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Stimulus-Dependent Dopamine Release in Attention-Deficit/Hyperactivity Disorder

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Attention-deficit/hyperactivity disorder (ADHD) is related to an attenuated and dysfunctional dopamine system. Normally, a high extracellular dopamine level yields a tonic dopaminergic input that down-regulates stimuli-evoked phasic dopamine responses through autoreceptors. Abnormally low tonic extracellular dopamine in ADHD up-regulates the autoreceptors so that stimuli-evoked phasic dopamine is boosted. The authors propose that these boosted phasic responses yield hypersensitivity to environmental stimuli in ADHD. Stimuli evoking moderate brain arousal lead to well-functioning performance, whereas either too little or too much stimuli attenuate cognitive performance. Strong, salient stimuli may easily disrupt attention, whereas an environment with impoverished stimuli causes low arousal, which is typically compensated for by hyperactivity. Stochastic resonance is the phenomenon that makes a moderate noise facilitate stimulus discrimination and cognitive performance. Computational modeling shows that more noise is required for stochastic resonance to occur in dopamine-deprived neural systems in ADHD. This prediction is supported by empirical data.

Keywords: ADHD, dopamine, stochastic resonance, noise, model

Attention-deficit/hyperactivity disorder (ADHD) is believed to depend on a dysfunctional and hypoactive dopamine (DA) system (Sagvolden, Johansen, Aase, & Russell, 2005; Solanto, 2002). There are two functionally related DA components, called *tonic* and *phasic* DA response (Grace, 1995, 2001). Phasic DA responses are evoked by environmental stimuli and consist of high concentrations of DA in the synaptic cleft that is rapidly inactivated through DA reuptake. Tonic levels of DA in the extracellular fluid down-modulate the phasic responses through presynaptic inhibitory autoreceptors (Grace, 2000, 2001). Flexibility and rigidity are core states in maintaining goal-directed behavior. Handling flexibility and rigidity simultaneously places high demands on cognitive functioning and DA transmission in the brain. In this article we show that such demands, often difficult for children with ADHD to achieve, can be managed if the environmental conditions are adapted to ADHD requirements.

In this article we propose that abnormally low tonic DA levels in ADHD cause a relative up-regulation in the efficiency of phasic response, which behaviorally leads to *hypersensitivity* to environmental stimuli. Depending on the nature of the environmental stimulation, the phasic responses may lead to low, well-adapted, or high DA levels. Earlier research has shown how moderate levels of DA are beneficial for cognitive performance in general (Goldman-Rakic, Muly, & Williams, 2000). Here, however, we emphasize how environmental stimulation influences cognitive efficiency by means of the mediating effect of the phasic DA levels. Strong, salient, irrelevant stimuli may easily disrupt concentration, leading to attentional problems, whereas an impoverished environment may be compensated for by hyperactivity. However, moderate levels of arousing stimuli may be beneficial for cognitive performance.

We propose a neurocomputational model in which the level of DA is modeled by the gain parameter of the sigmoid function (Servan-Schreiber, Printz, & Cohen, 1990). This model can be expressed at the single-cell level, without simulating complex networks. The signal-to-noise ratio (SNR) is influenced by a statistical phenomenon called *stochastic resonance*, in which a signal presented under the detection threshold can be detected if noise is added (Moss, Ward, & Sannita, 2004). Stochastic resonance is a counterintuitive phenomenon in which well-adjusted noise levels facilitate information acquisition, improve performance, or amplify signals in natural and human-made nonlinear systems. A moderate level of noise is beneficial for performance, whereas either too little or too much noise attenuates performance (Manjarrez, Diez-Martinez, Mendez, & Flores, 2002; Moss et al., 2004). Our simulations show that for low DA levels, more external noise is needed for high cognitive performance. The hypodopaminergic state in individuals with ADHD leads to an enhancement in cognitive performance in noisy environments compared with a normal population (Söderlund, Sikström, & Smart, 2007).

This article is organized as follows. A short introduction to ADHD is followed by a presentation of the proposed model. The model is then supported by reviewing and fitting empirical data

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An Excel spreadsheet for calculating the predictions of the moderate brain arousal model is available at http://www.lucs.lu.se/People/Sverker.Sikstrom/MBA_demo.xls.

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regarding how environmental stimuli, such as interstimulus intervals (ISIs), attention-focusing stimuli, and attention-removing stimuli, influence cognitive performance. Finally, the model is compared with current ADHD theories.

ADHD

ADHD is a developmental disorder characterized by behavioral impairments in three domains: inattention, impulsivity, and hyperactivity. ADHD is one of the most commonly diagnosed childhood psychiatric disorders, influencing approximately 3%–5% (Barkley, 1997) or 3%–7% (American Psychiatric Association, 1994; Castellanos & Tannock, 2002) of the childhood population. ADHD is about three times more common among boys (9%) compared with girls (3.3%) (Szatmari, Offord, & Boyle, 1989).

There seems to be consensus regarding multiple etiologies of ADHD. Heritability is one factor (Nigg & Hinshaw, 1998). Evidence exists for genetic linkages, primarily in DA-related pathways (Fisher et al., 2002; Smalley et al., 2002) and in the nicotinic system, which, in addition to acetylcholine release, also promotes DA release (Kent et al., 2001). The genes of interest are DA transporter gene (DAT1), DA receptor genes (DRD4, DRD5), DA beta-hydroxylase (DBH), serotonin receptor and transporter genes (HTR1B, 5-HTT), and synaptosomal-associated protein 25 (SNAP 25). SNAP 25 is associated with the release of exocytotic DA and is affected by amphetamine. Small odds ratios are consistent with the idea that the vulnerability to ADHD is mediated by many genes with small effect (Faraone et al., 2005; Mill et al., 2005).

Environmental variables have also been found to be prominent risk factors, including early deprivation (Kreppner, O'Connor, & Rutter, 2001), maternal smoking (Kotimaa et al., 2003; Mick, Biederman, Faraone, Sayer, & Kleinman, 2002), and family psychosocial problems (Biederman et al., 1995), as well as problems during pregnancy, delivery (Rowland, Lesesne, & Abramowitz, 2002), and infancy (Harrison & Sofronoff, 2002). Some of the above-mentioned factors might also interact with parental genotype (Castellanos & Tannock, 2002).

Children diagnosed with ADHD can be characterized by specific behavioral and brain patterns. Recently, a consensus statement signed by a consortium of distinguished ADHD researchers summarized the distinguishing features of ADHD (Barkley et al., 2002). These included greater harm through increased mortality, morbidity, or impairment in major life activities (i.e., education, social relationships, family, and occupational functioning). Children with ADHD are also more prone to physical injury and accidental poisoning. These behavioral deficits have been linked to several specific brain regions (frontal lobe, basal ganglia, and cerebellum). Neurological studies show that individuals with ADHD display less brain electrical activity and less reactivity to stimulation, smaller volumes of brain matter, and less metabolic activity. Studies of identical and fraternal twins show a high genetic contribution to these traits (70% to 95% of trait variability in the population; Barkley et al., 2002).

A number of cognitive deficits are associated with ADHD. These include shortened delay gradients (characterized by attempts to avoid delay and delayed rewards; e.g., Sagvolden et al., 2005); deficits in response inhibition (deliberate suppression of a response to achieve a goal, e.g., go/no-go responding; Nigg, 2001), executive functioning (e.g., rule-governed and problem-solving functions; Barkley, 1997), and working memory (e.g., visuospatial working memory; Westerberg, Hirvikoski, Forssberg, & Klingberg, 2004); and increased variability in performance (e.g., inter- and intraindividual variability in performance, Leth-Steensen, Elbaz, & Douglas, 2000; reaction time distributions, Castellanos, Sonuga-Barke, Milham, & Tannock, 2006), temporal processing, and sustained attention (e.g., poor performance in vigilance testing, continuous performance tests; Corkum & Siegel, 1993; Koelega, 1995; Stins et al., 2005).

Current theories emphasize different psychological concepts to account for cognitive function and deficit in ADHD. Inhibition theory (Barkley, 1997) emphasizes an inability to inhibit a prepotent or ongoing response. Dual-pathway theory (Sonuga-Barke, 2003) identifies an executive dysfunction circuit (a mesocortical pathway related to inattention) and a delay aversion circuit (a mesolimbic pathway related to motivation). Dynamic developmental theory stresses altered reinforcement patterns and deficient extinction of previously reinforced behavior, as well as an inability to identify error signals (due to stunted phasic DA responses), leading to maladaptive behaviors (Sagvolden et al., 2005). The cognitive–energetic model (Sergeant, 2000) proposes that a reduction of the energetic level (cognitive processing, effort, and executive functioning) underlies the failure to inhibit in individuals with ADHD. Optimal stimulation theory (Zentall & Zentall, 1983) argues that hyperactivity arises from low levels of arousal and serves to maintain an optimal arousal level. These models are further elaborated later in the article.

DA Modulates Neural Efficiency in ADHD

Hyper- or hypofunctioning of the DA system causes impairments in cognitive performance. DA modulates neuron responses by increasing the SNR through enhanced differentiation between background, or efferent (internal), firing and afferent (external) stimulation. This in turn implies that DA produces a suppressive influence on spontaneous activity through the indirect pathway (extending from the prefrontal cortex [PFC] through the *external segment* of the globus pallidus and thalamus) that produces a net inhibition on other cortical output areas (Solanto, 2002). Insufficient activity in this pathway results in excessive motor output, explaining its apparent inhibitory actions. Simultaneously, through the parallel direct pathway (projecting through the *internal segment* of the globus pallidus), cortical signals are amplified (via disinhibition), causing an enhanced excitability in response to afferent driven transient stimulation (Cohen, Braver, & Brown, 2002). DA malfunctions can be conceptualized as increased levels of internal neural noise that decrease the SNR, which plays a critical role in working memory (Nieoullon, 2002), attention, motor control (Sagvolden et al., 2005), and reward/motivation (Schultz, 2002), where impairments are seen in ADHD.

Three DA systems have been implicated in ADHD. These include (a) a dysfunctioning mesolimbic system that influences reinforcement patterns and gives rise to delay aversion, hyperactivity in novel situations, impulsiveness, and so forth; (b) a hypofunctioning mesocortical DA pathway that causes attention response deficiencies and poor executive functions; and (c) a dysfunctioning nigrostriatal branch that causes impairments in motor functions and nondeclarative habit learning and memory, as expressed in clumsiness (Sagvolden et al., 2005; Solanto, 2002; Sonuga-Barke, 2003).

Modeling DA in ADHD

DA has been implicated as a factor in several other different clinical groups outside of the ADHD field, and explicit computational models have been proposed. For example, DA has successfully been modeled in aging (Li, Lindenberger, & Sikström, 2001; Li & Sikström, 2002; Sikström, 2007), schizophrenia (Smith, Becker, & Kapur, 2005), addiction (Redish, 2004), and Parkinsonism (Frank, Seeberger, & O'Reilly, 2004).

Detailed modeling offers high fidelity to the underlying biological system but is more difficult to connect to the behavioral level. General characteristics of the DA systems can be modeled by changing the gain parameter in the sigmoid function (Servan-Schreiber et al., 1990). This parameter modifies how responsive the output of a neural cell is to stimulation. Furthermore, a modest increase in the gain parameter raises the SNR, yielding improvements in performance. Although other approaches have been used to model DA (Durstewitz & Seamans, 2002), and with different levels of details, they share the common feature of modulating the SNR.

Few computational models have been proposed for ADHD. A noticeable exception is Frank and colleagues (Frank, 2006; Frank & O'Reilly, 2006; Frank, Santamaria, O'Reilly, & Willcutt, 2007; Frank, Scheres, & Sherman, in press), who suggested a neurocomputational model for ADHD and other clinical groups. In this basal ganglia–prefrontal cortex (BG-PFC) model, the role of the frontostriatal circuits is emphasized. The model is based on the go and no-go circuitries that interdependently connect basal ganglia (striatum) with PFC and have opposing effects on the selection of action. Go neurons facilitate the execution of a response in cortex through the direct pathway (substantia nigra–globus pallidus [internal segment]–thalamus–cortex), where inhibition is inhibited, resulting in a go response. The second circuit produces an opposing force, where neurons produce no-go activity by suppressing competing responses through the indirect pathway. This pathway passes globus pallidus (external segment) via subthalamic nucleus back to globus pallidus (internal segment), where the inhibition is restored, resulting in a no-go response (Solanto, 2002). DA modulates the relative balance between the competing go and no-go pathways via the facilitating D_1 receptors and the inhibiting D_2 receptors. In the BG-PFC model, Frank et al. (in press) simulated DA depletion and found emergent oscillatory activity in basal ganglia nuclei. These oscillations are characteristic of Parkinson tremor and are eliminated by simulated subthalamic nucleus lesions. The model shows how basal ganglia can participate in a wide range of cognitive functions, from low-level procedural learning to high-level working memory tasks (Frank & O'Reilly, 2006). The basal ganglia are essential for motor responses, and phasic DA bursts mediate go learning whereas DA suppression mediates no-go learning. Accordingly, ADHD is thought of as a disorder in action selection, and the BG-PFC model suggests that dysregulation of DA is caused by stunted phasic DA release, similarly to the dynamic developmental theory (Sagvolden et al., 2005). The results indicate a reduced basal-ganglia/DA signaling that causes a decrease in go signaling in which appropriate behaviors will not be reinforced, which in turn raises the threshold for updating working memory. Reduced signaling within basal ganglia will therefore lead to apparent hypofrontality owing to reductions in selective maintenance of task-relevant information and, furthermore, increased distractibility.

Furthermore, the BG-PFC model includes norepinephrine (NE) firing neurons in locus coeruleus, and dysfunctional NE transmission in ADHD leads to distractibility and increased variability. Similarly to DA, NE firing has tonic and phasic components, with phasic NE bursts occurring under focused attention. NE release increases the SNR by inhibiting nontarget stimulation. High tonic NE diminishes phasic inhibitory firing, and accordingly, the SNR decreases and variability increases. Thus, phasic NE release leads to sharper cortical representation and decreased variability. ADHD is proposed to be characterized by intermediate high tonic and low phasic NE levels, which accounts for the resulting variability (Frank et al., in press). In sum, deficits related to DA dysfunction cause distractibility, insufficient working memory updating, and insufficient reinforcement learning. Deficits related to NE dysfunction cause variability according to the BG-PFC model. The model furthermore proposes that distractibility and working memory impairment should be independent of increased variability—that is, DA and NE transmission should be independent. However, this proposal may be questioned, because methylphenidate (MPH) acts on both NE and DA transporters, suggesting dependence between NE and DA transmission during MPH administration (Berridge et al., 2006; Devilbiss & Berridge, 2006).

In addition, the BG-PFC model predicts that low striatal DA levels in ADHD lead to larger deficits in go learning from positive reinforcement as compared with no-go learning. This was supported by the finding that MPH medication improved go learning but not no-go learning; however, the interaction was nonsignificant (Frank et al., 2007). Accordingly, the BG-PFC model suggests a reduced sensitivity to immediate rewards, in opposition to earlier findings in ADHD (e.g., Sonuga-Barke, 2005). Data supporting reduced reward sensitivity in ADHD were recently found in two experiments in which participants performed at the same level as controls in responding to reinforcements with regard to accuracy, delay aversion, and reaction times, and ADHD participants were found to be less susceptible to immediate rewards (Scheres et al., 2006; Scheres, Milham, Knutson, & Castellanos, 2007). These partly contradictory data regarding the sensitivity to immediate reinforcements illustrate the necessity to include the entire experimental context before conclusions can be made. That is, if the experimental setting provides a moderate brain arousal state in ADHD participants, they may perform at the same level as controls, which could be an alternative explanation for the data noted above (Frank et al., 2007; Scheres et al., 2006, 2007).

Behavioral observations reveal that children with ADHD are easily overaroused and excitable in their responses to rewards and even more visibly frustrated when past rates of reinforcement decline. Children with ADHD show stronger negative affect compared with controls in learning tasks when given noncontingent negative feedback. In general, greater emotional reactivity has also been reported in the social interactions of such children (Barkley, 1998). Furthermore, children with ADHD show (a) greater emotional reactivity to emotionally charged immediate events, (b) fewer anticipatory emotional reactions to future (emotional) events, (c) decreased ability to act on others' emotions, (d) less ability to induce and regulate emotional drive in goal-directed behaviors, and (e) greater dependence on external sources affecting drive, motivation, and arousal (Barkley, 1997).

To conclude, it is still an open research question whether the above-sketched emotional reactions are caused by stunted phasic DA release, where children with ADHD, owing to a floor effect, do not detect what to approach or what to avoid. The alternative interpretation, proposed by the model introduced in this article, is that excessive phasic DA makes children with ADHD "go" on the first impulse (i.e., excessive go responding), thus interfering with task-specific attention. The value of elaborated neurocomputational models like the BG-PFC model and the model proposed here is that they provide researchers with distinct and testable predictions. Despite many similarities between the models, they also pose a crucial question that future experiments must address, namely, the role of phasic DA in ADHD. Two prominent theories of tonic and phasic DA in ADHD are extensively reviewed in the following sections.

Tonic and Phasic DA

DA is divided into phasic and tonic components. Phasic DA refers to the spike-dependent release of DA from axon terminals into the synaptic cleft in response to action potentials caused by a relevant external stimulus (Grace, 1995) or a reward signal that mediates new learning (Schultz, 1998). Tonic DA refers to the presence of low concentrations of DA in the extracellular fluid outside the synaptic cleft.

Tonic levels are continuous and modulate phasic reactivity. Autoreceptors in the presynaptic cell are activated when the tonic level is too high and suppresses spike-dependent phasic DA release, whereas low tonic levels increase phasic release (Grace, 1991, 1995). It is suggested that excessive tonic DA transmission results in excessive stability of neuronal activity with inhibited phasic DA release and is associated with cognitive rigidity. Low tonic levels, in contrast, cause neuronal instability and boosted phasic responses (Bilder, Volavka, Lachman, & Grace, 2004; Grace, 1995). Excessive phasic transmission is suggested to cause instability in neuronal activation states and is associated with cognitive symptoms such as failure to sustain attention, distractibility, and excessive flexibility.

Effects of stimulant drugs on tonic and phasic DA: Two hypotheses. MPH, in particular, and amphetamine are the most frequently used treatments for ADHD (Greenhill, 2001). Despite the widespread use of MPH, its actions at the neurocellular level are not yet fully understood. There is consensus about some of the effects of stimulant medication in ADHD. Both MPH and amphetamine increase extracellular DA (Carboni, Imperato, Perezzani, & Di Chiara, 1989; Schiffer et al., 2006; Volkow et al., 2001). MPH acts by blocking DA reuptake via DA transporters (i.e., inhibition of presynaptic DA uptake; Bergman, Madras, Johnson, & Spealman, 1989; Krause, Dresel, Krause, Kung, & Tatsch, 2000), and amphetamine acts by blocking DA reuptake and by increasing terminal DA release (Carboni et al., 1989). A standard therapeutic dose of MPH (0.5 mg/kg) is estimated to block approximately 60% of DA transporters (Volkow, Wang, Fowler, & Ding, 2005). In brain areas where DA density is high, such as striatum, DA transporter activity is the most important mechanism of DA inactivation, and MPH will exert a substantial increase of extracellular DA levels (Schmitz, Benoit-Marand, Gonon, & Sulzer, 2003). Converging evidence indicates that increased DA transporter binding (i.e., overactive DA transporters) in ADHD (Spencer et al., 2005) leads to low levels of extracellular, tonic DA. The therapeutic effect of medication has been related to striatal DA increase, which is proposed to decrease background firing rates and increase the SNR in striatal cells (Kiyatkin & Rebec, 1996). Furthermore, behavioral effects of MPH medication are seen in various cognitive abilities, such as inhibition (van der Meere, Gunning, & Stemerdink, 1999), vigilance and reaction time (Greenhill, 2001), and motor hyperactivity (Porrino, Rapoport, Behar, Ismond, & Bunney, 1983).

There are two prominent hypotheses regarding the effects of stimulant medication on phasic (pulsatile) DA release. Seeman and Madras (1998; 2002) proposed an MPH-related relative or absolute attenuation in phasic DA. MPH blocking of DA transporters raises the extracellular DA level; presynaptic autoreceptors get activated and diminish phasic DA release, resulting in a net decrease of DA (Seeman & Madras, 1998) or a reduced amplitude of phasic DA relative to tonic levels (Seeman & Madras, 2002). Volkow et al. (2005) suggested an MPH-related increase in phasic DA. This occurs because DA transporter blocking increases extracellular DA, leading to a net increase of both tonic and phasic DA cell firing (Volkow et al., 2005). The framework proposed in this article suggests the possibility of integrating these apparently contradictory views by discussing them in a context of absolute and relative DA levels. In particular it is suggested that MPH decreases the relative influence of phasic compared with tonic DA.

Volkow and colleagues (2005) suggested that stimulant medication leads to a DA accumulation in the synapse and a general amplification of DA signals that result from both tonic and phasic cell firing that will not be counteracted by autoreceptors. Using a positron emission tomography (PET) technique, Volkow et al. showed that stimulant medication (e.g., MPH) increases extracellular DA in healthy adults (Volkow, Fowler, Wang, Ding, & Gatley, 2002; Volkow, Wang, et al., 2002; Volkow et al., 2001, 2005). However, this PET technique is based on averaging data for 30–60 s, making it intractable to draw conclusions about phasic DA on millisecond timescales (Schultz, 2002). This view has also been implied by Sagvolden et al. (2005), in that the dynamic developmental theory claims that a dysfunction of the phasic–tonic DA system in ADHD results in stunted phasic DA responses; however, the neurophysiological support for this view is unclear (see V. A. Russell, de Villiers, Sagvolden, Lamm, & Taljaard, 1995, p. 348).

The amount of MPH and speed of uptake is crucial for medication (Volkow, 2006). Reinforcing effects occur when MPH elicits large and fast DA increases that mimic those of phasic DA firing, whereas therapeutic effects occur when MPH elicits slow, steady-state DA increases that mimic those of tonic firing. Whether presynaptic autoreceptors and postsynaptic DA receptors are activated differently by the *indirect acting* DA agonist MPH was experimentally investigated at different doses of MPH on rats; no dose was found that acted selectively at presynaptic autoreceptors (Ruskin et al., 2001). However, selective presynaptic autoreceptor activity has been found while studying the Nur 77 receptor, which has an important role in adaptation and homeostatic regulation of dopaminergic systems (Levesque & Rouillard, 2007). Nur $77^{-/-}$ knockout mice are spontaneously hyperactive and have been found to be selectively sensitive to low doses of *direct acting* D_2 agonists (quinpirole .025 mg/kg ip), which act mainly at presynaptic autoreceptors and reduce hyperactivity (Gilbert et al., 2006).

The effect of quinpirole in reducing hyperactivity was about twofold stronger in Nur $77^{-/-}$ as compared with Nur $77^{+/+}$ mice (Gilbert et al., 2006).

Further support for Volkow et al.'s view is given by a microdialysis experiment on rodents where a 5-mg/kg MPH dose caused an increase in synaptic DA by 3.6 times (Schiffer et al., 2006). However, the doses were high (MPH 5 mg/kg, amphetamine 2.5 mg/kg) and not directly comparable to therapeutic doses of MPH (typically MPH 0.3–1.0 mg/kg) (Solanto, 2000). Furthermore, intraperitoneally administered MPH is four times as efficient in increasing plasma levels compared with oral delivery. This means that the dose used by Schiffer et al. (5 mg/kg ip) should be equivalent to a 20-mg/kg oral dose (Berridge et al., 2006).

The studies referred to above (Ruskin et al., 2001; Schiffer et al., 2006; Volkow et al., 2001, 2004) investigated the effects of MPH in normal, healthy participants or rodents. It is unclear whether these findings can be generalized to DA transmission in ADHD. It is known that those with ADHD respond differently to MPH medication, as seen in both human (Vaidya et al., 1998, 2005) and rodent studies (V. A. Russell et al., 1995; V. A. Russell, de Villiers, Sagvolden, Lamm, & Taljaard, 2000). Furthermore, DA transporter knockout mice respond differently to MPH (their hyperactivity decreases) compared with mice with intact DA transporter function (they become hyperactive; Giros, Jaber, Jones, Wightman, & Caron, 1996). Of note, in the above referenced studies by Volkow et al., an increase in DA binding was found only in striatum and not in PFC, the crucial area for goal-oriented cognitive performance.

It is generally acknowledged that autoreceptors inhibit DA release; however, there are disagreements regarding onset and duration times of DA-release autoinhibition. The estimated duration of axon terminal release autoinhibition ranges from milliseconds up to several seconds (Benoit-Marand, Borrelli, & Gonon, 2001; Schmitz et al., 2003). DA release is tonically depressed during basal firing via autoinhibition. During a burst firing, little inhibition occurs during the first three spikes; however, this is followed by attenuation of DA release (Schmitz et al., 2003). The fast (i.e., phasic) time-dynamic properties of presynaptic autoinhibition are not captured in microdialysis experiments. Instead, in Schiffer et al.'s (2006) experiment, both extracellular and synaptic DA increase was measured as a response to therapeutic doses of MPH and amphetamine, where the DA was measured by microdialysis averaged over 5 min. The within-event time dynamics makes it difficult to estimate phasic DA release; however, time dynamics might be captured in the near future using nano techniques.

Schmitz et al. (2003) proposed that inhibition of DA release through autoreceptors may serve to increase the SNR of the DA signal in response to target burst firing versus baseline firing. Only synapses that are coincidently activated by cortical inputs and the DA afferent signal (from substantia nigra) will enhance the DA signal, whereas synapses not activated by coincident cortical inputs will remain unchanged or depressed (i.e., neural noise) (Schultz, 2002). ADHD is characterized by a reduced capacity in making these couplings owing to a hypofunctional PFC. At the systems level, DA exerts a focusing effect whereby only the strongest inputs pass through the striatum to external and internal pallidum (internal and external pathways, i.e., go and no-go). This system benefits from a nonlinear bistable threshold mechanism in generating action potentials. The phasic, bottom-up DA reward alert signal has to be modulated or processed by a top-down governed reward discrimination or representation system. The salience of stimulus and task seems to have a large impact on the DA-related effects of stimulant medication. Volkow et al.'s (2004) and Schiffer et al.'s (2006) experiments did not involve any conditioning task, which might have changed autoreceptor function and extracellular DA levels. Evidently, behavioral effects of MPH medication in children with ADHD were found to be context (or stimulus) dependent—for example, effects were larger in the classroom as compared with the playground (Swanson et al., 2002).

The second hypothesis, proposed by Seeman and Madras (2002), suggests that low doses of MPH elevate tonic DA, which in turn diminishes phasic DA release. MPH increases extracellular DA by DA transporter blockade and causes diminished phasic DA release through stimulation of the presynaptic autoreceptor, which down-regulates postsynaptic receptor activation (Seeman & Madras, 1998). The DA transporter, presynaptic D_2 autoreceptors, and diffusion regulate extracellular levels of DA in the synapse. In striatum in particular the DA transporter reuptake constitutes 95% of DA clearance (Lapish, Kroener, Durstewitz, Lavin, & Seamans, 2007), so a DA transporter blocker like MPH will have a pivotal effect on extracellular levels in striatum. At stimulant doses typically given as medication, the elevated resting extracellular DA lowers phasic DA response (compared with baseline) by acting on presynaptic D_2 autoreceptors at nerve terminals, which in turn inhibits the stimulated release of additional DA (Davis, Heffner, & Cooke, 1997; Silvia, King, Lee, Xue, & Caron, 1994; Suaud-Chagny, Buda, & Gonon, 1989).

In our view, the relative strength of phasic to tonic DA decreases with administration of MPH. That is, MPH decreases the relative importance of tonic compared with phasic DA, leading to an increased SNR, improvement in cognitive tasks, and less reliance on distractor stimuli. Support for this suggestion comes from the following findings. Normal resting level of extracellular (tonic) DA in the synaptic cleft is low (4 nM) and transiently rises at least 60-fold (250 nM) during a normal nerve impulse. The transiently elevated extracellular level falls back (in milliseconds) by diffusion and DA transporters (Seeman & Madras, 2002). However, in the presence of MPH, through the block of DA transporters, there is a larger increase in resting (tonic) DA levels (about sixfold) than the increase in stimulus-triggered (phasic) release of additional DA (i.e., twofold) (Seeman & Madras, 2002). This suggests that stimulant medication influences phasic release less than tonic firing, thus reducing the importance of phasic DA relative to tonic firing. Furthermore, higher doses (above 1–2 mg/kg) raise the resting level of extracellular DA more (14- to 35-fold) (Shetty & Chase, 1976) than the pulsatile DA output (sevenfold) (Gonon, 1988). These high levels of both tonic and phasic DA cause widespread stimulation of postsynaptic DA receptors that overcomes the presynaptic inhibition of further DA release. This presynaptic feedback loop via autoreceptors is very frequency dependent and operates most efficiently at low and intermediate ranges of nerve stimulation frequency (Langer, 1997). This dependence on stimulus frequency reflects the physiological relevance of DA modulation and can explain the biphasic effects of MPH and sensitivity to ISIs. Thus, presynaptic autoreceptor modulation can occur through changes in both DA resting (tonic) levels and phasic burst frequencies (Benoit-Marand et al., 2001). Further effects of ISIs are discussed below.

Actions of low doses of stimulants appear to be qualitatively distinct from those of higher doses. At higher doses of stimulants, both DA and NE efflux increases widely throughout the brain (Kuczenski & Segal, 2002). In contrast, low doses of MPH show a minimal influence of DA and NE efflux in subcortical areas (nucleus accumbens) but an increased influence in PFC (Berridge et al., 2006). It is interesting to note that medication yields a larger increase of NE than DA in PFC and is combined with dampened spontaneous and evoked NE discharge in locus coeruleus. It is hypothesized that the increase of DA and NE efflux in PFC combined with the decrease by the same transmitters subcortically contributes to the behavioral and cognitive actions of low-dose psychostimulants (Devilbiss & Berridge, 2006). Similarly to DA, there is an inverted U curve between NE transmission and working memory performance (Arnsten, 2001). The effects of the neural mechanisms underlying these therapeutic actions are poorly understood, but MPH raises DA and NE levels in the NE-transporter-rich and DA-transporter-poor frontal cortex (Madras, Miller, & Fischman, 2005), possibly leading to a dissociation between cortical and subcortical regions. Furthermore, this is consistent with the suggested subcortical hyperactivity and prefrontal hypoactivity of DA transmission.

There is circumstantial evidence that a variety of cognitive tasks depend on a relatively narrow range of tonic and phasic discharge (in locus coeruleus) (Clayton, Rajkowski, Cohen, & Aston-Jones, 2004). Only at the lowest dose tested did MPH produce a significant, though relatively modest, suppression of the SNR of phasic discharge (Devilbiss & Berridge, 2006). It is possible that this facilitates attention and suppresses responses to distracting (attention-removing) environmental stimuli. Thus, MPH may facilitate signal processing within cortical regions associated with attention and impulsivity, like PFC. To conclude, we propose, with the above noted arguments, that it is not the phasic level per se (in absolute measures) that is the main determinant of cognitive performance but rather the relation (ratio) between excitatory and inhibitory actions induced by tonic and phasic neural firing.

Furthermore, the effects of medication are dependent on individual baseline levels or the relative levels of tonic and phasic DA. That is, as suggested by Grace (2001), a low tonic baseline DA level will be up-regulated by MPH, and the high phasic release will be down-regulated. The opposite occurs if the tonic baseline is high or normal; MPH will increase tonic levels only marginally but will up-regulate phasic DA release. Low doses of MPH will restore a dysfunctional balance between phasic and tonic DA transmission. Thus, only high doses and/or intravenous delivery of stimulant medication will cause a general boost of phasic DA release irrespective of baseline DA levels. This may also explain the differences between individuals with ADHD and controls in functional MRI (fMRI) or PET activation patterns after medication.

Hyperactivity and poor impulse control may result from excess DA activity in striatum and nucleus accumbens. Hyperactivity has been induced in rats by delivery of a D_2 agonist (Hoffman & Wise, 1992), whereas neuroleptic treatment (D_2 blocker) reduces ADHD symptoms (Barkley, 1998; Popper, 2000). Further support for a hyperdopaminergic subcortical model is that adolescents with ADHD show increased striatal activity on PET relative to controls (Ernst et al., 1999) and that levels of homovanillic acid in cerebrospinal fluid correspond both with severity of symptoms and with response to stimulants (Castellanos et al., 1996). For example, 0.5 mg/kg of dextroamphetamine administrated to hyperactive children lowered the spinal fluid level of homovanillic acid, which is a major metabolite of DA, by 34%, and was accompanied by a clinical improvement of their hyperactive syndrome (Shetty & Chase, 1976). A reduced DA transmission in PFC can result in subcortical hyperdopaminergic activity while inhibitory projections from PFC disappear (Deutch & Young, 1995). Thus, loss of inhibitory control and self-regulation in ADHD may be the result of a decrease in frontal cortical modulation of subcortical systems by descending corticostriatal dopaminergic projections (Taylor & Jentsch, 2001).

Grace (2001) has proposed a model of DA transmission in ADHD that integrates many of the foregoing observations. He suggested that, possibly because of reduced stimulation from PFC, children with ADHD have low tonic DA activity in limbic regions, leading to high phasic activity in nucleus accumbens and other subcortical areas. By blocking DA transporters, extracellular DA levels will increase and phasic DA levels will decrease, via autoreceptors, back to normal levels. Of note, the intersubject variability for MPH-induced increases in extracellular DA levels was much larger (50%) as compared with the variability in the number of receptors affected by DA transporter blockade (18%) (Volkow, Wang, et al., 2002). Furthermore, no correlation was found between the effects of MPH-induced DA transporter blockade and extracellular DA levels. This may reflect individual differences in internal noise levels (i.e., DA tone), which in turn means that the net effect of MPH on phasic DA release is determined by tonic DA levels. If DA tone is low, there will be a net decrease of phasic DA release through autoreceptor feedback inhibition, whereas a high tonic level will result in a net increase of DA release, as suggested by Grace (2001, p. 148). This means that PET scans in which extracellular DA levels are assessed at the group level might be misleading, in that some participants show increased DA levels and some show decreased DA levels. Finally, it is worth mentioning that general learning problems are not a hallmark of ADHD; for example, in certain conditions episodic memory performance is at the same level as seen in controls (Rashid, Morris, & Morris, 2001; Söderlund et al., 2007).

Desensitizing of postsynaptic DA receptors. Low doses of MPH raise extracellular (tonic) DA levels and generate lower postsynaptic activation, partly through desensitization, resulting in reduced behavioral hyperactivity (Seeman & Madras, 2002). Dopaminergic receptors are metabotropic, and the transduction is linked to second messenger cascades (G-protein-coupled receptors), which make neurotransmission slower than direct acting (e.g., voltage-gated) ion channels. These second messenger actions generally last from seconds to minutes; they do not mediate rapid behaviors but rather serve to modulate the efficacy of fast synaptic transmission (e.g., ionotropic receptors) by modulating release, sensitivity, or electrical excitability (Kandel, Schwartz, & Jessel, 2000, p. 248). DA receptors exhibit the property of desensitization, the progressive inactivation of a receptor due to the continuous presence of a transmitter. Although the mechanism is not well understood, the rate of desensitization can be modulated by several second messenger pathways (Kandel et al., 2000). Stimulant medication by agonists like MPH, amphetamine, and nicotine can evoke this effect. This desensitization acts on different timescales and is modulated by agonist concentration. Fast-acting current K^+ channel desensitizing operates on 20-s timescales (Leaney et al.,

2004), whereas in slow-acting current K^+ channels it takes up to 20 min to reach the maximum effect of desensitizing (Wooltorton, Pidoplichko, Broide, & Dani, 2003). These effects occur predominantly in midbrain regions such as ventral tegmental area and substantia nigra (Wooltorton et al., 2003)—that is, areas that are proposed to be hyperactive in ADHD (Biederman & Faraone, 2005).

Summary of the relative importance of phasic and tonic DA. In our view, the literature reviewed above suggests the following interpretation of phasic and tonic DA. In unmedicated ADHD, phasic DA is relatively more important at the expense of tonic DA, whereas drug medication emphasizes tonic DA relative to phasic DA. That is, the important contrast is the ratio between phasic and tonic DA levels, which decreases following administration of MPH. This perspective may be contrasted with the view that the relevant comparison is the absolute DA levels, where MPH administration increases the phasic levels. The latter view has been advocated by, for example, Sagvolden et al. (2005; Volkow, Fowler, et al., 2002) and is sometimes computationally implemented in the error-driven learning mechanisms, such as the temporal differences algorithm for explaining DA effects on learning (Rescorla & Wagner, 1972; Schultz, 2002; Sutton & Barto, 1990). These two views would make very similar predictions given that the phasic levels would change whereas the tonic levels are constant. However, the data reviewed above suggest that the tonic levels increase more than the phasic levels, yielding a decrease in the phasic-to-tonic ratio following MPH administration. This decrease in phasic sensitivity following the increase in tonic levels may be connected to the desensitizing of postsynaptic DA receptors, as reviewed above.

Stochastic Resonance

Stochastic resonance is the statistical phenomenon in which stimuli presented under a detection threshold can be detected in the presence of noise (see Moss et al., 2004, for a review). Stochastic resonance is a ubiquitous phenomenon; it exists in any system with noise and signal that requires the passing of a threshold. A signal below the detection threshold cannot be detected. However, adding noise to the signal allows information about the signal to pass the threshold so that the signal can be detected. This phenomenon also occurs if the signal frequently is above the detection threshold, and where adding moderate noise increases the discriminability between the probabilities of the threshold being passed with and without the signal, thus paradoxically increasing the SNR. However, with excessive noise, discriminability deteriorates so that performance as a function of noise follows an inverted U-shaped curve.

Stochastic resonance has been identified in a number of naturally occurring phenomena, for example, in explaining the dramatic climate changes that created ice ages despite very small external forces acting on the climate system (Benzi, Parisi, Sutera, & Vulpiani, 1982). Further applications are in optical systems such as the fluctuations in bistable ring laser systems, and in electronic and magnetic systems such as analogue electric simulators, electron parametric resonance, and superconducting quantum interference devices (Gammaitoni, Hänggi, Jung, & Marchesoni, 1998).

Stochastic resonance has also been experimentally demonstrated to occur in sensory systems in animals and humans. In particular, it has been found in the neural system and in behavioral data. In neural systems, thresholds exist because of the all-or-none (bistable) nature of action potentials and can be modeled by a nonlinear activation function (Gammaitoni et al., 1998). The first stochastic resonance experiment in sensory biology was conducted on the mechanoreceptors of a crayfish (Douglass, Wilkens, Pantazelou, & Moss, 1993). Stochastic-resonance-enhanced perception and changed feeding behaviors in the paddlefish have also been demonstrated (D. F. Russell, Wilkens, & Moss, 1999). Among humans, stochastic resonance has been found in several modalities, for example, in auditory (Morse & Evans, 1996; Zeng, Fu, & Morse, 2000) and in vision and tactile modalities (Laming, 1986; Manjarrez et al., 2002; Wells, Ward, Chua, & Inglis, 2005), where moderate noise improves sensory discrimination.

In fMRI scans, a moderate noise level increased neural cortical activity more than too little or too much noise did (Simonotto et al., 1999). However, the effect of stochastic resonance from random exposure to visual stimuli (noise and target) to the right and left eye separately seemed to occur in primary visual cortex and not in the retina, at least after the optic chiasm (Mori & Kai, 2002). Because stochastic resonance can improve the ability of a sensory system to detect weak stimuli, it can be used to elevate sensory thresholds—for example, in patients with cochlear implants (Behnam & Zeng, 2003). Gluckman et al. (1996) showed that small amounts of superimposed noise amplified subthreshold stimuli in an isolated hippocampal preparation. Effects of stochastic resonance have also been found in cognitive performance. Auditive noise improved the speed of arithmetic computations in a normal population (Usher & Feingold, 2000). In bistable moving systems driven by external periodic input, the presence of a moderate noise produced a periodic output that was much stronger than the input (Hu, Nicolis, & Nicolis, 1990). This phenomenon is the hallmark of stochastic resonance and can be mimicked by carrying water on a tray. This nonmonotonic relationship between performance and noise level, as an arousal source, is reminiscent of the Yerkes–Dodson law, where an inverted U-shaped relationship between performance and arousal level is observed (Heath, 2000).

The Moderate Brain Arousal (MBA) Model

Overview

The MBA model is based on the neurophysiological finding of phasic and tonic DA and the statistical phenomenon of stochastic resonance. (A computational implementation of the MBA model can be downloaded from http://www.lucs.lu.se/People/Sverker.Sikstrom/MBA_demo.xls.) In the model, it is assumed that the total DA level is the sum of the largely constant tonic level and the variable, stimulus-dependent phasic level. The tonic level is stimulus independent. The tonic level is lower for those with ADHD than for others because of altered DA transporter function, DA metabolism (Kirley et al., 2002), and hetero- and autoreceptor function (Grace, 2001). However, owing to low tonic levels in ADHD, autoreceptors up-regulate the efficiency of the stimuli-evoked phasic responses relative to the tonic responses so that they are larger for individuals with ADHD than for others (Grace, 1995). This regulatory system functions as a homeostatic control, and it includes a presynaptic feedback system, glutamate-driven heteroreceptors, and DA-driven (D_2) autoreceptors (Grace, 1995).

The model predicts that poorly adjusted DA levels in environments with impoverished stimuli frequency or excessive DA-release inducing stimuli lead to diminished cognitive performance and make those with ADHD hypersensitive to environmental stimuli. In contrast, normal individuals have higher tonic levels, yielding a lower sensitivity to environmental stimuli, and their total DA levels are adaptively maintained near an optimum.

Consistent with earlier DA models (Li & Sikström, 2002; Servan-Schreiber et al., 1990), the level of DA in the MBA model is modulated by the gain parameter in the sigmoid activation function. A low DA level corresponds to a low gain, yielding a relatively more linear input–output relation compared with a high DA level and high gain. The neural system is influenced by stochastic resonance as the signal plus noise passes a threshold during generation of action potentials. The low DA level in ADHD shifts performance on the stochastic resonance curve (inverted U curve) to the right, so that the neural system in a person with ADHD may operate on that part of the curve where noise is beneficial for performance, whereas under the same conditions, a person with a normal system operates on the part of the curve where performance declines (see Figure 5 later in article).

It is suggested that moderate noise is necessary for well-functioning signal transmission in the brain. Because of the neuron's highly nonlinear threshold activation function, a single neuron's sensitivity to incoming signals is enhanced by a moderate level of signal-unrelated activity (Gluckman, So, Netoff, Spano, & Schiff, 1998). Temporal co-occurrence of multiple action potentials is necessary to generate an action potential (Gluckman et al., 1998). Our model proposes that the low level of extracellular DA in ADHD produces an insufficient neural noise level, which leads to a poorly functioning signal transmission. This is consistent with a hypoarousal model for ADHD. To compensate for low internal neural noise, it is suggested that children with ADHD require more external noise to achieve high performance. Further indirect support for our model is provided by electroencephalogram (EEG) evidence, which suggests hypoarousal in ADHD (Barry, Clarke, & Johnstone, 2003; Barry, Johnstone, & Clarke, 2003). The brain's tonic level of DA plays a crucial role in maintaining the required noise or arousal level for efficient information processing.

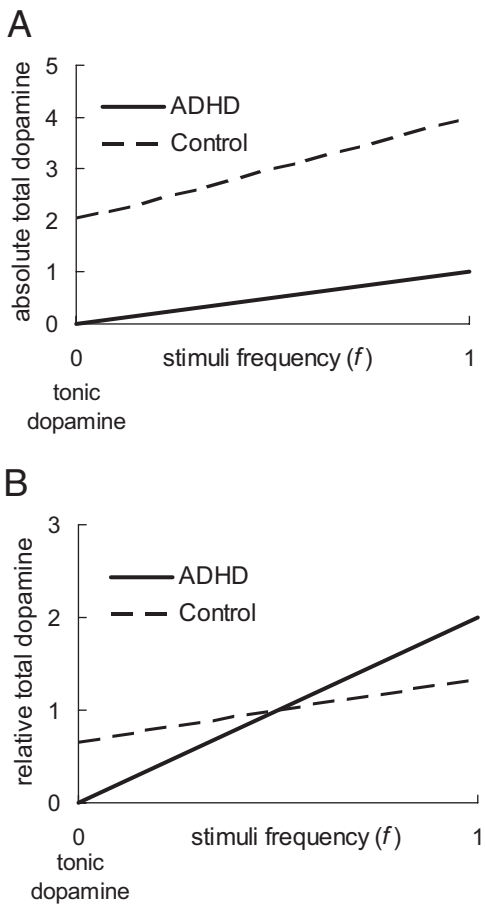

Figure 1. Panel A shows the absolute total dopamine (DA) levels, and Panel B shows the relative total DA levels (i.e., DA modified by presynaptic autoreceptors and/or postsynaptic DA receptors) as a function of stimuli frequency. The tonic DA levels are represented at a stimuli frequency of zero. The phasic DA levels are represented in the slope of the curves. Absolute and relative tonic DA is lower in attention-deficit/hyperactivity disorder (ADHD) systems compared with control systems. However, the phasic relative (but not the absolute) DA is larger for ADHD systems compared with control systems. The moderate brain arousal model is based on the relative DA levels.

Tonic and Phasic DA Levels

The tonic DA level (β_t) is the level of DA in the absence of stimuli or in impoverished stimuli environments. Phasic DA (β_p) is the DA released at the onset of a stimulus, and the time-averaged DA response when stimuli are presented at a frequency (f) is $\beta_p f$. The total DA ($\beta > 0$) equals the phasic DA plus the tonic DA:

$$\beta = \beta_t + \beta_p f, \quad (1)$$

where we impose the restriction that $\beta > 0$ for all f.

Absolute and Relative DA Levels

The MBA model makes a distinction between absolute (Figure 1A) and relative DA levels (Figure 1B), where performance in the model is dependent on the relative levels. The relative DA level is the efficiency of DA following modulation from presynaptic autoreceptors and/or adaptation of postsynaptic DA receptors (as described in the literature review above). In particular, the relative phasic DA level is up-regulated when the tonic DA level is low, making the relative phasic DA level larger for persons with ADHD than for persons without ADHD.

The mapping between absolute and relative DA levels can be modeled in the following way. It is assumed that presynaptic autoreceptors and/or postsynaptic adaptation change on a slow timescale that down-regulates the efficiency of high DA levels. This adaptation is implemented by rescaling the absolute DA into the relative DA levels so that the total DA integrated over a range of frequencies is the same for the neural systems in persons with and without ADHD. We set this adaptation factor to the total absolute DA integrated over a range of stimuli frequencies (0 to f_{max}), which is equivalent to the area under the curve in Figure 1A. The adaptation factor is larger for the neural systems in persons without ADHD than for those in persons with ADHD. It changes slowly and is for practical purposes assumed to be constant during

the simulations discussed in this article. The relative DA in Figure 1B is then equal to the absolute DA level divided by the adaptation factor.

The following illustrative example corresponds to Figure 1A and 1B. The absolute tonic DA is larger for control (2) than for ADHD (0), where the tonic levels correspond to the hypothetical state of a stimuli frequency of zero ($f = 0$). The same is true for the absolute phasic DA, where the phasic DA corresponds to the slopes—that is, it is smaller for ADHD (1) than for control (2). The adaptation factor (i.e., area under the total DA curve) in the frequency interval 0 to 1 is 0.5 for ADHD and 3 for control. The relative DA in Figure 1B is obtained by dividing the absolute DA with the corresponding adaptation factor. The results show a larger relative phasic DA for ADHD (2) than for control (0.67), whereas the relative tonic level is larger for control (0.67) than for ADHD (0).

In summary, low tonic levels in ADHD modulate phasic responses through a compensatory mechanism by which stimulus-dependent phasic answers are up-regulated by presynaptic autoreceptors and/or postsynaptic adaptation. This means that relative phasic DA in the neural systems in ADHD persons is more sensitive to environmental stimuli than that in the neural systems of persons without ADHD. However, in stimuli-impoverished environments, the adaptation cannot fully compensate for the lower tonic DA, and the total DA level is lower for ADHD than for normal systems. The MBA model bases its prediction on the relative DA levels, and unless stated otherwise, we refer to relative DA levels simply as DA levels.

Performance in the MBA Model

Performance in the MBA model is assumed to depend on the information (measured by entropy) carried in the neural activity evoked by external stimulation and internal neural noise. Neural activity is modeled by the sigmoid activation function, where the gain models the total DA level (Li & Sikström, 2002; Servan-Schreiber et al., 1990). The input to the sigmoid function is the noise (N) plus the signal (S) scaled by the gain (β), plus the bias term (T). The sigmoid function is

$$p(N) = \frac{1}{1 + \exp[-\beta(S + N) + T]}. \quad (2)$$

Figure 2A shows the sigmoid activation function for ADHD (shallow slope) and for control (steep slope) systems in a stimulus-impoverished environment where the neural system of a person with ADHD has less total DA than the neural system of a person without ADHD. The signal is presented as a smooth line, and the signal with added noise, as the fluctuating line. The flatter line in ADHD indicates that reaction on external stimulation occurs more at random compared with control.

A spike occurs in Figure 2B when the neural input activity is above the activation threshold. The more distributed pattern of threshold crossings in ADHD depicts less focus on attention, a hallmark of ADHD. An effect of this is an exaggerated semantic priming effect, seen in both ADHD and schizophrenia (Kiefer, Ahlegian, & Spitzer, 2005).

According to standard information theory, entropy measures how much information there is in a signal (Shannon, 1948). An intuitive understanding of information entropy relates to how much uncertainty is related to a certain probability distribution, where the entropy is higher for a higher degree of uncertainty. Mathematically, entropy is a product of the probability of an outcome times the log of the inverse of this probability summed over probability distribution. As with other models of stochastic resonance (Moss et al., 2004), the performance in the MBA model is based on entropy. The sigmoid function ($p[N]$) could be interpreted as the probability that a neural cell is firing. The entropy is based on this probability and is calculated by integrating over the noise distribution. The noise (N) is normally distributed, with a mean value of zero and a variance of σ_N^2:

$$C\frac{1}{f}\int_{-\infty}^{\infty}\frac{e^{-\left(\frac{N}{2\sigma_N}\right)^2}}{\sqrt{2\pi\sigma_N}}p(N)\log[1/p(N)]dN, \quad (3)$$

where the scaling parameter, C, is for fitting with empirical data and the $1/f$ factor represents the study time for which an encoded stimulus is presented. The predicted performance in the MBA model is based on Equation 3.

Support of the MBA Model

Individuals With ADHD Are Hypersensitive to Environmental Stimuli

Generally speaking, the MBA model suggests that under well-adjusted environmental conditions, individuals with ADHD perform as well as others; however, their performance attenuates when the environmental conditions are poorly adjusted. Changes in environmental stimuli influence phasic responses and performance more in ADHD than in others. Additionally, changes in environmental stimuli lead to larger fluctuations in total DA (Figure 1B), activity, and performance (Figures 3 and 4) for individuals with ADHD compared with others.

The MBA model suggests that where environmental stimuli alter DA levels through stimulus-evoked phasic responses, cognitive performance is modified depending on the interaction between the DA system and the environmental stimulation. The relation between DA and performance shows an inverted U-shaped curve, in which either too low or too high levels attenuate performance. In *hypodopaminergic* states (D_1 transmission in PFC), facilitation via DA agonists improves working memory performance. In *hyperdopaminergic* states the opposite occurs—that is, inhibition via DA antagonists improves performance (Goldman-Rakic et al., 2000). An arousal state in which cognitive performance is well tuned is called moderate brain arousal, whereas high brain arousal and low brain arousal are states that attenuate performance. How much arousal is needed for high performance depends on the complex interaction among the cognitive task, the experimental setting (e.g., ISIs), and the state of the participant (e.g., internal neural noise and DA levels in ADHD and controls).

The MBA model suggests that the boosted (excessive) phasic DA responses in ADHD cause hypersensitivity to environmental stimuli and (a) increased dependence on ISIs of task-related stimuli. External stimulation can be either (b) attention removing or (c) attention focusing. In the former case, sensitivity to task-irrelevant stimuli causes inattentiveness, whereas in the latter case salient

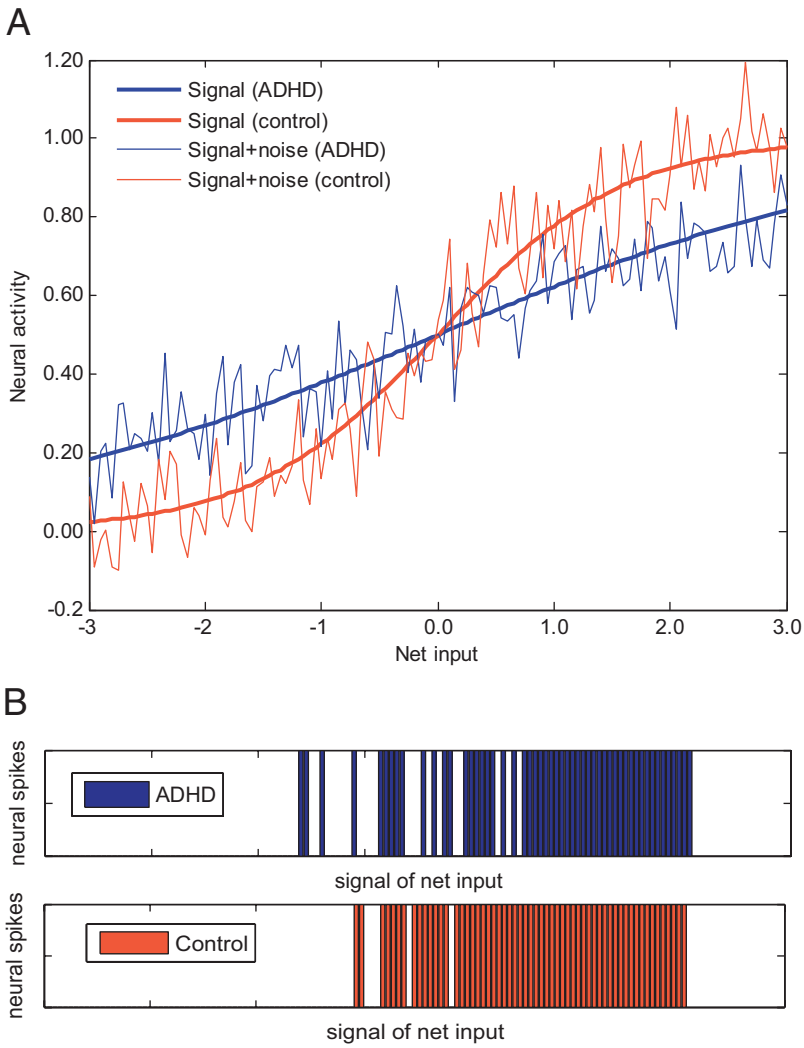

Figure 2. A: Signal and noise in the sigmoid activation function for attention-deficit/hyperactivity disorder (ADHD) and control systems. The *y*-axis represents the neural activity (i.e., spike frequency) as a function of net input on the *x*-axis. The smooth lines represent the sigmoid function, and the noise lines represent the sigmoid with added Gaussian noise. The shallow curve line represents ADHD with a low gain parameter, and the steep curve represents control with a high gain parameter. B: Single spikes as a function of signal in the net input for ADHD and control systems. Each vertical line represents a single neural spike that is generated when the signal plus noise exceeds a threshold in Panel A. The lower gain in ADHD systems makes the spike distribution less distinct than for higher gain in control systems.

task-related stimuli focus attention. An increase of both inter- and intraindividual variability in individuals with ADHD performance increases both inter- and intraindividual variability in performance. Furthermore, individuals with ADHD perform better in moderately noisy environments as a result of the stochastic resonance phenomenon. Below we review evidence for the MBA model.

Individuals With ADHD Are Sensitive to ISIs

We suggest that the hypersensitivity to environmental stimuli makes individuals with ADHD particularly vulnerable to ISIs. In ADHD, ISIs have a great impact on cognitive performance, with short, intermediate, and long ISIs corresponding to high, moderate, and low brain arousal states, respectively. Here empirical evidence for the MBA model is reviewed. In general, children with ADHD have been found to be sensitive to ISI manipulations. Studies indicate that impairments can be found for both long and short ISIs.

Performance is impaired when long ISIs are used, and unlike normal controls, children with ADHD do not benefit in performance for prolonged ISIs. This result has been found in paired-association tests (Conte, Kinsbourne, Swanson, Zirk, & Samuels, 1986; Dalby, Kinsbourne, Swanson, & Sobol, 1977). Furthermore, performance of individuals with ADHD was found to be better in an intermediate study-time condition compared with both short and long ISI conditions. Stimulant medication (MPH) abolished these differences (Conte & Kinsbourne, 1988).

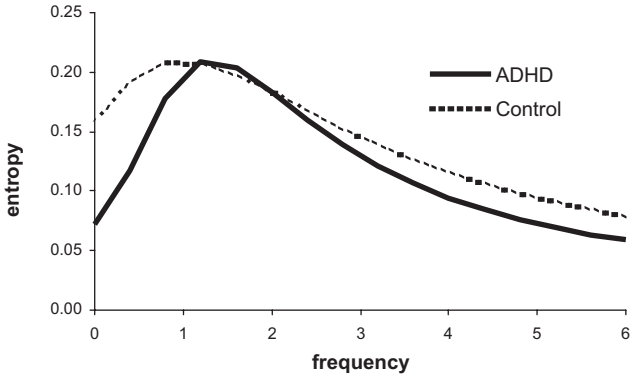

Figure 3. Performance (entropy) as a function of stimuli frequency. The *y*-axis shows the predicted performance as measured by information entropy in the moderate brain arousal model as a function of stimuli frequency (*f*). The attention-deficit/hyperactivity disorder (ADHD) system has lower performance than the control system for high and low, but not for moderate, stimuli frequencies. All parameter values were set to 1 except the following: $T = 4$, $\beta_t(\text{ADHD}) = 0$, and $\beta_p(\text{ADHD}) = 1.5$.

In go/no-go tests, individuals with ADHD showed best performance in the intermediate study interval (4 s) and worst performance in short (1-s) and long (8-s) intervals (van der Meere et al., 1999; van der Meere, Stemerdink, & Gunning, 1995); this effect was also found with MPH or clonidine medication (van der Meere et al., 1999). In a moderately fast condition (2 s), individuals with ADHD showed the same performance as controls, but their performance deteriorated in the slower (6 or 8 s) conditions (Börger & van der Meere, 2000a; Wiersema, van der Meere, Roeyers, Van Coster, & Baeyens, 2006). Greater heart rate variability and less adaptation to task in terms of heart rate deceleration (before go signals) and acceleration (after go signals) were found in the ADHD group during the slow condition (Börger & van der Meere, 2000a). In an EEG study, an attenuated parietal P300 was found among ADHD children in the slow condition, indicating that they did not allocate enough effort to adjust to a potentially underactivated state (Wiersema et al., 2006). In a motor presetting experiment, a larger sensitivity for increased ISI was found among hyperactive children (van der Meere, Vreeling, & Sergeant, 1992).

In a matching familiar figures test, children with ADHD performed poorly on slow (15-s) and fast (5-s) trials but as well as controls on moderate (10-s) trials (Sonuga-Barke, 2002a). In a similar picture memory task, children with ADHD were faster but made more errors while using self-imposed presentation times, whereas they performed as well as controls when using externally imposed presentation times (Sonuga-Barke, Taylor, & Heptinstall, 1992).

In a sustained attention task (the continuous performance task), prolonged ISIs led to deteriorated performance and increased heart rate variability (Börger et al., 1999). Looking aside during long ISIs was used as a method to speed up perceived time of passage (Börger & van der Meere, 2000b). When a slow presentation rate was used in a continuous performance task, both reaction times and deterioration in performance over time were greater for children with ADHD compared with normal controls; however, MPH medication abolished these differences (van der Meere, Shalev, Börger, & Gross-Tsur, 1995).

Time perception may be conceived of as a low brain arousal task, and individuals with ADHD have been found to perform poorly in this task. Short intervals were underestimated and long intervals overestimated by children with ADHD, whereas intermediate intervals were best estimated. Controls generally underestimated increasingly with longer duration intervals (12, 24, 36, 48, and 60 s). A distractor (jack-in-the-box popping up) did not affect control children, whereas ADHD children were significantly less accurate when distracted, particularly in short durations (36 s or less). No effects of MPH were evident (Barkley, Koplowitz, Anderson, & McMurray, 1997). The distractor may be seen as increasing brain arousal to a moderate level during long latencies and to a high level under short latencies. Impairments in time discrimination for ADHD in which size errors interacted with time durations have been found in two studies (Smith, Taylor, Rogers, Newman, & Rubia, 2002; Toplak, Rucklidge, Hetherington, John, & Tannock, 2003).

Slow responses and large variability in performance have been found for children with ADHD in stop tasks (Scheres, Oosterlaan, & Sergeant, 2001) and in finger tapping for 1,000-ms ISIs (Rubia, Taylor, Taylor, & Sergeant, 1999). Finger tapping may be considered a low brain arousal task in which performance by those with ADHD should improve with shorter ISIs, and consistent with this view there were no deficiencies in motor timing ability for ISIs less than 1,000 ms (i.e., for 263 to 875 ms) (Tiffin-Richards, Hasselhorn, Richards, Banaschewski, & Rothenberger, 2004).

In temporal judgments (time estimation, production, and reproduction), children with ADHD also perform as well as controls at very short intervals (Brown & Vickers, 2004). In the visual half-field tasks (a perceptual task), ADHD children had faster reaction times, which would be indicative of faster interhemispheric transfer. Ivry (2003) suggested that this might be due to arousal effects, or that tasks with short intervals of less than 1 s are cerebellar tasks whereas tasks longer than 1 s involve frontal regions. In Brown et al.'s (2004) experiments, MPH did not affect the results at all. In a speech perception task consisting of identifying syllables for 10, 70, or 500 ms, the main effect was a decrement with decreasing ISIs; however, no interaction effects were found for ADHD versus control children in the different ISIs (Breier, Gray, Fletcher, Foor-

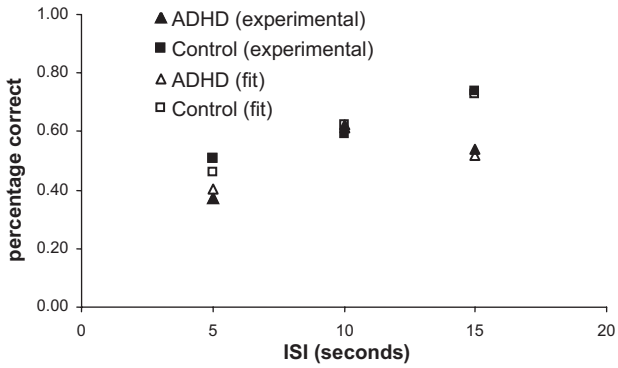

Figure 4. Proportion of correct recall as a function of interstimulus interval (ISI) in the moderate brain arousal model. Experimental data (Sonuga-Barke, 2002a) for attention-deficit/hyperactivity disorder (ADHD) and control groups are shown as solid symbols for 5-, 10-, and 15-s ISIs. Fitted data are shown as open symbols.

man, & Klaas, 2002). The increasing inaccuracy in the performance of those with ADHD with longer target durations suggests that time reproduction errors are dependent on the poorly adjusted state induced by a slow event rate (Sergeant, Piek, & Oosterlaan, 2006); however, performance improves with feedback (McInerney & Kerns, 2003). In a time perception experiment using 400-, 2,000-, and 6,000-ms intervals, there was no difference in mean performance between those with ADHD and controls. However, standard deviation variability was significantly larger in the 2,000- and 6,000-ms conditions, thus indicating a deficit in time perception (Toplak et al., 2003).

To summarize, in our view there is an abundance of data indicating that ISI influences performance of individuals with ADHD differently from controls in a wide variety of tasks. Several studies show a pattern where those with ADHD perform better in moderate ISIs compared with slow and fast ISIs. The pattern that individuals with ADHD perform worse in long rather than moderate ISIs seems particularly clear, whereas the evidence that they perform worse in short compared with moderate ISIs is somewhat more mixed. However, these results should be viewed in light of the fact that the time interval needed for moderate stimulation varies highly depending on the specific task setting and the experience of the participants. In some tasks (e.g., time perception, finger tapping) it may be particularly difficult, because of a task's inherent qualities, to achieve a too high brain arousal state simply by manipulating ISIs, and in these conditions poor performance in those with ADHD would not be expected even for very short ISIs.

This would seem to indicate that particular experimental conditions and individual differences have to be taken into account before one can estimate an intermediate ISI. This may not be possible to achieve on a group level or simply by diagnosis type, because this level is influenced by the participant's internal baseline noise level, specific experience, and skill at a particular task. It would therefore be advantageous to adjust the stimulation level individually to the particular settings and tasks (in the same way that medication levels are often set on an individual basis in ADHD).

Fitting the MBA Model to ISI Data From Sonuga-Barke (2002a)

The MBA model predicts that children with ADHD perform as well as controls for moderate presentation rates, whereas their performance is lower than controls' for shorter and longer presentation rates. This is predicted because the level of DA in ADHD systems is strongly dependent on stimulus frequency, which controls the phasic input. For moderately long presentation rates the DA level is well adjusted, or at a moderate level of brain arousal, whereas for longer and shorter presentation rates the DA levels are, respectively, too low (low brain arousal) or too high (high brain arousal). However, in normal systems the DA level is largely dependent on the tonic DA level rather than the phasic inputs and is therefore less influenced by the presentation rate.

The MBA model was fitted to the data from Sonuga-Barke (2002a) using Equation 3 (which indirectly uses Equations 1 and 2). The total DA was calculated from Equation 1, using tonic DA level, phasic DA level, and fast ($f = 1/5$), intermediate ($f = 1/10$), and slow ($f = 1/15$) presentation rates, respectively. To minimize the number of free parameters in the model, we fit the model only by adjusting the DA levels and the overall level of performance. Other parameters that were not essential for fitting were set to a standard value of 1 (i.e., $S = \sigma_N = 1$). The bias term in the sigmoid function was set so that the overall activity was low ($T = 4$, which yields reasonably low activity around .01 to .1 depending on other parameters). This value was chosen because the biological neural system typically operates at low neural levels and because the stochastic resonance phenomenon is pronounced at this parameter regime. Five parameters were adjusted so that the mean squared error was minimized ($MSE = 0.0009$): β_p (ADHD) = 22.4, β_p (control) = 8.9, β_t (control) = 0.0, β_t (ADHD) = –1.4,[1] and $c = 0.45$. That is, the total DA levels varied more for the ADHD group (0.1, 0.8, and 3.1) compared with the control group (0.5, 0.8, and 1.7 for fast, moderate, and slow presentation rates, respectively). The results in Figure 4 show a reasonably good fit to the empirical data.

Consistent with the MBA model predictions and Grace's (Grace, 2001) tonic–phasic DA model, the fit produced considerably lower tonic DA and considerably higher phasic DA levels for the ADHD group compared with the control group. The results show similar performance for the ADHD and control groups for intermediate presentation rates but attenuated performance for slow and fast rates.

It should be noted that the fit of the model is not due merely to an adjustment of a flexible model. First, the number of parameters in the model is smaller than the number of fitted data points. Second, and more important, the qualitative predictions of the model hold true for all allowed parameter settings. By allowed parameter settings, we mean biological findings that constrain the parameters—for example, that the phasic DA level is relatively lower for ADHD than for normal neural systems—which give rise to a number of predictions in the model. The model could not be tuned to account for qualitatively different outcomes of the data, and it is therefore potentially possible to falsify. Fits of similar quality are obtained when the standard parameters are set to different values.

[1] The negative value of tonic DA, produced by the fit, can be explained by averaging the DA across time. That is, following a stimulus onset, phasic DA release is maintained over a longer time period, possibly owing to recurrent activation, so that the tonic DA levels never fall below zero. To eliminate DA floor effects in the model, we have imposed the restriction that the total DA is always greater than zero for any f (see the text near Equation 1). However, the negative value of β_t in the fits for ADHD indicates that the total DA levels are at a floor effect (i.e., near zero total DA) for hypothetical frequency of stimulation that are lower than the experimental conditions. Arguably, most environments have reasonably large stimuli levels, either naturally included in the external environment, self-generated by actions from the individual (possibly related to hyperactivity in ADHD), or internally generated by a continuous communication between neural cells, so that the DA levels are always well above zero. According to this perspective, the phasic DA would be related to all input that the neural cells receive (not necessarily time-locked to the onset of an external stimulus as the term is commonly used), whereas the tonic DA would be related only to spontaneous DA release in the absence of input to the cell. This interpretation suggests that cells with zero tonic DA levels would lack spontaneous firing, whereas cells with positive DA would be able to fire in the absence of neural input. In particular, for the fitted experimental conditions, the total DA levels were always larger than zero.

Attention-Removing Stimuli

Attention can be easily distracted in individuals with ADHD due to their low tonic DA level. This makes these individuals hyperreactive to all kinds of external stimulation. We define attention-removing stimuli as sudden changes in environmental stimuli that are irrelevant to the measured cognitive task. Examples of attention-removing stimuli are sudden speech utterances, novel classroom activities, and distracting sounds. According to the MBA model, these stimuli cause a sudden boosted phasic DA response in individuals with ADHD that makes them withdraw attention from the relevant cognitive task and causes deterioration in performance.

Data on attention-removing stimuli exist for various distractors, both external and within particular tests. External distractors, such as dropping books or the experimenter sorting papers or walking across the testing room, had a more negative effect on word recall tasks for ADHD compared with control children (Higginbotham & Bartling, 1993). In the presence of highly appealing toys, but not when they were absent, ADHD children (7–12 years old) spent half as much time watching a TV program. Recall of program content did not differ between groups (Landau, Lorch, & Milich, 1992). However, when recall tasks required structured knowledge of relations among events (in TV programs) controls outperformed ADHD children in the toy-present condition (Lorch et al., 2000). Among younger children (4–6 years old), the decrements in cognitive performance were more pronounced in the toy-present condition, but the difference between groups remained significant (Sanchez, Lorch, Milich, & Welsh, 1999). Exposure to videotaped classroom-based activity significantly increased both omission and commission errors for ADHD children compared with controls while a continuous performance task was completed (Rickman, 2001). Speech sound also negatively affected the performance of children with ADHD in auditory discrimination tasks (Corbett & Stanczak, 1999). During an outing to a zoo in which children were required to walk a marked route as quickly as possible, the ADHD group manifested inhibition deficits in terms of interference control, taking longer than controls to complete the route (Lawrence et al., 2002).

Task distractors in selective attention tasks affected both reaction times and accuracy more negatively in an ADHD group compared with controls (Brodeur & Pond, 2001). Congruent and incongruent flankers in flanker tasks made reaction times longer and increased the number of errors committed by ADHD children (Crone, Jennings, & van der Molen, 2003; Shalev & Tsal, 2003). The short distance between target and distracting flankers also contributed to more errors (Shalev & Tsal, 2003).

In signal-detection tasks, children with ADHD showed no differences compared with controls when the stimuli were presented binaurally to both ears (Pillsbury, Grose, Coleman, Conners, & Hall, 1995). However, when noise was added to the contralateral ear, more false alarms in the signal-detection task were committed by the ADHD group compared with controls (central masking, random shift between ears) (Breier, Gray, Klaas, Fletcher, & Foorman, 2002). An auditory tone and a masker tone were used in a signal-detection task (Gray, Breier, Foorman, & Fletcher, 2002). The results revealed no differences between the ADHD group and controls in a quiet condition without masker. However, when uncertainty was added by means of the random selection of one ear for the presentation of the stimulus and the opposite ear for the masker tone, the ADHD group committed more false alarms than the control group. This suggests that individuals with ADHD have difficulty switching attention between ears. These findings resonate with findings obtained in dichotic listening, where increased top-down control is required to identify syllables presented in a forced left ear condition, whereas there is a right ear preference as far as attention is concerned (Hugdahl et al., 2003). When more uncertainty was added in the auditory tone and masker tone, the false alarm rate increased to the same level for both groups. In a high-uncertainty condition, both control and ADHD children were impulsive (Gray et al., 2002). Stimulus predictability is therefore considered to be attention focusing, whereas stimulus unpredictability, using random ear switching and masker tone frequency, is considered to be attention removing.

Highly appealing external distractors, such as toys (Lorch et al., 2000), animated cartoons, or watching television, had a more negative effect for ADHD compared with control children (Blakeman, 2000; Bunner, 1998). However, when the distractor was of low appeal (i.e., the random presentation of letters) this effect disappeared (Blakeman, 2000). Attention-removing stimuli need to be of particular significance in order to create phasic responses that are sufficient to cause withdrawal of the participant's attention.

Incongruent Stroop conditions are another example of a task where interfering stimuli (e.g., the word *red* written in green letters) removes attention from task-related stimuli (e.g., the naming of the color green). The MBA model predicts poorer performance for individuals with ADHD compared with controls. The Stroop experiment also includes congruent control conditions (e.g., reading of the word *red* printed in red color and color naming of colored dots). Typically the congruent conditions are self-paced and are conducted with the instructions to perform the task as fast as possible. This leads to short ISIs and, according to the MBA model, to a high brain arousal state and poorer performance in those with ADHD compared with controls. Because the magnitudes of the deficits depend on a complex interaction of various environmental variables, the MBA model makes no explicit predictions as to whether the deficits are larger in congruent or incongruent conditions; however, the incongruent condition is considered attention removing.

In a meta-analysis of the Stroop effects, van Mourik, Oosterlaan, and Sergeant (2005) found that ADHD children performed worse than controls in word reading (congruent), color naming (congruent), and interference (incongruent). The effect sizes for word reading ($d = 0.49$) and color naming ($d = 0.58$) were larger and more homogeneous than the effect size for incongruent interference ($d = 0.35$). In another meta-analysis, by Homack and Riccio (2004), the effect sizes were slightly larger, particularly in the interference condition: word reading ($d = 0.60$), color naming ($d = 0.65$), and interference ($d = 0.75$). Different theoretical accounts have been suggested for the slow processing speed typically found in ADHD, as shown in congruent Stroop task performance (Sergeant, Oosterlaan, & van der Meere, 1999): for example, a general PFC hypofunctioning (Zang et al., 2005), itself reflecting a poorly adjusted activation state (Sergeant, 2000; Sergeant et al., 1999), or abnormalities in brain structure (van Mourik, Oosterlaan, & Sergeant, 2005).

Prolonged interference latencies in Stroop task performance have been explained via two theoretical perspectives: the sequential model and the parallel distributed processing model (MacLeod, 1991). The earlier of the two, the *sequential model*, claims that reading must be completed before color naming can begin (MacLeod, 1991). If the Stroop effect depends principally on inhibition, incongruent Stroop results should be more obvious because there is strong evidence for ADHD being an inhibitory disorder, as measured in various tests (Barkley, 1997; Nigg, 2001). The sequential model (MacLeod, 1991) has been abandoned in favor of the *parallel distributed processing model*, which claims that strength rather than speed, in these two competing processes, determines the degree of interference (MacLeod, 2005). A computational model was proposed by Cohen, Dunbar, and McClelland (1990), according to which parallel processing along multiple dimensions occurs simultaneously and buildup practice for the word pathway is greater than for the color pathway, a feature accounted for by interference. This process can, however, be tuned by attention mechanisms in the frontal (and parietal) executive networks (Corbetta & Shulman, 2002). The anterior cingulate cognitive division plays a pivotal role in attentional processing by modulating stimulus selection and mediating response selection (Bush et al., 1999), two crucial abilities in interference tasks such as the Stroop. In an fMRI study it was found that the ADHD group failed to activate the anterior cingulate cognitive division during the interference condition in a Stroop test, indicating hypoactivity as compared with normal controls, and relied on more distributed prefrontal activation patterns (Bush et al., 1999). Furthermore, interference suppression and inhibition are mediated differently, and children with ADHD showed deviating patterns from controls during fMRI scans in frontostriatal circuits (Vaidya et al., 2005).

Even if effect sizes for Stroop interference conditions are sometimes smaller than in color naming and word reading conditions, poor results in other interference tasks point toward a deficient interference control in ADHD (e.g., Crone et al., 2003; Lawrence et al., 2002). Impaired performance in Stroop and other interference tasks may be indicative of an underlying neurological disorder related to PFC dysfunction (Homack & Riccio, 2004). Children with ADHD also show major problems in responding to a central target flanked by adjacent incongruent distractors and when searching for a conjunctive target in a high-density display (Shalev & Tsal, 2003). These results suggest that individuals with ADHD are unable to restrict visual attention to a limited spatial area in order to selectively process relevant information and to ignore irrelevant information.

The effects of stimulant medication on inhibition and interference may shed new light on the character of these abilities. Nicotine is known to improve attention and memory task performance (Rezvani & Levin, 2001), and MPH has been found to ameliorate ADHD symptoms (Greenhill, 2001). Both nicotine and MPH affect the DA system, but in different ways. MPH blocks DA transporters, thus leading to a strong (e.g., 35-fold; Volkow et al., 2001) increase of tonic DA. This leads to a powerful stimulation of presynaptic autoreceptors and causes a marked attenuation of phasic DA release (Grace, 2000). A higher DA tone and a diminished phasic release facilitate inhibition and increase the SNR. Nicotine, similarly to alcohol and morphine, activates DA release by increasing DA neuron spike activity. However, it does not affect DA transporter function and therefore increases tonic DA level only moderately (e.g., twofold). This is of particular importance in ADHD children where an overactive DA transporter function is proposed (e.g., Krause, Dresel, Krause, la Fougere, & Ackenheil, 2003). This subcortical phasic spike activation leads to increased postsynaptic DA receptor stimulation and increased corticostriatal activation (Grace, 2000).

The effects of MPH and nicotine on ADHD participants performing Stroop tests were tested in three studies. Stroop interference speed was not improved by MPH in any of the studies (Bedard, Ickowicz, & Tannock, 2002; Potter & Newhouse, 2004; Scheres et al., 2003); however, MPH improved naming speed in the Bedard et al. (2002) study, and stop-signal reaction time was improved in the Potter and Newhouse (2004) study. In addition, flanker task and stop paradigm performance improved in the Scheres et al. (2003) study. Positive effects of MPH are also found on tasks of vigilance (e.g., continuous performance tasks) and impulse control (e.g., go/no-go tasks). The positive effects of MPH on inhibition have also been confirmed in other studies (e.g., Boonstra, Kooij, Oosterlaan, Sergeant, & Buitelaar, 2005).

Nicotine, in contrast to MPH, has been found to ameliorate Stroop interference speed but not stop-signal reaction time performance. Nicotine promotes phasic DA release in striatum, which projects onto PFC via ventral tegmental area. However, nicotine is still capable of mediating reinforcement as a result of neuron firing and overflow from the synaptic cleft (Grace, 2000). It has been shown that direct stimulation of DA neurons (3–4 Hz) elicits DA-related behaviors without marked changes in extracellular DA levels (Grace, 2000). The reinforcing effect of nicotine seems to promote interference control that requires the maintenance of two simultaneous processes: the inhibition of a faster process (word reading) and the responding with a slower process (color naming). A Stroop interference control task could therefore be conceived of as a high-DA task. Positive effects of nicotine are also found among normal controls and in different clinical groups such as schizophrenics and Alzheimer's disease patients, for whom nicotine may work by increasing the SNR (Rezvani & Levin, 2001). Chronic exposure may help to reduce the density of DA transporters (Levin, Conners, Silva, Canu, & March, 2001). The divergent effects of MPH and nicotine on inhibition and interference indicate that these tasks are mediated differently (Potter & Newhouse, 2004).

MPH has been found to facilitate inhibition in various tasks for children with ADHD—for example, prepulse inhibition during attended but not ignored prestimuli (Hawk, Yartz, Pelham, & Lock, 2003). However, the effect of MPH disappeared when ISIs were prolonged in an experiment by Hawk et al. (2003). Furthermore, in paced, auditory serial-addition tasks (where participants added random numbers from 0 to 9, with ISIs of 200 ms, and gave vocalized answers), with number generation as a control condition, MPH improved task performance and reduced regional cerebral blood flow in PFC and increased subcortical activity (basal ganglia and cerebellum) in both the experimental and the control conditions (Schweitzer et al., 2004). Schweitzer et al. (2004) suggested that the task-related decrease in regional cerebral blood flow was due to improved filtering out of task-irrelevant stimuli by way of MPH-mediated DA release in PFC. Increases in DA (tonic) have been shown to cause reductions in the firing activity of PFC neurons. An effect of DA is to enhance resistance against distractors, thereby boosting executive function performance (Schweitzer

et al., 2004). According to Schweitzer et al. (2004), the neural systems of persons with ADHD might show different activation patterns in executive function tasks, relying on basal ganglia and motor cortex rather than PFC activity. This results in a greater reliance on the neuroanatomy associated with visual, spatial, and motor processing than on the neuroanatomy associated with verbal strategies (Fassbender & Schweitzer, 2006).

Attention-Focusing Stimuli

Hypersensitivity to environmental stimuli in children with ADHD may also focus attention on the current task. This means that a salient stimulus related to the task evokes strong phasic responses in individuals with ADHD that focus attention on the current task. Examples of highly focusing stimuli are moving, novel, or colored objects in complex environments, such as those typically found in computer games, whereas more repetitive, stationary, or familiar objects are scored low on attention focusing.

The simplest form of attention-focusing stimulation is to manipulate stimulus properties. For example, Zentall and colleagues found that different kinds of stimulation (colors, size, movement) helped cognitive performance in a spelling task as long as the stimulation could be mapped to the target (and not to distractors) (Zentall, 1986; Zentall & Dwyer, 1989; Zentall, Falkenberg, & Smith, 1985; Zentall & Kruczek, 1988; Zentall, Zentall, & Barack, 1978; Zentall, Zentall, & Booth, 1978). In this context, hyperactivity is explained as a homeostatic response in an environment with too low levels of sensory input (Zentall & Zentall, 1983). Thus, relevant stimuli, such as color and location, can be used to direct attention to targets in a visual scene, according to Corbetta and Shulman (2002). In conclusion, colors can serve as attention focusing if they are used as within-test stimuli and do not interfere with the target stimulus.

Cognitive performance among children with ADHD is often assessed with tasks that demand working memory. As reviewed below, there are studies indicating that children with ADHD perform worse than controls under low working memory load but that this difference disappears as working load increases. These findings could be interpreted in the MBA model as an improvement in performance as the workload moves from low to moderate brain arousal. However, it is difficult to draw any firm conclusion on this aspect, as these studies use only two working memory levels; a more direct test of the MBA model would also require a high brain arousal state. First we review studies supporting the idea that an increase in working memory load improves performance in individuals with ADHD as they move from a low to moderate brain arousal state. Later we discuss the possibility that excessive working memory load leads to a high brain arousal state and lower performance in those with ADHD.

Videogames provide a more complex form of attention-focusing stimulation in which several crucial variables can be manipulated, such as ISIs, feedback rate, and working memory load. When a videogame task (high attention = focusing stimuli) was compared with a match-to-sample task (low attention), group differences occurred (Bunner, 1998). The high-attention task was defined as a high-interest task, and low-attention task as a low-interest task. In the high-interest (focusing stimuli) videogame, the ADHD and control groups performed at the same level, but in the low-interest (low-attention) task, the ADHD group performed worse (Bunner, 1998). In a simple target videogame and an adventure videogame, no differences were found in the level of performance (as measured by errors and rule violations) between ADHD and control groups (Lawrence et al., 2002), which is consistent with the idea that these conditions provide highly focusing stimuli. Furthermore, in an advanced videogame, a cartoon distractor did not affect performance negatively for the ADHD group, and this resistance to distraction remained even when working memory load was increased (Farrace-Di Zinno et al., 2001). During videogames, a cartoon distractor increased self-talk for ADHD children but did not attenuate performance; self-talk worked rather as a self-pacer (i.e., with focusing stimuli providing moderate brain arousal) (Lawrence et al., 2002).

Houghton et al. (2004) found a significant interaction between groups (ADHD vs. control) and working load in a videogame scenario. In the high-load condition a game rule had to be kept in mind (indirect maneuvering on the target). In the low-load condition participants maneuvered directly on the target. The ADHD group performed worse than controls in the low-load condition and at the same level in the high-load condition. The ADHD group also spent more time on the high-load condition compared with the low-load condition (Houghton et al., 2004). When working memory buffers were tested, children with ADHD performed as well as controls at increasing memory loads. However, decrements in response times were found in the ADHD group when the two tasks were performed concurrently (Karatekin, 2004). Increasing memory load in a selective attention task was found to affect the event-related potential (ERP); a prolonged, load-related positivity was found in normal controls (Gomarus, Althaus, Wijers, & Minderaa, 2006). Event-related desynchronization was mainly affected by stimulus load. In a comparison of alphabet tasks (low load) and math tasks (high load), children with ADHD were less distracted by external distractors and performed as well as controls in the high-load condition (Zentall & Shaw, 1980).

The effects of MPH in individuals with ADHD have been found to vary with working load in complex visual search tasks (Berman, Douglas, & Barr, 1999). In both low and high working load conditions, providing MPH to participants with ADHD caused error rate to diminish. MPH prolonged time on task and improved performance in the high-load condition. Furthermore, the higher the MPH dose was, the lower was the error rate (Berman et al., 1999). These findings were also confirmed in PET studies, where the effects of MPH diminished the SNR in brain activity, an effect that was larger in salient tasks compared with neutral tasks. That is, task-specific stimuli enhanced performance (Volkow et al., 2001, 2005).

To summarize, the above cited studies support the idea that increasing memory load improves performance in individuals with ADHD as they go from a low to moderate brain arousal state. However, excessive memory load may also lead to a high brain arousal state and lower cognitive performance. This suggests that controlling parameters influencing brain arousal is essential for making reliable predictions. A lack of appropriate control may lead to inconsistent results. In particular, this suggests that performance of those with ADHD would be highly variable depending on particular experimental conditions that influence the arousal level and that a lack of appropriate control would lead to equivocal results. Consistent with this view, working memory studies of ADHD have had variable results. An early review by Pennington

and Ozonoff (1996) concluded that there was no impairment among children with ADHD. More recent studies have revealed inconsistent results, some showing no working memory impairment (Kerns, McInerney, & Wilde, 2001) and others finding impairment (Karatekin & Asarnow, 1998; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). A meta-analysis addressed these inconsistent results and differentiated tests according to modality (verbal vs. spatial), processing level (memory storage vs. memory storage and manipulation), and moderating variables (reading or learning disabilities). The results revealed a general deficit in working memory processes for children with ADHD, with moderating variables having an effect on visuospatial but not verbal working memory (Martinussen, Hayden, Hogg-Johnson, & Tannock, 2005).

This is further exemplified by Vaidya et al.'s (1998) experiment, in which the effects of MPH in a go/no-go test within an fMRI study were measured. Activation in the frontal and striatal brain areas was assessed, and the tasks were equated in the number of key presses, that is, they were classified as either response controlled (6) or stimulus controlled (12), where the presentation rates were equated in the number of go tasks (no-go 50%) to control for response characteristics of the go and no-go trial blocks. This means that in the stimulus controlled go condition, ISIs were 1.4 s, and in the response-controlled condition ISIs were 3 s. (Each block lasted 25 s and six blocks were presented, which made the entire task last 3 min including instructions.) Results revealed differences between ADHD and control participants in striatal activity after MPH medication. ADHD participants showed increased activity, whereas controls showed decreased activity. However, this was valid only for the stimulus-controlled task (i.e., short ISIs) and not the response-controlled task (i.e., long ISIs). Furthermore, the MBA model also predicts greater variability (as discussed below) in ADHD, which might be a significant determinant of ADHD in cases where group means do not differ.

ADHD-Related Variability in Performance

Individuals with ADHD show greater variability in performance compared with controls (Castellanos et al., 2005; Leth-Steensen et al., 2000). This ADHD-related variability has been found both between and within participants. Increased variability is also found among older adults (Hultsch, MacDonald, & Dixon, 2002) and in childhood (Williams, Hultsch, Strauss, Hunter, & Tannock, 2005). DA transmission changes over a life span and deteriorates with age (Backman et al., 2000; Erixon-Lindroth et al., 2005). Variability has several neuromodulatory correlates such as an altering of DA functions, which has been implicated in aging and ADHD. Increased variability is strongly linked to frontal brain regions and is a more sensitive measure of dysfunctions as compared with group means in cognitive tests such as response latencies in episodic recall and choice reaction time (MacDonald, Nyberg, & Backman, 2006). Leth-Steensen et al. (2000) let participants perform a simple color-key matching task and found that those with ADHD had extremely large response time variability and slightly larger mean response times compared with controls. Comparisons with a younger control group ruled out the possibility that the data could be accounted for simply by the overall longer response time. Castellanos et al. (2005) used the Eriksen flanker task, where participants are instructed to respond *left* or *right* to a target arrow that is flanked with task-irrelevant arrows pointing in either the same or the opposite direction as the target arrow. Participants with ADHD had a larger variability in this task. In finger-tapping and anticipation tasks, participants with ADHD showed significantly more intraindividual variance compared with controls (Toplak & Tannock, 2005). In a time perception study, ADHD children with severe problems showed more intravariability (Toplak et al., 2003). Wider performance distributions have also been shown in various attention-demanding tasks, including sustained attention (continuous performance tasks), selective attention (conjunctive search), orienting attention (cost–benefit), and executive attention (Stroop) (Tsal, Shalev, & Mevorach, 2005).

The MBA model predicts ADHD-related variability because of a hypersensitivity to stimuli changes. Stimuli-evoked phasic DA responses are up-regulated by autoreceptors, yielding a large impact on behavioral performance. This means that a small variability in stimuli is up-regulated to a large variability in behavioral performance in ADHD. Stimuli's impact on performance was explored using the fits to Sonuga-Barke's (2002a) data. The predicted variability across the three ISI levels in Sonuga-Barke's data was 0.124 for ADHD and 0.114 for control, which agrees well with the empirical data (0.123 for ADHD and 0.117 for control). In the context of simulating this phenomenon, variability may be introduced both by internally generated stimuli, such as thoughts, self-generated associations, and task instructions, and by external stimuli, such as changes in ISI and novel stimuli.

Power-spectrum analysis has revealed that reaction time in the Eriksen flanker task varies over time with a predictable frequency of approximately 0.07 Hz, and that the amplitude of this variability was larger for ADHD than for control participants (Castellanos et al., 2005). This time-dependent variability may be compared with a 0.1-Hz variability found in heart rate and in neural activity of globus pallidus and subthalamic cells in immobilized rats (Ruskin et al., 2001). These oscillations are induced by the DA agonist apomorphine and terminated by the DA antagonist haloperidol. A speculative hypothesis is that these slow oscillations may be generated by the tonic–phasic feedback loop that, via autoreceptors, would form characteristic performance variability over time. In this context, a small variability in tonic DA in the ADHD system would be up-regulated to large variability in phasic responses.

Benefit of Moderate Noise Through Stochastic Resonance for Individuals With ADHD

The MBA model predicts an improvement in cognitive performance by children with ADHD in environments with moderate external noise levels. The basic assumption is that noise in the environment, through the perceptual system, introduces internal noise in the neural system. According to the stochastic resonance phenomenon, moderate noise is beneficial for cognitive performance in threshold-based systems, whereas both excessive and insufficient noise are detrimental. Figure 5 shows the predicted performance as a function of noise (for parameter settings, see fits below). The simulations show that the stochastic resonance curve is shifted to the right for ADHD, associated with a low gain (see Figure 2A), compared with controls. Thus, individuals with ADHD need more noise to achieve a high performance compared with controls.

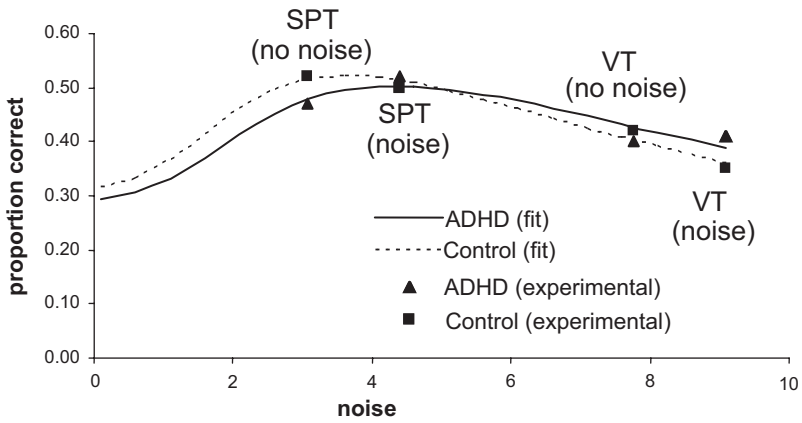

Figure 5. Proportion of correct recall as a function of noise intensity, divided into attention-deficit/hyperactivity disorder (ADHD) and control systems, in the moderate brain arousal model. The lower dopamine level in the ADHD system shifts the stochastic resonance curve to the right, indicating that more noise is needed for high performance compared with in the control system. Experimental data from Söderlund et al. (2007) are shown for ADHD and control groups, with the subject-performed task (SPT) assumed to have less internal noise than the verbal task (VT). Conditions with and without external auditory noise are also displayed.

We define noise as smooth and continuous environmental stimuli that are irrelevant to the cognitive task. Examples of noise stimuli that generate stochastic resonance are continuous white auditory noise and background music. It is important to emphasize the difference between attention-removing stimuli, discussed in the earlier section, and noise, as presented here. The former are abruptly presented stimuli that switch attention from the current task when they are introduced, whereas the latter is continuously and smoothly presented background noise that stimulates neural activity while maintaining attention to the current task.

It is proposed that this type of external background activity compensates for the reduced neural background activity in ADHD. Moderate external noise serves as an attention-focusing stimulus that produces a moderate brain arousal state. In a normal population, irrelevant acoustic noise of random frequency tones improved participants' reaction times in solving multiplication problems, in line with the MBA model. Intermediate noise (77 dB) improved reaction times the most, whereas both lower and higher noise levels caused deterioration in performance. This experiment used six noise levels ranging from 50 to 90 dB (Usher & Feingold, 2000). Consistent with the MBA model, favorite music served as a noise stimulus that enhanced performance of children with ADHD in solving arithmetic problems (a 33% increase of correct answers), whereas silence or speech did not. Controls performed equally well in all three conditions, although an interaction was found (Abikoff, Courtney, Szeibel, & Koplewicz, 1996). Rock music stimulation (Gerjets, Graw, Heise, Westermann, & Rothenberger, 2002b) also had a significant diminishing effect on the number of errors in a continuous performance task for the ADHD group but caused no change in performance for controls. A condition in which participants were screened off (to minimize distraction) during a continuous performance task was beneficial for controls (compared with a no-screen condition) but did not affect performance for the ADHD group. Of interest, it was also found that performance of the ADHD group improved significantly over time in the distracted (no-screen) condition, coming close to controls' performance by the end of the testing session. Distractive noise (music) used as external stimulation for the ADHD group (Gerjets et al., 2002b) served to generate a state of moderate brain arousal.

Further studies provide support for the hypothesis that noise facilitates performance in ADHD. For example, Kinsbourne and colleagues (1992, as cited in Abikoff et al., 1996) found that white auditory noise enhanced performance in a paired-associates learning test. White auditory noise also had a positive effect on the ADHD group and a negative effect on controls in an episodic memory test (Söderlund et al., 2007).

In a large population study of environmental stressors (Stansfeld et al., 2005), the effects of exposure to external aircraft and road traffic noise on children were studied. A population of 2,844 children between the ages of 8 and 12 was studied without taking diagnosed subgroups into account. Aircraft noise (here classified as an attention-removing stimulus owing to its sudden onset) caused impairments in reading comprehension and recognition memory. Of note, exposure to road traffic noise (here classified as attention focusing) was associated with increasing performance levels in episodic memory tests for the entire group (Stansfeld et al., 2005).

One theory of language impairments suggests that an increase in attention through the use of white or pink noise improves language performance (Johnsson, Segnestam, & Lacerda, 2002). This finding is explained by similar acoustic inputs adding to each other and, when they correlate around the same auditive coordinates, generating stochastic activity, which produces meaning from auditive noise. Concepts such as the magnet effect and emergent phonology are used to explain this phenomenon (Lacerda & Linblom, 1998).

Fitting the MBA Model to Stochastic Resonance Relevant Data From Söderlund et al. (2007)

Söderlund et al. (2007) investigated the influence of auditory white noise in ADHD. In a subject-performed task (SPT) condition, participants were given short verbal commands (e.g., "lift the

pen") and were instructed to perform them motorically. In a verbal task (VT) condition, participants encoded the commands without enactment. Twelve commands were presented for 9 s each, followed by a free-recall test. (See Nilsson, 2000, for details about experimental setup and design.)

The ADHD and control groups performed equally well in both the SPT and the VT conditions when results were summed. However, the ADHD group performed better in the presence of auditory white noise compared with silence, whereas the control group performed better in silence compared with auditory white noise. In particular, ADHD participants benefited from noise in the SPT condition, whereas performance was attenuated for controls in the VT condition.

The MBA model was fitted to the Söderlund et al. (2007) data, where external auditory noise was assumed to evoke noise in the neural system. Parameters used for fitting were the noise level, the overall performance, and the relative level of DA for the ADHD group (compared with controls). To minimize the number of parameters, we set other parameters to standard values of 1 (similarly to the fit of the Sonuga-Barke, 2002a, data above), that is, $S = \beta(c) = 1$ and $T = 4$. The silent SPT condition was modeled with a certain amount of baseline noise (σ_N[silent SPT]). The auditory noise conditions were modeled by adding (σ_N[noise]) noise to the silent SPT condition. The VT conditions were modeled by adding (σ_N[VT]) noise to the SPT conditions (i.e., they were associated with poorer performance compared with the SPT conditions; similar results are obtained if the VT conditions are modeled with a lower signal than the SPT conditions). The predicted performance was calculated using Equation 3 (and Equation 2). The total DA (β) was used as a parameter in the model (i.e., Equation 1 was not used because the experiment did not manipulate ISI). The mean squared error was minimized to 0.00029 by adjusting the five parameters to β(ADHD) = 0.88, s_N(silent SPT) = 1.34, σ_N(noise) = 0.75, σ_N(VT) = 2.68, and $C/f = 3.15$.

The results in Figure 5 show the proportion of correct recall as a function of noise. The two VT conditions (on the right side of the curve) have lower performance due to elevated noise levels compared with the two SPT conditions (on the left side). Stochastic resonance is apparent in the figure because performance increases with moderate noise. For the ADHD group, low DA levels shift the stochastic resonance curves to the right so that more noise is needed for efficient performance compared with controls. In the SPT condition performance of the ADHD group improves with noise levels, whereas there is no significant difference in the control group. In the VT condition noise does not influence performance in the ADHD group, whereas performance attenuates in the control group.

The fit above is based on the assumption that external auditive noise, through activation of the neural system, gives rise to internal neural noise. A complementary view is that the external auditive noise, through activation of the neural system, increases the DA release. According to this perspective, the ADHD data will have a right-shifted stochastic resonance curve owing to lower levels of DA, so that more noise is required for high cognitive performance. This noise-induced DA model was fitted to the Söderlund et al. (2007) data by adding DA in the noise conditions (β[noise]). The VT and SPT tasks were modeled (as above) by adding noise (σ_N[VT]) in the VT conditions. The following five parameter values were obtained by the fit: β(ADHD) = 1.34, $\beta(c) = 1.8$, β(noise) = 0.54, s_N(VT) = 0.70, and $C/f = 2.4$. Other parameters were set to the standard values, $S = \sigma_N = 1$ and $T = 4$. The results show a reasonably good fit to the empirical data ($MSE = 0.00016$). This suggests the possibility that noise may induce DA, leading to a noise-induced rightward shift of the performance curve for ADHD compared with control data. We find this view of auditory noise inducing DA to be complementary to the view that auditory noise induces internal noise.

The qualitative predictions of the model hold true for all reasonable parameter settings of the model. That is, it is not possible to adjust the parameters (within the allowed, or biologically constrained, values) to obtain qualitatively different predictions. In particular, it is the lower DA levels for ADHD neural systems that drive the prediction that noise is more beneficial for cognitive performance in individuals with ADHD than in others. The number of fitted parameters was smaller than the number of data points, and fits of similar quality were obtained when standard parameters were set to different values.

The fitted parameters also revealed similar values across experiments. For example, the total DA levels ($\beta_t + \beta_p f$) in Sonuga-Barke's (2002a) data were fitted in the range from 0.1 to 3.0, and in the Söderlund et al. (2007) data in the range from 1.3 to 2.3, in the noise-inducing-DA fit where DA was allowed to vary freely. In the noise-inducing-internal-noise fit, the control DA levels were fixed to the standard value; however, when the DA levels were allowed to vary, they converged to values between 0.59 and 0.70. The fact that these DA values are slightly lower than the values obtained in the Sonuga-Barke fit was expected given that Söderlund et al.'s data were collected in a less arousing setting (i.e., where one word was presented every 9 s, whereas Sonuga-Barke's task involved discrimination between six different stimuli during 5 to 15 s).

In the Söderlund et al. (2007) noise-inducing-internal-noise data, the noise levels were fitted, whereas this parameter was held constant in Sonuga-Barke's (2002a) fit. When the Söderlund et al. fit was constrained so that the average noise levels were identical to Sonuga-Barke's data (i.e., 1), the DA levels converged to an average value of 1.6, which is well within the range of DA levels in Sonuga-Barke's fit, indicating that fits can be obtained where the parameter values are similar across conditions. Other comparable parameters were set to standard values and were identical.

Conflicting Results

The MBA model suggests that performance of individuals with ADHD depends on several factors. For example, it depends on whether stimuli are attention removing or attention focusing, and noise can act in both ways depending on its character and onset. Furthermore, ISIs affect performance through brain arousal, and individuals with ADHD generate more variable data in general. These predictions naturally follow from a few basic neurophysiologically based principles on which the model is based. Despite these simple assumptions, the predictions depend on several factors. Given the MBA model, experimental conditions could be set up that would provide straightforward predictions. However, the large number of experiments that we have used to validate our account were obviously designed with other purposes in mind. Thus, the stimuli used in these experiments sometimes fall into more than one category, and in some cases the methods are not

sufficiently explicit to allow specific predictions. These circumstances sometimes make predictions difficult or ambiguous. As reviewed above, we believe that our account has ample empirical support; however, we focus here on predictions that are problematic and on conflicting results.

Geffner, Lucker, and Koch (1996) conducted an auditory speech discrimination test (picture pointing and word recall tests) with three noise/distractor conditions: cafeteria sound (nonmeaningful speech), continuous meaningful speech, and fan noise (nonmeaningful nonspeech). According to our definition, the fan noise and possibly the nonmeaningful speech (cafeteria sound) should be considered attention-focusing noise, whereas the meaningful speech should be considered an attention-removing stimulus. However, ADHD participants performed less well than controls in all three conditions. Explicit predictions are problematic in these experiments because the ISIs were undefined in the word list, picture pointing, and discrimination tests (Geffner et al., 1996).

Furthermore, our model suggests a complex interaction between ISI and noise levels. Noise levels used by Geffner et al. (1996) in the word test were SNR +10 dB, with words presented at 50 dB above hearing level. The discrimination test was administered at a "comfortable" listening level, with noise randomly changing between SNR +6 and SNR −6 dB. In a stochastic resonance experiment, Usher and Feingold (2000) showed that noise levels are essential for performance in a normal population. In this experiment, in which participants solved arithmetic problems under different noise levels, the best performance was found for 77 dB, and no effects could be seen under 50 dB. This indicates that the noise levels were too low in Geffner et al.'s experiment for achieving high performance.

Zentall and Shaw (1980) presented high and low levels of linguistic classroom noise while children performed auditory processing tasks, alphabet tasks, and mathematical tasks. Whether classroom noise should be considered to be attention removing or attention focusing depends on the salience of the speech sounds (i.e., to what extent the content of the spoken language is understandable). In this experiment hyperactive children showed more motor activity and impaired results in the high-noise condition, whereas controls showed the opposite performance results and activity patterns. However, the differential effects of linguistic noise were less pronounced when the task was new and more challenging, suggesting that task difficulty may play a role in the effects of overlapping stimulation on both groups.

Discussion

In this article we have suggested that individuals with ADHD are hypersensitive to environmental stimulation. In impoverished environments, neural transmission is relatively more dependent on tonic than phasic DA, and low tonic DA levels in ADHD yield poor cognitive functioning. However, in moderately arousing environments, stimulus-evoked phasic DA responses compensate for the low tonic DA level to enhance cognitive performance. These phasic responses are up-regulated by autoreceptors in the ADHD system, whereas in normal systems the phasic responses are down-regulated through continuous tonic DA stimulation. Hyperactivity may be a self-regulating mechanism that raises DA to moderate levels. However, sudden environmental changes or excessive environmental stimulation may generate too much phasic DA, which causes a switching of attention from the current task, attention deficit, and poor cognitive performance.

Cognitive performance in individuals with ADHD is vulnerable to surrounding conditions and to poor adaptation to environmental demands. The MBA model suggests that under well-adjusted environmental conditions it is possible for those with ADHD to perform at the same level as others, whereas under poor conditions their performance is worse. This prediction is consistent with, and suggests a reason for, the divergent experimental findings, with some studies showing poorer performance for participants with ADHD (e.g., Bedard et al., 2003; Nigg, 2001; Oie, Sunde, & Rund, 1999; Paule et al., 2000) and other studies showing the same performance as controls (e.g., Farrace-Di Zinno et al., 2001; Lawrence et al., 2002; Rashid et al., 2001). Furthermore, it provides a comprehensible framework for how experimental conditions influence performance that would help explain results of studies in which explicit manipulations yield either equal or lower performance for ADHD compared with control participants (Sonuga-Barke, 2002a).

We have also suggested that moderately continuous noisy environments are beneficial for cognitive performance in individuals with ADHD, as compared with environments with too much or too little noise. The basic assumption, described above, is that the noisy environment, via the perceptual system, raises noise levels in the neural system. This can also be thought of as raising the arousal level in the brain, because well-tuned noise levels enhance signal transmission and information processing by increasing the SNR. According to the stochastic resonance phenomenon, moderate noise is beneficial for performance in threshold-based systems. Simulation results show that more noise is needed by those with ADHD, who are associated with low DA levels (i.e., low gain), to reach high cognitive performance. Consistent with these predictions, empirical data indicate that participants with ADHD perform better in surroundings with auditory noise, traffic noise, music, and so forth (Abikoff et al., 1996; Gerjets et al., 2002b; Söderlund et al., 2007; Stansfeld et al., 2005).

An alternative explanation to the stochastic resonance phenomenon is that external noise produces prolonged, continuous phasic DA release, which also raises tonic DA levels. This in turn would raise the total DA levels to a state of moderate brain arousal that is beneficial for performance in those with ADHD. Consistent with empirical behavioral data, this noise–DA theory would predict that individuals with ADHD benefit more from noise than others. However, the noise–DA hypothesis would also predict that excessive noise harms performance of those with ADHD more than others and that they would have a narrower level of well-tuned noise levels (SNR) than others. Looking at the available evidence, we are inclined to be more supportive of the stochastic resonance hypothesis than the noise–DA hypothesis. More data would be required to rule out either of these hypotheses; however, these proposals do not contradict each other and could be valid simultaneously. Furthermore, it is unclear whether continuous smooth noise causes continuous activation of the DA system or whether phasic response would be attenuated by habituation following prolonged exposure to noise.

Response variability is a ubiquitous finding in ADHD research, across a variety of tasks, states, and environmental factors. In coherence with the proposed hypersensitivity to environmental

variables, the MBA model predicts larger variability in individuals with ADHD compared with others.

Although the present article has focused on DA transmission, there are certainly other factors that may contribute to ADHD behavior. For example, a recent neurocomputational model suggests that NE may also play a pivotal role in the clinical syndrome of ADHD (Frank et al., 2007). Apart from biochemistry in the brain, environmental factors such as parenting and societal styles predict ADHD behavior (see Sagvolden et al., 2005, p. 9). These environmental factors can be either positive or negative for the behavioral outcome. In particular, the MBA model suggests that DA levels interact with several environmental factors, such as white noise, ISIs, and working load. These effects may also carry longtime changes in higher level cognition such as self-esteem and mood (Sagvolden et al., 2005). This strong interaction between DA and behavior suggests that it is difficult to draw causal conclusions regarding whether DA transmission is causing an effect on behavior or whether the environment is influencing the DA levels. Nevertheless, there is a high genetic contribution to the traits of ADHD and the associated DA systems.

Further evidence of stochastic resonance is provided by a selective positive effect of noise in older people, who are associated with lower DA levels than younger people. The stochastic resonance phenomenon has been successfully modeled in aging research, and simulations showed that older participants required more noise for successful signal detection as compared with normal controls (Li, von Oertzen, & Lindenberger, 2006).

Comparing the MBA Model With Current ADHD Theories

In searching for the underlying causes of ADHD, it would be useful to identify relevant neuroscience and psychological constructs that differentiate between persons with and without ADHD. Examples of such constructs are (a) delay aversion, (b) deficit in arousal/activation regulation, and (c) motor inhibition deficit, or hyperactivity (Castellanos & Tannock, 2002). Here we examine whether there are any relevant measurable units that can encapsulate these constructs and reveal their relation to current ADHD theories and the MBA model.

The mechanisms underlying ADHD are not fully known, and current models take different perspectives. Some emphasize process factors (top-down) in the frontal cortex and stress inhibition as the core deficit in ADHD (Barkley, 1997). Other models stress subcortical and brain stem loci as regions of interest and include state factors and bottom-up processes such as energetic factors (Sergeant, 2000), optimal stimulation (Zentall & Zentall, 1983), delay aversion (Sonuga-Barke, 2002b), and altered reinforcement and extinction deficit (Sagvolden et al., 2005).

Delay aversion. Delay aversion refers to an intolerance for waiting and is manifested as a tendency to select an immediate reward rather than a larger delayed reward. Sonuga-Barke (2002b) argued that delay aversion is an acquired characteristic that is based on fundamental abnormalities in reward mechanisms. Individuals with ADHD display a faster decline in the effectiveness of reinforcement as the delay between behavior and reward increases, resulting in a shorter delay gradient. Escape or avoidance of delay is also well documented for ADHD in behavioral studies (Kuntsi, Oosterlaan, & Stevenson, 2001; Sonuga-Barke, De Houwer, De Ruiter, Ajzenstzen, & Holland, 2004; Sonuga-Barke, Taylor, & Heptinstall, 1992; Sonuga-Barke, Taylor, Sembi, & Smith, 1992; Tripp & Alsop, 2001).

Solanto et al. (2001) showed that a certain subgroup of individuals with ADHD show delay aversion whereas another subgroup show inhibitory failure. Delay aversion, as measured by the choice-delay task, correlated with a broad range of ADHD characteristics, such as teacher ratings of impulsivity, hyperactivity, conduct problems, and gross motor activity. In contrast, inhibitory failure, as measured by the stop-signal task, taps into a more discrete dimension of executive control.

Dual-pathway theory proposes a reward circuit that is modulated by the mesolimbic DA pathway, involving ventral tegmental area, orbitofrontal cortex, and amygdala. Inattention, impulsiveness, and overactivity are all defined as delay aversion features in ADHD and are explained by an allocation of attention to environment aspects that speeds up the perceived passage of time in order to avoid the experience of delay (Sonuga-Barke, 2003, 2005). Thus, individuals with ADHD cannot benefit from prolonged time at task (ISI) in the way that controls can (Sonuga-Barke, 2002a; Sonuga-Barke, Taylor, & Heptinstall, 1992). This view is complementary to the MBA model, according to which prolonged ISIs produce insufficient phasic responses, thus generating too little DA and resulting in a low brain arousal state.

In dynamic developmental theory, delay aversion and response disinhibition are viewed as extinction deficits (Sagvolden et al., 2005). According to this theory, low tonic DA levels and stunted phasic DA responses to external stimulation produce shorter delay-of-reinforcement gradients, while it takes more time and effort to build up sufficient DA levels via reinforcement for proper learning. Furthermore, in dynamic developmental theory extinction does not work properly in ADHD, owing to a floor effect. The relatively low value of reinforcement (i.e., stunted phasic DA response) results in less synaptic depression, thereby causing situational maladaptation (Sagvolden et al., 2005).

However, dynamic developmental theory is inconsistent with the tonic–phasic DA model (Grace, 1991, 1995), according to which low tonic DA levels are associated with elevated phasic DA responses. The MBA model proposes, consistent with the tonic–phasic model (Grace, 1991, 2001), low tonic and relatively elevated phasic DA responses in ADHD. In accordance with the MBA model, elevated phasic baseline DA levels cause a ceiling effect in DA response, by which immediate reinforcement reaches a high DA level, which overshadows and suppresses competitive delayed reinforcement (Sonuga-Barke, Taylor, Sembi, & Smith, 1992). As a consequence of the ceiling effect, a withdrawal of a reward and its consequent shutdown of phasic DA response would also produce a much greater negative effect on someone with ADHD (Grace, 2001). Nevertheless, both dynamic developmental theory and the MBA model propose shortened and steeper delay gradients in ADHD, in accordance with compelling behavioral data. Although several practical implications of the two models are similar, the MBA model elaborates on possible interventions that influence cognitive performance (e.g., noise, ISI, and working load manipulations).

Deficit in arousal/activation regulation. The MBA model proposes that external stimuli (i.e., bottom-up processes) may withdraw attention from the current task (i.e., top-down processing) if brain arousal is poorly tuned. The PFC plays an important role in

this process. A unique feature of PFC neurons is their ability to hold information online in the presence of interfering stimuli (Arnsten & Li, 2005). In a recent study, moderate doses of MPH improved PFC performance, whereas high doses produced perseverative errors (Arnsten & Dudley, 2005). That is, appropriate tuning is associated with the moderate brain arousal state in task-related areas. Adaptation failures to environmental demands are here considered a hallmark of ADHD.

Dynamic developmental theory (Sagvolden et al., 2005) claims that if response contingencies are appropriate, encounters with changing situations can serve as attention-focusing stimulation. These changes explain the relative calmness of children with ADHD in novel situations and why they can stay focused in highly reinforcing environments (e.g., playing videogames) or while performing hazardous acts (e.g., ski jumping). In these conditions high DA levels are produced so that attention is maintained despite stunted phasic release (through synaptic summation and modulatory effects via second messengers, a property of DA) (Sagvolden et al., 2005). In contrast, the MBA model suggests that novel environmental stimuli cause elevated (i.e., not stunted) phasic DA response, thus leading to focused attention on task-relevant stimuli.

The cognitive–energetic model focuses on energetic levels. This model is supported by the finding that an externally applied event rate (ISIs) alters the participants' energetic state, giving rise to both over- and underarousal (Sergeant, 2000). As confirmatory evidence, MPH has been found to have the same effect as an increased event rate, with both being seen as state-regulating factors (van der Meere et al., 1999). Effort has also been manipulated through working load and was found to have a positive effect on cognitive performance in ADHD (Sergeant, 2000).

According to the optimal stimulation model, Zentall and Zentall (1983) argue, hyperactivity stems from low levels of arousal and serves to maintain a well-tuned arousal level. Hyperactivity, impulsivity, and a short attention span should be seen as a form of self-stimulation to achieve a nicely tuned arousal level. Behaviors supporting this view are reward-seeking and stimulation-seeking behaviors, often seen in ADHD (Zentall & Zentall, 1983). Different kinds of stimulation (colors, size, movement) have also been found to help cognitive performance in spelling tasks, for example, provided the stimulation can be mapped to a target and not to distractors (Zentall, 1986; Zentall & Dwyer, 1989; Zentall et al., 1985; Zentall & Kruczek, 1988; Zentall, Zentall, & Barack, 1978; Zentall, Zentall, & Booth, 1978).

Behavior therapy programs that systematically use response contingencies have been found less effective than stimulant drug treatment (Greenhill, 2001; Greenhill, Findling, & Swanson, 2002). The long-term effects of behavior therapy in which inhibition is systematically trained are very small in individuals with ADHD (Barkley, 1998, 2002), owing to their strong aversive reaction to withdrawal of reinforcements. Cognitive–behavioral interventions, self-monitoring training, and self-control techniques have not so far been generalized beyond the treatment context in ADHD patients (Solanto, 2001).

Motor inhibition/hyperactivity. Children with ADHD are more active than other children, a fact that has been found even during sleep registered by a movement monitor (Porrino, Rapoport, Behar, Sceery, et al., 1983). Recent theories consider hyperactivity to be compensation for lack of external stimulation (Barkley, 1997; Sergeant, 2000; Sonuga-Barke, 2003; Zentall & Zentall, 1983). In low-stimuli environments ADHD children allocate their attention to aspects of the environment that speed up the perceived passage of time. This can be done through motor stimulation, fidgeting, self-pacing, and so forth (Sonuga-Barke, 2002b, 2003). Dynamic developmental theory considers hyperactivity a primary symptom in ADHD due to a dysfunctioning nigrostriatal DA branch (Sagvolden et al., 2005).

According to Solanto (2001, 2002), motor activity is controlled by direct and indirect DA pathways, involving cortical and subcortical areas. Depletion of DA in the direct pathway results in difficulties in initiating movement (go movements), as seen in individuals with Parkinson's disease. Hyperactivity can be seen as either excessive DA activity in the direct pathway (too much go activity) or insufficient inhibitory tone in the indirect pathway (too little no-go activity). Castellanos (1997) suggested that ADHD is distinguished by a *hypodopaminergic* transmission in PFC and a *hyperdopaminergic* transmission subcortically (e.g., in the basal ganglia). Consistent with this idea, providing MPH increased PFC activity for children with and without ADHD; however, children without ADHD showed decreased striatal activity, whereas those with ADHD showed increased activity in striatum (Vaidya et al., 1998).

Time–action and dose–response curves for motor and cognitive effects of MPH diverge. MPH causes longer lasting reduction in motor activity and larger effect sizes compared with changes in cognitive performance (Solanto, 2002). These differences may be related to the fact that D_2 receptors are more abundant in striatum and D_1 receptors are more represented in PFC (Goldman-Rakic, Castner, Svensson, Siever, & Williams, 2004; Goldman-Rakic et al., 2000). Tonic stimulation acts on D_2 receptors through autoreceptors, whereas D_1 receptors are activated postsynaptically on phasic input (Onn, Wang, Lin, & Grace, 2006). Whereas DA transporter density is high in striatum and low in PFC, the effects of MPH are differentiated. Levels of extracellular DA rise more in striatum than in PFC, which heightens the threshold for action–inhibition through D_2 receptors (Madras et al., 2005). This in turn makes the subcortical projections of afferent input sparser and more salient; only the strongest impulses remain in PFC mediated by D_1 receptors (Seamans & Yang, 2004). To conclude, increased subcortical DA (D_2) activity raises the inhibitory tone (D_1) in PFC and diminishes locomotor activation.

The MBA model suggests that motor activity can, depending on the task, be either attention removing or attention focusing. When motor activity works as a focusing stimulus, it is top-down driven, with motor activity connected to target stimuli and serving as a brain arouser (toward a moderate arousal level). Stimulus-dependent DA release resulting from task-related activities makes the target stimuli become more salient, yielding a stable working memory and stable network representations (Seamans & Yang, 2004). However, motor activity can also be attention removing when one is attending to irrelevant external stimulation. When irrelevant stimuli are attended to, target stimuli lose their salience. This results in multiple inputs impinging on PFC simultaneously and working memory buffers getting overloaded, viewed as a high brain arousal state.

In conclusion, with the exception of dynamic developmental theory, the models of ADHD reviewed above do not propose specific neuronal mechanisms as underlying the behavioral symp-

toms of ADHD. These models propose deficits in loosely defined cognitive functions. Although the models provide descriptive and verbal guidance, they have not been computationally implemented and therefore do not provide detailed quantitative predictions. The MBA model suggests that biologically plausible neural mechanisms—stochastic resonance and tonic and phasic DA—contribute significantly to the cognitive and behavioral deficits observed in ADHD. The model can therefore generate specific and testable predictions about performance in ADHD.

Benefit of Moderate Noise Through Stochastic Resonance for Individuals With ADHD

We are unaware of any previous attempts to map stochastic resonance to ADHD. However, the enhancing effect of noise in signal detection in normal populations is well documented (Moss et al., 2004; Simonotto et al., 1999; Wells et al., 2005). fMRI and ERP studies have found changes in neural activity due to noise (Novitski et al., 2003; Simonotto et al., 1999). Increased activity as measured by fMRI has been found in the visual cortex. ERP measurements showed increased latencies and changes of amplitudes in control participants during continuous performance tests. Participants with ADHD showed stunted amplitude, particularly in the P3a and P3b components, which argues for positive effects of extra stimulation such as noise (Banaschewski et al., 2003; Brandeis et al., 2002). Stochastic resonance is also well documented in animal neurons (Douglass et al., 1993) as well as in the human visual system (Simonotto et al., 1999).

Current ADHD theories have not addressed the beneficial effects of noise. Surprisingly few experiments have explored the possibilities of stimulation through noise. There are only two exceptions. Abikoff et al. (1996) attributed the enhancing effect to increased level of general appeal, which counteracts boredom, and Gerjets, Graw, Heise, Westermann, and Rothenberger (2002a, 2002b) accounted for the positive effect with Zentall and Zentall's (1983) optimal stimulation theory. In an attempt to create an action–theoretical framework integrating different explanations of ADHD, Gerjets et al. also suggested motivational factors, in accordance with Sonuga-Barke's delay aversion theory (Sonuga-Barke, 2002b), and arousal anomalies, in line with Sergeant's cognitive–energetic model. In his model, Sergeant claimed that energetic failures underlie inhibitory dysfunctions and arousal (Sergeant, 2000).

To conclude, current models of ADHD contradict proposals of the MBA model to some extent. However, the cognitive–energetic model, the dual-pathway model, and optimal stimulation theory are consistent with the MBA model regarding energetic levels and arousal. These models emphasize the dynamic interplay between top-down and bottom-up processes. Dynamic developmental theory is also consistent with the models listed above regarding the importance of DA. However, it suggests that stimuli cause stunted DA responses in ADHD, which contradicts both the MBA model and Grace's tonic–phasic DA model. No compelling evidence is provided to support the dynamic developmental theory on this matter.

Future Experiments That Would Differentiate Between Theories

Earlier in this article we reviewed evidence from available data that is relevant for differentiating between various theories. However, a crucial question is how to design new experiments that are particularly tailored for testing the MBA model against competitive theories. Perhaps one of the most straightforward tests would be to conduct a stochastic resonance experiment on individuals with and without ADHD. For example, one might present an auditive signal under the detection threshold in the presence of auditive noise that is varied in loudness. The MBA theory predicts that individuals with ADHD would show higher signal-detection rate under conditions of louder noise compared with controls. Such data are not available in the literature; however, preliminary data from our laboratory are clearly consistent with the model's predictions. ERPs between 250 and 500 ms following the onset of a signal have peaks at louder noise for individuals with ADHD compared with controls. These peaks match the peaks in the behavioral data well (Sikström, Smart, Kallioinen, Åberg, & Söderlund, 2006). The behavioral and EEG peaks in these data could be used to tune individual noise levels to find the best cognitive performance levels among children with ADHD. To our knowledge, none of the previously suggested theories makes predictions consistent with these data as they are currently formulated.

EEG measures reveal elevated relative theta power and reduced relative alpha and beta, together with elevated theta–alpha and theta–beta ratios, in ADHD (Barry, Clarke, & Johnstone, 2003). Deviations between ADHD and control persons are also found in ERP measures, particularly in N1 (larger amplitude) and P3 (smaller amplitude) waves (Barry, Johnstone, & Clarke, 2003; Brandeis et al., 2002). It would be of considerable interest to investigate whether white noise would abolish these EEG deviations. Manipulations could be made at different noise levels and in both visual and auditive modalities. One prediction is that for a well-adjusted and individually determined noise level, these differences in EEG patterns will disappear, and cognitive measures of behavioral level will improve. A second prediction is that more noise will be needed in those with ADHD as compared with a normal population. Antisaccade (Munoz & Everling, 2004) and dichotic listening (Hugdahl et al., 2003) are additional paradigms where the MBA model could be tested. In these experiments, the effects of white noise could be compared with the effects of ISIs.

Future Applications of the MBA Model

The MBA model can be used to understand several shortcomings in cognitive functioning where changes in the DA system have been identified. Cognitive changes and alterations in DA transmission are found in various illnesses and conditions. Hypofunctioning DA systems are seen in normal aging and Parkinsonism (Erixon-Lindroth et al., 2005; Goldman-Rakic et al., 2000). Hyperfunctioning DA systems are seen in Huntington's disease and Tourette syndrome but also in stress and amphetamine psychosis (Castner & Goldman-Rakic, 2004; Goldman-Rakic et al., 2000; Nieoullon, 2002). A more complex form of dysregulation consisting of both hyperfunctioning (subcortical) and hypofunctioning (prefrontal) DA transmission is present both in ADHD and in schizophrenia. Despite the similarities in DA transmission in these disorders, there are great differences in their cognitive functioning, indicating that other factors may be involved (Bilder et al., 2004; Goldman-Rakic et al., 2004; Grace, 2001). In spite of the differences between these groups, it would be of great interest to investigate whether the MBA model could be applied and used to

develop proper training programs for different kinds of cognitive disturbances. Future research will focus on this topic.

Converging evidence suggests that DA transmission is crucial for cognitive performance. If top-down processing can be reinforced by noise, this could have interesting applied implications for clinical groups, as well as for normal populations. Our own empirical data show that low-achieving pupils benefit from white auditive noise in cognitive performance (Söderlund, Sikström, & Loftesnes, 2007; Söderlund et al., 2007).

The MBA model may be used to create an appropriate and adaptive environment for individuals with ADHD, especially in school settings. Klingberg and colleagues have attained remarkable results with Robomemo, a computer game that trains working memory (Klingberg et al., 2005; Klingberg, Forssberg, & Westerberg, 2002). In this context, the MBA model can serve as a tool for individually tailoring treatments for children with ADHD. Computerized training programs are particularly interesting because crucial variables can be manipulated easily and precisely. This provides us with the hope of creating long-term changes as an alternative to short-term medications. Future research should further explore the effect of white noise and stochastic resonance in the context of learning and ADHD.

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