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Impulsive aggression and response inhibition in Attention-Deficit/Hyperactivity Disorder and Disruptive Behavioral Disorders: findings from a systematic review

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Highlights

- Impulsive aggression and dysfunctional response inhibition are present in ADHD and DBDs.
- Broad fronto-striatal-cerebellar dysfunctions have been implicated in ADHD and DBDs.
- Prefrontal and cingulate cortical deficits are associated with IA in ADHD.
- Severe widespread cortico-subcortical breakdowns are associated with IA in DBDs.
- RI deficits have been attributed to hypoactivity in the lateral PFC, insula, and amygdala.
- It remains unclear whether reduced gray matter volumes relate to ADHD and DBDs, or if they are present as an IA epiphenomenon.

Abstract

Background: Although impulsive aggression (IA) and dysfunctional response inhibition (RI) are hallmarks of attention-deficit/hyperactivity disorder (ADHD) and disrupted behavioral disorders (DBDs), little is known about their shared and distinct deviant neural mechanisms.

Aims and Methods: Here, we selectively reviewed s/fMRI ADHD and DBD studies to identify disorder-specific and shared IA and RI aberrant neural mechanisms.

Results: In ADHD, deviant prefrontal and cingulate functional activity was associated with increased IA. Structural alterations were most pronounced in the cingulate cortex. Subjects with DBDs showed marked cortico-subcortical dysfunctions. ADHD and DBDs share similar cortico-limbic structural and functional alterations. RI deficits in ADHD highlighted hypoactivity in the dorso/ventro-lateral PFC, insula, and striatum, while the paralimbic system was primarily dysfunctional in DBDs. Across disorders, extensively altered cortico-limbic dysfunctions underlie IA, while RI was mostly associated with aberrant prefrontal activity.

Conclusion: Control network deficits were evidenced across clinical phenotypes in IA and RI. Dysfunctions at any level within these cortico-subcortical projections lead to deficient cognitive-

affective control by ascribing emotional salience to otherwise irrelevant stimuli. The clinical implications of these findings are discussed.

170 words (max. 170)

Keywords: impulsive aggression; response inhibition; ADHD; DBDs; fMRI; sMRI; prefrontal cortex; cingulate cortex; paralimbic system; control; top-down ;emotional salience.

1. Background

Impulsive aggression (IA) is a major concern in many psychiatric disorders. Evolutionarily, aggression was paramount to securing territory, food, and mating partners, thus, aiding survival. It is currently defined as any behavior violating social norms that is intended to inflict verbal or physical injury or death, or to cause havoc (Anderson & Bushman, 2002). Aggression can be proactive or *reactive*. While the former is premeditated and goal-directed, the latter (known as *impulsive*) is unplanned and driven by anger in response to perceived provocation (Barratt et al., 1999; Geen, 2001).

Response inhibition (RI) deficits often relate to IA (Pawliczek et al., 2013; Raaijmakers et al., 2008). The inability to inhibit habitually dominant responses in selecting goal-appropriate behaviors likely leads to aggression via frustration (Breuer et al., 2015; Diamond, 2013; Osumi et al., 2012; Ricciardi et al., 2013; Strüber et al., 2008). RI deficits, high emotional intensity, and impulsivity, *inter alia,* characterize attention-deficit/hyperactivity disorder (ADHD), disrupted impulse-control and conduct disorders (hereafter, disruptive behavioral disorders; DBDs) and support a frustration-aggression framework (Achterberg et al., 2016; Bari & Robbins, 2013; Dambacher et al., 2013; Ende et al., 2016). Thus, the failure to inhibit overpowering impulses that are modulated by frustration, hostility, moral disengagement, and self-regulation may be a proximal cause of IA (Deater-Deckard et

al., 2010; Rubio-Garay et al., 2016). A comprehensive neurobiological understanding of IA and RI is currently needed to facilitate the understanding of impulsive-aggressive psychopathology.

IA and RI deficits are hallmarks of ADHD and DBDs. Here, we use the term DBDs to collectively refer to conduct, oppositional defiant, and symptomatologically related intermittent explosive disorders (CD, ODD, and IED, respectively). It is estimated that 4 to 12% of the general population meet the criteria for ADHD (Wilens and Spencer, 2010), 5 to 15% meet those for CD/ODD (Moffitt et al., 2008), and 5 to 7% meet those for IED (Kessler et al., 2006) at some point during the lifetime. This highlights the necessity of a multisystem neurobiological framework of IA and RI (Fig. 1) both within and between ADHD and DBDs, as this could aid the development of therapeutic interventions.

ADHD and DBDs (including intermittent explosive disorder, IED) are associated with emotional lability (for ample reviews see Nigg, 2017, 2001; Skirrow et al., 2009). Negative mood, which is auxiliary to IA, may automatically increase the risk of aggression via repetitive aversive stimulation (for a review, see Berkowitz, 1989) and maladaptive reinforcement of hostile attributional biases (Chen et al., 2012; Crick and Dodge, 1994; but see Banaschewski et al., 2012). For instance, in an ADHD cohort study, emotional dysregulation increased the risk of negative occupational and social outcomes beyond the risk predicted by hyperactive and impulsive symptoms (Barkley and Fischer, 2010). Hence, emotional lability might reflect hyperexcitability, reduced frustration tolerance, and dampened inhibitory control (Shaw et al., 2014) which ultimately reinforce one another as individuals with labile emotions unsuccessfully attempt to regulate their emotional fluctuations (Stucke and Baumeister, 2006). Similarly, neuropsychological tests of emotional control suggest the processing of emotional stimuli is impaired in ADHD and DBDs alike as reviewed elsewhere (Johnson et al., 2015; van Stralen, 2016). Inappropriate internalized or externalized responses may thus be associated with more than one neurological pathway responsible for emotional dysregulation in ADHD and DBDs. Therefore, ADHD-CD/-ODD and IED-diagnosed individuals are more likely to engage in “hot” information processing (De Brito et al., 2013; Nigg, 2017) which places them at a high risk for developing aggressive behaviors.

The substantial overlap between impulsive aggression and irritability should also be noted. Individuals showing high degrees of emotional lability typically exhibit low frustration tolerance. Generally, measures of IA and irritability are highly correlated and relate equally to social impairments (Van Meter et al., 2016). Within DSM-5, chronic and severe irritability is found as a diagnostic feature across most disruptive, impulse-control, and conduct disorders. It is, therefore, possible that irritability is a sensitive trait (present for extended periods of time) in many cases with externalizing behaviors (Brotman et al., 2017) which could potentiate emotion dysregulation and foster aggressive outbursts (Coccaro et al., 2016). For instance, ADHD and IED youths show at least a few of the following pervasive symptoms that render emotion regulation dysfunctional: distractibility, hyperarousal, insomnia, racing thoughts or inability to follow-through with an idea/action, or intrusiveness (APA, 2013; Brotman et al., 2017). Since these symptoms are rather chronical and not episodic, only little frustration is needed to reach a severely irritated state that culminates in impulsive aggression.

INSERT FIGURE 1 ABOUT HERE

2. Disruptive, impulse-control, and conduct disorders

Disorders in the "disruptive, impulse-control, and conduct disorders" group of the DSM-5 (APA, 2013) share similar inhibitory control dysfunctions. A recurrent diagnosis theme focuses on an array of behaviors (malicious or not) aimed at infringing on societal norms. ADHD behaviors, on the other hand, are likely the consequence of symptom frustration, which then appears malicious, unlike the purposeful maliciousness exhibited in DBDs (Chandler, 2012; Ostrov and Godleski, 2009). Moreover, the latter diagnostic group shows a high prevalence of callous-unemotional (CU) traits, such as lack of guilt, inability to empathize, or the callous use of others (Barry et al., 2000; Frick et al., 2005). These traits are risk factors for IA and delinquency in DBDs (Barry et al., 2000). Where possible, we address CU traits as predictors of deficient emotion regulation and RI.

Although featured in the DSM-5's "disruptive, impulse-control, and conduct disorders" and "personality disorders" chapters, we avoid discussing antisocial personality disorder (APD), as its

diagnosis emphasizes callous indifference and lack of remorse (Azizli et al., 2016), thus, falling beyond the scope of this review. APD is more strongly associated with psychopathy and criminal activities (De Brito et al., 2013; Raine et al., 2010) than it is to impulse-control deficits *per se.* Relative to CD/ODD, it is speculated that APD involves rather "chronicised" neural dysfunctions (Müller et al., 2008). Thus, regarding DBDs, we focus on CD, ODD, and IED because their symptom severity places them on a rather similar behavioral IA spectrum (Fig. 2).

INSERT FIGURE 2 ABOUT HERE

3. State of the art

In typically developing subjects, it has been found consistently that RI activates the fronto-striatal circuitry (Aron & Poldrack, 2006; Lijffijt, et al., 2005; Liu et al., 2012; Young et al., 2009) as well as fronto-cerebellar loops (Durston et al., 2011; Kucyi et al., 2015). These altered functional networks foster the emergence of aggressive behaviors (for ample reviews, see Rosell and Siever, 2015; Nigg, 2017; Sonuga-Barke et al., 2016). In addition, overriding impulsive behaviors seems to rely on the functional integration of cortico-subcortical networks which align emotional processing with goal-directed actions (Muhlert & Lawrence, 2015; Mujica-Parodi et al., 2017).

In response to direct or perceived provocation during Taylor Aggression Paradigms (TAP), neurotypical individuals have shown IA-related functional activations in the insular and ventral/dorsal medial prefrontal cortices (Dambacher et al., 2013; Emmerling et al., 2016; Krämer et al., 2007; Repple et al., 2017; Lotze et al., 2007). Additionally, impaired RI in intermediate phenotypes (i.e., healthy individuals showing high trait aggression) has been associated with motor impulsivity and dampened activity of the pre-supplementary motor area (pre-SMA) and motor cortex (Pawliczek et al., 2013). On the other hand, the neural network of successful RI in GNG/SST tasks appears to overlap with IA neural architecture in the motor and dorsal anterior cingulate cortices, anterior insula, and the dorsal striatum (Baumeister et al., 2014; Dambacher et al., 2013; Meyer-Lindenberg et al., 2006). In response to IA and RI, a couple of studies have found a hyperactive and volumetrically reduced limbic system across healthy, genetically at-risk for violence subjects (Foley et

al., 2004; Meyer-Lindenberg et al., 2006). Altogether, preliminary evidence shows consistent overlap in the anterior insula (aI) suggesting its core involvement in motor impulsivity and reactive aggression.

Meta-analytic findings of ADHD revealed structural abnormalities in the prefrontal, anterior and posterior cingulate cortices (PFC, ACC, and PCC, respectively), the temporal cortices, insula, basal ganglia, and the cerebellum (Castellanos & Proal, 2012; Fernandez-Jaen et al., 2015; Frodl & Skokauskas, 2012; Peng et al., 2013; Pironti et al., 2014; Roman-Urrestarazu et al., 2016). The identified functional changes were found to mirror the structural alterations outlined above (Cortese et al., 2012; Cubillo et al., 2011; Dibbets et al., 2010; Rubia et al., 2011; Rubia, 2011). Hypoactivation of frontostriatal regions including the inferior frontal cortex, striatum, supplementary motor, dorsolateral prefrontal, anterior cingulate, and inferior parietal cortices were observed in many studies. Similarly, CD/ODD structural MRI (sMRI) findings revealed reduced gray matter volume(s) (GMv) in the anterior insular, orbitofrontal cortex (OFC), and basal ganglia (Fairchild et al., 2014, 2011; Passamonti et al., 2010). Functional deficits were associated with reduced neural activity in the dorsolateral PFC (DLPFC), ACC, insula, amygdala, and caudate (Fairchild et al., 2011, 2014; Sterzer et al., 2005) during face processing in CD/ODD subjects, but with exaggerated amygdalar reactivity and diminished OFC activity (McCloskey et al., 2016), together with morphometric alterations in the amygdala and hippocampus (Coccaro et al., 2015) in IED individuals in similar tasks.

Although the genetic evidence for cognitive-behavioral endophenotypes such as RI or IA has been reviewed elsewhere (Gallo and Posner, 2016; Gizer et al., 2009; Klein et al., 2017; Montalvo-Ortiz et al., 2017; Oruche et al., 2016; Stergiakouli et al., 2016), it is worthwhile mentioning that polygenic risk scores obtained from ADHD case-control GWAS were found to be particularly higher in those ADHD cases with comorbid aggression (Hamshere et al., 2013). Similarly, heritable RI deficits have been observed in ADHD subjects and their unaffected siblings (Bédard et al., 2010; Durston et al., 2008). Thus, identifying the neural substrates of IA and RI across disorders might also facilitate future studies on the genetic architecture of endophenotypes, using novel techniques that selectively target certain brain regions or circuitries.

Despite high heterogeneity and few disorder-specific findings (for a review, see Noordermeer, 2016), current evidence indicates that broad fronto-striato-cerebellar network dysfunctions account for IA and RI deficits in ADHD and DBDs. Traditionally, IA and RI neurocognition has been considered separately, yielding limited information on their overlap, directionality, and associated cortico-subcortical breakdowns. Here, we aim to clarify the individual and shared neural substrates of IA and RI in ADHD and DBDs.

4. The current review

The Research Domain Criteria (RDoC) proposed an integrative multisystemic approach accounting for measures of functional circuitry, genetic, and molecular variance in an attempt to explain the clinically relevant variability in mental disorders (Insel et al., 2010; Sanislow et al., 2010). This can be extended to most psychopathological behaviors, including IA. However, because of its myriad of forms, a current caveat in aggression research is the lack of a universally accepted and empirically supported IA framework. Efforts should converge to develop a systemic socio-biologically valid IA nosology. Investigating the disorder specificity and overlaps of IA across clinical phenotypes and integrating these perspectives into robust and scalable findings are the first steps in reaching this goal. The objectives of this review are thus two-fold: *(1)* to synthesize the disorder-specific brain-behavior correlates of IA and RI from a structure-function perspective, and *(2)* to identify and evaluate the extent to which IA and RI neurocognitive phenotypes overlap in ADHD and DBDs. Considering the degree of behavioral and clinical overlap in ADHD and DBDs and their potentially shared genetic risk factors, the current review is important for highlighting the need for better patient stratification and for the development of individualized therapeutic strategies.

5. Measuring impulsive aggression and response inhibition

IA and inhibitory control are neither unitary nor static constructs. They develop nonlinearly, from early life throughout adulthood, in stages corresponding to typical maturation phases (McGirr et al., 2008; for a review see Nigg, 2017). On a behavioral level, dissociating between IA and RI remains difficult. While RI has been traditionally defined as a relatively simple process of overriding planned or already initiated actions (Barkley, 1997) thereby causing impulsive conduct (Bari and

Robbins, 2013), IA has been associated with more complex processes including not only actions characterized by little or no forethought or consideration of consequences (Ramírez and Andreu, 2006), but also choosing short-term gains over long-term ones (Madden and Johnson, 2010; Nigg, 2017).

Experimentally, IA is most commonly assessed with the Taylor aggression paradigm (TAP; Taylor, 1967), the Point Subtraction Aggression paradigm (PSAP; Cherek, 1981), or the hot sauce paradigm (HSP; Lieberman et al., 1999). Common to all these paradigms is the infliction of unpleasant psycho-physiological stimulation (i.e., noise blast or muscle pain stimulation, monetary/status loss, or administering spicy sauce). Normally rigged to the disadvantage of the participant, regular loss or unfair treatment is associated with exhibiting impulsive-aggressive behaviors (i.e., punishment). IA is conceptualized as the intensity and/or duration of unpleasant stimulation/monetary loss that a real participant is administering to an alleged opponent. Extensive neuropsychological test batteries and personality assessments complement experimental IA measurements. Behavioral assessments are useful in delimiting a rash and transient *state of anger* from a more permanent and chronic *trait anger*.

RI is mostly evaluated using the go/no-go (GNG) and stop-signal task (SST). The former involves withholding a no longer required motor response (also termed action restraint), while the latter assesses a context-dependent ability to cancel an ongoing motor response (known as action cancellation; Bennett et al., 2009; Schachar et al., 2007; Steinbeis et al., 2012). Conceptually similar, both tasks involve repeated motor response execution in response to predefined stimuli (i.e., visual, auditory), while on a minority of trials a “stop”/”no-go” signal instructs participants to suppress a habitual response (Littman and Takács, 2017). Correctly responding to a “no-go” target involves adequate inhibitory control over a prepotent response. The commission error rate (i.e., not withholding a “go” response upon “no-go” stimulus presentation) is the main dependent measure in GNG tasks, with fewer errors indicating better RI abilities. This has been shown to correlate with measures of cognitive control and aggression in ADHD (Van Goozen et al., 2016). Other dependent variables in the GNG task are reaction times (RTs) in response to “Go” trials and intraindividual RT

variability - the latter also representing a marker of inhibitory inefficiency (Vaurio et al., 2009). Stopping, however, as a function of the SST requires a rapid control mechanism preventing the execution of an initiated motor behavior while continuously monitoring and adjusting performance (Verbruggen and Logan, 2008). Performance in the SST is modeled as a race between the “go” and the “stop” process. The stop-signal reaction time (or stop process latency) is then estimated using an independent race model (Logan et al., 2014). For instance, an SST variant assesses proactive slowing or participants’ likelihood of responding slower in anticipation of upcoming “stop” signals. Here, differential and often adaptive stop-signal probabilities are used to manipulate subjects’ expectancies. The extent of slowing yields an index of proactive control. In order to isolate brain activity specifically associated with the cancellation of an already initiated response, variants of selective stop tasks have been introduced that include a so-called “ignore condition”. This condition is thought to control for effects of novelty and sensory properties (Albert et al., 2013; Etchell et al., 2012; Sharp et al., 2010) using similar sequences of events and equal probabilities of occurrence as in “stop” trials.

Another widely applied RI task is the Flanker task which measures the ability to suppress responses that are inappropriate in a particular context (reviewed in Davelaar and Stevens, 2009; Mullane et al., 2009). Here, a target is flanked by non-target stimuli which correspond either to the same directional response as the target (congruent flankers), to the opposite response (incongruent flankers), or to neither (neutral flankers). Dependent variables are the RT differences between conditions which reflect a measure of response interference. In addition, the Simon task has been applied in several studies, which is a spatial compatibility task (reviewed in Mullane et al., 2009). In this task, the stimulus, either a word, letter, or symbol, is shown on the right or left side of the computer screen. The participant is instructed to press the right or left button based on the content of the stimulus rather than its location. A congruent trial, for example, could be the word "left" shown on the left side of the screen, while an incongruent trial might be the word "left" on the right side of the screen. Again, RT differences between conditions reflect the amount of response conflict.

6. Methods and study selection

We performed a systematic literature search in PubMed (www.ncbi.nlm.nih.gov/pubmed), PsychINFO (http://ovidsp.tx.ovid.com/sp-3.28.0a/ovidweb.cgi), and Web of Knowledge (https://apps.webofknowledge.com) using the following search and MeSH-equivalent terms in any possible combination: *impulsivity, (dis)inhibition, action/response inhibition, motor control, effortful control, aggression, provocation, retaliation, retribution, punishment, tit-for-tat, Taylor Aggression, point subtraction, hot sauce, go/no-go task, and stop signal*. The search was conducted through to January 2017. Two authors monitored the database search and retrieval. The results were restricted to f/sMRI studies published in peer-reviewed, English-language journals within the past decade (2006-2017). The included studies met the following criteria: (1) the ADHD and DBD diagnosis was based on the DSM-IV/5 or ICD-9/10 criteria, (2) the healthy control group had no medication history or psychological/psychiatric insult, (3) inhibitory deficits and IA were assessed experimentally (task-based) and diagnostically; for sMRI studies, the assessment of the association between RI/IA and structural alterations was compulsory, and (4) participants' full-scale IQ was not lower than 70. We excluded publications where (1) the study was a meta-analysis, literature review or a case-study, (2) the study was a commentary or addendum to previously published data, or (3) the full-text was unavailable after contacting the corresponding authors. The included studies were forward-citation tracked using the Publish or Perish software (Harzing, 2016). This yielded three additional studies that met the inclusion criteria. Three hundred eighty studies were initially retrieved, and then title- and abstract-screened. After the full-text evaluations, 41 studies meeting the inclusion criteria were incorporated in the systematic review (Fig. 3; cf. PRISMA guidelines, Moher et al., 2009). The included studies accounted for 2540 individuals, 972 patients (790 with ADHD, 96 with CD, 18 with ODD, and 68 with IED) and 1568 healthy controls. The small sample size of neuroimaging studies continues to be an ongoing caveat. Nevertheless, we deem it necessary to provide a general preliminary account of the available findings to date. As the number of currently available studies for each of these conditions is too small to conduct quantitative analyses of the shared and distinct

neural mechanisms underlying IA or RI in ADHD and DBDs (such as e.g., an ALE meta-analysis), within this review, we compare and discuss the findings on a qualitative level.

INSERT FIGURE 3 ABOUT HERE

7. Results and Discussion

First, we report the disorder-specific functional and structural findings of IA in ADHD and DBDs and address their overlap, which is then followed by the RI findings. Last, we integrate the IA and RI findings to provide an account of the neural overlap across these disorders. Given the high network heterogeneity, we report and discuss the findings within each section. Although it is beyond the scope of the current review, summarizing healthy functional and structural IA and RI imaging findings aids in the understanding of clinical phenotypes. Together with a general overview of the included studies and sample characteristics, detailed findings of healthy simulated aggression and response inhibition are available in the supplemental materials.

7.1 IMPULSIVE AGGRESSION

7.1.1 Impulsive aggression in ADHD *(2 fMRI studies, 3 sMRI studies)*

ADHD subjects showed less bilateral temporoparietal junction (TPJ), PCC, and precuneus functional activity, further modulated by trait impulsivity (Bubenzer-Busch et al., 2016; Cha et al., 2015), than neurotypical individuals.

On a structural level, path modeling and multiple linear regression analyses identified reduced cortical thickness and generally decreased GMv as predictors for IA etiology. Specifically, the findings converged on right-lateralized GMv reductions in the prefrontal lobe, and the medial parietal and occipital cortices, as well as in the superior temporal sulcus (Cha et al., 2015; McAlonan et al., 2007; Sasayama et al., 2010). Subcortically, reduced GMv were found in the globus pallidus, bilateral amygdala, and temporal poles. White matter volume (WMv) reductions were seen along a bilateral temporo-occipital gradient (McAlonan et al., 2007).

Behaviorally, ADHD children were more revengeful than healthy controls (Bubenzer-Busch et al., 2016). Moreover, the ADHD subjects subtracted almost four times more points in the low relative to the high provocation condition. The drive for punishment was predicted by reduced nucleus

accumbens volumes and this effect was partly mediated by impulsivity but not trait aggression scores (Cha et al., 2015). Altogether, these findings suggest steeper delay-discounting and lower frustration tolerance thresholds in the face of trivial events. This likely renders ADHD individuals more aggressive compared to controls.

Discussion

ADHD subjects showed generally decreased fronto-striatal activity associated with dysfunctional social cognition, anticipation, and error detection, as evidenced by hypoactive TPJ and PCC. The TPJ, comprising the inferior parietal lobule and caudal parts of the superior temporal sulcus (Abu-Akel and Shamay-Tsoory, 2011), *inter alia*, is involved in social cognition, empathy (Lombardo et al., 2010), theory of mind (ToM), and reorienting of attention (Corbetta et al., 2008; Krall et al., 2015). Within IA, an underactive TPJ might *fail to break* ADHD subjects' moral judgement and encourages retaliation when provoked. In neurotypical individuals, the ACC signals the presence of internal conflict (Boes et al., 2008), which dampens the desire to aggress. Hence, decreased ACC and PCC activity in ADHD might indicate impaired moral judgement. The absence or impairment of adequate reasoning likely leads to IA. This, however, does not fully account for retaliation. Prior studies of healthy controls showed increased PCC activity during task-monitoring conditions involving monetary incentives (Engelmann et al., 2009; Small et al., 2005). Here, the PCC might regulate visual attention and top-down control unlike in IA, where the PCC modulates responses to provocation (Leech and Sharp, 2014). Since the adaptation of behaviors to constantly changing environmental cues is affected by, and co-occurs with attentional lapses in ADHD, the roles of the PCC and TPJ in IA appear crucial in controlling the state of arousal. As such, reduced cingulate activity fits well with the behavioral symptoms of ADHD.

Complementary to the functional findings, reduced GMv in the temporal poles and globus pallidus likely reflect dysfunctional decision-making, empathic responses, and emotion regulation. The temporal poles and globus pallidus are involved in socio-emotional processing (Olson et al., 2007), as well as in the regulation of voluntary movement (Filion et al., 1988), and are linked to cortical structures by loop circuits mediating cognitive, emotion, and motor behaviors. Temporal pole

damage leads to unstable mood states with rapidly changing cycles of irritation (Glosser et al., 2000). This trade-off between movement regulation and emotional control likely suggests the involvement of RI either as a precursor or a consequence of IA, though the directionality of the effect is difficult to ascertain. Altogether, findings suggest a deficient cognitive reappraisal of salient stimuli, which is typical for subjects with ADHD (Ochsner and Gross, 2005). The scarcity of available studies, however, deems it necessary for a generalization of these findings to be cautious.

Summary: Functional neurobehavioral correlates of IA in ADHD were found to be associated with deficits in the prefrontal and cingulate cortices, as well as in moral cognition areas (for a meta-analytic review, see Bzdok et al., 2012), which likely suggests a failure to adjust behaviors to incoming feedback. Furthermore, the parietal and occipital cortices, frontal gyrus, and dorsal striatum were structurally altered. IA-related GMv reductions in ADHD were greater with a CD, but not an ODD, comorbidity. Although not adequately robust, the findings suggest IA - RI interrelatedness, although the temporal sequence is still under debate.

7.1.2 Impulsive aggression in DBDs *(3 fMRI studies, 10 sMRI studies)*

The studies identified shared functional deficits in the ventromedial prefrontal cortex (vmPFC), OFC, ACC, and periaqueductal gray (PAG; Bubenzer-Busch et al., 2016; White et al., 2016) in CD/ODD. More pronounced and widespread functional deficits were outlined in CD instead of ODD, and the deficit magnitude increased with a CD-ADHD comorbid diagnosis. This provides preliminary support for a precursory role of ODD in CD. The vmPFC-amygdala connectivity was significantly reduced in CD/ODD during retaliation and provocation. In contrast, IED showed increased functional activity in the left amygdala, ACC, and anterior insula (Coccaro et al., 2007; Coccaro et al., 2016). Bearing in mind the limited power of the studies, these findings cannot convincingly outline a comprehensive IA picture in DBDs.

Structurally, whole-brain (WB) and region of interest (ROI) analyses showed pronounced GMv reductions in CD/ODD in the dorsal anterior insula, the bilateral temporal lobes, left amygdala and left hippocampus, and across the orbitofrontal and ventromedial prefrontal regions (De Brito et al., 2009; Fairchild et al., 2011, 2013; Huebner et al., 2008; Sterzer et al., 2007), and the claustrum

(Fahim et al., 2011; Hummer et al., 2015; Michalska et al., 2015). Regression analyses with self-reported CU traits as predictors showed that, relative to both CD/-CU (CD without CU traits) and controls, CD/+CU (CD with CU traits) subjects had increased GMv in the insula and posterior hippocampus (De Brito et al., 2009). Overall, CD boys showed 6% less global GMv relative to controls (Huebner et al., 2008). The right striatum showed the most reduced GMv in girls (Fairchild et al., 2013). Similarly, IED subjects showed reduced GMv in the OFC, ACC, and the left insula and left uncus (Coccaro et al., 2016). Structural shape and surface alterations in the bilateral anterior amygdala and hippocampus head and tail were additionally seen in IED (Coccaro et al., 2015; Coccaro et al., 2016).

Behaviorally, IA was positively associated with punishment intensity which further increased with the presence of CU traits (White et al., 2016). Additionally, DBD-diagnosed subjects were readier to punish relative to healthy controls as indexed by decreased retaliation speed (i.e., less time needed to select a costly option). Generally, findings suggest a readiness to punish even the slightest of offense. This is supported by heightened activity of the basic threat circuitry which might be sensitized to favor defensive instead of freezing or fleeing behaviors in response to minimally threatening events.

Discussion

Reduced activity and cortical thickness in the vmPFC were found to predict aggression in adolescents (Strenziok et al., 2011a, 2011b), suggesting the vmPFC's critical role in modulating state anger (Meyer-Lindenberg et al., 2006). As part of a regulatory mechanism, the vmPFC and cingulate cortex control emotional arousal and extinguish amygdalar hyperreactivity (for a review, see Ochsner & Gross, 2005; Paus, 2001). Disrupted vmPFC-amygdala functional connectivity is a known feature and a potential IA risk factor in DBDs, irrespective of CU traits (Frick and Dickens, 2006). Thus, given the evidence that the vmPFC and cingulate modulate amygdalar activity by inhibition (Sotres-Bayon, 2004), and since inhibitory deficits have been found in ADHD and DBD, the observed reduction in vmPFC-amygdala coupling strength and decreased GMv provide a potential mechanistic account for the increased retaliation.

However, diminished GMv and less functional activity of the OFC, together with a hypoactive amygdala, do not necessarily affect the decoding of emotional states (Bachevalier and Loveland, 2006). Instead, these might result in an inability to adequately modulate emotional states as social cues change, which lend themselves to IA in DBDs. This interpretation is consistent with work that has linked hypoactive and volumetrically smaller amygdalar regions, basolateral complexes, and insular and cingulate cortices with sustained attention and timing difficulties across different clinical phenotypes (Kaufman et al., 2003; Menon & Uddin, 2010; Plessen et al., 2006; Sasayama et al., 2010). Although tentatively one might directly link disrupted vmPFC function to IA, whether this is instead an indication of a global shared biomarker across all DBDs is still unclear and warrants further research.

Despite high heterogeneity and limited power, an interesting observation remains in the increased GMv in CD/+CU individuals that possibly hinges on slowed fronto-striatal maturation, which is consistent with delayed emotional pruning (De Brito et al., 2009). Similar abnormalities have been seen in criminal psychopaths (Yang and Raine, 2009). The callous-unemotional neural substrate of successful psychopaths has been found to positively correlate with increased GMv in the amygdala and the hippocampal formation, as well as to predict violent recidivism (Yang et al., 2005). Similar alterations in the amygdalo-hippocampal formation, including the parahippocampus (i.e., uncus), have been observed in IED. Altogether, these findings speak to an IA profile characterized by severe structural alterations in the amygdala, hippocampus, anterior cingulate and orbitofrontal cortices.

Studies of IED reported high levels of trait anger and hostility. Behaviorally, these were found to be correlated with a *feeling of dyscontrol* (Coccaro et al., 2007), which appears to be overwhelming and distressful. Relative to all other psychiatric groups, higher anger was found to correlate with severe corticolimbic dysregulations in IED (Coccaro et al., 2016; Look et al., 2015). This possibly reflects an attentional bias similar to the one evidenced in ADHD. However, unlike ADHD or CD/ODD, IA in IED was found to be more intense and arousing and was associated with heightened feelings of gratification following outbursts (Look et al., 2015). Although the neural correlates of IED

mimic the ones of CD/ODD, IA behaviors in IED appear to be beyond the aggressive episodes commonly met in CD/ODD or other psychiatric disorders.

Summary: The dysfunctional and structurally altered areas in DBDs were found to be the vmPFC, OFC, ACC, amygdala, insula, and the hippocampus. GMv was found to decrease proportionally with age, particularly in the temporal cortex, fusiform gyrus, and portions of the cerebellum. Caution is advised when generalizing these findings, as the number of studies investigating IA from a development perspective is limited. Nevertheless, the findings outline a DBD subject profile of an individual who fails to anticipate prospective loss before making decisions, thus, compensating with impulsive punitive behaviors (Fairchild et al., 2008), with the rather out-of-context IA behaviors likely suggesting symptom worsening instead of diagnosis outgrowing. Given the high comorbidity rates, we were unable to distinguish CD- and ODD-specific profiles.

7.1.3 Impulsive aggression overlap in ADHD and DBDs

The findings of brain-behavior correlates revealed large functional IA network overlaps in ADHD and DBDs. Shared functional deficits were seen in the VMPFC, the orbitofrontal and cingulate cortices, TPJ, insula, amygdala, and hippocampus. Globally reduced GMv were observed in both disorder groups, although reliable structural alterations were confined to the ACC and amygdala. Both clinical phenotypes were found to share significant ACC dysfunctions, albeit they were left-lateralized in DBDs relative to the more bilateral deficits in ADHD. These lateralized findings have to be considered preliminary, as they are awaiting support from more high-powered studies. Though being less structurally altered, the amygdala showed severe functional anomalies in ADHD relative to DBDs. On the other hand, functional and structural prefrontal abnormalities, left-lateralized amygdalar structural alterations, and global GMv reductions were observed in DBDs. Furthermore, inward structural shape alterations of the amygdala were consistent across IED studies regarding IA. Despite robustness concerns, our qualitative findings fit a recent high-powered quantitative review implicating the amygdala (and its functional deficits) as a key region underlying ADHD pathogenesis (Hoogman et al., 2017). Whether reduced GMv primarily relate to ADHD, DBD, or are present in both as an epiphenomenon of IA pathogenesis remains debatable.

The propensity of IA appears to be associated with structural and functional cortico-subcortical breakdowns in a network comprising the *dorsomedial* (Janssen et al., 2015; Lotze et al., 2007), including the pre-SMA (Jimura et al., 2014; Li et al., 2008), *ventromedial* (White et al., 2016), and *ventrolateral PFC* (Pliszka et al., 2006) including the insula and inferior frontal gyrus (Costa Dias et al., 2013; Devito et al., 2013; Liu et al., 2012). Subcortically, the loops extend to the ventral striatum (Cha et al., 2015; Costa Dias et al., 2013; Rubia et al., 2008), globus pallidus, putamen, caudate and thalamic regions in a left-lateralized manner (Dambacher et al., 2013). These networks are responsible for appropriate behavioral regulation in response to environmental demands (Durston et al., 2011), including attentional, cognitive and emotional control. Emotional salience, thus, virtually hijacks top-down affective control (particularly obvious in IED) in the lack of accurate basic expectations.

Abnormalities in the insular cortex are related to pathological social behaviors. Marked TPJ disruptions in children with DBDs yield severe empathizing and mentalizing difficulties (Sterzer & Stadler, 2009). However, since the anterior TPJ clusters are putatively connected to the ventral PFC and anterior insula (Mars et al., 2012), and given the latter's intrinsic coupling with the cerebellum (Bolo et al., 2015), this likely reflects the joint operations of the fronto-striatal and fronto-cerebellar circuits. The anterior insula might, therefore, serve as an integration hub for autonomic responses and subjective arousal (Critchley, 2005), while the TPJ supports reorienting of attention and social cognition (Dugué et al., 2017), which is further downregulated by the PFC. Additionally, the ventral striatum is responsible for aligning goal-driven behaviors with anticipated rewards (Ness & Beste, 2013; Simões-Franklin et al., 2010). Frustration arises when the timing of events is mismatched with an inappropriate behavioral outcome or goal-directed interference (Breuer et al., 2015). Thus, the end result of frustration is IA.

Alternatively, in light of the TPJ-inferior frontal gyrus (IFG) hypoactivity in CD and ADHD subjects, one could speculate that the performance monitoring networks are corrupted. We suspect this makes CD/ODD and ADHD subjects care less about their mistakes, in spite of negative feedback. Instead, they retaliate aggressively (Rubia et al., 2006). This likely feeds the dysfunctional motivation

loop characterizing the disorders (Rubia, 2011). Symptom recovery in ADHD supports this view, as it relies on the better integration of prefrontal regions (Francx et al., 2015; Nelson & Trainor, 2007; Shaw et al., 2015; Szekely et al., 2017). Likewise, these performance monitoring networks strengthen until young adulthood, suggesting continuous prefrontal maturation (see Tamnes et al., 2013 for a review).

7.2 RESPONSE INHIBITION

7.2.1 Response inhibition in ADHD *(4 fMRI studies)*

Relative to controls, inhibitory deficits in ADHD were found to be associated with deviant functioning of the ventrolateral and dorsolateral prefrontal cortices, the ACC, and the insula. S*uccessful inhibition* yielded higher activity in the right superior temporal gyrus (STG) and right inferior parietal lobule (rIPL; Pliszka et al., 2006), middle/superior frontal cortex, ACC, bilateral insula, occipital cortex (Janssen et al., 2015; Pliszka et al., 2006; Rubia et al., 2008), left anterior PFC, thalamus, and nucleus accumbens (Costa Dias et al., 2013). Decreased left-lateralized DLPFC and parieto-temporal activity was also reported (Rubia et al., 2008). *Failed inhibition* revealed hypoactivity of the bilateral premotor cortex (Pliszka et al., 2006), right insula, ACC (Janssen et al., 2015), ventrolateral and dorsolateral PFC (VL/DLPFC; Rubia et al., 2009).

In general, behavioral data indicated greater intraindividual variability in RTs to “Go” signals in subjects with ADHD (Janssen et al., 2015; Pliszka et al., 2006; Rubia et al., 2008, 2009) who also show longer SSRTs and have reduced slopes on inhibitory functions (e.g., Pliszka et al., 2006). When examining task performance separately for diagnoses, CD boys show more errors relative to ADHD and control boys and these errors were associated with higher reaction times (Rubia et al., 2009). Similarly, ODD boys were less accurate and showed increased stop latencies relative to healthy boys.

Discussion

Increased STG activity was consistently found across the ADHD literature, suggesting diminished attentional resource availability. A vital node of the amygdala-PFC pathway, together with the rIPL, the STG relays visually salient information to prefrontal areas (Arzimanoglou et al., 2005). Children and adolescents with ADHD performing oddball tasks, for instance, showed reduced

activity in the bilateral STG, amygdala, parietal cortices, including the rIPL, and parahippocampal gyri (Booth et al., 2005; Rubia et al., 2007; Stevens et al., 2007). The same areas are intrinsically involved in social cognition (Green et al., 2015), particularly during face perception, thus, providing a potential speculative directional link, from RI deficits to IA. Additional VLPFC hypoactivity that was found during attentional tasks supported the slowed ability to reorient attention to perceptual contexts (Langenecker et al., 2007; Page et al., 2009). As such, events occurring outside a temporary locus of attention are either left unattended or are addressed at inappropriate times (Levy and Wagner, 2011). In other words, during a motor inhibition task, attention might be locked on the mere task of pressing a button, resulting in ADHD subjects failing to observe the "Go" to "No-Go" transition. Several failed inhibition trials might then serve as a prompt for aggression (Breuer et al., 2015; Osumi et al., 2012; Shiels et al., 2010). Given the blunted inhibitory control in ADHD (Nigg, 2017; Pauli-Pott et al., 2017) and the highly reactive insula and DLPFC during failed inhibition, it is not unlikely that IA emerges as an RI deficit consequence. Overall, the rather posterior pattern of hypoactivity during attentional tasks in ADHD coincides with prior findings and suggests reduced attentional resources and difficulties in integrating and processing rapidly changing information.

Although impulsivity in ADHD might not be equally high across development, it might lead to more mistakes when motor stopping is needed. For instance, deviant VM/DMPFC functioning, as well as striatal-VM/DMPFC hypoactivity, is modulated by trait impulsivity (Costa Dias et al., 2013; Forman et al., 2004; Kaufman et al., 2003). As such, it might be that, in addition to motor inhibition, cortico-subcortical activity during RI relies on social cognition (Ray Li et al., 2006). Taken together, the findings support accounts of reduced response inhibition, reduced error monitoring, and reduced responsiveness to negative feedback, which all characterize ADHD.

Summary: The areas primarily involved in inhibition difficulties were found to be the VL/DLPFC, ACC, insula, temporal gyrus, inferior parietal lobule, and the accumbens. Additional areas (i.e., rIPL) are likely recruited to compensate for off-task mind wandering in an attempt to stay on track with the task demands. This might indicate a dysfunctional top-down regulatory mechanism rather than attentional deficits *per se*.

7.2.2 Response inhibition in DBDs *(5 fMRI studies)*

Relative to controls, DBD subjects showed increased activity in the frontal and middle temporal lobes, including the right inferior frontal gyrus (rIFG), PCC, and striatum, during *successful inhibition* (White et al., 2016). This only held true for CD boys (Rubia et al., 2008). Decreased activity in bilateral temporo-parietal regions was found in CD more than in ADHD or ODD boys (Rubia et al., 2009). In ODD boys, the bilateral inferior/right middle frontal gyrus and the insula were hypoactive, while dorsolateral parts of the bilateral frontal gyrus were hyperactive (Zhu et al., 2014). *Failed inhibition* revealed hypoactivity in the posterior cingulate gyrus of CD relative to healthy boys (Rubia et al., 2010, 2011, 2013). We could not identify any study reporting on RI in IED.

Discussion

Increased rIFG activity is critical for successful inhibition (Aron et al., 2004). The rIFG has been found to be involved in general attentional processes implicating salience detection (Boehler et al., 2011) and risk-aversion (Christopoulos et al., 2009). Congruent with early findings, a hyperactive rIFG in DBDs might indicate global inhibitory control difficulties. The rIFG might have to "work harder" to ensure a neurotypical-like performance. Alternatively, it might be that DBD subjects perceive response inhibition tasks as risky since they cannot predict when a stopping behavior is needed. Increased rIFG activity, thus, plays a role in monitoring events trial-by-trial but might also reflect arousal in the face of trial and risk uncertainty. The inhibitory signal might, thus, be a cue to accept a risky option.

The ventral attentional network, including the inferior frontal cortex (IFC), TPJ, and the insula, has been implicated in stimulus-driven attentional control (Aron et al., 2014a, 2014b; Corbetta et al., 2008; Eckert et al., 2009). This network is recruited by unexpected or infrequently occurring events (i.e., no-go trials). Here, the rIFC's role is to pause or stop (completely or temporarily) an action via its putative connections with the basal ganglia (Aron et al., 2014b). The increased rIFC activity would, therefore, facilitate the orientation of attention and information processing (Eckert et al., 2009). Breakdowns at any level might lead to RI deficits. The hypoactive IFC observed in boys with pure ODD

likely indicates sustained attention difficulties, while the extent of the deactivation speaks to the disorder severity.

Left temporo-parietal (Downar et al., 2000; Weidner et al., 2009) and bilateral TPJ activity (Serences et al., 2005) were also noted in the emergence of attentional deficits. The findings indicate an underactive insula and TPJ during RI in DBDs and reduced GMv in the amygdala extending to the insula and rIFG in CD adolescents (Fairchild et al., 2013). It is possible that a hypoactive insula is linked to its structural abnormalities in DBDs, which then leads to inhibitory deficits (Zheng et al., 2017). Overall, it appears that the paralimbic system is primarily deficient in DBDs during inhibition and reward trials (Rubia et al., 2010, 2011, 2013). Although speculative, higher activation clusters in adjacent regions could reflect compensatory strategies. Despite prior evidence of the co-occurrence of ODD and anxiety disorders in terms of shared risks (see Drabick et al., 2010 for a review), our qualitative findings primarily confirm the link between ODD and CD.

Summary: The areas consistently involved in inhibition difficulties in DBDs were found to be the PFC, including the OFC, IFG, and temporo-limbic networks. Similar to ADHD subjects, CD/ODD individuals showed hypoactive PFC and insula clusters. We suspect that the involvement of the ventral attention system relates to attentional bottom-up mechanisms triggered more by internal memory-based information and less by sensorial stimuli (Cabeza et al., 2012).

7.2.3 Response Inhibition overlap in ADHD and DBDs

During inhibition and impulse-control trials, ADHD- and DBD-diagnosed subjects showed aberrant functioning of the vmPFC, middle/superior temporal and parietal cortices, ACC, and TPJ circuitry. Adequate RI functioning relies on the fronto-parieto-striatal networks. Breakdowns at any between or within network-level unarguably lead to inhibitory deficits.

The vmPFC is a crucial cortico-subcortical relay that coordinates the information flux (Roy et al., 2012). It plays a role in top-down control, including inhibiting fear responses by regulating the activity of the insula, the amygdala, and the ACC (Quirk et al., 2003). However, the vmPFC might not be necessary for affective cognition *per se* (see Roy et al., 2012). Nevertheless, both clinical phenotypes show marked deficits in inhibitory control and social decision-making (Boes et al., 2009;

Tranel et al., 2002) that involve the vmPFC. Depending on the extent of the functional alterations, a hypoactive vmPFC might lead to either inefficient decision making, as seen in ADHD and ODD, or to the behavioral *dyscontrol* observed predominantly in IED. The behavioral consequences are likely rooted in affective dysregulations via the vmPFC's projections to the amygdala. For instance, studies on impulsive affective murderers showed decreased vmPFC activity and increased subcortical activity (Raine et al., 1998; Seo et al., 2008). Similar results were found in DBD subjects, with neural imbalances enhancing actions driven by negative emotions. Since the dysfunctions are widespread, lower prefrontal cortex activity cannot counteract emotional salience and, thus, results in inappropriate motor behaviors.

The reviewed studies indicate that prefrontal hypoactivity also correlated with antisocial behaviors. Additionally, while failed inhibition increased BOLD activity in the ACC and TPJ of healthy subjects, ADHD subjects showed decreased activity within these structures. This failure of contextual information integration feeds into social cognition dysfunctions and might lend itself to poor self-control. Despite some convergence, it remains unclear how different functions served by the vmPFC are attributable to its cytoarchitectonic heterogeneity.

7.3 Overlap between impulsive aggression and response inhibition across disorders

Marked functional cortico-subcortical alterations associated with IA and RI are seen across disorders. Dorsolateral prefrontal circuit abnormalities render the organization of information in preparation for response facilitation dysfunctional. This might increase inhibition, delay-discounting, and unplanned aggression. Furthermore, the absence of adequate ACC monitoring over orbitofrontal networks hinders the integration of limbic modulation. An inability to sustain appropriate behavioral responses consequently arises. Note, however, that most of the studies reviewed included age-matched children and adolescents. Relative to prefrontal areas, the limbic system develops faster and ontogenetically earlier (Steinberg, 2007). As such, impulsive aggressive behaviors might be by-products of an overriding desire for reward, rebelliousness, and *dodging* of social conventions based on exacerbated emotional salience that ultimately hijacks top-down control. Therefore, it might be the functional underdevelopment at young ages that increases the likelihood of impulsive aggression

and susceptibility to poor outcomes. Acknowledging the clinical, methodological, and sample size heterogeneity, these findings should be interpreted cautiously given evidence supporting the outgrowing of age-dependent behavioral symptoms (McAuley et al., 2014).

Structurally, cingulate-fronto-insular regional thinning and decreased GMv are common in both ADHD and DBDs. Both clinical phenotypes show structural alterations in the temporal and parietal lobes, OFC, ACC, insula, amygdala, and the hippocampus. Cingulate cortex deficits are hypothesized to increase the likelihood of aggressive CD behaviors irrespective of sex (Fahim et al., 2012; Fahim et al., 2011; Fairchild et al., 2013). This extends to IED subjects and fits well with the placement of IED on the severe end of the IA behavioral spectrum. Similarly, OFC abnormalities fail to constrain affective impulses because of altered functional coupling with other prefrontal and limbic areas (Fahim et al., 2011). CD/ODD subjects showed reduced global GMv in the posterior temporal areas during late adolescence compared to childhood stages, which converge with ADHD findings. PFC GMv deficits were reported in both clinical phenotypes, yet structural PFC alterations were not found in individuals with pure ADHD. Likewise, morphometric studies agree on the severely reduced global GMv in youths with CD relative to ADHD or ODD youths. In line with the developmental maturation hypothesis, GMv are expected to steadily increase in adolescence for CD/ODD subjects and decrease in controls upon the conventional completion of the cortical maturation process. Irrespective of cortical development, cognitive-affective regulation impairments are likely attributable to the joint operations of fronto-striatal and fronto-cerebellar loops (Nigg and Casey, 2005) that appear to overlap in RI and IA.

It should be noted that, although the overall topographic organization of different frontostriatal circuits has been well described (Alexander et al., 1986; Bostan et al., 2013; Middleton and Strick, 2000), more recent evidence suggests that fibers from functionally diverse cortical areas also overlap within the striatum (Draganski et al., 2008). These regions of overlap may be the striatal equivalents of cortical hub connections for integrating information across multiple cortical areas that represent different components of decision processes or for associating values to actions and stimuli (Averbeck et al., 2014). Hence, the striatum is a site of convergence that allows integration of

information spread across diverse prefrontal cortical areas. The ventral striatum, in particular, is an important hub in adapting goal-driven behaviors to anticipated rewards (Ness and Beste, 2013; Simões-Franklin et al., 2010). In ADHD, for instance, a hypoactive ventral striatum may foster impulsive reward-seeking and delay-discounting behaviors (Tomasi et al., 2015). If rewards are not attained, frustration tolerance decreases which might increase the likelihood of aggression. On the other hand, hypoactive TPJ-IFG in ADHD with or without comorbid CD might suggest that performance monitoring networks are corrupted. One might further speculate that this makes CD subjects careless during inhibition trials as they perseverate responding improperly in spite of negative feedback (Rubia et al., 2006). This might relate to the dysfunctional motivation loop that characterizes the disorders. More generally, cortico-subcortical loops appear to modulate cognitive control of affect (Öngür and Price, 2000) and might be responsible for attentional and emotional regulation in response to environmental demands (Durston, van Belle, & de Zeeuw, 2011).

Altogether, the findings revealed shared deficits in a broad control network involving extensive cortico-subcortical projections. Dysfunctions at any level within this circuit were associated with deficient cognitive-affective control by ascribing increased emotional salience to otherwise irrelevant stimuli. Despite varying degrees of severity, one could speculatively see ADHD as a precursor of more chronic-like asocial aggressive behaviors and psychopathy. Dysfunctional social cognition and an inability to withhold ongoing behaviors, together with the finding that ADHD co-occurs at above chance levels with affective disorders (Pliszka et al., 2006), offers some preliminary support. Importantly, and in line with a recent meta-analytic connectivity modeling study (Alcalá-López et al., 2017), we are now able to qualitatively show that affective cognition is not reached via disparate regions. Instead, so-called “social” regions are engrained in putative higher-order cognitive processing mechanisms that harness adequate affective control.

7.4 Response inhibition does not (necessarily) precede impulsive aggression

Corroborating evidence supported an account where RI and IA emerge from improper regulation of first-order emotional representations (i.e., immediate sensations). Likewise, dispositional higher-order emotional modulation and self-regulation (i.e., conscious awareness of IA

behavioral consequences) are mostly discounted. Adequate control over IA involves two neural circuits: (1) an emotional regulation and processing loop responsible for the increased likelihood of showing aggressive antisocial behaviors that is modulated by the insula and amygdala, and (2) a fronto-cerebellar loop responsible for response inhibition (for a review, see Rubia et al., 2014). The second network is intimately involved in the short-temperedness and out-of-proportion aggressive behaviors of IED patients. Additionally, failed inhibition and IA showed common regional activity in the insula and the ACC. It is tentative to speculate that, at least in the case of neurotypical individuals, failing to inhibit a prepotent/ongoing behavior might lead to gradually increasing frustration, which then generates a rash behavior (Breuer et al., 2015). One dysfunctional loop likely inflicts damage on the other circuit leading to RI deficits and IA. Nevertheless, at this stage the evidence does not allow causal inferences on the IA-RI temporal sequences. It remains open whether impaired inhibitory control precedes IA or whether breakdowns in the circuits mediating IA are modulated by symptomatology, emerge secondary to RI deficits or vice-versa.

8. Agenda for further research

Research unanimously agreed that younger children show more physical and impulsive aggression than older children (Connor et al., 2004). Consistent with normal development, cognitive ability progresses in ensuring adequate goal-setting and planning behaviors. Despite increasing evidence showing that girls engage in subtle relational aggression while boys mostly display overt aggression, sex differences are still scarcely assessed throughout development. Future research should address sex differences paralleled by typical and atypical development, as this will help to integrate the neurobiological bases of IA and RI. We believe upcoming research would benefit from more longitudinal, prospective research designs. These provide a critical account of the causation of patterns over time. Similarly, the gap between a categorical DSM diagnosis and the framework proposed by the RDoC needs to be bridged, which would provide more effective, faster, and comprehensive diagnoses of developmental samples. This would also substantially increase the precision of targeted interventions. While it may not be immediately applicable for clinical purposes, it is possible to envision how research on basic neural circuitry and functional psychopathology can

readily translate into therapeutic and preventive interventions as the RDoC framework encourages interdisciplinary actions.

9. Potential concerns

Several points of this qualitative synthesis warrant comment. First, the studies reviewed here examined individuals at a single time point. The conclusions based on cross-sectional designs rely on the assumption that every tested individual developed somewhat similarly to the members of the group each individual was assessed against. This restricted inferences regarding the neurodevelopmental trajectories to a single given time. Second, the limited availability of female samples across the reviewed studies precluded a thorough observation of sex-specific effects. Third, we were unable to track detailed information regarding comorbidities with early trauma exposure, family violence, post-traumatic stress disorders, etc., yet adverse and traumatic life events play an important role in the etiology of childhood psychopathology. Not controlling for these confounds might have skewed the results and contributed to brain abnormalities and/or overlaps such as those reported in the sections above. Fourth, differences in the results of the reviewed investigations may have been caused by diverse (and often small) sample sizes, different s/fMRI data analysis pipelines, and group heterogeneity. Rather concerning is also the degree of variability in the anatomical localization of brain activity and the generally small effect sizes reported across studies (for a review, see Jimura et al., 2014). Fifth, future research needs to address additional outcome measures (i.e., resting-state functional connectivity, neuropsychological and genetic markers) for evaluating the effectiveness of individualized therapy in order to treat the manifoldness of the impulsive aggressive construct. Sixth, the qualitative comparison of the neural correlates IA and RI across disorders in this review has to be considered with caution as subjects included in the original neuroimaging studies were rarely free of comorbid disorders. Thus, the overlap might have been artificially increased by the presence of multiple disorders within a subject. Last, although well-validated, it remains open whether laboratory-based aggression paradigms assess “real-life” aggression. Disagreements focus largely on the intended harmfulness and the subjective evaluation of how unpleasant an aggressive behavior is thought out to be (Ferguson and Rueda, 2009; Tedeschi and Felson, 1994). Additionally,

dependent measures of aggression (e.g., frustration or negative affect) correlate modestly with unitary aggression constructs (Carlson et al., 1989 but see Giancola and Chermack, 1998; Ritter and Eslea, 2005). Association strength, however, increases when accounting for intent and the effects seem modulated by age. For instance, children may perceive scenarios introduced by aggression paradigms as a "follow the leader" game, thus complying with imposed role models. Contrastingly, youth may exhibit more sophisticated behaviors such as balancing distributive and retributive justice (Smilansky, 2006). Either way, these instrumentally coercive behaviors are implemented to achieve a terminal goal (see Tedeschi and Felson, 1994 for an ample discussion). In the absence of intent assessment, it cannot be explained why a subject may choose coercion over other means of influencing alleged opponents. Likewise, it remains unclear why one may engage in retaliatory behaviors instead of using alternative response strategies. Aggressive behaviors, therefore, must be assumed to be caused by the intent to harm and the belief that a recipient wants to avoid the consequence of the exerted behavior. Hence, understanding aggressive motives post-hoc becomes challenging particularly across different age groups since moral cognition unarguably shape retaliatory behaviors. Future research may try to examine subjective motivation in disaggregating instilled aggressive tendencies from mere reflections of tit-for-tat competitive behaviors.

10. Conclusions

This qualitative review provided an account of functional and structural ADHD and DBDs findings in relation to impulsive aggression and response inhibition. Adequate control over impulsive aggression and successful response inhibition rely on the functional integration of fronto-striatal and fronto-cerebellar circuits that monitor ever-changing social cues. Despite considerable heterogeneity, the evidence suggests a role of deviant cortico-subcortical functional activity and structural alterations in the emergence of IA and RI. A deficient cognitive control process is well-supported in ADHD and DBDs, as was evidenced by dysfunctional dorsolateral and ventromedial prefrontal structures, including the orbitofrontal, cingulate, and insular cortices. Further, dysregulated limbic regions extending to the basal ganglia, together with globally reduced gray matter volumes support a model of dysfunctional cognitive control. Nevertheless, it remains open to

discussion whether the driving force is predominantly an inhibitory deficit or an excessively increased perception of emotional salience, which then interrupts the top-down control of emotions. Thus, further work is needed to parse out the reciprocal IA-RI associations, with a particular focus on IA and simulated aggression. Likewise, the need for developmental multisystem research accounting for the biopsychosocial basis of impulse-control is of utmost importance since aggressive behaviors are currently most often typified in the lay community as *mad, sad or bad,* with ADHD- and DBDs-diagnosed individuals unjustly falling into the latter taxonomy.

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Figure Captions

Figure 1. **Response Inhibition and Impulsive Aggression: behavioural specificity, overlap, and common disorders**. The diagram illustrates possible biopsychosocial mechanisms underlying RI and IA as well as some of the commonest DSM-5 diagnoses. Inhibitory control anger, hostility, and IA appear on the same behavioural continuum represented by cognitive, emotional, and behavioural components (Spielberger et al., 1983). It seems that, if automatic motor and physiological reactions interfere with goal-directed behaviours, negative affect could arise and generate rudimentary feelings of anger (Berkowitz, 1974, 1993). As such, RI likely emerges before IA from impaired attentional mechanisms, timing mismatches, tendencies to perseverate with stereotype actions/behaviours, or other mechanisms alluded to in text. That RI deficits might appear following dysfunctional emotion-regulation should also not be discounted. Although under considerable debate, it appears the two constructs are interrelated and inter-correlated. Note that while there is overlap in terms of motor and timing difficulties, these likely occur at different stages of the response process. Hence different clinical phenotypes appear based on symptom severity. Abbreviations: IED = Intermittent Explosive Disorder; CD = Conduct Disorder; ODD = Oppositional Defiant Disorder; ADHD = Attention-Deficit/Hyperactivity Disorder; BPD = Borderline Personality Disorder; APD = Antisocial Personality Disorder.

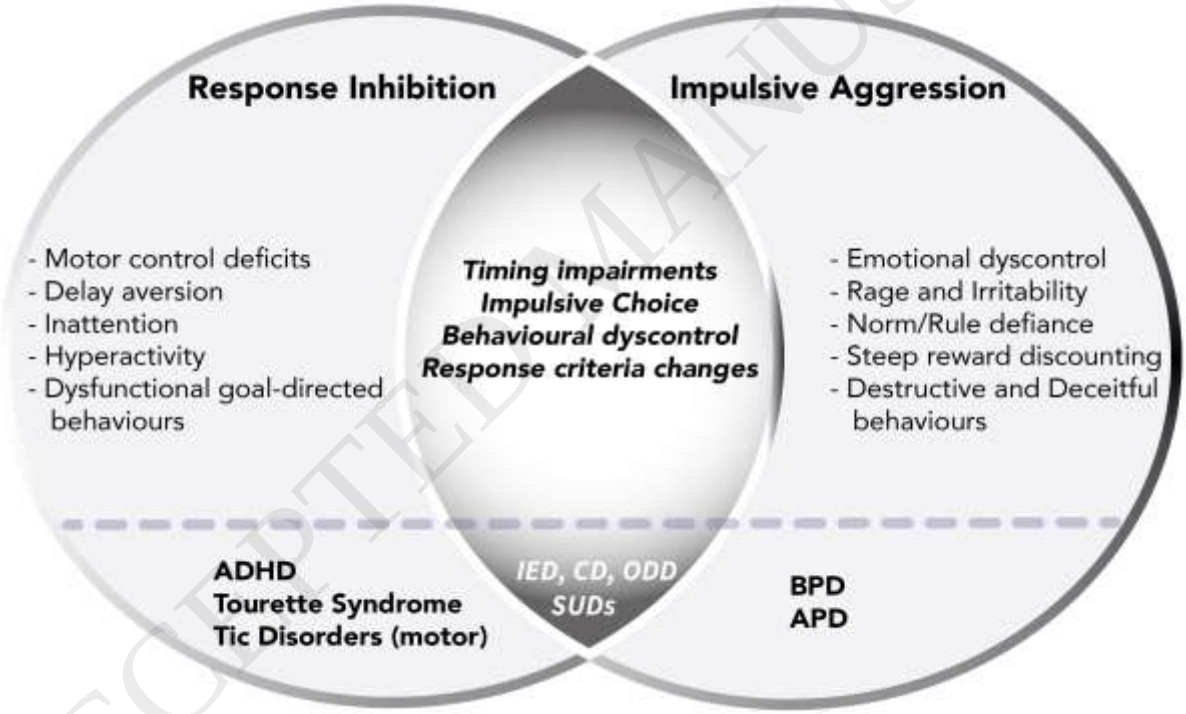

Figure 2. **DSM-5 diagnostic criteria for CD, ODD, IED along a prospective IA continuum.** On one hand, there is ODD for which diagnostic criteria are rather equally distributed between behaviours (defiance and retaliation) and emotions (irritation and hostility) (Burke et al., 2002). Conversely, severely dysfunctional emotion regulation of IED sufferers feeds into disproportionate anger outbursts enhancing the propensity of irrational hostile behaviours (Coccaro, Kavoussi, Berman, & Lish, 1998; McCloskey et al., 2016). Somewhere amid the spectrum lies CD for which poorly controlled, often antisocial impulses give room for behaviours aimed at violating social norms (Foster & Jones, 2005).

Figure 3. **Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram illustration of the study selection process.**