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*REGULAR ARTICLE*

# The neurobiology of oppositional defiant disorder and conduct disorder: Altered functioning in three mental domains

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**Abstract**

This review discusses neurobiological studies of oppositional defiant disorder and conduct disorder within the conceptual framework of three interrelated mental domains: punishment processing, reward processing, and cognitive control. First, impaired fear conditioning, reduced cortisol reactivity to stress, amygdala hyporeactivity to negative stimuli, and altered serotonin and noradrenaline neurotransmission suggest low punishment sensitivity, which may compromise the ability of children and adolescents to make associations between inappropriate behaviors and forthcoming punishments. Second, sympathetic nervous system hyporeactivity to incentives, low basal heart rate associated with sensation seeking, orbitofrontal cortex hyporeactiviy to reward, and altered dopamine functioning suggest a hyposensitivity to reward. The associated unpleasant emotional state may make children and adolescents prone to sensation-seeking behavior such as rule breaking, delinquency, and substance abuse. Third, impairments in executive functions, especially when motivational factors are involved, as well as structural deficits and impaired functioning of the paralimbic system encompassing the orbitofrontal and cingulate cortex, suggest impaired cognitive control over emotional behavior. In the discussion we argue that more insight into the neurobiology of oppositional defiance disorder and conduct disorder may be obtained by studying these disorders separately and by paying attention to the heterogeneity of symptoms within each disorder.

The last decade has seen a remarkable increase in important studies on the neurobiology of oppositional defiant disorder (ODD) and conduct disorder (CD), together referred to as the disruptive behavior disorders (DBDs; American Psychiatric Association, 2000). Previous reviews have presented the neurobiology of children and adolescents with antisocial behavior from the perspective of various neurobiological systems such as the hypothalamus–pituitary–adrenal system (HPA axis), the autonomic nervous system (ANS), and the serotonergic system (van Goozen & Fairchild, 2008; van Goozen, Fairchild, Snoek, & Harold, 2007). In the present review, we aim to provide a coherent picture of the neurobiology of ODD and CD within a conceptual framework of three mental domains: punishment processing, reward processing, and cognitive control. In this framework some hypotheses (e.g., on punishment and reward processing) are included on the etiology of similar adult disorders that have been generated decades ago (Lykken, 1957; Quay, 1965). Recently, studies in children and adolescents have been conducted that support these hypotheses more specifically than has been done in the past (e.g., Gao, Raine, Venables, Dawson, & Mednick, 2010a, 2010b; Rubia, Halari, et al., 2009; Rubia, Smith, et al., 2009; Sijtsema et al., 2010). The mental domains in this framework are defined in terms of their functions (e.g., the processing of punishment cues) that are physically realized by the various neurobiological systems (e.g., ANS, HPA axis, serotonin). This conceptualization of neurobiological systems in terms of functions allows for the inclusion of environmental factors such as parenting and peer group characteristics (Matthys & Lochman, 2010) because it is the environment that provides the input for the processing of punishment and reward.

We primarily focus on studies including clinical samples of children and adolescents with ODD and CD and children and adolescents with these disorders and/or psychopathic or callous–unemotional (CU) traits, that is, the affective factor of psychopathy (Frick & White, 2008). ODD has often been regarded as a milder form and a possible precursor of CD, and therefore the samples of many studies consist of both children and adolescents with ODD and children and adolescents with CD, here referred to as DBDs. In addition, many studies have been conducted in children and adolescents with ODD and CD comorbid with attention-deficit/hyperactivity disorder (ADHD); when discussing these studies, comorbidity with ADHD is mentioned explicitly. In order to better understand the development of ODD and CD we also discuss several nonclinical community studies that classify subject groups on the basis of aggressive behavior, antisocial behavior, and delinquent behavior.

According to the conceptual framework presented here, adequate functioning of the three mental domains is necessary for adaptive social behavior and development. Children need to be sensitive to punishment cues in order to learn to

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refrain from inappropriate behaviors. Likewise, normative sensitivity to reward cues is a prerequisite condition for learning appropriate behaviors and for seeking pleasure in natural rewards such as constructive peer group activities. Finally, in order to behave appropriately, adequate cognitive control of emotions, thought, and behavior is necessary. Although we are aware that the three mental domains are closely interconnected, the separate presentation of these domains aims to help our understanding of the pathophysiology of ODD and CD and provide leads for future research.

## Punishment Processing

Lack of fear in children can explain poor socialization because low fear of punishment would reduce the effectiveness of conditioning (Lykken, 1957). For a long time, low levels of arousal, assessed using basal skin conductance and heart rate, have been interpreted as markers of low levels of fear (Raine, 1993). In agreement, reduced skin conductance in anticipation of punishment is a robust finding in adult criminal and psychopathic individuals (Fowles, 2000). It has been proposed that these individuals do not learn to make successful associations between (stimuli associated with) antisocial acts and (stimuli associated with) punishments. This type of learning is crucial for children because it results in anticipatory fear whenever children consider behaving inappropriately. Learning to refrain from inappropriate behaviors is based on aversive conditioning, for instance, learning to associate hitting another child with subsequent punishment or the perception of the distress of the victim. This learning process may be impeded in ODD and CD either because of a lack of presentation of appropriate punishments by adults or by the child's decreased punishment sensitivity. The latter results in less affective discomfort (e.g., less fear, guilt, and remorse) occasioned by committed or anticipated antisocial behavior (Kochanska, 1993).

### *ANS*

The ANS, which comprises the sympathetic and the parasympathetic branches, regulates several vital functions on a moment-to-moment basis. Although there is a long tradition of research of the ANS in children, adolescents, and adults with antisocial and aggressive behavior (for a meta-analysis, see Lorber, 2004), poor electrodermal fear conditioning as a risk factor for later aggressive behavior and criminality has only recently been demonstrated in young children (Gao et al., 2010a, 2010b).

In a prospective study, fear conditioning using electrodermal responsivity was assessed in children at ages 3, 4, 5, 6, and 8. It was shown that poor fear conditioning from ages 3 to 8 years is associated with aggression at age 8 (Gao et al., 2010a). Furthermore, it appeared that poor fear conditioning at age 3 predisposes an individual to crime at age 23 (Gao et al., 2010b).

Besides this important series of studies that demonstrate poor fear conditioning in young children as a risk factor for developing aggressive and criminal behavior, psychopathy-prone adolescent boys relative to healthy controls have also been found to display reduced electrodermal activity in anticipation of and in response to an aversive stimulus. However, no differences were found between antisocial nonpsychopathic boys and antisocial psychopathy-prone boys. Thus, the antisocial component of psychopathy may be associated with skin conductance hyporesponsivity (Fung et al., 2005). In another study, children and adolescents with CD comorbid with ADHD showed low skin conductance responses to aversive stimuli as well as to (positive and negative) emotional stimuli and to neutral pictures, compared to children and adolescents with ADHD only and healthy controls (Herpertz et al., 2005). The authors concluded that this general autonomic hyporeactivity may reflect a deficit in associative information-processing systems that normally produce adaptive cognitive–emotional reactions.

Basal skin conductance activity has also been considered to be a marker of punishment sensitivity, although it is much less specific than skin conductance reactivity to aversive stimuli (for a critique, see Fowles, 1980). In Lorber's (2004) meta-analysis, it was found that children with conduct problems demonstrate lower basal skin conductance activity than controls (Cohen $d = -0.30$). Consistent, lower basal skin conductance levels were found in preschool children with aggressive behavior as compared to nonaggressive preschoolers (Posthumus, Böcker, Raaijmakers, van Engeland, & Matthys, 2009) and in school-aged children with DBDs half of whom also had comorbid ADHD as compared to healthy controls (van Goozen, Matthys, Cohen-Kettenis, Buitelaar, & van Engeland, 2000). In addition, in a follow-up study of 7- to 12-year-old children treated for DBDs, lower basal skin conductance activity was a predictor of externalizing problems and of maintenance of DBDs in adolescence (van Bokhoven, Matthys, van Goozen, & van Engeland, 2005).

### *HPA axis*

In addition to the ANS, responsiveness to aversive stimuli and stress is mediated by a neural circuit network comprising the HPA axis and the amygdala (LeDoux, 2002). Cortisol secretion by the adrenal cortex is controlled by adrenocorticotropic hormone released from the pituitary, which is regulated by corticotrophin-releasing hormone from the hypothalamus. Corticotrophin-releasing hormone is released in response to stress and subsequent activation of the amygdala and prefrontal cortex. Reduced cortisol reactivity to stress has been found in children with DBDs, many of whom had comorbid ADHD (van Goozen et al., 1998, 2000). Low cortisol responsivity during stress appears to be specific to DBDs. In a study that examined children with DBDs, children with ADHD, and healthy controls, only children with DBDs showed a blunted cortisol response (Snoek, van Goozen, Matthys, Buitelaar, & van Engeland, 2004).

### *Amygdala*

The amygdala is involved in the allocation of subjective value to stimuli in the internal and external environment (Balleine

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& Killcross, 2006; Cardinal, Parkinson, Hall, & Everitt, 2002; Phelps & LeDoux, 2005). The amygdala has been widely implicated in learning and expressing the association of certain undesirable behaviors with punishment, as shown by studies on Pavlovian fear conditioning and passive avoidance learning (Phelps & LeDoux, 2005). Impaired functioning of the amygdala associated with decreased aversive stimulus-reinforcement associations is thought to be characteristic of psychopathic individuals (Blair, 2007).

A number of studies on structure and function of the amygdala have been performed in children and adolescents with CD or conduct problems with or without psychopathic characteristics. In adolescents with early-onset CD, most of whom were comorbid with ADHD, reduced gray matter volumes were found in a variety of brain regions, including the amygdala, relative to healthy controls. Regression analyses indicated that CD symptoms were primarily correlated with gray matter reductions in limbic brain structures such as the amygdala and prefrontal cortex (Huebner et al., 2008). In addition, reduced gray matter volumes in the left amygdala have been found in adolescents with CD relative to healthy controls (Sterzer, Stadler, Poustka, & Kleinschmidt, 2007). In contrast, one study failed to find structural deviances of the amygdala in boys with CU traits (De Brito et al., 2009). Although the boys in this study had conduct problems, the presence of ODD or CD was not assessed. Thus, the negative findings could have been due to the presence of a less severe form of psychopathology in these boys.

Findings from a functional magnetic resonance imaging (fMRI) study suggest left amygdala hyporeactivity to negative emotional stimuli in children and adolescents aged 9 to 15 years with CD. However, it should be noted that the majority of participants was also diagnosed with ADHD and the amygdala hyporeactivity was only found in those subjects with low anxiety levels (Sterzer, Stadler, Krebs, Kleinschmidt, & Poustka, 2005). Likewise, in an fMRI study, DBD children and adolescents (aged 10–17 years) with CU traits, many of whom also had comorbid ADHD, were found to have reduced amygdala responsiveness during the presentation of fearful facial expressions in comparison to healthy controls and youth with ADHD. It is interesting that this study's functional connectivity analyses demonstrated greater correlations between the amygdala and ventromedial prefrontal cortex in healthy controls and youth with ADHD relative to those with DBDs and CU traits (Marsh et al., 2008). In another fMRI study, boys with conduct problems and elevated levels of CU traits who also had ADHD symptoms showed less right amygdala activity to fearful faces compared with healthy controls; these differences remained after controlling for ADHD symptoms (Jones, Laurens, Herba, & Viding, 2009). Thus, these studies reveal evidence of deficits in amygdala function in children and adolescents with DBDs or conduct problems with or without psychopathic or CU traits.

In contrast, enhanced activity of the amygdala has also been observed. CD adolescents, most of whom also had comorbid ADHD relative to healthy controls, showed enhanced left amygdala activation in response to negative pictures as compared to neutral pictures, an effect that was not observed in a patient control group with ADHD only (Herpertz et al., 2008). Likewise, when perceiving others in pain, enhanced activation in the left amygdala was observed in adolescents with CD, most of whom were comorbid with ADHD, compared with healthy controls. It is important that amygdala activation was correlated with adolescents' sadism scores. It may be that enhanced activation of the amygdala in CD adolescents elicited by viewing pain in others reflects enjoyment and excitement as the amygdala is involved in not only the processing of negative affect but also the processing of positive affect, as was found in a study with a small sample size (Decety, Michalska, Akitsuki, & Lahey, 2009).

Some studies with indirect measures of amygdala function are also relevant to mention here. Children with psychopathic characteristics but without DBDs showed selective impairments in the recognition of sad and fearful facial expressions (Blair, Colledge, Murray, et al., 2001). Likewise, adolescents with many CU traits but without DBDs showed reduced attention to other people's eyes during a facial emotion task relative to adolescents with few CU traits, thus accounting for their problems with fear recognition (Dadds, El Masry, Wimalaweera, & Guastella, 2008). Several studies have also been conducted using the startle reflex. In one study it was shown that children with DBDs, the majority of whom also had comorbid ADHD relative to healthy controls, had a blunted response to auditory stimuli that normally elicit a startle reflex. Furthermore, there was a negative correlation between delinquency in the children with DBDs and their startle responses while viewing unpleasant pictures (van Goozen, Snoek, et al., 2004). In a second study, attenuation of the eye-blink startle reflex was found both in youth with early-onset CD and in youth with adolescent-onset CD relative to healthy controls. ADHD symptoms did not affect the startle reflex (Fairchild, van Goozen, Stollery, & Goodyer, 2008).

### *Neurotransmitters*

On the neurochemical level, studies examining serotonergic (5-HT) and noradrenergic neurotransmission in the central nervous system are particularly relevant. Studies have revealed that 5-HT neurotransmission has, among other functions, been implicated in the sensitivity to punishment and aversive signals (Cools, Roberts, & Robbins, 2008). Acute tryptophan depletion, thought to result in decreased 5-HT functioning, has been shown to selectively inhibit the recognition of fearful facial expressions (Harmer, Rogers, Timbridge, Cowen, & Goodwin, 2003). The effect of tryptophan depletion on fear recognition was later shown to occur only in carriers of the short allele of the promotor region (i.e., the section that regulates the transcription process) of the 5-HT transporter (*5-HTT*) gene (Marsh et al., 2006) and to depend on individual threat sensitivity (Cools et al., 2005). This may also explain why a subsequent study failed to find an effect of

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acute tryptophan depletion on fear recognition (aan het Rot, Coupland, Boivin, Benkelfat, & Young, 2010).

5-HT has specifically been associated with aggression (Nelson & Trainer, 2007; Siever, 2008). Genetic studies of the 5-HT system in individuals with aggressive behavior have demonstrated an association between a polymorphism in the promoter region (i.e., the section that regulates the transcription process) of the *5-HTT* gene and aggression in two studies with children, that is in a general population sample (Haberstick, Smolen, & Hewitt, 2006) and in a clinical sample of children with a DBD the majority of whom had comorbid ADHD (Beitchman et al., 2006). This polymorphism has also been found in one study with adolescents with CD (Sakai et al., 2006). However, *5-HTT* polymorphisms have also been associated with numerous other forms of psychopathology including depression that may relate more generally to susceptibility to negative affect (Caspi, Hariri, Holmes, Uher, & Moffitt, 2010).

Various measures can be used to assess 5-HT activity. These include measurement of the principal 5-HT metabolite, 5-hydroindoleacetic acid (5-HIAA), in the cerebrospinal fluid or in plasma; measurements of 5-HT in whole blood; pharmacological challenge studies using a drug or a dietary manipulation that is known to affect central nervous system 5-HT functioning; and measurements of 5-HT receptor activity in blood platelets. In general, studies on neurotransmitters in ODD and CD have been confounded by ADHD comorbidity. Furthermore, studies have often focused on correlations between measures of neurotransmitter levels and aggression or conduct problem measures. We here pay specific, but not exclusive, attention to studies that compare DBD children with healthy controls and refer to the review by van Goozen et al. (2007) for additional information. According to a meta-analysis in adults, there is an inverse relationship between cerebrospinal fluid 5-HT and antisocial behavior (Cohen effect size, $d = -0.45$; Moore, Scarpa, & Raine, 2002). An inverse relationship between 5-HIAA and aggressive behavior has also been found in the cerebrospinal fluid of children and adolescents with DBDs and/or ADHD (Kruesi et al., 1990) and in the plasma of children with DBDs with or without ADHD (van Goozen, Matthys, Cohen-Kettenis, Westenberg, & van Engeland, 1999). In the latter study, no differences were found in plasma 5-HIAA between DBD subgroups with or without ADHD. However, the results from studies investigating whole-blood 5-HT in children and adolescents with CD, most of whom were comorbid with ADHD, appear contradictory: no difference with healthy controls was found in one study (Rogeness, Hernandez, Macedo, & Mitchell, 1982) whereas in another study a positive relation was found between whole-blood 5-HT and aggression (Unis et al., 1997).

Challenge studies with fenfluramine in children with ADHD and aggressive behavior, using the prolactin response as an indirect measure of brain 5-HT functioning, have shown mixed results (Halperin et al., 1994, 1997). No clear relationship between prolactin response and aggression in children with or without ADHD was found (Schultz et al., 2001). However, a longitudinal study demonstrated that lower prolactin responsivity to fenfluramine (indicating lower 5-HT functioning) in 9-year-old children with ADHD predicts the emergence of antisocial personality disorder in early adulthood (Flory, Newcorn, Miller, Harty, & Halperin, 2007). Furthermore, a challenge study with sumatriptan, a selective 5-$HT_{1B/1D}$ receptor agonist, demonstrated that the growth hormone response was enhanced in children with ODD. There were no differences on baseline and peak growth hormone levels between ODD subgroups with and without ADHD comorbidity (Snoek et al., 2002). These findings suggest that the sensitivity of 5-$HT_{1B/1D}$ receptors is increased in ODD. Because 5-$HT_{1B/1D}$ receptors can function as autoreceptors providing negative feedback on 5-HT release mechanisms (Hoyer, Hannon, & Martin, 2002), their hypersensitivity is likely to contribute to lower 5-HT activity in ODD.

Platelet membranes that show similarities to pre- and postsynaptic membranes of 5-HT neurons in the central nervous system have been used to estimate central 5-HT functioning. An inverse correlation has been shown between platelet markers of 5-HT function and aggression in children and adolescents with CD, the majority of whom were also diagnosed with comorbid ADHD (Birmaher et al., 1990). However, no difference in 5-HT function was found between children and adolescents with DBDs and/or ADHD and controls (Stoff et al., 1991).

Taken together, there is support for an inverse relationship between 5-HT measures and aggressive behavior in children and adolescents with ODD and CD, although this relationship is less clear than in adults. The relationship between altered 5-HT function and ODD or CD is supported by reports that risperidon and lithium, which both affect 5-HT function, reduce disruptive behavior in the DBDs (Findling et al., 2000; Malone, Delaney, Luebbert, Cater, & Campbell, 2000). 5-HT neurotransmission has been implicated in sensitivity to punishment and aversive signals (Cools et al., 2008). Hence, the reduction in 5-HT function that accompanies ODD and CD may contribute to the altered impact that punishment and aversive learning have on behavior in ODD and CD. Paradoxically, though, acute depletion of 5-HT appears to enhance the neural and behavioral responsiveness to punishment (Cools et al., 2008). Therefore, if altered function of 5-HT directly contributes to the behavioral deficits in ODD and CD, it is likely to be the consequence of long-lasting reductions in 5-HT function that result in a series of adaptations in this system that contribute to the reduced punishment sensitivity in ODD and CD.

Noradrenergic neurotransmission may also play an important role in behavioral arousal associated with punishment (Berridge & Waterhouse, 2003). If signals associated with punishment do not lead to the noradrenergically driven increase of attention and change in emotional state, these signals become less meaningful. Levels of the metabolite 3-methoxy-4-hydroxyphenylglycol in the cerebrospinal fluid, as well as dopamine-β-hydroxylase (the enzyme that converts dopamine into noradrenaline) in plasma, have been used as an indirect way to measure central noradrenergic ac-

tivity. Kruesi et al. (1990) found a negative correlation between 3-methoxy-4-hydroxyphenylglycol in cerebrospinal fluid and lifetime history of aggression in children and adolescents with DBDs or ADHD. Similarly, low plasma dopamine-β-hydroxylase has been shown in children and adolescents with CD (Rogeness, Javors, Maas, & Macedo, 1990), although this finding was not replicated in a study examining adolescents with CD, many of whom also had comorbid ADHD (Pliszka, Rogeness, Renner, Sherman, & Broussard, 1988). In sum, there is some evidence to suggest decreased noradrenergic functioning in the DBDs.

### *Interim summary of punishment processing*

Studies on electrodermal fear conditioning, cortisol reactivity to stress, serotonergic and noradrenergic neurotransmission, and, although less consistent, the amygdala function indicate that reduced sensitivity to aversive cues and punishment plays a role in the development of ODD and CD. Specifically, learning to refrain from inappropriate behaviors based on aversive conditioning, that is, making the association between inappropriate behavior and punishment, seems to play a role in the development of the ODD and CD from early childhood on. According to Blair (2004), this dysfunctional moral socialization is specifically associated with instrumental antisocial behavior. There is, however, no research in children and adolescents that has demonstrated the specificity of the relation between impaired sensitivity to aversive/punishment cues and instrumental/proactive antisocial behavior or aggression.

## Reward Processing

It has been suggested by Quay (1965) that psychopathy is characterized by low basal reactivity to stimulation, so that more sensory input is needed for the maintenance of pleasant affect in the psychopathic individual. Thus, the psychopath is motivated to change this unpleasant state of stimulus deprivation by seeking stimulation. Below, we argue that recent research supports the hypothesis that reduced reward sensitivity in ODD and CD explains stimulation/thrill/sensation-seeking behavior such as rule breaking, as an attempt to experience a pleasant level of emotional stimulation that is difficult to achieve through the regular sources of pleasure for healthy individuals. In addition, the learning of appropriate behaviors may be compromised in ODD and CD because of a reduced sensitivity to reward.

### *ANS*

The pre-ejection period (PEP) of the heart, which is an index of sympathetic nervous system activity, is considered to be a peripheral marker of reward sensitivity (Beauchaine, 2001). PEP nonreactivity to monetary incentives has been shown in preschoolers with ODD and ADHD relative to controls (Crowell et al., 2006), in male school children and adolescents with DBDs (Beauchaine, Gatzke-Kopp, & Mead, 2007), and in aggressive boys with conduct problems (Beauchaine, Hong, & Marsh, 2008). These results point toward reduced reward sensitivity in boys with conduct problems.

In addition, heart rate has also been linked to reward processing (Fowles, 1980), whereby low resting heart rate may reflect reduced reactivity to rewarding stimuli associated with an unpleasant state. In support of this interpretation, preschool boys who chose to watch videotapes of intense anger had lower basal heart rates than boys who chose to watch videotapes of mild anger. Thus, boys with a lower heart rate level might have sought a higher level of stimulation to experience a pleasant emotional state (El-Sheikh, Ballard, & Cummings, 1994). A longitudinal general population study found that sensation seeking in boys at age 13.5 and 16 mediated the relation between low resting heart rate at age 11 and rule breaking at age 16 (Sijtsema et al., 2010). This relation was not mediated by behavioral disinhibition. This study therefore shows that sensation seeking mediates the relationship between heart rate and rule breaking only in adolescence but not in preadolescence. The study also supports stimulation-seeking theory, which states that rule breaking in adolescence serves to alleviate the unpleasant state of stimulus hyporeactivity associated with low resting heart rate, to experience a pleasant level of emotional stimulation.

School-age children with DBDs with and without ADHD have been found to have a lower resting heart rate than healthy controls. There were no differences in resting heart rate between subgroups with or without ADHD comorbidity (van Goozen et al., 2000). Moreover, over the years many studies have demonstrated lower resting heart rate in children and adolescents with antisocial behavior. In a meta-analysis by Ortiz and Raine (2004), the effect size (Cohen *d*) for resting heart rate in children and adolescents with antisocial behavior was −0.44. Lorber (2004) has subsequently conducted a meta-analysis of heart rate effects in groups of children with more specifically defined forms of antisocial behavior. The effect size of resting heart rate in children with aggressive behavior was −0.51, whereas in children with conduct problems it was −0.34.

### *Amygdala*

Although the amygdala has been widely implicated in negative emotions such as fear, an increasing amount of evidence indicates that the amygdala is associated with valence detection rather than just fear and punishment (Sander, Grafman, & Zalla, 2003). Furthermore, it is well established that the amygdala is involved in positive emotions and appetitive learning as well (Balleine & Killcross, 2006; Cardinal et al., 2002). Therefore, a dysfunctional amygdala may likely result in disturbances in positive emotions and stimulus-reinforcement learning. Thus, reduced gray matter volumes in the amygdala in adolescents with CD discussed above (Huebner et al., 2008; Sterzer et al., 2007) may also result in altered reward processing.

*Cerebral cortex*

Cues and actions associated with reward are processed in the orbitofrontal cortex (Rolls, 2004). Blair (2004) has argued that orbitofrontal cortex dysfunctioning is involved in the modulation of reactive aggression. Specifically, as the orbitofrontal cortex is involved in the computations of expectation of reward and violations of expected reward result in frustration, orbitofrontal dysfunction may be associated with reactive aggression. Evidence for orbitofrontal dysfunction in CD comes from an fMRI study that assessed brain activation during a continuous performance task measuring sustained attention and the effects of reward on performance. Children and adolescents with CD without ADHD showed underactivation in the right orbitofrontal cortex during the reward condition relative to healthy comparison subjects and children and adolescents with ADHD without CD (Rubia, Smith, et al., 2009). This hyposensitivity to reward is consistent with the psychophysiological studies discussed above (Beauchaine et al., 2007; Beauchaine et al., 2008; Crowell et al., 2006), as well as with the study by Herpertz et al. (2005) discussed earlier that showed a generalized deficit in autonomic responding. Deficient functioning of the orbitofrontal cortex may result in compromised stimulus-reinforcement learning in CD (Rubia, 2011). Abnormalities in reward computations that are mediated by the orbitofrontal cortex may lead to enhanced frustration and facilitate reactive aggression (Rubia, Smith, et al., 2009), as suggested by Blair (2004). This specific association with reactive aggression and related uncontrolled disruptive symptoms, however, has not been explicitly studied in children and adolescents with CD.

Finally, in the study by Rubia, Smith, et al. (2009), CD individuals showed decreased activation in paralimbic regions of the insula, hippocampus, and anterior cingulate cortex and cerebellum during the sustained attention condition. These findings suggest that CD is characterized by reduced brain activity in paralimbic regions that contribute to attention networks through their role in motivation (Rubia, Smith, et al., 2009). This is especially relevant with respect to the possible role of dopamine in ODD and CD.

*Neurotransmitters*

Lower activity of brain dopamine systems could result in a reduced salience of positive emotional stimuli in the environment, or a lack of motivation to exert effort to obtain rewards (Berridge, 2007). Low motivation to obtain natural rewards associated with unpleasant affect may incite individuals to search unnaturally strong reinforcers such as drugs. A recent study showed that psychopathic traits (assessed in a community sample) predicted an increased nucleus accumbens dopamine response to amphetamine (Buckholtz et al., 2010). Although seemingly at odds with the view of hypoactive dopamine systems, it is very well possible that low baseline dopamine activity is associated with adaptive changes such as reduced sensitivity of D2 autoreceptors, which result in an increased dopamine response when this system is pharmacologically challenged with psychostimulant drugs.

Genetic studies have found aggression and ODD and CD symptoms to be associated with variations in the structure of the gene encoding the dopamine D4 receptor (DRD4). The DRD4 gene was associated with maternal report of problems with aggression at age 4 (Schmidt, Fox, Rubin, Hu, & Hamer, 2002), as well as with ADHD with comorbid conduct problems (Holmes et al., 2002). Moreover, genetic studies of catechol-*O*-methyltransferase (*COMT*) and monoamine oxidase A (*MAOA*) show an association between lower levels of bioavailable catecholamines in the brain and the DBDs. COMT is an enzyme that metabolizes dopamine, adrenaline, and noradrenaline into inactive forms. The short form of *COMT* is responsible for the substitution of methionine (met) for valine (val). Carriers of the short isoform of the valine allele have significantly more *COMT* activity than carriers of the methionine allele. Therefore, the val/val genotype is argued to more rapidly inactivate catecholamines as compared to the val/met genotype. Thus, the val/val genotype may be associated with lower levels of bioavailable catecholamines in the brain, including dopamine. Together with the evidence suggesting that *COMT* plays an important role in prefrontal cortex function (Winterer & Goldman, 2003), a link between *COMT* and early antisocial behavior has been proposed (Thapar et al., 2005). The first evidence in support of the *COMT*–DBD link was reported by Thapar et al. (2005), who found a relation between antisocial behavior in ADHD and the presence of the val/val genotype. Likewise, Caspi et al. (2008) have shown that ADHD subjects with the val/val genotype displayed more symptoms of CD, were more aggressive, and were more likely to be convicted of criminal offenses than methionine carriers. In addition, evidence was found for involvement of the valine variant in ADHD comorbid with ODD (Qian et al., 2009). These studies suggest a relationship between lowered catecholaminergic activity, including dopamine, and ODD or CD.

Although a polymorphism in the promoter region of the gene encoding *MAOA* conferring low levels of *MAOA* expression (resulting in high levels of dopamine) has been found to be associated with antisocial behavior (albeit in interaction with environmental risks; Caspi et al., 2002; Foley et al., 2004), high *MAOA* activity (resulting in low levels of dopamine) has also been found in children with externalizing and aggressive behavior (Lee et al., 2004; van der Vegt et al., 2009). In sum, results of studies on *MAOA* in ODD and CD are inconsistent.

To study dopamine functioning, measurements of homovanillic acid (HVA), the metabolite of dopamine, have been used. No correlation of HVA in cerebrospinal fluid and aggression has been demonstated in children and adolescents with DBDs and/or ADHD (Kruesi et al., 1990). In addition, no correlation between HVA in plasma and conduct problems in hospitalized children was found (Rogeness, Javors, Maas, Macedo, & Fischer, 1987). In contrast, low HVA plasma levels in children with DBDs with or without ADHD were

found; plasma HVA levels between DBD subgroups with or without ADHD did not differ (van Goozen et al., 1999). In sum, based on these studies there is limited evidence of decreased dopaminergic functioning in children and adolescents with ODD and CD.

Studies of the effectiveness of psychostimulants, which enhance dopaminergic and noradrenergic neurotransmission by blocking the reuptake and/or enhancing the release of these neurotransmitters (Fone & Nutt, 2005), may give insight into the neurochemical mechanisms of ODD and CD. These studies have been conducted primarily in ADHD, but in view of the substantial comorbidity of the DBDs with ADHD (Angold, Costello, & Erkanli, 1999), it is no surprise that many studies have investigated the effect of psychostimulant drugs, such as methylphenidate and amphetamine, in subjects with ADHD with or without DBD or DBD symptoms. The effect of psychostimulants on disruptive behaviors has been examined in a number of studies and in one meta-analysis.

In an important early study on the effect of methylphenidate on disruptive behaviors in children with disruptive, inattention, and hyperactivity symptoms, methylphenidate was an effective treatment for many children with disruptive behavior (Taylor et al., 1987). In this study, hyperactivity was the predictor of the effectiveness of methylphenidate. Specifically, it was hyperactivity rather than defiance that predicted the degree to which defiance was reduced. In another study, the efficacy of methylphenidate was investigated in children and adolescents with CD; two-thirds of the participants also met criteria of ADHD (Klein et al., 1997). Methylphenidate was shown to reduce antisocial behavior. This effect was independent of severity of the children's initial ADHD symptoms, in contrast to the findings of the study by Taylor et al. (1987). Thus, the Klein et al. study (1997) shows an independent influence of methylphenidate on antisocial behavior.

Connor, Glatt, Lopez, Jackson, and Melloni (2002) have conducted a meta-analysis of the effect size for psychostimulants on overt and covert aggression-related behaviors in children and adolescents with ADHD. Examples of overt aggression are physical assault, malicious teasing of others, and temper tantrums, whereas examples of covert aggression are lying, stealing, and vandalism. In 24 of the 28 reviewed studies, ADHD was the primary diagnosis. Of the 24 studies in which ADHD was the primary disorder, 17 studies had CD or ODD as comorbid diagnoses. In two studies CD was the primary diagnosis with ADHD as a comorbid disorder, and in two studies mental retardation was the primary diagnosis with ADHD and CD as comorbid disorders. The overall weighted mean effect size was 0.84 for overt aggression and 0.69 for covert aggression. However, in studies in which ADHD was the primary diagnosis, increased prevalence of either ODD or CD led to diminished effect sizes for overt aggression. Thus, although psychostimulants affected aggression in children with ADHD, ODD and CD appeared to moderate the effect.

With respect to the behavioral mechanism of action of psychostimulants, methylphenidate has been shown to exert positive effects on cognitive performance by increasing task salience (Volkow et al., 2004). Because incentive salience or "wanting" is particularly influenced by dopaminergic neurotransmission (Berridge, 2007), an increase in incentive salience by psychostimulants might explain why parents of children and adolescents with DBDs treated with methylphenidate report improvement in their children's attention and motivation to comply and otherwise to engage more positively in social interactions. It may be that methylphenidate improves function of paralimbic regions in children and adolescents with ODD and CD because these regions have been shown to play a role in attention networks in CD (Rubia, Smith, et al., 2009). Taken together, there is some evidence of decreased dopaminergic functioning associated with ODD and CD based on genetic studies, studies of the metabolite of dopamine, and pharmacological studies.

### *Interim summary of reward processing*

Studies on the ANS suggest hyposensitivity to reward, and decreased dopaminergic functioning may be associated with reduced salience of environmental stimuli in ODD and CD. These factors make adolescents more vulnerable for stimulation/thrill/sensation seeking or reward seeking, which may manifest in antisocial and delinquent behavior. Healthy individuals will usually not percieve these forms of behavior as pleasurable, but they may be experienced as positive in ODD and CD individuals because they improve an unpleasant state of stimulus deprivation, which may manifest in boredom. In addition, reward seeking may make adolescents with ODD or CD vulnerable for substance abuse. Substances of abuse have much larger rewarding effects than natural rewards such as food and sex, and they enhance the incentive salience of associated stimuli in the environment through their effects on dopaminergic neurotransmission (Berridge, 2007; Fone & Nutt, 2005). Reduced reward sensitivity and deficient functioning of the orbitofrontal cortex may also result in compromised stimulus-reinforcement learning of appropriate behaviors in children and adolescents with ODD or CD. Finally, orbitofrontal cortex dysfunctioning in CD may be associated with reactive aggression owing to abnormalities in computations of expectation of reward.

## Cognitive Control

Whereas limbic brain structures, such as the amygdala, are involved in the allocation of subjective value to stimuli in the internal and external environment, frontal cortical structures are involved in the top-down control of behavior. Specifically, the paralimbic system comprising orbitofrontal, superior temporal, cingulate cortices, and limbic brain regions, mediates the cognitive control of emotion and motivation (Blair, 2004). The explicit control of thought, emotion, and action is also referred to as executive functions (EFs; Séguin & Zelazo, 2005). EFs include mental processes such as planning, working memory, inhibition of inappropriate responses, flexibility in adaptation to environmental changes, and deci-

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sion making (Nigg, 2006). These functions serve to optimize behavior in changeable environments. Due to maturation of the frontal cortex with age (Durston et al., 2001), cognitive control over behavior increases in children and adolescents.

### *EFs*

According to a meta-analysis of studies in school-aged children, adolescents, and adults with externalizing disorders, the average mean effect size (Cohen *d*) of a variety of EF measures for the groups with antisocial behavior (criminality, delinquency, CD, psychopathy, antisocial personality disorder) was 0.62, whereas the effect size for CD was 0.36 (Morgan & Lilienfield, 2000). The possible role of ADHD comorbidity in EF impairments in CD was not examined in this study. However, another meta-analysis revealed that EF deficits in CD are likely due to the presence of comorbid ADHD (Pennington & Ozonoff, 1996). In contrast, a meta-analysis showed that deficits in response inhibition were found not only in elementary school children with ADHD but also in children with DBD without comorbid ADHD (Oosterlaan, Logan, & Sergeant, 1998). Likewise, impairments in inhibition have been found in preschool children with aggressive behavior when compared with nonaggressive preschoolers, and these impairments were maintained after controlling for attention problems (Raaijmakers et al., 2008).

The results of studies in DBDs are less inconsistent when motivational factors are involved in EFs. In this respect, the distinction has been made between "cool" cognitive EFs mediated by lateral inferior and dorsolateral frontostriatal and frontoparietal networks and "hot" EFs that involve motivation and are mediated by orbitofrontal and medial prefrontal networks and underlying limbic structures including the amygdala (Rubia, 2011). Impairments in hot EFs may result in perseverative behavior, which involves the inability to show adaptive behavioral responses to changes in the environment. For example, the tendency to continue a previously rewarded response that is now punished, in other words, response perseveration, has been demonstrated in children and adolescents with DBDs (Daugherty & Quay, 1991; Matthys, van Goozen, de Vries, Cohen-Kettenis, & van Engeland, 1998; Matthys, van Goozen, Snoek, & van Engeland, 2004; Shapiro, Quay, Hogan, & Schwartz, 1988; van Goozen et al., 2004) and in children with psychopathic tendencies (O'Brien & Frick, 1996). In one study, boys with ODD showed not only response perseveration but also decreased punishment sensitivity (Matthys et al., 2004). Thus, children with DBDs seem to have difficulties in stopping their ongoing behavior in response to punishment cues. However, it cannot be excluded that decreased reward sensitivity in these children induces an increased search for rewards in order to achieve a pleasant affective state. Response perseveration is thought to be the result of impaired functioning of the orbitofrontal cortex (Schoenbaum, Roesch, Stalnaker, & Takahashi, 2009).

Blair (2004) suggested that dysfunctions of the orbitofrontal cortex in individuals with antisocial behavior may be associated with impaired decision making. To assess impaired decision making in patients with damage to the ventromedial prefrontal cortex (consisting of the medial prefrontal cortex and the orbitofrontal cortex), the Iowa gambling task was developed by Bechara, Damasio, Damasio, and Anderson (1994). This decision-making task simulates real-life decisions involving reward, punishment, and uncertainty of outcomes. Specifically, in this task it is not possible to calculate the net gains and losses when making decisions. Instead, one needs to develop an estimate or intuition of which choices are risky and which ones are profitable in the long run. Therefore, this task is supposed to assess affective or intuitive decision making. Impaired functioning on this task and similar tasks, indicating favoring immediate rewards despite long-term punishments, has been shown in young adults with psychopathic characteristics (van Honk, Hermans, Putman, Montagne, & Schutter, 2002); children and adolescents with psychopathic tendencies (Blair, Colledge, & Mitchell, 2001), adolescents with ADHD or CD (Ernst et al., 2003); children with ODD, most of whom were comorbid with ADHD (Luman, Sergeant, Knol, & Oosterlaan, 2010); adolescents with CD, some of whom had comorbid ADHD (Fairchild et al., 2009); and adolescents with both DBDs and substance dependence (Schutter, van Bokhoven, Vanderschuren, Lochman, & Matthys, 2011).

Impaired functioning of the orbitofrontal cortex (Rubia, Smith, et al., 2009) may underlie compromised affective decision making in ODD and CD. The orbitofrontal cortex is involved in controlling reward-related and punishment-related behavior (Rolls, 2004). Specifically, the orbitofrontal cortex is responsible for calculating the value of reward outcome, including the assessment of trade-offs, determining how well the outcome satisfies current needs, and comparing the outcome with other potential reward outcomes (Schoenbaum et al., 2009). Thus, affective decision making in which quick decisions in everyday situations are made on the basis of intuition, regarding which solution is risky and which is profitable in the long run, may be compromised in ODD and CD. This type of deficit also occurs in other individuals who decide against their best interest and have difficulty learning from their mistakes, such as those with substance use disorders (Bartzokis et al., 2000; Bechara et al., 2001; Grant, Contoreggi, & London, 2000; Mazas, Finn, & Steinmetz, 2000).

### *Cerebral cortex*

With respect to possible structural deficits of the cerebral cortex, in a region of interest (ROI) study right temporal lobe and right temporal gray matter volumes were significantly reduced in children and adolescents with early-onset CD, the majority of who also had comorbid ADHD compared to controls. Prefrontal cortical volumes in these subjects were 16% smaller than controls, but the difference did not reach statistical significance (Kruesi, Casanova, Mannheim, & Johnson-Bilder, 2004). In a study with early-onset adolescents with CD (most of whom were comorbid with ADHD), whole

brain volume analysis showed reduced gray matter volumes in the left orbitofrontal region, bilaterally in the temporal lobes, and in the amygdala and hippocampus on the left side compared with healthy controls; the mean total gray matter volume was 6% smaller in the clinical group. Regression analyses indicated that CD symptoms were correlated primarily with gray matter reductions in limbic brain structures, including the amygdala and the prefrontal areas, whereas hyperactive/impulsive symptoms were correlated with gray matter abnormalities in the frontoparietal and temporal cortices (Huebner et al., 2008). In a community sample of adolescents with conduct problems, ADHD problems, and CU traits, whole brain volumetric analysis showed increased gray matter in the medial orbitofrontal cortex and the anterior cingulate cortex relative to their healthy twins, controlling for ADHD symptoms. It is interesting that the norm-typical negative correlation between age and cortical thickness was not found in the adolescents with conduct problems and CU traits, suggesting a delay of normal brain maturation in these brain structures (De Brito et al., 2009). In an ROI study, reduced gray matter volumes bilaterally in the anterior insula and in the left amygdala were found in adolescents with CD relative to healthy controls. Aggressive behavior appeared to be the strongest predictor for gray matter volume in the left and right insula, whereas attention problems were the strongest predictor for gray matter volume in the left amygdala (Sterzer et al., 2007). Finally, in an ROI study, structural deficits of the cerebellum have been found not only in ADHD but also in CD: children with ADHD only and those with comorbid ADHD and CD both differed from controls in the volume of the left and total posterior superior and inferior lobes of the vermis (Bussing, Grudnik, Mason, Wasiak, & Leonard, 2002). Vermal abnormalities are in agreement with the view that the cerebellum is involved in affective and cognitive processes (Schutter & van Honk, 2005).

With respect to functional impairments, the anterior cingulate cortex, which is involved in emotion processing and social functioning, has been studied in children and adolescents with DBDs. In an fMRI study by Stadler et al. (2007), children aged 9 to 15 years with CD, the majority of who also had comorbid ADHD, viewed negative pictures and showed a deactivation in the dorsal part of the anterior cingulate cortex, that is, the part involved in the cognitive control of emotional behavior, as compared to healthy controls. This abnormal suppression of neural activity may result in a failure to cognitively control emotional behavior. Likewise, abnormal right anterior cingulate cortex activation during the presentation of images with negative valence was shown in children and adolescents aged 9 to 15 years with CD, most of whom also had comorbid ADHD relative to healthy controls (Sterzer et al., 2005). In addition, in another fMRI study, children and adolescents with CD and children and adolescents with ADHD performed an inhibition task and showed reduced activation in the posterior cingulate compared to healthy controls. Children and adolescents with CD showed reduced activation in temporal–parietal regions during failed inhibition when compared with the other groups. Because participants obtained feedback about their inhibition failures, the results suggest that performance-monitoring networks are dysfunctional in CD when compared to ADHD and healthy controls (Rubia et al., 2008). Consistent with this notion is the observation that adolescents with psychopathic traits and ODD or CD, the majority of who also had comorbid ADHD, showed abnormal responses of the ventromedial prefrontal cortex during punished errors in a reversal learning task, as compared to adolescents with ADHD and healthy controls (Finger et al., 2008). According to Rubia et al. (2008), this could mean that adolescents with CD care less about their mistakes than adolescents with ADHD and healthy controls, which is in line with evidence that children with DBDs are undermotivated and respond less to negative feedback than controls (Matthys et al., 2004; van Goozen, Cohen-Kettenis, et al., 2004). As already discussed in the section on reward processing, lower responsiveness to reward outcome information within the orbitofrontal cortex has been shown in children and adolescents with CD (Rubia, Smith, et al., 2009). In line with this, less orbitofrontal responsiveness to stimulus-reinforcement exposure and rewards while performing a passive avoidance learning task was shown in adolescents with DBDs and psychopathic traits relative to comparison youths. Thus DBD adolescents with psychopathic traits seem to be less able to represent reward expectance values resulting in a higher vulnerability to impaired decision making (Finger et al., 2011). During interference inhibition and attention allocation, boys with CD only compared to controls showed reduced activation in the right middle and superior temporal and parietal regions; impaired functioning of these areas possibly accounts for attentional deficits in CD, causing more errors (Rubia, Halari, et al., 2009). Finally, during cognitive flexibility, when compared with control boys and ADHD-only boys, no disorder-specific brain underactivation was observed in boys with CD only (Rubia et al., 2010).

EFs are thought to heavily rely on optimal functioning of the prefrontal cortex. In this regard, the prefrontal dysfunctions that have been reported in CD are consistent with impairments in EF. Given the anatomical and functional heterogeneity of the prefrontal cortex, a more detailed understanding of prefrontal function in ODD and CD is necessary in order to appreciate how altered function of separate prefrontal subregions contributes to various mental and behavioral aspects of the DBDs. Finally, both neuroimaging and neuropsychological research has been biased in the selection of ROI (structural studies), paradigm selection (fMRI), and use of EF tasks, in that functions such as working memory and planning, and their associated neural systems, have not been systematically investigated in CD and ODD (Rubia, 2011).

The observed structural abnormalities in the cerebral cortex are paralleled by functional deficiencies in information processing. Electrophysiological (EEG) studies have found amplitude reductions of the P300 brain wave in children with DBDs (for a review see Cappadocia, Desrocher, Pepler, & Schroeder, 2009). The P300 is a cortically generated brain

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wave that is suggested to reflect online adjustment of mental representations in response to environmental changes. The P300 emerges around 300 ms over frontal and parietal regions in response to a stimulus that is relevant to the subject. It has been proposed that the P300 amplitude reductions represent a neurocognitive deficit of explicitly acknowledging and incorporating novel information in order to effectively guide behavior under changing conditions. The reduced P300 amplitude and its associated neurocognitive deficits could provide an explanation as to why children with DBDs show less flexibility in adjusting their behavior (Bauer & Hesselbrock, 1999; Baving, Rellum, Laucht, & Schmidt, 2006).

In addition to externally (exogenous) evoked brain activity, irregularities in the spontaneous (endogenous) generation of neural activity as reflected by the waxing and waning of brain oscillations across different frequency bandwidths have also been observed in various externalizing spectrum disorders. For example, significant reductions in the spontaneous generation of beta (13–30 Hz) oscillations in the EEGs of young adults have been observed in subjects with impulsivity and antisocial personalities (Houston & Stanford, 2005). These reductions have been interpreted as lowered levels of cortical arousal that set the stage for decreased cognitive control and increased impulsive behavior. In agreement, other studies have found that reduced beta activity relative to theta (4–7 Hz) activity is associated with disadvantageous decision making in healthy adult volunteers (Schutter & van Honk, 2005) and impulsive behavior found in patients with ADHD (Barry, Clarke, & Johnstone, 2003). In sum, electrophysiological studies provide further support for the view that the behavior in DBDs can at least in part be understood in terms of cortical abnormalities and subsequent impairments in attention and EF.

### *Neurotransmitters*

Proper function of the prefrontal cortex strongly depends upon monoaminergic inputs. One particular aspect that is pertinent to EF in ODD and CD is the notion that they modulate mental functions according to an inverted U-shaped function: dopaminergic, noradrenergic, as well as serotonergic activity needs to be at an optimum, whereby both increases and decreases from this optimal level lead to impaired function (Robbins & Arnsten, 2009). Dopaminergic neurotransmisson has been widely implicated in working memory, as well as in impulse control (Chamberlain, Müller, Robbins, & Sahakian, 2006; Dalley, Cardinal, & Robbins, 2004; Pattij & Vanderschuren, 2008; Robbins & Arnsten, 2009). A reduction in dopaminergic activity could therefore well play a role in the EF impairments in ODD and CD. Because it has been shown that psychostimulants activate the medial orbitofrontal cortex and the rostral part of the anterior cingulate cortex (Völm et al., 2004), the beneficial effect of methylphenidate on symptoms of ODD and CD in children and adolescents with these disorders and ADHD comorbidity (Turgay, 2009) may be the result of improved functioning of these structures.

In addition, noradrenergic neurotransmission has been implicated in working memory, behavioral inhibition, and the balance between optimizing task performance versus searching alternative behavioral strategies, whereas serotonergic neurotransmission plays an important role in behavioral flexibility (i.e., reversal learning), behavioral inhibition, and decision making (Aston-Jones & Cohen, 2005; Chamberlain et al., 2006; Dalley et al., 2004; Pattij & Vanderschuren, 2008; Robbins & Arnsten, 2009; Rogers et al., 1999). Therefore, the alterations in the function of these important modulatory neurotransmitters likely play a prominent role in the deficits in various EFs such as behavioral inhibition and decision making in ODD and CD. In this respect it is worth mentioning that atomoxetine, a selective noradrenaline transporter inhibitor, has been found to reduce ODD symptoms in children and adolescents with ADHD with or without ODD comorbidity (Newcorn, Spencer, Biederman, Milton, & Michelson, 2005).

### *Interim summary of cognitive control*

DBDs have been associated with structural deficits and impaired functioning of the paralimbic system comprising the orbitofrontal cortex, superior temporal lobes, and cingulate cortices. Likewise, impairments in executive or cognitive control functions have been shown in ODD and CD, especially when motivational factors (reward and punishment) are involved. Thus, compromised cognitive control over emotional behavior in ODD and CD may result in reactive aggression and related uncontrolled disruptive symptoms (e.g., losing temper). Furthermore, compromised processing of both punishment and reward cues in the orbitofrontal cortex leads to impaired representation of information on reinforcement expectations, increasing the risk of deficient decision making. Thus, children and adolescents with ODD or CD choose not to approach objects associated with reward and avoid those associated with punishment but instead choose actions that harm others.

## Discussion

In this review we have discussed neurobiological studies on ODD and CD within the conceptual framework of three mental domains. These domains are defined in terms of functions that are exerted by distinct, but partially overlapping neurobiological systems. Altered punishment processing, reward processing, and cognitive control seem to be associated with ODD and CD, although the causal role of the neurobiological systems in the development of these disorders clearly needs further study. For the sake of clarity, we have presented these mental domains and related neural substrates separately, but these domains and their neural underpinnings are, of course, closely interconnected. For example, the medial prefrontal and orbitofrontal cortices have dense reciprocal connections with the amygdala, and these structures provide a rich input into the striatum, including the reward-associated nucleus ac-

cumbens (Pitkänen, 2000; Voorn, Vanderschuren, Groenewegen, Robbins, & Pennartz, 2004). Furthermore, the different mental domains involved in ODD and CD can operate in a serial fashion: Before adequate cognitive control of emotions and related behavior by EF generated by the prefrontal cortex can take place, reward and punishment cues need to be processed appropriately by the ANS, the HPA axis, and the amygdala first. Thus, compromised stimulus-reinforcement information provided by the amygdala is represented as expectancy information in the orbitofrontal cortex (Blair, 2007; Finger et al., 2011), and impaired processing of this information in the orbitofrontal cortex may result in deficient decision making.

Research in the neurobiology of ODD and CD suffers from the assumption that ODD and CD are similar disorders, ODD being a milder form and a possible precursor of CD. Thus neurobiological studies have included children and adolescents with ODD and CD. Recent research, however, suggests that ODD is a separate disorder to be distinguished from CD in symptomatology, comorbidity, and development (Nock, Kazdin, Hiripi, & Kessler, 2007; Rowe, Costello, Angold, Copland, & Maughan, 2010; Stringaris & Goodman, 2009a, 2009b). With respect to symptomatology, a defiant/headstrong behavior cluster (argues with adults, defies adults' requests, deliberately annoys people, blames others) can be differentiated from an irritability cluster (temper tantrums, touchy or easily annoyed, angry, and resentful; Rowe et al., 2010; Stringaris & Goodman, 2009b). ODD may therefore be considered a mixed disorder of behavior and emotion. The defiant/headstrong behavior cluster is associated specifically with the development of CD whereas the irritability factor is associated specifically with the development of anxiety and mood disorders (Stringaris & Goodman, 2009a). The neurobiology of ODD therefore needs to be studied separately from CD.

One important aim in the study of the neurobiology of ODD is to investigate whether different neural systems are involved in the defiant/headstrong behavior cluster, possibly corresponding with the proactive/controlled type of aggression, and in the irritability cluster, probably corresponding with the reactive/undercontrolled subtype of aggression. Neurobiological research in adults and in animals suggests that different neural systems are involved in the proactive/controlled and the reactive/undercontrolled subtypes of aggression (Nelson & Trainor, 2007). When studying the neurobiology of the ODD symptom clusters and aggressive subtypes, the role of comorbidity with ADHD and other disorders (anxiety, depression) needs to be taken into account. With respect to ADHD, the present review clearly shows that neurobiological studies of ODD and CD often have been confounded by ADHD comorbidity. Only in a series of neuroimaging studies conducted by Rubia and colleagues (for a review see Rubia, 2011) has CD been studied separately from ADHD and in contrast with ADHD.

The conceptualization of ODD and CD as separate disorders also has consequences for research in the neurobiology of CD. The hierarchical rule of *DSM-IV-TR* precludes a diagnosis of ODD when the criteria of CD are met. In other words, when a subject fulfills criteria of both ODD and CD, the diagnosis of CD is given. Thus, in studies with subjects diagnosed with CD, it is unclear whether participants are comorbid with ODD or not. This may be important because CD subjects who fulfill ODD criteria may have symptoms belonging to the irritability factor of ODD, and the neurobiology of this CD subgroup may be quite different from the neurobiology of CD subjects who do not fulfill ODD criteria. Therefore, treating ODD and CD as fully separate disorders that may also be comorbid would be helpful for understanding the neurobiology of CD. Releasing the hierarchical rule that precludes a diagnosis of ODD when CD criteria are met is presently an issue that is being considered as a possible revision of *DSM-IV* criteria in developing *DSM-V* (Pardini, Frick & Moffitt, 2010). Besides, the neurobiology of CD may be furthered by making the distinction between proactive/controlled and reactive/undercontrolled aggression symptoms and by investigating the role of comorbidity with ADHD, anxiety, and mood disorders. There is also a need to further investigate the specific role of psychopathic or CU traits, and there is no clear reason why this should not be done in ODD as well.

The conceptualization of neurobiological systems in terms of functions allows for the inclusion of environmental factors to better understand the development of ODD and CD. The distinction between the three mental domains may help generate hypotheses to be tested in longitudinal developmental studies on ODD and CD in which measures of the corresponding neurobiological systems and environmental measures are both included. First, as children learn to refrain from inappropriate behaviors based on aversive conditioning, low punishment sensitivity resulting in fewer associations between inappropriate behaviors and punishment may put children at risk of developing the defiant/headstrong behavior cluster symptoms of ODD, the proactive/controlled aggression symptoms of CD, and CU traits, especially when environmental risk factors are involved such as inconsistent and harsh discipline. Second, low reward sensitivity may result in compromised stimulus-reinforcement learning of appropriate behaviors. This is an important issue that is often overlooked and that may help answer the question why some children developing ODD and CD do not learn to substitute inappropriate behaviors with appropriate behaviors, as developing children typically do. Of course, in such research the parenting characteristics in the families of these children need to be included as well. In addition, low reward sensitivity associated with an unpleasant affective state may put adolescents with ODD or CD at risk of substance dependence as the use of substances results in an intensively positive affective state that is difficult to achieve through the regular sources of pleasure. This risk is specifically enhanced when these adolescents become involved in deviant peer groups. Third, decreased cognitive control in children and adolescents may result in the irritability cluster of ODD symptoms, reactive/undercontrolled aggressive symptoms of CD, and risk-taking behaviors as a result of deficient decision making, especially when parents of these children and adolescents do

not present appropriate models of coping in situations of frustration because of difficulties in self-control themselves.

In conclusion, when compared with research on the neurobiology of ADHD, our knowledge of the neurobiology of ODD and CD is quite limited. Nevertheless, substantial progress has been made during recent years, specifically with respect to neuroimaging. The consideration of the functions of the various neural systems as described in the present framework of three mental domains may further our understanding of the etiology of these disorders.

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