysis. *Experimental Brain Research*, 133(1), 55-65.

Kufahl, P., Li, Z., Risinger, R., Rainey, C., Piacentine, L., Wu, G., Bloom, A., Yang, Z., Li, S.J. (2008). Expectation modulates human brain responses to acute cocaine: a functional magnetic resonance imaging study. *Biological Psychiatry*, 63(2), 222-230.

Kufahl, P.R., Li, Z., Risinger, R.C., Rainey, C.J., Wu, G., Bloom, A.S., Li, S.J. (2005). Neural responses to acute cocaine administration in the human brain detected by fMRI. *Neuroimage*, 28(4), 904-914.

Kunisato, Y., Okamoto, Y., Okada, G., Aoyama, S., Nishiyama, Y., Onoda, K., Yamawaki, S. (2011). Personality traits and the amplitude of spontaneous low-frequency oscillations during resting state. *Neuroscience Letters*, 492(2), 109-113.

Koenigs, M., Young, L., Adolphs, R., Tranel, D., Cushman, F., Hauser, M., Damasio, A. (2007). Damage to the prefrontal cortex increases utilitarian moral judgements. *Nature*, 446, 908-911.

Kohlberg, L. (1981). *The Philosophy of Moral Development. Moral Stages and the Idea of Justice*. San Francisco: Harper and Row.

Krajbich, I., Adolphs, R., Tranel, D., Denburg, N.L., Camerer, C.F. (2009). Economic games quantify diminished sense of guilt in patients with damage to the prefrontal cortex. *Journal of Neuroscience*, 29(7), 2188-2192.

Kyrios, M., Iob, M.A. (1998). Automatic and strategic processing in obsessive-compulsive disorder: Attentional bias, cognitive avoidance or more complex phenomena? *Journal Anxiety Disorders*, 12, 271-292.

LaBar, K.S., and Cabeza, R. (2006). Cognitive neuroscience of emotional memory. *Nature Reviews Neurosci*ence, 7(1), 54-64.

Lavy, E., van Oppen, P., van den Hout, M. (1994). Selective processing of emotional information in obsessive compulsive disorder. *Behaviour Research and Therapy*, 32(2), 243-246.

Lawrence, N.S., An, S.K., Mataix-Cols, D., Ruths, F., Speckens, A., Phillips, M.L. (2007). Neural responses to facial expressions of disgust but not fear are modulated by washing symptoms in OCD. *Biological Psychiatry*, 61(9), 1072-1080.

LeDoux, J.E. (1998). Fear and the Brain: Where have we been and where are we going? *Biological Psychiatry,* 44, 1129-1238.

LeDoux, J.E. (2000). Emotion circuits in the brain. *Annual Review of Neuroscience*, 23, 155-184.

Leistico, A.R., Salekin, R.T., de Coster, J., Rogers, R. (2008). A large-scale meta-analysis relating the Hare measures of psychopathy to antisocial conduct. *Law and Human Behavior*, 32, 28-45.

Levenston, G.K., Patrick, C.J., Bradley, M.M., Lang, P.J. (2000). The psychopath as observer: emotion and attention in picture processing. *Journal of Abnormal Psychology*, 109, 373-385.

Liddell BJ, Brown KJ, Kemp AH, Barton MJ, Das P, Peduto A, Gordon E, Williams LM. (2005). A direct brainstem–amygdala–cortical 'alarm' system for subliminal signals of fear. *NeuroImage*. 24, 235-243.

López-Solà, M., Pujol, J., Hernández-Ribas, R., Harrison, B.J., Ortiz, H., Soriano-Mas, C., Deus, J., Menchón, J.M., Vallejo, J., Cardoner, N. (2010). Dynamic assessment of the right lateral frontal cortex response to painful stimulation. *Neuroimage*, 50(3), 1177-1187.

Lorenz, A.R., and Newman, J.P. (2002). Deficient response modulation and emotion processing in low-anxious Caucasian psychopathic offenders: results from a lexical decision task. *Emotion*, 2(2), 91-104.

Ly, M., Motzkin, J.C., Philippi, C.L., Kirk, G.R., Newman, J.P., Kiehl, K.A., Koenigs, M. (2012). Cortical thinning in psychopathy. *American Journal Psychiatry* , 169(7), 743-749.

Lykken, D. T. (1957). A study of anxiety in the sociopathic personality. *Journal of Social and Abnormal Psychology*, 55, 6-10.

Maas, L.C., Lukas, S.E., Kaufman, M.J., Weiss, R.D., Daniels, S.L., Rogers, V.W., Kukes, T.J., Renshaw, P.F. (1998). Functional magnetic resonance imaging of human brain activation during cue-induced cocaine craving. *American Journal Psychiatry*, 155(1), 124-126.

MacCoon, D. G., Wallace, J. F., Newman, J. P. (2004). Self-regulation: the context-appropriate allocation of attentional capacity to dominant and non-dominant cues. In R. F. Baumeister and K. D. Vohs, (ed.), *Handbook of Self-Regulation: Research, Theory, and Applications.* (p. 422-446). New York: Guilford.

MacLean, P.D. (1949). Psychosomatic disease and the 'visceral brain': recent developments bearing on the Papez theory of emotion. *Psychosomatic Medicine,* 11, 338-353.

Macmillan, M. (2000). *An Odd Kind of Fame: Stories of Phineas Gage.* Cambridge, Massachusetts, USA: MIT Press.

Maltby, N., Tolin, D.F., Worhunsky, P., O'Keefe, T.M., Kiehl, K.A. (2005). Dysfunctional action monitoring hyperactivates frontal-striatal circuits in obsessive-compulsive disorder: an event-related fMRI study. *Neuroimage,* 24(2), 495-503.

Mancini, F., and Gangemi, A. (2004). Fear of guilt from behaving irresponsibly in obsessive-compulsive disorder. *Journal of Behavior Therapy and Experimental Psychiatry*, 35(2), 109-120.

Margulies DS, Kelly AM, Uddin LQ, Biswal BB, Castellanos FX, Milham MP. (2007). Mapping the functional connectivity of anterior cingulate cortex. *Neuroimage,* 37(2), 579-588.

Margulies, D.S., Vincent, J.L., Kelly, C., Lohmann, G., Uddin, L.Q., Biswal, B.B., Villringer, A., Castellanos, F.X., Milham, M.P., Petrides, M. (2009). Precuneus shares intrinsic functional architecture in humans and monkeys. *Proceedings of the National Academy of Sciences U.S.A.*, 106(47), 20069-20074.

Marsh, A.A., Finger, E.C., Fowler, K.A., Jurkowitz, I.T., Schechter, J.C., Yu, H.H., Pine, D.S., Blair, R.J. (2011). Reduced amygdala-orbitofrontal connectivity during moral judgments in youths with disruptive behavior disorders and psychopathic traits. *Psychiatry Research*, 194(3), 279-286.

Marsh, A.A., Finger, E.C., Mitchell, D.G., Reid, M.E., Sims, C., Kosson, D.S., Towbin, K.E., Leibenluft, E., Pine, D.S., Blair, R.J. (2008). Reduced amygdala response to fearful expressions in children and adolescents with callous-unemotional traits and disruptive behavior disorders. *American Journal of Psychiatry*, 165, 712–720.

Martinez-Montes, E., Valdes-Sosa, P.A., Miwakeichi, F., Goldman, R.I., Cohen, M.S. (2004). Concurrent EEG/fMRI analysis by multiway partial least squares. *Neuroimage.* 22(3), 1023-1034.

Mataix-Cols, D., Wooderson, S., Lawrence, N., Brammer, M.J., Speckens, A., Phillips, M.L. (2004). Distinct neural correlates of washing, checking, and hoarding symptom dimensions in obsessive-compulsive disorder. *Archives of General Psychiatry*, 61(6), 564-576.

McKiernan, K.A., D'Angelo, B.R., Kaufman, J.N., Binder, J.R. (2006). Interrupting the "stream of consciousness": An fMRI investigation. *Neuroimage*, 29(4), 1185-1191.

McNally, R. J. (1999). Information-processing abnormalities in obsessive-compulsive disorder. In W. Goodman, M. Rudorfer, and J. Maser (ed.), *Obsessive-compulsive disorder: contemporary issues in treatment*. Mahwah: Lawrence Erlbaum.

McNeil, D.W., Tucker, P., Miranda, R., Lewin, M.R., Nordgren, J.C. (1999). Response to depression and anxiety Stroop stimuli in posttraumatic stress disorder, obsessive-compulsive disorder, and major depressive disorder. *Journal of Nervous and Mental Disease,* 187, 512-516.

McNeil, J. and Warrington, E. (1993). Prosopagnosia: a face-specific disorder. *Quarterly Journal of Experimental Psychology*, 46(1), 1-10.

Mendez, M.F. (2009). The neurobiology of moral behavior: review and neuropsychiatric implications. *CNS Spectrums*, 14(11), 608-620.

Mendez, M.F., Anderson, E., Shapira, J.S. (2005). An investigation of moral judgment in frontotemporal dementia. *Cognitive and Behavioral Neurology*, 18, 193-197.

Menon, V., and Uddin, L.Q. (2010). Saliency, switching, attention and control: a network model of insula function. *Brain Structure and Function*, 214(5-6), 655-667.

Menzies, L., Chamberlain, S.R., Laird, A.R., Thelen, S.M., Sahakian, B.J., Bullmore, E.T. (2008). Integrating evidence from neuroimaging and neuropsychological studies of obsessive-compulsive disorder: the orbitofronto-striatal model revisited. *Neuroscience and Biobehavioral Reviews*, 32(3), 525-549.

Mitchell, D.G., Colledge, E., Leonard, A., Blair, R.J. (2002). Risky decisions and response reversal: is there evidence of orbitofrontal cortex dysfunction in psychopathic individuals? *Neuropsychologia*, 40(12), 2013-2022.

Moll, J., de Oliveira-Souza, R., Eslinger, P.J. (2003) Morals and the human brain: a working model. *Neuroreport*, 14(3), 299-305.

Moll, J., Zahn, R., de Oliveira-Souza, R., Krueger, F., Grafman, J. (2005). Opinion: the neural basis of human moral cognition. *Nature Reviews Neurosci*ence, 6(10), 799-809.

Montague, P.R. and Berns, G.S. (2002). Neural economics and the biological substrates of valuation. *Neuron*, 36(2), 265-284.

Moretto, G., Làdavas, E., Mattioli, F., di Pellegrino, G. (2010). A psychophysiological investigation of moral judgment after ventromedial prefrontal damage. *Journal of Cognitive Neuroscience*, 22(8), 1888-1899.

Moritz, S., Fischer, B.K., Hottenrott, B., Kellner, M., Fricke, S., Randjbar, S., Jelinek, L. (2008). Words may not be enough! No increased emotional Stroop effect in obsessive-compulsive disorder. *Behaviour Research and Therapy*, 46(9), 1101-1104.

Moritz, S., Jacobsen, D., Kloss, M., Fricke, S., Rufer, M., Hand, I. (2004). Examination of emotional Stroop interference in obsessive-compulsive disorder. *Behaviour Research and Therapy*, 42(6), 671-682.

Morris, J.S., Friston, K.J., Büchel, C., Frith, C.D., Young, A.W., Calder, A.J., Dolan, R.J. (1998). A neuromodulatory role for the human amygdala in processing emotional facial expressions. *Brain*, 121, 47-57.

Morris, J.S., Frith, C.D., Perrett, D.I., Rowland, D., Young, A.W., Calder, A.J., Dolan, R.J. (1996). A differential neural response in the human amygdala to fearful and happy facial expressions. *Nature*, 383(6603), 812-815.

Motzkin, J.C., Newman, J.P., Kiehl, K.A., Koenigs, M. (2011). Reduced prefrontal connectivity in psychopathy. *Journal of Neuroscience*, 31, 17348-17357.

Müller, J.L., Gänssbauer, S., Sommer, M., Döhnel, K., Weber, T., Schmidt-Wilcke, T., Hajak, G. (2008). Gray matter changes in right superior temporal gyrus in criminal psychopaths. Evidence from voxel-based morphometry. *Psychiatry Research,* 163(3), 213-222.

Müller, J.L., Sommer, M., Wagner, V., Lange, K., Taschler, H., Röder, C.H., Schuierer, G., Klein, H.E., Hajak, G. (2003). Abnormalities in emotion processing within cortical and subcortical regions in criminal psychopaths: evidence from a functional magnetic resonance imaging study using pictures with emotional content. *Biological Psychiatry*, 54, 152-162.

Murphy, F.C., Nimmo-Smith, I., Lawrence, A.D. (2003). Functional neuroanatomy of emotions: a meta-analysis. *Cognitive and Affective Behavioral Neuroscience,* 3, 207-233.

Naqvi, N.H., Rudrauf, D., Damasio, H., Bechara, A. (2007). Damage to the insula disrupts addiction to cigarette smoking. *Science*, 315, 531-534.

Nauta, W.J.H. (1971). The problem of the frontal lobe: a reinterpretation. *Journal of Psychiatric Research,* 8, 167-187.

Newman, J. P and Baskin-Sommers, A. R. (2011). Early Selective Attention Abnormalities in Psychopathy: Implications for Self-Regulation. In M. Poser (Ed), *Cognitive Neuroscience of Attention* (p.421-440). New York: Guilford Press.

Newman, J.P., Curtin, J.J., Bertsch, J.D., Baskin-Sommers, A.R. (2010) Attention moderates the fearlessness of psychopathic offenders. *Biological Psychiatry*, 67(1), 66-70.

Newman, J.P., Kosson, D.S. (1986). Passive avoidance learning in psychopathic and nonpsychopathic offenders. *Journal of Abnormal Psychology*, 95(3), 252-256.

Newman, J.P., Patterson, C.M., Kosson, D.S. (1987). Response perseveration in psychopaths. *Journal of Abnormal Psychology*, 96(2), 145-148.

Newman, J.P., Schmitt, W.A., Voss, W.D. (1997). The impact of motivationally neutral cues on psychopathic individuals: assessing the generality of the response modulation hypothesis. *Journal of Abnormal Psychology*, 106(4), 563-575.

Novara, C., and Sanavio, E. (2001). Compulsive checking and selective processing of threatening information. *Psychological Report,* 88, 1171-1181.

Ochsner, K.N., Bunge, S.A., Gross, J.J., Gabrieli, J.D. (2002). Rethinking feelings: an FMRI study of the cognitive regulation of emotion. *Journal of Cognitive Neuroscience*, 14(8), 1215-1229.

Ochsner, K.N., and Gross, J.J. (2005). The cognitive control of emotion. *Trends and Cognitive Sciecnes*, 9(5), 242-249.

Ochsner, K.N., Ray, R.D., Cooper, J.C., Robertson, E.R., Chopra, S., Gabrieli, J.D., Gross, J.J. (2004). For better or for worse: neural systems supporting the cognitive down- and up-regulation of negative emotion. *Neuroimage*, 23(2), 483-499.

Olatunji, B.O., Ciesielski, B.G., Zald, D.H. (2011). A selective impairment in attentional disengagement from erotica in obsessive-compulsive disorder. *Progress in Neuro-psychopharmacology and Biolological Psychiatry*, 35(8), 1977-1982.

Osumi, T., Nakao, T., Kasuya, Y., Shinoda, J., Yamada, J., Ohira, H. (2012). Amygdala dysfunction attenuates frustration-induced aggression in psychopathic individuals in a non-criminal population. *Journals of Affective Disorders*, 142(1-3), 331-338.

Papez, J.W. (1937). A proposed mechanism of emotion. *Archives of Neurology and Psychiatry,* 38, 725-743.

Pastor, M.C., Moltó, J., Vila, J., Lang, P.J. (2003). Startle reflex modulation, affective ratings and autonomic reactivity in incarcerated Spanish psychopaths. *Psychophysiology*., 40(6), 934-938.

Patrick, C.J., Bradley, M.M., Lang, P.J. (1993). Emotion in the criminal psychopath: startle reflex modulation. *Journal of Abnormal Psychology*, 102(1), 82-92.

Patrick, C.J., Cuthbert, B.N., Lang, P.J. (1994). Emotion in the criminal psychopath: fear image processing. *Journal of Abnormal Psychology*, 103(3), 523-534.

Patterson, K., Nestor, P.J., Rogers, T.T. (2007). Where do you know what you know? The representation of semantic knowledge in the human brain. *Nature Reviews Neuroscience*, 8(12), 976-987.

Perrett, D.I., Rolls, E.T., Caan, W. (1982). Visual neurones responsive to faces in the monkey temporal cortex. *Experimental Brain Research*, 47, 329-342.

Pessoa, L. (2008). On the relationship between emotion and cognition. *Nature Reviews Neurosci*ence, 9(2), 148-158.

Pessoa, L., McKenna, M., Gutierrez, E., Ungerleider, L.G. (2002). Neural processing of emotional faces requires attention. *Proceedings of the National Academy of Sciences U.S.A.*, 99, 11458-11463.

Phillips, M.L., Young, A.W., Senior, C., Brammer, M., Andrew, C., Calder, A.J., Bullmore, E.T., Perrett, D.I., Rowland, D., Williams, S.C., Gray, J.A., David, A.S. (1997). A specific neural substrate for perceiving facial expressions of disgust. *Nature*, 389(6650), 495-498.

Plutchik, R. (2001). The Nature of Emotions. *American Scientist,* 89, 344-350.

Pujol, J., Batalla, I., Contreras-Rodríguez, O., Harrison, B.J., Pera, V., Hernández-Ribas, R., Real, E., Bosa, L., Soriano-Mas, C., Deus, J., López-Solà, M., Pifarré, J., Menchón, J.M., Cardoner, N. (2011). Breakdown in the brain network subserving moral judgment in criminal psychopathy. S*ocial Cognitive and Affective Neurosciences*, 7(8), 917-923.

Pujol, J., Harrison, B.J., Ortiz, H., Deus, J., Soriano-Mas, C., López-Solà, M., Yücel, M., Perich, X., Cardoner, N. (2009). Influence of the fusiform gyrus on amygdala response to emotional faces in the non-clinical range of social anxiety. *Psychological Medicine*, 39, 1177-1187.

Pujol, J., Reixach, J., Harrison, B.J., Timoneda-Gallart, C., Vilanova, J.C,, Pérez-Alvarez, F. (2008). Posterior cingulate activation during moral dilemma in adolescents. *Human Brain Mapping*, 29(8), 910-921.

Pujol, J., Soriano-Mas, C., Alonso, P., Cardoner, N., Menchón, J.M., Deus, J., Vallejo, J. (2004). Mapping structural brain alterations in obsessive-compulsive disorder. *Archives of General Psychiatry*, 61(7), 720-730.

Pujol, J., Torres, L., Deus, J., Cardoner, N., Pifarré, J., Capdevila, A., Vallejo, J. (1999). Functional magnetic resonance imaging study of frontal lobe activation during word generation in obsessive-compulsive disorder. *Biological Psychiatry*, 45(7), 891-897.

Raichle, M.E., MacLeod, A.M., Snyder, A.Z., Powers, W.J., Gusnard, D.A., Shulman, G.L. (2001). A default mode of brain function. *Proceedings of the National Academy of Science U.S.A.*, 98, 676-682.

Raichle, M.E., and Mintun, M.A., 2006. Brain work and brain imaging. *Annual Review of Neuroscience*, 29, 449-476.

Raine, A., and Yang, Y. (2006). Neural foundations to moral reasoning and antisocial behavior. S*ocial Cognitive and Affective Neurosciences*, 1(3), 203-213.

Rainville, P. (2002). Brain mechanisms of pain affect and pain modulation. *Current Opinion in Neurobiology*, 12, 195-204.

Remijnse, P.L., Nielen, M.M., van Balkom, A.J., Cath, D.C., van Oppen, P., Uylings, H.B., Veltman, D.J. (2006). Reduced orbitofrontal-striatal activity on a reversal learning task in obsessive-compulsive disorder. *Archives of General Psychiatry* , 63(11), 1225-1236.

Reniers, R.L., Corcoran, R., Völlm, B.A., Mashru, A., Howard, R., Liddle, P.F. (2012). Moral decision-making, ToM, empathy and the default mode network. *Biological Psychology*, 90(3), 202-210.

Robins, L.N., Helzer, J.E., Weissman, M.M., Orvaschel, H., Gruenberg, E., Burke, J.D. Jr., Regier, D.A. (1984). Lifetime prevalence of specific psychiatric disorders in three sites. *Archives of General Psychiatry*, 41, 949-958.

Rolls, E.T. (2000). Précis of The brain and emotion. *Behavioral Brain Science*, 23(2), 177-191.

Rolls, E. T. (2005). *Emotion Explained.* Oxford: Oxford University Press.

Rolls, E.T., and Grabenhorst, F. (2008). The orbitofrontal cortex and beyond: from affect to decision-making. *Progress in Neurobiology*, 86(3), 216-244.

Rudebeck, P.H., Bannerman, D.M., Rushworth, M.F. (2008). The contribution of distinct subregions of the ventromedial frontal cortex to emotion, social behavior, and decision making. *Cognitive and Affective Behavioral Neuroscience*, 8(4), 485-497.

Salkovskis, P.M. (1985). Obsessional-compulsive problems: a cognitive-behavioural analysis. *Behaviour Research and Therapy*, 23(5), 571-583.

Salkovskis, P. M., and Forrester, E. (2002). Responsibility. In R. O. Frost, G. S. Steketee, (ed.), *Cognitive Approaches to Obsessions and Compulsions: Theory, Assessment and Treatment.* (45-61). Oxford: Elsevier.

Samhsa. (2007). Results from the 2006 National Survey on Drug Use and Health: National Findings. (Office of Applied Studies, NSDUH Series H-32, DHHS Publication No. SMA 07-4293).

Saxena, S., Brody, A.L., Schwartz, J.M., Baxter, L.R. (1998). Neuroimaging and frontal-subcortical circuitry in obsessive-compulsive disorder. *British Journal of Psychiatry Supplement*, 35, 26-37.

Schienle, A., Schäfer, A., Stark, R., Walter, B., Vaitl, D. (2005). Neural responses of OCD patients towards disorder-relevant, generally disgust-inducing and fear-inducing pictures. *International Journal Psychophysiology*, 57(1), 69-77.

Sergerie, K., Chochol, C., Armony, J.L. (2008). The role of the amygdala in emotional processing: a quantitative meta-analysis of functional neuroimaging studies. *Neuroscience and Biobehavioral Review*, 32(4), 811-830.

Shafran, R. (2005). Cognitive-behavioral models of obsessive-compulsive disorder. In: J. Abramowitz, A. C. Houts (ed.), *Concepts and Controversies in Obsessive- Compulsive Disorder* (229-252). New York: Springer.

Shapira, N.A., Liu, Y., He, A.G., Bradley, M.M., Lessig, M.C., James, G.A., Stein, D.J., Lang, P.J., Goodman, W.K. (2003). Brain activation by disgust-inducing pictures in obsessive-compulsive disorder. *Biological Psychiatry*, 54(7), 751-756.

Sheng, T., Gheytanchi, A., Aziz-Zadeh, L. (2010). Default network deactivations are correlated with psychopathic personality traits. *PLoS One*, 5(9), e12611. Singh, K.D., Fawcett, I.P. (2008), Transient and linearly graded deactivation of the human default-mode network by a visual detection task. *Neuroimage*, 41, 100-112.

Sommer, M., Rothmayr, C., Döhnel, K., Meinhardt, J., Schwerdtner, J., Sodian, B., Hajak, G. (2010). How should I decide? The neural correlates of everyday moral reasoning. *Neuropsychologia*, 48(7), 2018-2026.

Soriano-Mas, C., Pujol, J., Alonso, P., Cardoner, N., Menchón, J.M., Harrison, B.J., Deus, J., Vallejo, J., Gaser, C. (2007). Identifying patients with obsessive-compulsive disorder using whole-brain anatomy. *Neuroimage,* 35(3), 1028-1037.

Sprengelmeyer, R., Young, A.W., Calder, A.J., Karnat, A., Lange, H., Hömberg, V., Perrett, D.I., Rowland, D. (1996). Loss of disgust. Perception of faces and emotions in Huntington's disease. *Brain*, 119(Pt 5), 1647-1665.

Staub, E. (1978). Positive Social Behavior and Morality: Social and Personal Influences, Vol. 1. New York: Academic Press.

Strongman, K. T. (2003). *The Psychology of Emotion* (5th ed.). New York: Wiley.

Summerfeldt, L.J., and Endler, N.S. (1998). Examining the evidence for anxiety-related cognitive biases in obsessive-compulsive disorder. *Journal Anxiety Disorders*, 12(6), 579-598.

Sutton, S.K., Vitale, J.E., Newman, J.P. (2002). Emotion among women with psychopathy during picture perception. *Journal of Abnormal Psychology*, 111(4), 610-619.

Tamietto, M., de Gelder, B. (2010). Neural bases of the non-conscious perception of emotional signals. *Nature Reviews Neurosci*ence, 11(10), 697-709.

Tanabe, J., Tregellas, J.R., Dalwani, M., Thompson, L., Owens, E., Crowley, T., Banich, M. (2009). Medial orbitofrontal cortex gray matter is reduced in abstinent substance-dependent individuals. *Biological Psychiatry*, 65(2), 160-164.

Thomas, B.C., Croft, K.E., Tranel, D. (2011). Harming kin to save strangers: further evidence for abnormally utilitarian moral judgments after ventromedial prefrontal damage. *Journal of Cognitive Neuroscience*, 23(9), 2186-2196.

Tiihonen, J., Hodgins, S., Vaurio, O., Laakso, M., Repo, E., Soininen, H., Aronen, H. J., Nieminen, P., Savolainen, L. (2000). Amygdaloid volume loss in psychopathy. Society for Neuroscience Abstracts, 2017.

Tomasi, D., Volkow, N.D., Wang, R., Carrillo, J.H., Maloney, T., Alia-Klein, N., Woicik, P.A., Telang, F., Goldstein, R.Z. (2010). Disrupted functional connectivity with dopaminergic midbrain in cocaine abusers. *PLoS One*, 5(5), e10815.

Tsodyks, M., Kenet, T., Grinvald, A., Arieli, A. (1999). Linking spontaneous activity of single cortical neurons and the underlying functional architecture. *Science*, 286, 1943-1946.

Uddin, L.Q., Kelly, A.M., Biswal, B.B., Castellanos, F.X., Milham, M.P. (2009). Functional connectivity of default mode network components: correlation, anticorrelation, and causality. *Human Brain Mapping*, 30(2), 625-637.

Valente, A.A. Jr., Miguel, E.C., Castro, C.C., Amaro, E. Jr., Duran, F.L., Buchpiguel, C.A., Chitnis, X., McGuire, P.K., Busatto, G.F. (2005). Regional gray matter abnormalities in obsessive-compulsive disorder: a voxel-based morphometry study. *Biological Psychiatry*, 58(6), 479-487.

van den Heuvel, O.A., Veltman, D.J., Groenewegen, H.J., Cath, D.C., van Balkom, A.J., van Hartskamp, J., Barkhof, F., van Dyck, R. (2005). Frontal-striatal dysfunction during planning in obsessive-compulsive disorder. *Archives of General Psychiatry*, 62(3), 301-309.

Veit, R., Flor, H., Erb, M., Hermann, C., Lotze, M., Grodd, W., Birbaumer, N. (2002). Brain circuits involved in emotional learning in antisocial behavior and social phobia in humans. *Neuroscience Letters*, 328(3), 233-236.

Verdejo-García, A., and Bechara, A. (2009). A somatic marker theory of addiction. *Neuropharmacology*, 56 Supplement 1, 48-62.

Verdejo-García, A., Pérez-García, M., Bechara, A. (2006). Emotion, decision-making and substance dependence: a somatic-marker model of addiction. *Current Neuropharmacology*, 4(1), 17-31.

Verdejo-García A, Rivas-Pérez C, Vilar-López R, Pérez-García M. (2007). Strategic self-regulation, decision-making and emotion processing in poly-substance abusers in their first year of abstinence. *Drug and Alcohol Dependence*, 86(2-3), 139-146.

Via, E., Cardoner, N., Pujol, J., Alonso, P., López-Solà, M., Real, E., Contreras-Rodríguez, O., Deus, J., Segalàs, C., Menchón, J.M., Soriano-Mas, C., Harrison, B.J. (2013). Amygdala activation and symptom dimensions in obsessive-compulsive disorder. *British Journal of Psychiatry*, [Epub ahead of print].

Viard, A., Flament, M.F., Artiges, E., Dehaene, S., Naccache, L., Cohen, D., Mazet, P., Mouren, M.C., Martinot, J.L. (2005). Cognitive control in childhood-onset obsessive-compulsive disorder: a functional MRI study. *Psychological Medicine*, 35(7), 1007-1017.

Vignemont, F., Singer, T. (2006). The empathic brain: how, when and why? *Trends and Cognitive Sciecnes,* 10, 435-441.

Vincent, J.L., Patel, G.H., Fox, M.D., Snyder, A.Z., Baker, J.T., Van Essen, D.C., Zempel, J.M., Snyder, L.H., Corbetta, M., Raichle, M.E. (2007). Intrinsic functional architecture in the anaesthetized monkey brain. *Nature*, 447, 83-86.

Vitale, J.E., Brinkley, C.A., Hiatt, K.D., Newman, J.P. (2007) Abnormal selective attention in psychopathic female offenders. *Neuropsychology*, 21(3), 301-312.

Volkow, N., and Li, T.K. (2005). The neuroscience of addiction. *Nature Neuroscience*, 8(11), 1429-1430.

Volkow, N.D., Tomasi, D., Wang, G.J., Fowler, J.S., Telang, F., Goldstein, R.Z., Alia-Klein, N., Wong, C. (2011). Reduced metabolism in brain "control networks" following cocaine-cues exposure in female cocaine abusers. *PLoS One*, 6(2), e16573.

Vuilleumier, P., Armony, J.L., Driver, J., Dolan, R.J. (2001). Effects of attention and emotion on face processing in the human brain: an event-related fMRI study. *Neuron*, 30(3), 829-841.

Vuilleumier, P., Driver, J. (2007). Modulation of visual processing by attention and emotion: windows on causal interactions between human brain regions. *Philosophical Transaction of the Royal Society London B: Biological Sciences*, 362(1481), 837-855.

Vuilleumier, P., Richardson, M.P., Armony, J.L., Driver, J., Dolan, R.J. (2004). Distant influences of amygdala lesion on visual cortical activation during emotional face processing. *Nature Neuroscience*, 7(11), 1271-1278.

Weissman, M.M., Bland, R.C., Canino, G.J., Greenwald, S., Hwu, H.G., Lee, C.K., Newman, S.C., Oakley-Browne, M.A., Rubio-Stipec, M., Wickramaratne, P.J., et al. (1994). The cross national epidemiology of obsessive compulsive disorder. The Cross National Collaborative Group. *Journal of Clinical Psychiatry*, 55 Supplement, 5-10.

Wexler, B.E., Gottschalk, C.H., Fulbright, R.K., Prohovnik, I., Lacadie, C.M., Rounsaville, B.J., Gore, J.C. (2001). Functional magnetic resonance imaging of cocaine craving. *American Journal Psychiatry*, 158(1), 86-95.

Whalen, P.J., Rauch, S.L., Etcoff, N.L., McInerney, S.C., Lee, M.B., Jenike, M.A. (1998). Masked presentations of emotional facial expressions modulate amygdala activity without explicit knowledge. *Journal of Neuroscience***,** 18(1), 411-418.

White, S.F., Marsh, A.A., Fowler, K.A., Schechter, J.C., Adalio, C., Pope, K., Sinclair, S., Pine, D.S., Blair, R.J. (2012a). Reduced amygdala response in youths with disruptive behavior disorders and psychopathic traits: decreased emotional response versus increased top-down attention to nonemotional features. *American Journal Psychiatry*, 169(7), 750-758.

White, S.F., Williams, W.C., Brislin, S.J., Sinclair, S., Blair, K.S., Fowler, K.A., Pine, D.S., Pope, K., Blair, R.J. (2012b). Reduced activity within the dorsal endogenous orienting of attention network to fearful expressions in youth with disruptive behavior disorders and psychopathic traits. *Development and Psychopathology*, 24(3), 1105-1116.

Wilcox, C.E., Teshiba, T.M., Merideth, F., Ling, J., Mayer, A.R. (2011). Enhanced cue reactivity and fronto-striatal functional connectivity in cocaine use disorders. *Drug Alcohol Dependence*, 115(1-2), 137-144.

Williamson, S., Harpur, T.J., Hare, R.D. (1991). Abnormal processing of affective words by psychopaths. *Psychophysiology*, 28(3), 260-273.

Worhunsky, P.D., Stevens, M.C., Carroll, K.M., Rounsaville, B.J., Calhoun, V.D., Pearlson, G.D., Potenza, M.N. (2012). Functional Brain Networks Associated With Cognitive Control, Cocaine Dependence, and Treatment Outcome. *Psychology of Addictive Behaviors,* [Epub ahead of print].

Yang, Y., Raine, A., Colletti, P., Toga, A.W., Narr, K.L. (2010). Morphological alterations in the prefrontal cortex and the amygdala in unsuccessful psychopaths. *Journal of Abnormal Psychology*, 119(3), 546-554.

Yang, Y., Raine, A., Joshi, A.A., Joshi, S., Chang, Y.T., Schug, R.A., Wheland, D., Leahy, R., Narr, K.L. (2012). Frontal information flow and connectivity in psychopathy. *British Journal of Psychiatry* , 201(5), 408-409.

Yang, Y., Raine, A., Narr, K.L., Colletti, P., Toga, A.W. (2009). Localization of deformations within the amygdala in individuals with psychopathy. *Archives of General Psychiatry* , 66(9), 986-994.

Yang, Y., Raine, A., Narr, K. L., Lencz, T., Toga, A. W. (2006). Amygdala volume reduction in psychopaths. Society for Research in Psychopathology.

Zeier, J.D., Maxwell, J.S., Newman, J.P. (2009). Attention moderates the processing of inhibitory information in primary psychopathy. *Journal of Abnormal Psychology*, 118(3), 554-563.