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Neural Mechanisms of Low Trait Anxiety and Risk for Externalizing Behavior

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The Oxford Handbook of Externalizing Spectrum Disorders (*Forthcoming*)

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Abstract and Keywords

High trait anxiety and its neural substrate (the behavioral inhibition system [BIS]) are linked frequently to internalizing disorders. The authors propose that low BIS activity and reactivity (including reduced arousal and reduced attention) contribute to externalizing disorders. They argue that the BIS contributes to externalizing disorders largely through its prefrontal components, with more indirect effects on hippocampus and other subcortical components. BIS contributes to attention-deficit/hyperactivity disorder (ADHD) and similar symptoms in phenylketonuria (PKU) largely via its prefrontal components; conduct disorder through prefrontal and temporal components; and psychopathy through prefrontal, temporal, and amygdalar components. Furthermore, neurological damage to brain regions involved in more than one externalizing disorder underlie comorbidity among them. The authors propose that frontal and subcortical BIS dysfunction acts synergistically with other dysfunctional neural systems to generate externalizing disorders, and the variation in patterns of neural dysfunction accounts for phenotypic differences across externalizing disorders and their subtypes.

Keywords: behavioral inhibition system, attention-deficit/hyperactivity disorder, conduct disorder, psychopathy, externalizing disorders, anxiety

Introduction

Trait anxiety is a term that is most often linked to internalizing disorders. The most recent description of its key neural substrate, the behavioral inhibition system (BIS), focuses on anxiety as a consequence of high sensitivity of the septo-hippocampal system (Corr & McNaughton, 2012; McNaughton & Corr, 2004, 2008). By contrast, externalizing disorders are more often attributed to dysfunction in reward systems related to the behavioral approach system (BAS). However, the normal distribution of trait anxiety as a personality characteristic in the population suggests that abnormally low BIS sensitivity should be just as disadvantageous as abnormally high BIS sensitivity. Externalizing disorders, then, may involve either low sensitivity of the BIS, high sensitivity of the BAS (e.g., impulsivity; see Beauchaine, 2001; Beauchaine, Gatzke-Kopp, & Mead, 2007), or both. Importantly, the BIS controls not only behavioral inhibition but also arousal and attention, with key implications for externalizing disorders.

Our extension of the voluminous BIS literature to externalizing disorders is speculative in parts. Nevertheless, we believe that the general framework outlined here can illuminate the complex roots of these disorders, advance development of detailed theories of externalizing spectrum disorders, and explain phenotypic variation—including why these disorders share comorbid features.

The BIS

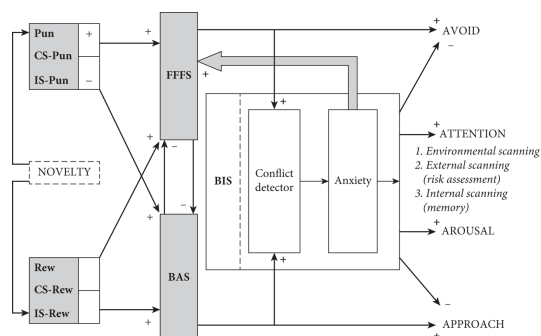
The concept of the BIS (Gray, 1975) originated in the fact that inhibition of behavior by aversive stimuli (e.g.,

approach–avoidance conflict) is sensitive specifically to anxiolytic drugs. Gray (1977) reviewed an extensive literature on behavioral effects of anxiolytics (i.e., barbiturates, alcohol, and benzodiazepines) on a wide range of behaviors assessed during reward, passive avoidance, classical conditioning of fear, escape, one-way active avoidance, two-way active avoidance, frustrative nonreward, discrimination learning, intermittent schedules in the Skinner box, reduction of reward, after effects of reward, and after effects of aversive stimuli. Across these diverse paradigms, anxiolytics did not impair simple approach or simple active avoidance behavior but did impair inhibition of prepotent behavior (passive avoidance) produced by approach–avoidance conflict (i.e., in the presence of conditioned signals of punishment). Gray concluded that a single system (i.e., the BIS) mediated anxiolytic-sensitive behavior and anxiolytic-sensitive autonomic reactions. Its key outputs were inhibition of prepotent behavior, increments in arousal, and increments in attention.

Defining anxiety in terms of the behavioral effects of anxiolytics was Gray's "philosopher's stone" (Corr, 2008). Although this approach ran the risk of tautology, its predictive value has now been confirmed in two ways. First, development of an ethological distinction between fear and anxiety (first extracted as different clusters of response and then identified as reactions to an immediate predator or uncertain threat, respectively) allowed for testing and confirmation of the proposal that anxiety, but not fear, is sensitive to anxiolytic drugs (Blanchard & Blanchard, 1990a, 1990b; Blanchard et al., 1997; for a review, see Gray & McNaughton, 2000). Second, the classical (γ -aminobutyric acid [$GABA_A$]) anxiolytic drugs that were used to develop the theory had side effects, such as anticonvulsant, muscle relaxant, and addictive actions, which may have accidentally given rise to the neural effects fundamental to the theory. However, serotonergic anxiolytic drugs, developed after the theory was proposed, shared none of these side effects yet retained the theoretically key neurophysiological effects of more classical anxiolytic drugs on hippocampal θ rhythm (McNaughton, Kocsis, & Hajós, 2007). They also shared key components of their behavioral profile in animal tests (for a review, see Gray & McNaughton, 2000). The predictive value of hippocampal θ was extended recently to pregabalin (Siok, Taylor, & Hajós, 2009)—a distinct third class of anxiolytics. Furthermore, a human scalp electroencephalogram (EEG) analogue of this anxiolytic-sensitive θ was demonstrated recently. This is a conflict-specific rhythmic activation that is sensitive to both classical and novel anxiolytic drugs (McNaughton, Swart, Neo, Bates, & Glue, 2013) and thus can be used as a specific measure of BIS sensitivity in humans.

The BIS controls processes that ultimately generate anxiety. The BIS inhibits conflicting prepotent behaviors, engages risk assessment, and elicits scanning of memory and of the environment. All of these function to resolve concurrent goal conflict. The paradigmatic example of its action is generation of anxiety by concurrent and equivalent activation of fear (or frustration) and approach systems; that is, approach–avoidance conflict. Goal conflict is resolved by increasing, through recursion in hippocampal-cortical loops, the negative valence of stimuli (held in cortical stores) until resolution occurs through either (a) avoidance, or if safety signals are detected in the concurrent scanning of the environment and memory stores, (b) approach (Gray & McNaughton, 2000). The main EEG signature of this recursive process is the θ rhythm, which is present when humans are engaged in emotionally salient personal rumination (e.g., Andersen et al., 2009; Moore, Gale, Morris, & Forrester, 2006; Moore, Mills, Marsham, & Corr, 2012).

Approach, Avoidance, Conflict, and Personality



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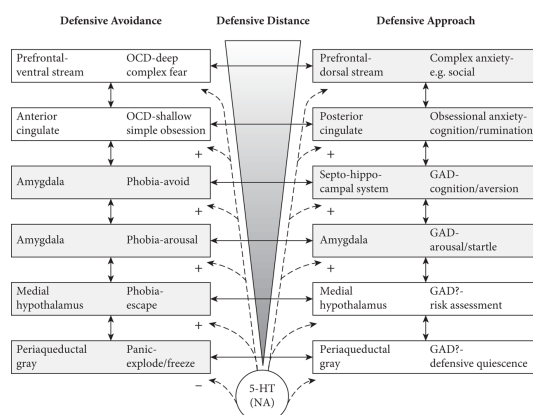
Figure 1 Overall relation of the behavioral inhibition system (BIS), fight-flight-freeze system (FFFS), and behavioral approach system (BAS). As indicated, the simplest way to activate the BIS is concurrently to

activate the FFFS and the BAS (i.e., face the animal with an approach–avoidance conflict). In this case, both simple approach and simple avoidance will be inhibited and replaced with environmental scanning (in the form of altered attention), external scanning (risk assessment behavior), and internal scanning of memory. Note that all of these scanning operations are aimed at detecting affectively negative information and involve an increase in the salience of such information. As a result, a secondary consequence of activation of the system is normally a shift of the balance between approach and avoidance tendencies in the direction of avoidance. The inputs to the system are classified in terms of the delivery (+) or omission (–) of primary rewards (Rew) or punishers (Pun) or conditional stimuli (CS) or innate stimuli (IS) that predict such primary events. (Adapted from Gray & McNaughton, 2000.)

Behavioral inhibition system theory describes “state” interactions among three motivation/emotion systems that control approach, avoidance, and approach–avoidance conflict, respectively (see Figure 1). The simple assumption that each of these systems can have a long-term “trait” sensitivity (reactivity) to its inputs (Gray, 1970) resulted in the reinforcement sensitivity theory (RST) of personality (Gray & McNaughton, 2000; McNaughton & Corr, 2004, 2008; for a summary see Corr, 2008). In more formal terms:

1. The fight-flight-freeze system (FFFS) mediates reactions that function to remove the animal from aversive stimuli of all types, conditioned and unconditioned (including frustrative reactions to omission of expected appetitive stimuli). The FFFS mediates fear, not anxiety. Critically, anxiolytic drugs (i.e., those lacking antipanic and antidepressant actions) do not affect the FFFS, but panicolytic drugs do. The associated personality trait is fear proneness, involving a greater tendency to avoidance/escape. The FFFS is composed of a hierarchy of neural modules. The neural level of a module is determined by the immediacy of threat—more formally, its *defensive distance* (Blanchard & Blanchard, 1990a; Blanchard, Griebel, Henrie, & Blanchard, 1997).
2. The BAS mediates reactions that function to bring the animal closer to appetitive stimuli of all types, conditioned and unconditioned (including relief reactions to safety signals). The associated personality traits are optimism, reward orientation, and (especially in very high BAS-active individuals) impulsivity. The BAS also appears to be organized hierarchically (Gray & McNaughton, 2000), but this organization—and its possible behavioral match “appetitive distance”—has not been subjected to the same detailed analysis as the FFFS.
3. The BIS is responsible for detection and resolution of goal conflict in very general terms (approach–approach, avoidance–avoidance, and approach–avoidance; see earlier discussion). Behavioral inhibition system outputs have evolved to resolve conflict by either permitting an animal to *enter* a dangerous situation (e.g., via cautious “risk assessment” behavior and scanning of memory) or to withhold entrance (e.g., via an increased level of avoidance). The function of BIS-generated behavior is to allow approach in potentially dangerous environments. This process involves blocking both approach and avoidance behaviors when neither are adaptive (this can result in “defensive quiescence,” which is similar to but involves a body posture distinct from freezing) and replacing them with risk assessment behaviors. The BIS is comprised of a hierarchy of neural modules parallel to those of the FFFS (McNaughton & Corr, 2004) and is affected by anxiolytic drugs, including those that lack antipanic and antidepressant actions (Blanchard & Blanchard, 1990b; Blanchard et al., 1997). A schematic of the FFFS, BAS, and BIS and their functional interactions appears in Figure 1.

Neurobiology of the BIS



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Figure 2 The defense system viewed in two dimensions and its relation to anxiety-related disorders. Two

parallel streams control behavior when danger is to be avoided or approached, respectively. Each has a hierarchy, with higher levels engaged at greater defensive distance. The separation of the amygdala into separate components and the placement of one component under the septo-hippocampal system is a modification of the equivalent diagram in Gray and McNaughton (2000). All parts of the system receive both fast, poorly digested (dirty) and slow well-digested (sophisticated) sensory information. The lowest level of the system is held to deal with the most basic response to threat: panic. This can be viewed as a normal response, a pathological symptom of other disorders, or the result of primary panic disorder depending on the cause of activity. Activity in response to threat or from other causes should always be seen as distributed across several parts of the system simultaneously both because of connections between the structures (double-headed arrows) and indirect links resulting from conditioning. Symptoms should not be equated with disorders, but we have assigned the control of particular symptoms/disorders predominantly to specific areas. GAD, generalized anxiety disorder; OCD, obsessive compulsive disorder.

The FFFS, BAS, and BIS each contain complex elements that are hierarchically structured but in a manner that yields integrative simplicity. There is more immediate “quick and dirty” control by lower neural levels and more complex or distant “slow and sophisticated” control by higher levels (LeDoux, 1994). Parallel activation of multiple parts of each system is followed by interactions between modules that “select” a particular level for control of current behavior. Urgent threat activates the periaqueductal gray and results in panic or attack, unless a module controlling escape is activated. If this happens, periaqueductal gray outputs (but not its activation) are inhibited. Similarly, activation of a module controlling avoidance inhibits escape behavior, replacing it with avoidance. Control of defensive behavior by the FFFS and BIS results in the two-dimensional system depicted in Figure 2 (McNaughton & Corr, 2008). The range from top to bottom of the FFFS and BIS maps onto a dimension of “defensive distance” (Blanchard & Blanchard, 1990a, 1990b). Loosely speaking, this represents urgency of perceived threat. Separation of the FFFS and BIS reflects a dimension of “defensive direction” either to avoid the source of danger (FFFS: fear) or to approach it cautiously (BIS: anxiety).

A number of components of the BIS are involved in psychological processes implicated in psychiatric disorders. First, detection of simple goal-related conflict is likely to have its main locus in the hippocampus but can involve all levels of the BIS, ranging from the periaqueductal gray, medial hypothalamus, amygdala, septo-hippocampal system, and posterior cingulate to the prefrontal dorsal stream (see Figure 2). Second, general attentional processing and arousal are modulated by aminergic neurotransmitter systems, principally acetylcholine and norepinephrine, with avoidance and behavioral inhibition modulated serotonergically. Third, more specific attentional/arousal processes, particularly fear-potentiated startle, are affected by amygdalar function. Critically for psychiatric disorder, output from the BIS increases negative cognitive biases and aversion, sending feedback to whatever aversive goal-linked areas provided the conflict input.

We should emphasize that two behavioral processes often linked to anxiety are not controlled by the BIS, as demonstrated by their insensitivity to anxiolytics. The first is obsession/compulsion. Although obsessions and compulsions can generate anxiety, they do so only if the compulsions conflict with other goals. Compulsions themselves (such as handwashing to escape infection) are generally simple avoidance behaviors (Rapoport, 1989) and are controlled by the FFFS (see Figure 2). These can, therefore, be normal behaviors, but, when excessive and when they interfere with functional behaviors, they represent obsessive-compulsive disorder (OCD). The second is action-stopping. This can be generated by output of the BIS to the motor system, which leaves activation of conflicting goal representations intact but prevents either of them from capturing the motor system. However, action-stopping can also be generated by stimuli that do not involve the BIS, and therefore it is not affected by anxiolytic drugs (McNaughton, Swart, Neo, Bates, & Glue, 2013). Action-stopping is often controlled by the inferior frontal gyrus or, under very tight time constraints, the presupplementary motor cortex (Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003; Floden & Stuss, 2006). There is evidence that the inferior frontal gyrus may be a target of BIS output to generate conflict-related stopping (Neo, Thurlow, & McNaughton, 2011; Shackman et al., 2009).

Personality and Clinical Comorbidity

Extremely high BIS sensitivity should generate levels of trait anxiety that rise to a level of clinical disorder. More specific personality predispositions (e.g., obsessiveness, panic proneness) depend on functions of particular component parts of the FFFS or BIS, whereas more general changes in defensive reactions (e.g., neuroticism, emotionality) may arise from the fact that the FFFS and BIS are both modulated by diffuse monoaminergic neural inputs and stress hormones. Long-term variation in this systemwide modulation alters *reactivity* of all parts of each

system. Critically, anxiolytic drugs (treated here as a proxy for a hormone that controls personality) alter defensive distance (i.e., magnitude of perceived threat and thus the level of the BIS that is in control of behavior) generally rather than altering any single module and, thus, any single behavior. That is, they manipulate a factor of anxiety proneness.

Benzodiazepines, which have strong anxiolytic properties, operate by modulating sensitivity of GABA_A receptors without activating them. The benzodiazepine site is likely to be the target of circulating “anxiety-specific” hormones. Importantly, some benzodiazepines can increase sensitivity to GABA, whereas others can decrease sensitivity. There is evidence for endogenous compounds that bind to benzodiazepine receptors and that may have such a hormonal action (see Gray & McNaughton, 2000). We might expect, then, that longer term increases in the reactivity of such a system could lead to a personality factor that would influence specific morbidity for generalized anxiety disorder and (unlike changes in the serotonin system) would not affect morbidity for OCD, panic disorder, or depression (although it would affect the extent to which anxiety resulted from and so was comorbid with those conditions). Conversely, longer term decreases in reactivity could provide vulnerability to a range of disorders of insufficient anxiety; namely, externalizing disorders. From this view, both extremely high and extremely low levels of anxiety would be dysfunctional—a proposition consistent with the maintenance of a normal distribution of this trait in the general population.

Serotonergic anxiolytics operate by binding to the 5-HT_{1A} receptor. The normal ligand for this receptor is serotonin, which is also released concurrently onto other 5-HT receptors. An endogenous, 5-HT_{1A}-specific hormone is unlikely. Changes in the 5-HT system (similar to effects of serotonin-selective reuptake inhibitors such as fluoxetine [Prozac]) would therefore be expected to produce concurrent variation in both the FFFS (trait fear) and the BIS (trait anxiety), thus generating a factor with broad-ranging effects, such as neuroticism.

These proposed effects of endogenous benzodiazepine and endogenous serotonin variation are broadly consistent with clinical and genetic data. For example, structural modeling of patients' ($n = 8,098$) symptoms (Krueger, 1999) extracts a higher order internalizing (e.g., depression and generalized anxiety disorder) factor that breaks down into lower order factors of “fear” and “anxious-misery,” which share about 50% of their variance (as do questionnaire measures of trait anxiety and neuroticism). Similarly, Kendler, Prescott, Myers, and Neale (2003) examined the genetic structure of 10 major psychiatric disorders in a sample of 5,600 twins. Genetic risk for internalizing disorders broke down into an “anxious-misery” factor (i.e., depression and generalized anxiety disorder) and a specific “fear” factor (i.e., animal and situational phobia). Their definition of fear may have been too narrow to capture the full range of FFFS functions, but their data suggest that some anxiety-related disorders are separate from at least some fear-related ones.

The BIS and Externalizing Disorders

Investigators have long argued that establishing links between psychological disorders and temperament/personality factors may be useful in advancing our understanding of diatheses, etiology, progression, prognosis, and treatment (e.g., Costa & Widiger, 1994; Harkness & Lilienfeld, 1997; Krueger & Tackett, 2003, 2006; Nigg et al., 2002; Tackett, 2006; Watson, Clark, & Harkness, 1994; Widiger & Trull, 1992; Widiger, Verheul, & van den Brink, 1999). The goal is to isolate and characterize neural processes that underlie these long-term stabilities in behavior (i.e., “personality”) with regard to specific disorders.

From the perspective of RST, motivational dysfunctions involved in externalizing disorders should result from distortions of operation of the FFFS, BAS, and/or BIS. Dysfunctional behavior can result from dysfunction of one of these systems in isolation but will also often result from dysfunction of systems acting in combinations (see, e.g., Beauchaine, 2001; Beauchaine, Katkin, Strassberg, & Snarr, 2001). In conditions involving a pure excess of approach behavior, the BAS is likely to be functionally dominant (see Zisner & Beauchaine, this volume). However, the BIS is often the core system because it is involved in the *regulation* of goal conflict detection and resolution. BIS dysfunction causes failure of inhibition of inappropriate behavior, which can be as important as excessive approach in generating externalizing symptoms. Also, as discussed later, the BIS plays important roles in attention, arousal, and cognitive processing (particularly negative cognitive biases). These often play central roles in the clinical presentation of externalizing disorders, and a dysfunctional BIS contributes motivation-driven dysfunction in these processes, thus supplementing dysfunction of primary systems such as attention.

All the externalizing disorders appear to involve BIS subprocesses (primarily in the frontal cortex) that normally act together with subcortical subprocesses to comprise “the BIS” as a whole. Although dysfunction or personality variation can be specific to the BIS, its outputs cannot be seen as occurring in isolation from the FFFS and BAS. The BIS is activated when there is goal conflict (i.e., when the BAS and FFFS are equally activated and require opposite behavior). Variation in or dysfunction of either the BAS or FFFS will therefore shift when the BIS is activated. Likewise, activation of the BIS leads to heightened activity in the FFFS. As discussed later, operations of these separate components can generate the complex motivations, emotions, and behaviors seen in externalizing disorders. We argue that variation in the precise pattern of dysfunction within not only the BIS, but also within the BAS and FFFS, is, in part, what differentiates among externalizing disorders. To substantiate this claim, we need to consider variation in dysfunction, particularly in prefrontal components of the BIS that, until now, have been poorly specified. In particular, its primary prefrontal component—the dorsal stream—is a substantial and highly differentiated part of the human cortex, all of which is represented by a single box in Figure 2.

ADHD and Phenylketonuria (PKU)

ADHD is one of the most common childhood disorders (see Hinshaw, this volume). At the broadest level, there are two primary forms: inattentive (ADHD-IA; e.g., distractibility and difficulty focusing on tasks for a sustained period) and hyperactive/impulsive (ADHD-HI; e.g., fidgeting, excessive talking, and restlessness). When present together, these symptom sets comprise ADHD combined type (ADHD-CT, which has now been downgraded to combined “presentation” in the *Diagnostic and Statistical Manual of Mental Disorders [DSM-5]*; see Drabick, Steinberg, & Hampton, this volume). The comparability of processes underlying ADHD symptoms and personality is supported by longitudinal studies that demonstrate that ADHD is fairly stable from childhood to adulthood, with more than half of those diagnosed in childhood continuing to have the same diagnosis in adulthood (Biederman et al., 1993). ADHD is highly heritable (Biederman, 2005; Faraone & Doyle, 2001; Hinshaw, this volume).

For our purposes, it is instructive to consider phenylketonuria (PKU) in parallel with ADHD. PKU is a well-known, genetically caused metabolic disorder with a radically different etiology (i.e., a double recessive gene) to that of ADHD. However, residual symptoms of PKU after dietary treatment overlap with features of ADHD and include both primary (sensory, motor) and executive (attention, working memory, planning) functions (for review, see Stevenson & McNaughton, 2013). Antshel and Waisbren (2003) described PKU as showing “ADHD symptom expression,” and there is a high prevalence of diagnosed ADHD among children with PKU (Antshel, 2010). Importantly, ADHD and PKU share a common major deficit in *failure of inhibitory control*, and it is here that the potential contribution of the BIS looms largest.

Both disorders have highly overlapping abnormalities of the frontal lobe and of the white matter connections between the frontal lobe and subcortical regions, such as the basal ganglia (Castellanos et al., 2002; Sowell, Toga, & Asarnow, 2000): “The most replicated alterations [in ADHD] ... include significantly smaller volumes in the dorsolateral prefrontal cortex, caudate, pallidum, corpus callosum, and cerebellum” (Seidman, Valera, & Makris, 2005, p. 1263). There are indications that reduced volume in dorsolateral prefrontal cortex, middle frontal gyrus, anterior cingulate cortex, inferior parietal cortex, temporal cortex, basal ganglia, and cerebellum remain in place during adulthood (Proal et al., 2011; Seidman et al., 2011; but see also Amico, Stauber, Koutsouleris, & Frodl, 2011). These structures are involved in motor control, reward processing, executive functioning, and inhibition of motor behavior.

Both ADHD and PKU are also associated with disturbances in dopaminergic (see Stevenson & McNaughton, 2013) and noradrenergic systems (e.g., Pliszka, 1998). We argue that, when integrating the neurology of all the externalizing disorders, reduced cortical dopamine (DA) results in failures to regulate subcortical DA that, in turn, produce impulsivity. Early results suggested increased DA transporter densities in the striatum (Krause, Dresel, Krause, Kung, & Tatsch, 2000), but, more recently, decreases in the striatum and nucleus accumbens, which may be partially lateralized (Volkow, Swanson, & Newcorn, 2010; Volkow et al., 2009), have been reported. Reduced DA, expressed both in mesocortical input to the dorsolateral prefrontal cortex and mesolimbic input to the nucleus accumbens, may account for some cognitive impairments in ADHD (Sonuga-Barke, 2005), as well as in PKU. But variations across individuals suggest “that additional pathology ... is necessary to account for the large differences in inattention observed” (Volkow, Wang, Newcorn, Fowler, et al., 2007, p. 1182; see also Volkow, Wang, Newcorn, Telang, et al., 2007).

Both ADHD (Beauchaine et al., 2001; Quay, 1997) and PKU (Stevenson & McNaughton, 2013) have been suggested to involve BIS dysfunction. With the possible exception of some hippocampal damage in PKU and some frontal-hippocampal disconnection in ADHD, the pattern of neurological disturbance suggests that both disorders involve damage to frontal rather than subcortical components of the BIS (Stevenson & McNaughton, 2013). Such relative frontal specificity of the BIS modules involved would be consistent with the common widespread frontal neuropathology in ADHD and PKU detailed in the previous paragraphs.

If low BIS sensitivity were the only dysfunction in an individual, we would predict (as illustrated in Figure 1) reduced behavioral inhibition (i.e., the capacity to inhibit prepotent goals and to resolve conflict by increased risk aversion), reduced attention (including both environmental and memory scanning), and reduced arousal. This set of symptoms covers a significant part of the description of ADHD-IA. However, there are both positive and negative features of the symptom profile that argue against any simple equation of ADHD-IA with global BIS dysfunction.

An example of a positive feature is stopping in the Stop-Signal Task (SST; Aron & Poldrack, 2006; Band, van der Molen, & Logan, 2003; Logan, Cowan, & Davis, 1984). It was predicted by the original BIS theory of ADHD (Quay, 1997) that affected children would show a longer stop signal reaction time (SSRT); that is, they would need more time for their inhibitory system to be effective in stopping the prepotent response. This hypothesis has been confirmed directly (Nichols & Waschbusch, 2004), and is consistent with related symptom variation in a nonclinical sample (Kooijmans, Scheres, & Oosterlaan, 2000). However, stopping behavior in the SST is not controlled by the BIS because it is not sensitive to anxiolytic drugs, despite their affecting concurrent goal conflict-related EEG activation (McNaughton et al., 2013). Stopping in the SST is controlled by the right inferior frontal gyrus (Aron et al., 2003), and, in people with ADHD, reduced activity in this area is linked to both poorer inhibition of “going” in the SST and to poorer inhibition of memory retrieval. The latter is likely to be the result of frontal-hippocampal disconnection (Depue, Burgess, Willcutt, Ruzic, & Banich, 2010). PKU deficits also appear to involve the inferior frontal gyrus, in addition to their similar involvement to ADHD in structures including the dorsolateral executive network (Christ, Huijbregts, de Sonnevle, & White, 2010).

An example of a negative feature is that, as noted earlier, as many as a third of children with ADHD have comorbid anxiety. If ADHD and anxiety simply reflect opposite poles of variation in global BIS function, this should not be possible. Comorbidity would be consistent with involvement of the BIS in ADHD if the observed anxiety arose from subcortical components of the BIS (such as the hippocampus and amygdala), whereas behavioral inhibition, arousal, and attention deficits in ADHD arise in prefrontal components (see Sauder, Beauchaine, Gatzke-Kopp, Shannon, & Aylward, 2012; Stevenson & McNaughton, 2013). It is important to re-emphasize that “the BIS” is not unitary. Rather, it represents a set of hierarchically organized processes (see Figure 2). In ADHD-IA, then, we appear to have dysfunction of prefrontal components of the BIS, but not of either subcortical components or of the overall modulation of the entire system by endogenous benzodiazepines, serotonin, or noradrenaline. Importantly, prefrontal BIS dysfunction would be combined with: a) reduced DA-related reactivity to reward stimuli; and, b) with dysfunction of additional non-BIS prefrontal and dopaminergic circuits controlling stopping and other functions such as working memory (Beauchaine & McNulty, 2013; Sauder et al., 2012).

The combined type of ADHD requires a more complex application of RST (Gomez & Corr, 2014). ADHD-CT is associated not only with relatively low cognitive control (BIS–) but also with high positive and negative emotionality (BAS+, FFFS+, respectively). The combination of BAS+ and FFFS+ results both in the generation of a greater tendency to make responses in the absence of conflict and in much higher levels of motivation under conditions of conflict (when the BAS and FFFS are equally activated). Given a dysfunctional BIS, this strong motivational activation is accompanied by a general inability to switch attention and behavior when a prepotent response is present.

In this view, a dysfunctional BIS could be involved in all types of ADHD and PKU. However, it should be noted that, in a standard challenge task such as the SST, the BIS biomarker (McNaughton et al., 2013) would be abnormally low only in those with the ADHD-IA subtype (in which arousal is low). With the CT subtype, the insensitive BIS would be subjected (for any given value of normal stimulus parameters) to a higher level of conflicting BAS and FFFS input than would neurotypical controls; thus, its activation could well be equivalent to or higher than neurotypicals, whereas the capacity of that activation to inhibit relevant behaviors would be subnormal (because these behaviors are more than normally activated). This process could give rise to the combination of impaired motor inhibition and anxiety.

In sum, disrupted frontal components of the BIS could account for a proportion of observed deficits in behavioral inhibition and attention in all types of ADHD and PKU. Conversely, reduced dopaminergic functioning must account for a range of deficits unrelated to the BIS (see Beauchaine & McNulty, 2013; Beauchaine, McNulty, & Hinshaw, this volume, Zisner & Beauchaine, this volume). We have linked a number of features of ADHD to some combination of BIS, BAS, and FFFS dysfunction. However, given the extent of frontal pathology, including white matter pathology, other features certainly require more local explanations. Nonetheless, consideration of the operation of the BIS, BAS, and FFFS should reveal core underlying deficits that may help to explain a wide range of specific symptoms (e.g., inattention, hyperactivity, and dysregulation of behavior), as well as their comorbidities with other conditions.

Conduct Disorder (CD)

We have already suggested that ADHD-IA and ADHD-CT both involve BIS– deficits but differ in that the latter have additional BAS+ and FFFS+ deficits. “With respect to externalising disorders in childhood, Quay suggested that ADHD and CD reflect different problems in the functioning of the BAS and the BIS. ADHD is characterised by an underactive BIS, whereas CD is associated with a BAS that dominates over the BIS: when cues for both reward and punishment are present, CD children focus on cues for reward at the expense of cues for punishment” (Matthys et al., 1998, p. 644; see also Matthys, Vanderschuren, & Schutter, 2013). Children with comorbid CD+ADHD combine these two patterns to have an even greater imbalance between BIS– and BAS+ (Matthys et al., 1998). Notably, many studies of CD are confounded by ADHD comorbidity, and comorbid ADHD+CD may be particularly prone to progress to more severe forms of externalizing psychopathology (Beauchaine, Hinshaw, & Pang, 2010; Beauchaine & McNulty, 2013), including psychopathy (Gresham, Lane, & Lambros, 2000; Lynam, 1998). In considering the neurobiology of CD, it is therefore important to try, as far as practical, to contrast “pure CD” with “pure ADHD,” given that we can already expect overlap between the two, albeit not as extensive as that between ADHD and PKU. Notably, however, this is very difficult in practice because CD often develops from ADHD (see Beauchaine, McNulty, & Hinshaw, this volume).

Matthys et al. (2013) reviewed studies that included comorbid ADHD+CD and linked reduced punishment sensitivity in CD to dysfunction in stress responding, serotonin, noradrenaline, and amygdalar dysfunction (with the latter showing, in addition, reduced gray matter volume); reduced responding to incentives to dysfunction in sympathetic responses, DA (see later discussion), and orbitofrontal cortex (OFC) function; and impaired executive function (cognitive control) to dysfunction of the OFC, superior temporal cortex, anterior cingulate cortex, and posterior cingulate cortex.

Pure CD, but not pure ADHD, has been associated with insular, right OFC, occipital cortex, and hippocampal dysfunction (Lockwood et al., 2013; Rubia et al., 2009b, 2010). Occasional reports of involvement of the anterior cingulate and hippocampus in ADHD could be due either to inclusion of CD cases in the sample or to differences in the tasks used to test the populations. CD appears to show somewhat more involvement than ADHD in temporal and parietal areas (Rubia et al., 2008, 2009a, 2010), whereas ADHD shows somewhat more involvement in the inferior frontal gyrus, the dorsolateral prefrontal cortex, and the posterior cingulate (Rubia et al., 2008, 2009a, 2009b, 2010; but see Lockwood et al., 2013). Unlike ADHD, CD does not appear to involve the ventrolateral prefrontal cortex (Rubia et al., 2009a, 2009b).

DA dysfunction appears to contribute to CD (Matthys et al., 2013). However, there are very few studies that do not involve comorbid ADHD+CD. There is evidence for dopaminergic abnormality as a vulnerability to development of CD among those with ADHD (see Beauchaine & McNulty, 2013). The DA-4 receptor gene, DRD4, is linked to carefully selected cases of ADHD combined with CD, but this linkage is not detected in more mixed ADHD samples (Holmes et al., 2002), and DRD4 may interact with the DRD2 gene to generate these effects. Similarly, DAT1 (a DA transporter gene) does not appear to be directly linked to CD (Schulz-Helik et al., 2008) but appears to interact with a lack of parental engagement (whether positive or negative) to predict future CD among children with ADHD (Lahey et al., 2011). There are also single-gene variants (in, e.g., COMT, necessary for DA synthesis, and D β H, necessary for conversion of DA to noradrenaline) that do not appear to be linked strongly to CD in isolation but show nonlinear synergies in generating CD in combination (Grigorenko et al., 2010).

Psychopathy

The classic picture of psychopathy comprises features of apparently good adjustment (e.g., adequate intelligence, charm) with features of definitely poor adjustment (e.g., behavioral deviance, parasitic existence) and underlying dysfunctions, including behavioral deficits (acting on impulsive whims), cognitive deficits (e.g., poor judgment), emotional and interpersonal deficits (e.g., shallow emotions; lack of empathy, remorse, and shame; and insincerity), motivational deficits (poorly motivated antisocial behavior), and ego distortion (egocentricity). About 1% of the general population and between 15% and 25% of the prison population may have clinically significant psychopathic features (Hare, 1996). Importantly, however, not all or even most individuals with psychopathy are identified and diagnosed, and many live “normal” lives (Babiak & Hare, 2007; Cleckley, 1941). What they have in common is a failure to regulate behavior adaptively—especially in relation to detection of goal conflicts and their appropriate resolution. Thus, on the face of it, psychopathy would appear to involve significant BIS dysfunction (see Fowles, 1980).

In common with other externalizing disorders, psychopathy appears to involve frontal dysfunction but may include greater involvement of the temporal lobes. There are increases in callosal white matter and decreases in gray matter in prefrontal cortex (right orbitofrontal, right anterior cingulate, left dorsolateral), the superior temporal gyrus, amygdala, and hippocampus (Müller et al., 2008; Weber, Habel, Amunts, & Schneider, 2008; Yang & Raine, 2009), which suggests major involvement of frontal-temporal-limbic circuits (Wahlund & Kristiansson, 2009). Dorsolateral prefrontal, amygdalar, and hippocampal involvements are consistent with a dysfunctional BIS. As with the other externalizing disorders, the BIS is clearly not the only frontal system involved, and amygdala dysfunction appears to extend beyond simple behavioral inhibition in passive avoidance tasks. There is “less amygdala responding and less amygdala-orbitofrontal functional connectivity in response to fearful expressions in youths with psychopathic traits” (Finger et al., 2011, p. 153).

As with the other externalizing disorders, dopaminergic alterations are also implicated. Neurochemical and neurophysiological hypersensitivity to d-amphetamine has been observed in the mesolimbic DA reward system among individuals with psychopathy (Buckholtz et al., 2010). However, the effect of d-amphetamine may not be exclusively dopaminergic because d-amphetamine also releases serotonin and noradrenaline (West, Van Groll, & Appel, 1995), and both the serotonergic and noradrenergic systems are implicated in emotion processing (Bijlsma, de Jongh, Olivier, & Groenik., 2010; Hung et al., 2011) and startle reactivity (Koch, 1999). Similarly, orbitofrontal and caudate responses to reward presentation during passive avoidance are blunted in CD cases with high levels of psychopathy (Finger et al., 2011). This suggests general hypofunction of the DA system (with resultant increased rebound sensitivity to DA when it is released). Such rebound sensitivity could explain why antisocial individuals are particularly prone to abuse DA agonists (Fridell, Hesse, Jaeger, & Kuhlhorn, 2008). A positive feedback loop has been suggested in which “chronic intake of drugs of abuse produces cortical dopaminergic hypofunction and other changes in cortical neurobiology that lead to impaired ability to gate or modulate subcortical dopamine function” (Jentsch & Taylor, 1999, p. 384; see also our later discussion of externalizing disorders and DA, especially Figure 3).

Impulse control takes different forms in “primary” versus “secondary” psychopathy (Fowles & Dindo, 2006; Karpman, 1941, 1949; Lykken, 1995). This distinction suggests that different roles are played by the FFFS and BAS, in addition to the BIS. Primary psychopathy is related to innate fearlessness and impaired socialization (FFFS–). In contrast, secondary psychopathy is related to normal fear sensitivity but reckless and impulsive behavior (BAS+), often leading to increased negative affect, formerly termed “neurotic psychopathy” (Blackburn, 1979; Hare, 1970). As argued by Corr (2010), both subtypes may be characterized by BIS dysfunction, specifically impaired goal conflict detection and resolution processes, which leads to inflexible and maladaptive behaviors that are difficult to change due to response inflexibility when behavior is inappropriately controlled by only one system (e.g., the BAS).

The idea that the BIS is defective in psychopathy is not new (see Fowles, 1980), but it has not previously taken into account differentiation between the FFFS and the BIS. The vast majority of previous research has relied on the pre-2000 BIS theory (Gray, 1982), which postulated that the BIS is activated by conditioned stimuli for punishment and nonreward. This earlier theory was typically interpreted in terms of the BIS serving as the main system mediating most forms of punishment (except the unconditioned variety) relevant to human motivation. As a result, there has been an unfortunate conflation of and confusion between FFFS-fear and BIS-anxiety in psychopathy research. We can now use revised RST to dig deeper into possible motivational roots of psychopathy.

Lykken (1995) argued that the fearlessness of primary psychopathy is associated with an underactive BIS coupled

with normal levels of BAS reactivity, leading to maladaptive behavior via impaired processing of stimuli associated with potential threats or punishment. Lykken also argued that secondary psychopathy is associated with an overactive BAS but normal levels of BIS reactivity, leading to impulsive and reckless behavior. As a consequence, individuals with secondary psychopathy experience relatively high levels of negative affect given their increased exposure to adverse outcomes. This theory is consistent with experimental research revealing that individuals with primary, or true, psychopathy may be differentiated from nonpsychopathic controls by a number of key features, especially autonomic underreactivity (e.g., as measured by electrodermal activity) to anticipated aversive stimuli (e.g., electric shock). Such data lend support to the hypothesis that individuals with primary psychopathy have an underreactive BIS and are generally low in fear/anxiety (see Fowles, 1980). As noted earlier, differentiation of fear and anxiety in these studies was not made clear. Indeed, Lykken related primary psychopathy to low fear, and then related low fear to the BIS, not the FFFS (see Fowles & Dindo, 2006, p. 13).

Research shows that, in general, individuals with psychopathy, when compared with controls, have higher scores on questionnaires designed to assess the strength of the BAS and lower scores on those designed to assess the strength of the BIS (e.g., Book & Quinsy, 2004). For example, among prison inmates ($n = 517$ males), Newman et al. (2005) tested Lykken's hypothesis by classifying individuals as either psychopathic or nonpsychopathic using the Psychopathy Checklist-Revised (PCL-R; Hare, 2003). Individuals with primary psychopathy had significantly lower BIS scores than their nonpsychopathic counterparts (as predicted by Lykken, BAS scores did not differ). In addition, individuals with secondary psychopathy had significantly higher BAS scores (also as predicted by Lykken), but their BIS scores were more inconsistent. Although these results may be interpreted as showing that individuals with psychopathy (especially primary) are underreactive to aversive stimuli, recent research suggests that their behavior may be better accounted for in terms of goal conflict detection and processing.

These data reveal that individuals with psychopathy are *not* always insensitive to punishment; rather, situational factors play a role (e.g., Newman & Kosson, 1986). In support of this claim, cognitive deficits are found using nonemotional stimuli (Newman et al., 1997). Such findings suggest that individuals with psychopathy are relatively unresponsive to contextual cues that are peripheral to their dominant response set (i.e., primary task), irrespective of whether the task involves emotional stimuli or not (Newman, Curtin, Bertsch, & Baskin-Sommers, 2010).

In a major re-evaluation of BIS theory in psychopathy, Wallace and Newman (2008) argued that individuals with psychopathy manifest disinhibition (i.e., decreased ability to regulate behavior to avoid adverse consequences) in situations in which avoidance of an adverse outcome requires overriding a prepotent response or modifying an existing behavioral goal. For those with primary psychopathy, selective attention is not appropriately reallocated in an automatic manner to processing of stimuli that are unrelated to their attentional focus. This conclusion is consistent with the finding that individuals with primary psychopathy do not have a general deficit in attentional focus: they perform as well as controls when task-specific stimuli are within their attentional focus. Rather, they lack the ability to shift their focus of attention when it has been captured by dominant stimuli in the environment. These may well be reward-related stimuli, but the issue is not that this subgroup is necessarily highly reward-oriented (which seems more of a problem with secondary psychopathy). This line of evidence suggests that, for individuals with primary psychopathy, there is an underactive FFFS (thus their low fear) and a dysfunctional BIS (thus their failure to modulate behavior in goal conflict situations). For individuals with secondary psychopathy, on the other hand, there is a dysfunctional BAS (once again with a dysfunctional BIS but perhaps with a normally functioning FFFS).

Blair, Mitchell, and Blair (2005) treat the BIS as if it is a single fear system and argue that, like other such theories, the BIS theory fails to account for the fractured relationship of different aspects of defensive behavior in psychopathy. However, they do not take into account either the FFFS/BIS distinction or the fact that both FFFS and BIS are hierarchically organized. Their model of psychopathy treats it as having three main strands: emotional dysfunction, antisocial and aggressive action, and impaired passive avoidance (Blair et al, 2005, fig. 8.1, p. 111). As with ADHD, these first two strands result from dysfunction of systems other than the BIS. At first glance, a passive avoidance deficit could indicate a general failure of the BIS. However, in generating their neural model of psychopathy, Blair et al. treat the main prefrontal component of the BIS (the dorsolateral PFC) as intact (which is consistent with a capacity of individuals with psychopathy to undertake planning but ignores the reported deficits in the left dorsolateral PFC) and focus on the amygdala as a primary source of deficit. In this context, it is important to note that one of the primary deficits they use to link psychopathy to the amygdala is fear-potentiated startle. This is a key test on the basis of which the amygdala was included in the BIS (Gray & McNaughton, 2000). Considerable

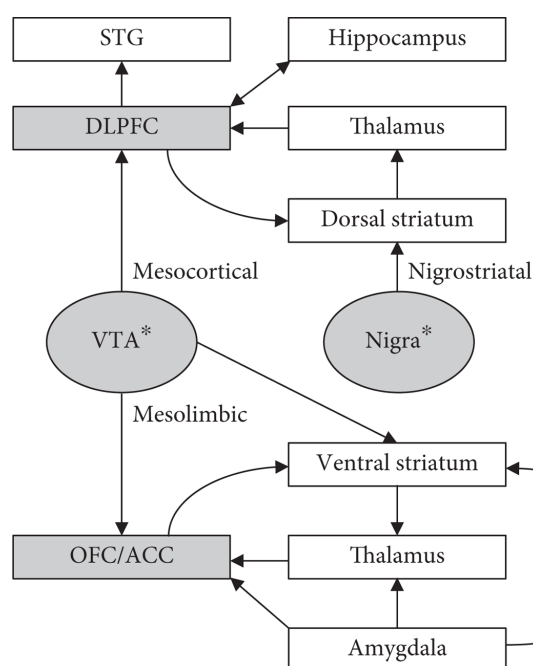
evidence points toward individuals with psychopathy having both impaired startle potentiation to aversive stimuli (e.g., Benning, Patrick, & Iacono, 2005; Herpertz et al., 2001; Patrick, Bradley & Lang, 1993; Vaidyanathan, Hall, Patrick, & Bernat, 2011) and amygdala dysfunction (see Blair, 2010; Gao, Glenn, Schug, Yang, & Raine, 2009).

An impaired BIS means that, in the context of goal conflicts, primary psychopathy will be associated with impaired ability to switch attention and modulate responses and, as a consequence, a failure to learn from exposure to aversive experiences (often such individuals do not even appreciate the significance of such experiences until it is too late). The BIS is unable to resolve this goal conflict for a number of reasons.

A dysfunctional BIS that fails to resolve FFFS–BAS conflict (or any other kind of goal conflict) would not provide appropriate cognitive control of executive and attentional resources sufficient to focus on salient stimuli in the environment. In addition, especially in secondary psychopathy where the BAS is overactive, a dysfunctional BIS would also fail to apply an effective brake on inappropriate prepotent behavior. As already discussed, inhibition of prepotent behavior and attentional control are different processes within the BIS.

Thus, according to the position adopted here, primary psychopathy is associated with an impaired FFFS and dysfunctional BIS (but a relatively normal BAS), and secondary psychopathy is associated with a hyperactive BAS and dysfunctional BIS. The role played by the FFFS in secondary psychopathy is difficult to discern because higher levels of negative affect experienced by individuals with secondary psychopathy may be entirely proportional to the degree of aversive stimuli they encounter.

The Neurology of Externalizing Disorders



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Figure 3 Simplified overview of systems involved in externalizing disorders (key components shaded). There is a largely shared direct dysfunction of dopamine (VTA/nigra), OFC/ACC, and higher levels of the behavioral inhibition system (BIS; DLPFC), with more indirect functional involvement of the amygdala and hippocampus. Psychopathy (and to a lesser extent conduct disorder) involves additional dysfunction (dashed boxes) of STG, hippocampus, and the amygdala. Attention-deficit/hyperactivity disorder (ADHD) involves disconnection of DLPFC from hippocampus (dashed arrow), whereas PKU involves hippocampal dysfunction. Dopamine systems have dysfunctional interactions with frontostriatal-thalamic circuits that can vary in detail among the disorders. ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; OFC, orbital frontal cortex; STG, superior temporal gyrus; VTA, ventral tegmental area. (Figure updated from two figures in Sonuga-Barke, 2005.)

Our review of ADHD, PKU, CD, and psychopathy suggests a partial overlap in terms of both the global symptom clusters and neurology. Much the same specific functional systems are implicated in each, with different degrees of involvement either in terms of their level of dysfunction or neural spread (i.e., the modules of each system that are

involved), both from disorder to disorder and from case to case. Similarly, much the same dysfunction in the global dopaminergic modulation of these systems occurs, again with some variation in degree and extent. This situation is summarized in Figure 3, which expands on the neurology of ADHD presented by Sonuga-Barke (2005).

Variation in the precise pattern of dysfunction (Table 1) presents as one or another type/subtype of disorder. In terms of the primary motivational systems on which we have focused, our global qualitative evaluations suggest differing patterns of contribution of the BAS, FFFS, and BIS to the different observed phenotypes, with some degree of BIS deficit serving as a common factor (Table 1: Phenotype; but see also our later discussion of DA). There is a fair degree of matching of these superficial phenotypic suggestions with the reported areas of cortical dysfunction. In particular, BIS dysfunction is suggested to be involved phenotypically in all cases, and, neurally, involvement of more frontal aspects of the BIS is observed with more moderate behavioral problems, with addition of more extensive temporal cortex (particularly superior temporal gyrus), amygdala (BIS-related components of which control fear-potentiated startle), and hippocampal involvement in terms of more problematic behavior. There is also a reasonable match between suggested phenotypic FFFS involvement and the extent to which anterior cingulate cortex and amygdala are involved. One potential exception here is that FFFS+ in the case of ADHD-CT appears to occur with a dysfunctional anterior cingulate cortex. One possibility is that this dysfunction is presenting as excessive output, or loss of inhibition, from the structure; the other possibility is that involvement of anterior cingulate is only occurring when ADHD is comorbid with CD (Rubia et al., 2009b, 2010) and does not contribute to FFFS-related changes. Another apparent exception is that the suggested BAS+ phenotype does not match in direction or pattern what would be expected in relation to the OFC. It may be that, again, dysfunction involves increased (particularly inappropriate) response generation; it may also be that BAS+ is driven more by subcortical (e.g., amygdala) involvement or by fairly directly related to changes in multiple DA systems.

Table 1 A Tentative Summary of Relations Between Motivational Phenotype and Neural Source.

Diagnosis		ADHD-IA	ADHD-CT	PKU	CD	PSYC-1	PSYC-2
Phenotype	BAS	0	+	as ADHD	+	0	+
	FFFS	0	+	as ADHD	0	—	0
	BIS	—	—	as ADHD	*	— —	— —
BAS Structures	OFC	0	0	0	—	—	—
FFFS structures	ACC	—	—	—	— —	— —	— —
	Amygdala	0	0	0	—	— —	— —
BIS structures	DLPFC	—	—	—	*	—	—
	Temporal	—	—	—	—	—	—
	STG	0	0	0	—	—	—
	Hippocampus	*	*	—	—	—	—
Other structures	White matter	—	—	—	0	+	+
	Insula	0	0	0	—	—	—
	MIFG	—	—	—	0	—	—
	Parietal	—	—	—	— —	0	0

Note that, with the exception of the amygdala and hippocampus, affected subcortical areas have been omitted, as have the posterior cingulate and the cerebellum. Subtypes of both ADHD and psychopathy (PSYC) have been assigned the same structural values (gray areas) because there is insufficient data to delineate their neural differences. Involvement of an area is indicated for major dysfunction (— —), dysfunction (—), minor dysfunction or disconnection (*), no reported involvement (0), and hyperactivity (+). ADHD-IA, ADHD inattentive subtype; ADHD-CT, ADHD combined subtype; PKU, phenylketonuria; PSYC-1, primary psychopathy; PSYC-2, secondary psychopathy; ACC, anterior cingulate cortex; BAS, behavioral approach system; BIS, behavioral inhibition system; DLPFC, dorsolateral prefrontal cortex; FFFS, fight-flight-freeze system; MIFG, medial or inferior frontal gyrus; OFC, orbital frontal cortex; STG, superior temporal gyrus.

Differences between disorders appear to result from variation in the relative involvement of different functional systems (such as the BAS, FFFS, and BIS) that reflect relatively minor variations in the position of the “geographic” boundaries of a relatively continuous area of pathogenesis. For example, the degree of BIS involvement appears to involve the spread of the boundary of dysfunction from dorsolateral prefrontal cortex to include the hippocampus and then the superior temporal gyrus and the amygdala. From this view, combinations of patterns of damage shown in Table 1 would be frequent and would present as one or another type of comorbidity (e.g., ADHD + psychopathy). Consistent with this view of a topographically variable zone of neural dysfunction, approximately 60% of children with ADHD also have a diagnosis of oppositional defiant disorder and/or CD (see Beauchaine, McNulty, & Hinshaw, this volume; Beauchaine et al., 2010; Levy, Hawes, & Johns, this volume). Conversely, as many as 70% of those in clinical samples with CD have comorbid ADHD (Beauchaine et al., 2001). In fact, it

appears that “comorbidity between CD and the hyperactive/impulsive subtype of ADHD ... represents a particularly virulent condition, characterised by a strong genetic loading, increased rates of aggression, and elevated risks of future antisocial behaviour ... and score [high] on measures of psychopathy” (Beauchaine et al., 2001, p. 610; see also Finger et al., 2011, p. 152; Gresham, Lane, & Lambros, 2000). Conversely, most of those with ADHD do not develop psychopathy because the neural level of the BIS involved is different (with primarily prefrontal involvement in ADHD and temporal cortex, amygdalar, and hippocampal involvement in psychopathy) and is combined with differences in other systems (notably opposite changes in white matter tracts such as the corpus callosum).

The idea of involvement of only some modules of the BIS in some disorders also accounts for the fact that, in ADHD samples, 30% can have comorbid anxiety disorders (Pliszka, 1998; Spencer, Biderman, & Wilens, 1999). In such comorbid cases, prefrontal hypofunction related to externalizing disorder may be counterbalanced by subcortical (e.g., amygdalar, hippocampal) hyperfunction in internalizing disorder. The lack of equivalent anxiety + psychopathy comorbidity would be accounted for, in this model, by the more substantial involvement of subcortical components of the BIS in hypofunction. Interestingly, in this context, the presence of internalizing disorder has been reported to involve a lesser reduction in hippocampal volume than that normally seen with externalizing disorders (Sauder et al., 2012). This pattern suggests an interaction at this key nodal point of the BIS of descending frontal and ascending subcortical influences. As with the hippocampus and the BIS, comorbid internalizing disorder has been reported to ameliorate reduced volumes of both the putamen and anterior cingulate cortex among those with externalizing disorders (Sauder et al., 2012). Consistent with this finding, comorbid anxiety appears to normalize the impaired inhibition seen in children with ADHD in the Stop Signal Task (Manassis, Tannock, & Barbosa, 2000). Moreover, effective inhibition is associated with resilience to development of both ADHD and CD in response to psychosocial adversity (Nigg, Nikolas, Friderici, Park, & Zucker, 2007).

The comparison of the etiologies of PKU and ADHD (Stevenson & McNaughton, 2013), in particular, suggests that quite different primary insults can result in distorted neural development that qualitatively converges on a common core pathology of particular frontal and temporal lobe structures (i.e., equifinality). PKU and ADHD involve opposite changes in plasma levels of large neutral amino acids but (through different routes) result in similar deficiencies in the brain of the precursors of DA and (perhaps to a lesser extent) serotonin. Similar final common-path arguments can be made for different etiological variants of ADHD (Swanson et al., 2007). Manipulation of DA transmission alters connectivity in default mode (frontal rather than hippocampal) frontoparietal and frontoinsular networks that include many of the structures listed in Table 1 (Cole et al., 2013). Changes in functional connectivity during development could lead to relatively consistent distortions of the affected areas, with the result that early impaired dopaminergic transmission would affect frontal components of the BIS via changes in the default mode network. However, “disordered DA” is not a simple unitary explanation for the pattern of developmental pathology. “The unbalanced presence of dopamine in various areas of the brain can result in a broad spectrum of outcomes, including cognitive, personality and psychiatric deficiencies. ... Variations in the COMT, MAOA, MAOB and DBH genes [can all be linked] to psychopathology in general and conduct problems in particular [and] can interact with each other enhancing nonlinearly the likelihood of a negative outcome” (Grigorenko et al., 2010, p. 160), with the locale and extent of DA disturbance depending of the precise genetic or environmental cause.

Separately from the etiological contribution of DA is the issue of the role of the overlapping dopaminergic deficits in externalizing disorders and the related pattern of OFC deficits, which contrasts with our phenotypic designation of BAS+. This issue is complex. Pre- and postsynaptic DA receptors may produce disparate functional outcomes resulting in an inverted-U response relationship, with both low and high DA levels resulting in the same pattern of dysfunction (see, e.g., Plichta & Scheres, 2014). Similarly, “paradoxical effects are observed, by which drugs improve performance in individuals with suboptimal DA and poor performance but impair performance in individuals with already optimized DA and good performance” (Cools, Sheridan, Jacobs, & D’Esposito, 2007). Loss of cortical DA can “lead to impaired ability to gate or modulate subcortical dopamine function and [an] associated augmentation in the control of behaviour by reward-related stimuli ... reduced basal dopamine turnover ... [and a] greater dopaminergic response to stress” (Jentsch & Taylor, 1999). In externalizing disorders, including drug abuse, there appears to be a “reward deficiency syndrome” in which deficiency in the DA system results in abnormal behavior (impulsivity, drug taking) that tends to result in some restoration of the level of dopaminergic input to the BAS that would normally have been produced by normal behavior (Blum et al., 2000). From this view, the designated BAS+ of Table 1 is correct in that the output from the BAS (i.e., approach) is increased as a greater amount of reinforcement is required to deliver normal levels of hedonic tone (in the form of DA). However, we must

enter a caveat in that whereas the quantitative output is increased, the qualitative output (in the form of adaptive response selection) is decreased. We can thus reconcile the reduced volume of frontal components of the BAS (which provide more limited machinery for goal selection and so a more restricted range of goal choices) with increased responding to those goals that are selected via reduced DA release into cortical areas and the tendency to opposite reactions of cortical and subcortical control of DA (Jentsch & Taylor, 1999).

Conclusion

Overall, externalizing disorders appear to arise from a number of quite different proximal developmental causes via largely similar neural substrates (DA, white matter, large neutral amino acids) that are selectively effective on largely similar prefrontal and temporal lobe circuits. All include damage to some, often frontal, components of the BIS, thereby sharing characteristics of low trait anxiety, at least in terms of higher order goals with relatively large defensive distances (McNaughton & Corr, 2004). Although only prefrontal modules of the BIS are involved, this allows for comorbidity of externalizing and internalizing disorders, resulting from opposite frontal and subcortical dysfunctions, respectively. In neonates, DA dysfunction appears to include generation of developmental abnormality of the targets of dopaminergic neurons in dorsolateral frontal and temporal regions of the default mode network, including the hippocampus, thus generating hypofunction of the BIS of varying extents.

All externalizing disorders also include some type of DA hypofunction that, paradoxically, underlies some forms of impulsivity that can be characterized as a quantitative (but not qualitative) increase in BAS function. Definitions and neural source may be important here because ventral striatal DA synthesis is more positively correlated with extravagance than with simple impulsivity (Lawrence & Brooks, 2014). We argue that the quantitative increase in BAS output is accompanied by impaired function of frontal components of the BAS, which results in a decrease of the functional quality of its outputs. (The same may well be true for FFFS+.) In addition, all externalizing disorders include non-BIS prefrontal dysfunction, which contributes to executive deficits.

On the basis of this view, the externalizing disorders share a general class of hypodopaminergic-related disturbances of neural development including hypofunction of the BIS, coupled with varying disturbances of the BAS, FFFS, and other (particularly executive-related) systems (Table 1). In cases where only higher levels of the BIS are compromised, hyperactivity of lower levels appears to provide a degree of counterbalance and potentially contributes to resilience. The BIS as a whole, therefore, appears to be important in relation to the risk of externalizing behavior, but it is clear that, in all cases, its failure of inhibition is acting in tandem with the excessive generation of inappropriate behaviors caused by hypodopaminergic impulsivity. Thus, excessive observed goal approach is the result of both an increased approach tendency and a reduced capacity for negative consequences to generate conflict and so prevent approach.

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