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Functional and Structural MRI Studies on Impulsiveness: Attention-Deficit/Hyperactive Disorder and Borderline Personality Disorders

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1. Introduction

Impulsive behavior is characterized a tendency to initiate behavior without sufficient/adequate consideration of consequences. It typically refers to ill-conceived, premature or inappropriate behavior that may be self-destructive or harmful to other individuals (Chamberlain and Sahakian, 2007). Pathological impulsiveness is associated with impaired performance on neuropsychological tests of attention and executive function and with neuroimaging evidence for structural and/or functional correlates, particular in frontal lobe regions (Congdon and Canli, 2005; Crews and Boettiger, 2009; Rubia et al., 2007). Impulsive behavior is a major component of several neuropsychiatric disorders, including schizophrenia, ADHD, substance abuse, bipolar disorder, and borderline and antisocial personality disorders. The notion of impulsiveness incorporates a multidimensional construct consisting of a range of inter-related factors including novelty-seeking and reckless behavior, lack of planning ability and self-control whereby mechanistic relations evolve from its role in initiating action (Barratt and Patton, 1983; Moeller et al., 2001). The construct incorporates motor impulsiveness, inability to tolerate delays, lack of planning and an incapacity for self-control.
Impulsiveness, with or without aggressiveness, has been associated with a range of personality disorders and other psychopathologies (Haden and Shiva, 2008; Krishnan-Sarin et al., 2007; Palomo et al., 2007a; Reynolds, 2006; Shiva et al., 2009), with impulse control difficulties often of primary diagnostic importance (e.g., Pfefferbaum & Wood, 1994; Quirk and McCormick, 1998). A variety of linear regression analyses based upon several self-report questionnaire studies including a range of cognitive-emotional personal attributes have indicated that impulsiveness is predicted by negative affect, amotivation and depressiveness and counterpredicted by positive affect and internal locus of control in healthy volunteers (Palomo et al., 2008a, b; but see also Miller et al., 2009). Cyders et al. have discussed the influence of positive urgency, acting rashly under extreme positive affect, and negative urgency as central risk factors for impulsive and maladaptive behavior (see also Cyders and Smith, 2008a, b; Cyders et al., 2009, 2010; Zapolsky et al., 2009).

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The inability to formulate decisions and plan actions presents a critical component of impulsiveness expressed in male offenders classified as both non-psychopathic and psychopathic (Dolan et al., 2001), euthymic and depressed bipolar patients, depressed unipolar patients and healthy controls (Peluso et al., 2007) and male forensic psychiatric in-patients facing severe criminal charges (Haden and Shiva, 2008). In a large-scale study of pathological gamblers, Ma Alvarez-Moya et al. (2010) identified four subtypes: Type I, (disorganized and emotionally unstable) showed schizotypic traits, high levels of impulsiveness, substance and alcohol abuse, and early age of onset, as well as other psychopathological disturbances;Type II (schizoid) showed high harm avoidance, social aloofness, and alcohol abuse; Type III (reward sensitive) showed high levels of sensation-seeking and impulsiveness but did not express psychopathological impairments; Type IV (high functioning)demonstrated a globally-adaptive personality profile, low levels of substance and alcohol abuse or smoking, without psychopathological disturbances but rather good general functioning. Thus, even among a broad population of pathological gamblers there exists a wide spectrum of cognitive and executive variability that requires the pathophysiological analysis of structure and function that magnetic resonance imaging may provide.

Individuals whose behavior is associated with high levels of impulsiveness frequently show general impairments over a wide range of neurocognitive tasks including tests of executive functioning (Dolan and Park, 2002; Keilp et al., 2005; Rogers, 2003), cognitive tasks demanding response control (Harrison et al., 2009; Potter and Newhouse, 2004) and cognitive flexibility [verbal fluency] (Barratt et al., 1997; Vieregge et al., 1997). The control of choice and decision-making processes seems to be modulated primarily by the eventual consequences of affective and cognitive appraisal with reinforcement/avoidance of actions directed by the underlying neural circuits (Beck et al., 2009; Frank and Claus, 2006; Koenigs and Tranel, 2007; Rustichini, 2005). Functional neuroimaging studies have implicated brain regions involved both in reinforcement and response inhibition. For example, financial rewards evoke differential patterns of recruitment in striatal and orbitofrontal cortex, as reflected in fMRI studies (Elliott and Deakin, 2005; Elliott et al., 2003). Other brain regions have been implicated in the different expressions of impulsiveness, including the inferior frontal gyrus, anterior cingulate cortex, regions of the prefrontal cortex (i.e. ventrolateral and dorsolateral), amygdala and the basal ganglia, insula and hippocampus (Love et al., 2009; Lee et al., 2009; Park et al., 2010). Gender effects have also been reported. For example, Lejuez et al. (2007) found that among 152 individuals in a residential substance-use treatment program, female subjects (37% of the sample) expressed greater use of crack/cocaine (current and lifetime heaviest) and were significantly more likely to show crack/cocaine dependence than their male counterparts. The female subjects expressed greater impulsiveness and higher levels of negative emotionality than their male counterparts, and were more likely to have suffered abuse during childhood. Impulsiveness presented a risk factor in the relationship between gender and crack/cocaine dependence and was also predictive of the quantity of drugs consumed and the duration of the dependency. These authors found no gender differences for any other forms of substance abuse (alcohol, cannabis or hallucinogens). Dysfunctional response to reinforcing stimuli, whether appetitive or aversive, appears to be a critical factor in the psychopathy of substance use and impulsiveness-related personality disorders (Petry, 2002).

Research indicates that in selecting among competing available behaviours immediate rewards are typically favoured over delayed rewards, such that with increasing delays the valuation of a future reward is reduced (known as *temporal discounting*; Ainslie, 1975).

Recent functional neuroimaging studies have explored the neural basis of temporal discounting, indicating that different (but overlapping) distributed networks are engaged as a function of the delay between decision and reward. Making choices between payoffs available at different points in time reliably engages a decision-making circuit that includes medial and/or dorsolateral prefrontal cortex (mPFC; dlPFC), posterior cingulate cortex (PCC), and ventral striatum (VS). However, evidence for specific functional roles in the decision making process across this distributed network is limited. Theoretical claims include the possibility that one or more of these regions: (1) is sensitive to the value of rewards discounted by a function of delay ('subjective value'); (2) is differentially sensitive to the availability of an immediate reward; and (3) is implicated in general/nonspecific impulsive and/or planned decision-making. Using event-related fMRI, Ballard and Knutson (2009) showed that although activation of the nucleus accumbens, mesial prefrontal cortex, and posterior cingulate cortex was correlated positively with future reward magnitude, the activation of the dorsolateral prefrontal cortex (DLPFC) and posterior parietal cortical (PCC) region was correlated negatively with future reward delay (see also Sripada et al., 2011). They found individuals expressing greater impulsiveness displayed diminished nucleus accumbens activation to the magnitude of future rewards and greater deactivations to delays of future rewards in the mesial prefrontal cortical, DLPFC, and PCC. Their observations imply that whereas the mesolimbic dopamine projection regions show greater sensitivity to the magnitude of future rewards, lateral cortical regions show greater (negative) sensitivity to the delay of future rewards, potentially reconciling different neural accounts of temporal discounting.

Motor impulsivity occurs when individuals act ‘on the spur of the moment’, inadequately inhibiting inappropriate response tendencies. Go/No go task performance (a measure of the ability to inhibit a prepotent response tendency) is typically impaired in neuropsychiatric patient groups for whom impulsivity is a common feature (Durston et al., 2003, 2006; Rubia et al., 1999) whereas in healthy controls the relationship between Go/No go performance and impulsiveness is not straightforward (Helmers et al., 1995; Keilp et al., 2005). In children with attention deficit hyperactivity disorder (ADHD), fMRI studies of Go/No go task performance have shown reduced activation in the ventrolateral prefrontal cortex (VLPFC), anterior cingulate cortex, mesial prefrontal cortex and/or caudate region in comparison to age-matched normally developing controls (Casey et al., 1997; Plitzka et al., 2006; Tamm et al., 2004). Activation of the VLPFC (particularly right hemisphere) is linked to response inhibition (Aron et al., 2004). The right VLPFC and DLPFC are implicated in the relationship between response inhibition and impulsivity (Asahi et al., 2004; Horn et al., 2003; Passamonti et al., 2006). Using fMRI, Goya-Maldonado et al. (2010) examined the relationship between trait impulsivity (BIS-11) and brain activation during motor response inhibition in an uncued Go/No go task. They obtained a significant positive correlation between motor impulsivity and bilateral activation of the VLPFC, suggesting that individuals expressing high levels of motor impulsivity show stronger recruitment of the VLPFC in order to maintain task performance. In an fMRI study examining neural activation during a food specific Go/No go task in adolescent girls, Batterink et al. (2010) required subjects to inhibit prepotent responses to appetizing foods. It was found that body mass index correlated with response inhibition at both behavioural and neural levels: greater weight was positively correlated with impulsiveness and negatively correlated with activation in frontal regions associated with inhibitory control (including superior and middle frontal gyrus, VLPFC, mPFC, and orbitofrontal cortex). It should be noted also that bulimia nervosa is associated with response inhibition deficits and higher impulsiveness (BIS-11) scores (Kemps and Wilsdon, 2010).

Comorbid aspects of clinical impulsiveness remain an issue in the pathophysiology of neuropsychiatric disorders (Palomo et al. 2007b). Both ADHD and pediatric bipolar disorder (PBD) are characterized by inattention, impulsiveness, lack of behavioural inhibition and deficits in cognitive flexibility and sustained attention (Galanter and Leibenluft, 2008; Pavuluri et al., 2006), the latter generally associated with emotional dysregulation, elated mood, irritability, increased energy and disinhibition (Pavuluri et al., 2007, 2008; Pavuluri and Passarotti, 2008). Children with PBD were found to show less activation in the VLPFC in a response inhibition stop-signal task (Leibenluft et al., 2007). In a color-naming Stroop task, PBD patients demonstrated elevated activation in the putamen and thalamus compared with healthy controls (Blumberg et al., 2003). A recent fMRI study of response inhibition in PBD patients, ADHD patients and healthy controls implicated (in the context of similarly impaired behavioral performance in both patient groups) a more focal role for VLPFC and anterior cingulate involvement in PBD (as indicated by *reduced* activation in these regions). The inhibitory impairment in ADHD was associated with more extensive prefrontal and temporal involvement. A distributed network of brain regions, within which the prefrontal cortex is of particular importance, is therefore likely to drive observed response inhibition impairments observed both in PBD and ADHD patients.

A central aspect of adaptive, as opposed to maladaptive, risky decision-making requires monitoring the value of behavioural options, possibly mediated through a 'teaching signal' expressed as a reward prediction error (PE) in the striatum. The involvement of higher level cognitive control associated with PFC might be necessary for mobilization of executive processes. Park et al. (2010) employed fMRI and a reinforcement learning task to investigate the neural mechanisms underlying maladaptive behavior in human male alcohol-dependent patients. They observed that in these patients the expression of striatal PEs was intact. Nevertheless, an abnormal functional connectivity between striatum and DLPFC predicted impairments in learning and in the magnitude of alcohol craving shown by the patients. Their findings confirm the structural abnormalities in the DLPFC that are associated with substance abuse. It is evident that frontostriatal connectivity exerts a pivotal role in the adaptive updating of action values and that impaired behavioural regulation in alcoholism may be associated with deficient interactive functionality of this system.

Definitions of impulsiveness vary from considerations of lack of persistence, patience and resistence to delayed rewards, boredom-thresholds, risk-taking behaviors and sensation-seeking behaviors to impaired understanding of the future implications of a given behavior (Barratt, 1994; Buss and Plomin, 1975; Eysenck, 1993; Logue, 1995). The intimate role of faulty timing behavior/time estimation as a non-specific factor in impulsiveness has been established in laboratory settings (cf. Evenden and Ko, 2005; Rivalan et al., 2007), with particular relevance in ADHD (Barkley et al., 1997, 2001; Meaux and Chelonis, 2003; Sonuga-Barke et al., 1992; Toplak et al., 2006). In healthy adults, the frontal cortex, basal ganglia and cerebellum are linked generally to timing functions with long or short delay intervals (Ivry and Spencer, 2004; Meck and Benson, 2002; Wiener et al., 2010). Various aspects of time processing have been addressed in individuals afflicted with ADHD, whether children/adolescents (McInerney and Kerns, 2003; Radonovitch, 2004; Smith et al., 2008) or adults (Gilden and Marusich, 2009; Marx et al., 2019; Seri et al., 2002).

Developmental trajectories of impulsive behavior bear essential outcome-expectancies for eventual disorder pathophysiology (cf. Grall-Bronnec et al., 2010). Valko et al. (2010) studied the developmental trajectory of the time-processing deficit that has been postulated as a neuropsychological candidate endophenotype for ADHD in 33 children and 22 adults with ADHD. They found that the children and adults displayed different patterns of deficit in the discrimination of brief intervals (600 – 1,500 msecs) in Go/No go and continuous performance tasks and concluded that time-processing deficits, though expressing different age-related forms, were present in adulthood. It is likely that the manifestation of the time-processing deficit in adult ADHDs may be more closely related to the fundamental processes of arousal and/or time perception with a peripheral role of executive function and response inhibition.

Recent research on the role of excessive alcohol consumption in the development of impulsive behaviors indicates that premorbid/baseline levels of impulsivity can predict the likelihood of increased impulsive behaviours following heavy drinking (White at al., 2011). This longitudinal study of boys assessed annually for 10 years until age 18 and again in their mid twenties indicated that a "moderate" (rather than "high" or "low") level of premorbid impulsiveness was the greatest risk factor for eliciting increased impulsive behaviors following heavy drinking. Basal levels of positive affect, a characteristic invariably counter-predictive for impulsiveness, appear related to outcomes of risk perception (drinking, getting into fights) in adolescents and young adults (Haase and Silbereisen, 2010). The notion of disturbed functional connectivity (see above) in frontal-striatal circuits bears consideration. Konrad et al. (2010) observed reduced fractional anisotropy (FA) and elevated mean diffusion bilaterally in orbitomedial prefrontal and right anterior cingulate cortex using voxel-based analyses in adult patients with ADHD compared with healthy controls. Impulsiveness was associated with FA in right orbitofrontal fibre tracts whereas attention was associated with DTI parameters in the right superior longitudinal fasciculus.

Rubia et al. (2009b) have argued that impulsive behavior is distinguished on the basis of a timing disturbance, with suboptimal recruitment of prefrontal, cingulate, striatal and cerebellar regions during temporal processing. They present the case that impulsiveness in ADHD is a dysfunction in temporal processing that may be reversed by acute treatment with a dopamine (DA) reuptake inhibitor. Valera et al. (2010) used fMRI to study paced and unpaced finger-tapping in a sample of 20 unmedicated adult ADHD patients and 19 healthy controls, matched for age, gender and IQ. They found that the ADHD adults expressed greater 'clock' (paced/unpaced tapping variation linked to a central clock rather than motor implementation) rather than motor variability that was consistent with a central timing locus for the atypical movements. Relative to healthy controls, the ADHD patients demonstrated reduced activity in several regions associated with sensorimotor timing, i.e. prefrontal and precentral gyri, basal ganglia, cerebellum, inferior parietal lobule, superior temporal gyri and insula. They concluded that (i) the ADHD abnormalities persisted into adulthood, and (ii) these abnormalities arose from the atypical functioning of corticocerebellar and corticostriatal timing circuits (see also Coull and Nobre, 2008; Smith et al., 2008; Terry et al., 2009).

A plethora of neuropsychological evidence indicates that abnormalities in executive functioning, particularly with regard to behavioural inhibition, are dysfunctional in in ADHD (Barkley, 1997; Chamberlain et al., 2010; Lambek et al., 2011; Mattison and Mayes, 2012). Arendts et al. (2010) have presented evidence of visual cortex abnormalities in adults with ADHD, using voxel-based morphometry of high resolution MRI scans, that may be related to impairments in early-stage, "subexecutive" attentional mechanisms. Accordingly, a neurocognitive model of ADHD presents the disorder as executive dysfunction originating from disturbances in the fronto-dorsal striatal circuit and associated dopaminergic branches (e.g. the mesocortical pathway). Nevertheless, a motivation-based account of altered reward processing, consisting of fronto-ventral striatal reward circuits and those meso-limbic branches that terminate in the ventral striatum and nucleus accumbens, implicates the avoidance of delay due to disturbances in the reward centres (Dalen et al., 2004; Sonuga-Barke, 2002, 2003; Sonuga-Barke et al., 2003). Sonuga-Barke et al. (2008) have argued that while executive dysfunction and delay aversion are implicated in ADHD neither is necessary for ADHD nor specific to the disorder. Several studies focused on the neural basis of individual differences in reward sensitivity have implicated the ventral striatum as a core component of the human reward system (Sescousse et al., 2010).

Adaptive, planned decision-making involves the selection of a particular behavior from several available options on the basis of a valuation of potential costs and benefits. Neuroimaging studies of delay and effort discounting suggest that there may be distinct valuation subsystems involved in the assessment of different types of costs (Prevost et al., 2010). The ventral striatum and the ventromedial prefrontal cortex represent the increasing subjective value of delayed rewards, whereas a distinct network comprised of the anterior cingulate cortex and the anterior insula, represent the decreasing value of an effortful option. Hahn et al. (2010) have shown that dopamine transporter variation (i.e., differences in DA availability affecting synaptic plasticity within the ventral striatum) moderates the association between ventral striatum-reactivity and trait reward sensitivity. In order to analyse further the contribution of reward processes, Carmona et al. (2009) applied a manual region-of-interest approach to assay for ventral striatum volumetric (MRIcro) alterations in 42 ADHD children/adolescents (age range: 6-18 years) compared to 42 healthy controls matched for age, gender and handedness. ADHD children/adolescents displayed marked reductions in both right and left ventro-striatal volume. Furthermore, the volume of the right ventral striatum was correlated negatively with the hyperactivity/impulsivity rating given by the mothers of the ADHD children/adolescents. Reduced volume of the ventral striatum is also associated with cognitive decline in the elderly (de Jong et al., 2012; see also Sripada et al., 2011).

The notion that ADHD symptoms are linked to altered reinforcement sensitivity has gathered momentum (cf. Luman et al., 2010). In an fMRI study comparing neural activity within the striatum in ADHD adolescent individuals and healthy controls, Scheres et al. (2007) observed reduced ventral striatal activation during reward anticipation in the ADHD group. Consistent with other studies, ventral striatal activation was negatively correlated with parent-rated hyperactive/impulsive symptoms across the entire sample. Both frontal-striatal and fronto-cerebellar circuits, necessary for the prediction of occurrence and timing of behaviourally-relevant are also implicated in expectancy violations. For example, Durston et al. (2007) have found fMRI evidence that individuals with ADHD have diminished cerebellar activity in response to violations of stimulus timing and diminished ventral prefrontal and anterior cingulate activity to violations in stimulus timing and identity (relative to healthy age matched controls).

The dysfunctional processing of reward, in combination with a limited capacity to tolerate delay in reward, may offer an important feature of ADHD. Reinforcement Sensitivity Theory, as a conceptual notion, involves three basic brain systems: the Behavioral Approach System and the Behavioral Inhibition System (both of which activate in response to stimulus signalling events), and the fight-fright-freeze system (which responds to actual aversive stimuli; Gray, 1982; Gray and McNaughton, 2000). Gray's impulsivity notion, reflecting trait reward sensitivity, deals with the extent to which environmental stimuli activate the Behavioral Approach System (Gray, 1991). Higher Behavioral Approach System activation due to increased trait reward sensitivity is implicated in 'disinhibitory' disorders, including ADHD and alcoholism (Franken et al., 2006; Mitchell and Nelson-Gray, 2006; Sher and Trull, 1994). Using fMRI in an appetitive task, Beaver et al. (2006) showed that the tendency to pursue Behavioral Approach System rewards was linked to a fronto-striatal-amygdala-midbrain network activation whereas Barros-Loscertales et al. (2006) describe a negative correlation between dorsal striatum/prefrontal cortex volumes and trait reward sensitivity using voxel-based morphometry. Hahn et al. (2009) studied the relationship, in 20 healthy subjects, between impulsiveness, according to Gray's notions, and event-related fMRI BOLD-response to reward anticipation in brain regions associated with reward processing. Higher trait reward sensitivity was related to cues for potential reward. Thus, the anticipation of reward during a monetary incentive delay task elicited activation in key components of the human reward circuitry, including the ventral striatum, orbitofrontal cortex and amygdala. Plichta et al. (2009) examined brain activation, with fMRI, in 14 adults with ADHD and 12 healthy controls in a task which required choosing between two monetary reward options based on immediate versus delayed reward conditions. For both immediate and delayed rewards, ADHD patients showed hyporesponsiveness of the ventral-striatum reward system compared with healthy controls. In the ADHD individuals, delayed rewards also elicited hyperresponsiveness in the dorsal caudate nucleus and the amygdala: in both structures neural activity correlated significantly with self-rated ADHD symptom severity. The authors concluded that hyperactivation, incremental along the ventral-dorsal caudate nucleus extension and amygdala, substantiates the delay aversion hypothesis. The spectre of temporal discounting (see above), in one form or another, emerges as a plausible mediating factor in the expression, both neural and functional, of impulsiveness in ADHD (see also, Rogers et al., 1999).

Given the cross-national prevalence of 3.4 % for adult ADHD (Fayyad et al., 2007), the potential and current problems associated with the disorder pose a bleak clinical reality. Functional imaging studies of children and adolescents with ADHD have implicated dysfunction of the VLPFC and DLPFC, anterior cingulate, insula, amygdala, hippocampus and ventral striatum (e.g. Amico et al., 2011; Kobel et al., 2010; Rogers et al., 1999; Sasayama et al., 2010; Sheridan et al., 2010); in adult ADHD similar regions are implicated (e.g. Depue et al., 2010a, b; Dillo et al., 2010; Schneider et al., 2010). For example, Schneider et al. (2010) observed (during a continuous performance Go/Nogo test) reduced activity in the caudate nuclei, anterior cingulate cortex and parietal cortical structures in ADHD, together with increased activity in the insular cortex, and that this was associated with the symptoms of impulsiveness and inattention. This widespread regional dysfunction was linked to symptom-profile severity in adults with a history of childhood ADHD, whether or not they qualified for a full ADHD diagnosis in adulthood. Such findings illustrate an important role for MRI in the characterization of neurodevelopmental trajectories (see also, Giedd and Rapoport, 2010; Wilens and Spencer, 2010).

Structural MRI studies indicate broad pathological heterogeneity in ADHD (e.g., Filipek et al., 1997; Mostofsky et al., 2002; Overmeyer et al., 2001; Semrud-Clikeman et al., 2006). Qiu et al. (2009) have published evidence that ADHD in boys may be associated with reduced basal ganglia volumes compared with boys with normal development. Large deformation diffeomorphic metric mapping (LDDMM) indicated that the two groups differed markedly with regard to basal ganglia morphology: bilateral volumetric compression was observed in the caudate head and body and anterior putamen, as well as in the left anterior globus pallidus and right ventral putamen. Coversely, volumetric expansion was observed in the posterior putamen. The authors concluded that the observed deviations from normal brain development involved multiple frontal-subcortical control loops that included circuits with premotor, oculomotor and prefrontal cortex regions. The relevance of developmental trajectories in impulsive disorders was illustrated further by Christakou et al. (2010) who demonstrated that age-related reductions in choice impulsivity were associated with changes in activation in the VLPFC, ACC, ventral striatum, insula, inferior temporal gyrus and posterior parietal cortex. They indicate that the maturational pattern of functional connectivity incorporates activation-coupling between the VLPFC and DLPFC, and the parietal and insular cortices during selection between delayed options, and between the ventromedial PFC and the ventral striatum. Maturational mechanisms within limbic frontostriatal circuitry form the basis of post-pubertal reductions in impulsive choice with age increments linked to activation coherence in networks modulating inter-temporal decision-making (Christakou et al., 2010).

Borderline Personality Disorder (BPD), the most common personality disorder clinically, is characterized by severe and persistent emotional, cognitive, behavioural and interpersonal impairments (American Psychiatry Association, 2000); a pervasive pattern of instability in affect regulation, impulse control, interpersonal relationships, and self-image are linked to the clinical signs of emotional dysregulation, impulsive aggression, repeated self-injury, and chronic suicidal tendencies (Lieb et al., 2004). Some patients are able to sustain a certain level of social and occupational functioning, while others experience a very high level of emotional distress (cf. Jordanova and Rossin, 2010). There is often rapid fluctuation from periods of confidence to despair. Early-life stress exerts damaging effects on brain development (Archer, 2010a, b; Archer et al., 2010b) and neuroimaging studies (e.g. Koenigsberg et al., 2009) have yielded important insight into the role of the hypothalamic-pituitary-adrenal (HPA) axis in BPD (see Wingenfeld et al., 2010 for review).

Patients with BPD have shown volumetric reductions of the hippocampal and (in some cases) amygdala regions in structural MRI studies (Brambilla et al., 2004; Driessen et al., 2000; Schmahl et al., 2003), with or without comorbid aggression or depression (Zetzsche et al., 2006, 2007). Krull et al. (2010) reviewed the multi-dimensional aspect of BPD from phenotypic, genetic, and endophenotypic perspectives. One major feature is the comorbid expression of the disorder with posttraumatic stress disorder which occurs in 50%-70% of patient populations (Zanarini et al., 1998b; Zimmermann and Mattia, 1999) with marked hippocampal volume reductions (Bremner et al., 1997, 2003; Stein et al., 1997; Zlotnick et al., 2003). Both BPD and PTSD share etiologic factors, e. g., trauma, symptom profiles (such as hyperarousal or dissociation states), and neurobiological factors (such as aberrant patterns of neural activation in prefrontal cortex and limbic regions; Schmahl and Bremner, 2006). Amygdala-deactivation has been indicated in BPD patients comorbid for PTSD but not those without PTSD (Kraus et al., 2009). Schmahl et al. (2009) compared a group of BPD with PTSD (n = 10) and a group of BPD without PTSD (n = 15) with 25 healthy female controls applying T1- and T2-weighted MRIs for manual tracing and 3-dimensional reconstruction of the hippocampus and amygdala. They found that the hippocampal volumes of BPD patients with PTSD were lower than those of the healthy female controls concomitant with significant correlations between impulsiveness and hippocampal volumes in these patients. These results and similar observations underlie the necessity of comorbidity considerations in BPD (Bahorik and Eack, 2010; Joshi et al., 2012; Rüsch et al., 2010).

BPD and antisocial personality disorders (ASPD) present common characteristics such as high levels of impulsiveness (Becker et al., 2005; Paris, 1997) and marked comorbidity (Chabrol and Leichsenring, 2006; Zanarini et al., 1998). Nevertheless, Völlm et al. (2004) have provided fMRI evidence that ASPD and BPD patients recruit different brain regions when successfully inhibiting pre-potent responses. Employing a Go/No Go task, they found that for healthy controls the main focus of activation during response inhibition was in the prefrontal cortex, in particular the right dorsolateral and the left orbitofrontal cortex. For ASPD and BDP patients, the active regions expressed a more bilateral and extended pattern of activation across the medial, superior and inferior frontal gyri extending to the anterior cingulate cortex. Völlm et al. (2009) studied the effects of positive (financial reward) and negative (financial loss) outcomes on blood-oxygen-level dependence (BOLD) responses in Cluster B (ASPD and BPD) patients (n = 8) and healthy controls (n = 14). They observed that: (i) there was an absence of prefrontal responses and reduced BOLD signal in the subcortical reward system of the patient group but not the control group, and (ii) for the patient group, but not control group, impulsiveness scores were correlated negatively with prefrontal responses during both reward and loss. The authors concluded that the response system to reward/loss in Cluster B was dysfunctional.
One prevailing notion is that emotional instability in BPD stems from an interaction of emotional vulnerability and an invalidating environment mediated hypersensitivity and hyperreactivity to emotional stimuli together with delayed return to baseline arousal level (Linehan, 1993; Linehan et al., 1999; Reeves et al., 2010). Niedtfeld et al. (2010) have found that both negative and neutral picture-presentations can lead to stronger activation of the amygdala, insula, and anterior cingulate cortex in patients with BPD compared with healthy controls. Structurally, a significant 24% reduction of the left orbitofrontal and a 26% reduction of the right anterior cingulate cortex in BPD in comparison to controls has been observed (Tebartz van Elst et al., 2003). Other studies show volumetric reductions of the hippocampus, orbitofrontal cortex and amygdala in BPD (Domes et al., 2009; Lis et al., 2007) and „ enhanced emotional-cue related activation in the amygdala (Donegan et al., 2003; Minzenberg et al., 2007), and middle and inferior temporal regions (Guitart-Masip et al., 2009) known to be involved in the processing of facial features carrying emotional content. Dyck et al. (2009) suggest that a selective deficit of BPD patients in rapid and direct discrimination of negative and neutral emotional expressions may in large part underlie their difficulties in social interactions.
In BPD, fronto-limbic neural dysfunction has been implicated in the expressions of emotional dysregulation and impulsivity. Using structural MRI and impulsiveness instrument, Takahashi et al (2009), examined the insular cortex volume and its relationship to clinical characteristics in a first-presentation teenage BPD sample of 20 BPD (5 male participants) and 20 healthy controls (5 male participants). They found no association between the insular volume and parasuicidal episodes, trauma exposure, or comorbid Axis I disorders; nevertheless, the BPD participants with a history of violent episodes during the previous 6 months showed a smaller insular volume bilaterally compared with those without such episodes. In addition, the right anterior insular volume in the BPD participants correlated negatively with the impulsiveness score. The potential relationship between the insular cortex volume and impulsiveness expression seems specific to BPD. Whittle et al. (2009) investigated anterior cingulate cortex volume in a first-presentation teenage BPD population with minimal exposure to treatment. Fifteen female BPD patients and 15 healthy female control participants underwent MRI scanning. Anterior cingulate cortex volumes

were estimated with a method that accounts for inter-individual variation in sulcal morphology with measurements between the two groups compared. ANOVA revealed a decrease in volume of the left anterior cingulate cortex in BPD patients compared with control participants that correlated with parasuicidal behavior and impulsivity. Anterior cingulate cortex volumetric asymmetry correlated also with fear of abandonment symptoms, implying that these volumetric abnormalities early in the course of BPD may relate to the clinical correlates of the disorder. Krause et al. (2010) explored the neural correlates of script-driven imagery of self-injurious behavior in female BPD patients and healthy controls. When imagining the reactions to a situation triggering self-injurious behavior, BPD patients showed significantly less activation in the orbitofrontal cortex but increased activity in the DLPFC. Imagining the self-injurious act itself was associated with a decrease in the mid-cingulate in the patient group. Together, these structural and functional neuroimaging findings suggest that frontal, insular, mid- and anterior cingulate regions and medial temporal lobe structures may be critically involved in the impaired regulation of impulse and affect observed in BPD (e.g., Soloff et al., 2008).

In conclusion, the notions of aberrant reward learning, dysregulated response inhibition and pathological hypersensitivity to temporal delays in reinforcement form the essential behavioural endophenotype of impulsiveness that is witnessed in ADHD and BPD, as well as in compulsive gambling, addictive disorders and dopamine dysregulation syndrome. Developmental trajectories of impulsive behaviors and the damaging effects of early-life trauma on brain development bear essential outcome-expectancies for eventual understanding of etiopathogenesis. Structural and functional resonance imaging has served to provide a point of convergence for the resolution of neurobehavioural, epigenetic and neurodevelopmental factors.

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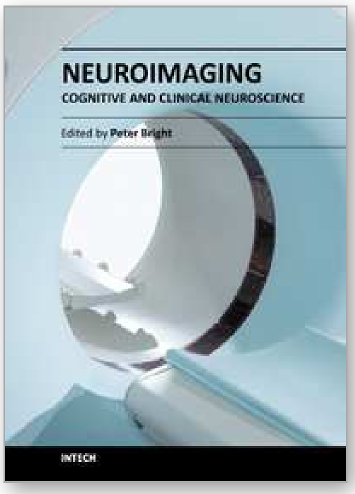

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The rate of technological progress is encouraging increasingly sophisticated lines of enquiry in cognitive neuroscience and shows no sign of slowing down in the foreseeable future. Nevertheless, it is unlikely that even the strongest advocates of the cognitive neuroscience approach would maintain that advances in cognitive theory have kept in step with methods-based developments. There are several candidate reasons for the failure of neuroimaging studies to convincingly resolve many of the most important theoretical debates in the literature. For example, a significant proportion of published functional magnetic resonance imaging (fMRI) studies are not well grounded in cognitive theory, and this represents a step away from the traditional approach in experimental psychology of methodically and systematically building on (or chipping away at) existing theoretical models using tried and tested methods. Unless the experimental study design is set up within a clearly defined theoretical framework, any inferences that are drawn are unlikely to be accepted as anything other than speculative. A second, more fundamental issue is whether neuroimaging data alone can address how cognitive functions operate (far more interesting to the cognitive scientist than establishing the neuroanatomical coordinates of a given function - the where question).

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