Changes in sleep-wake behavior may be more than just an epiphenomenon of ADHD

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Abstract: Sleep disturbances are common for children with attention-deficit/hyperactivity disorder (ADHD) and are of great clinical significance. Brain dopamine plays an important role for both ADHD symptoms and sleep-wake regulation. We therefore suggest that one basic aspect of integrative brain-behavior relationship such as the sleep-wake cycle may certainly be addressed in a dynamic developmental theory of ADHD.

Attention-deficit/hyperactivity disorder (ADHD) represents one of the most common, socially important, and scientifically debated child psychiatric disturbances (Buitelaar & Rothenberger 2004). Hence, we must be grateful to Sagvolden et al. for carefully analyzing a large number of data concerning ADHD and proposing a unique functional schema to explain the complexity and heterogeneity of ADHD phenotypes. However, in a general theory of ADHD, one basic aspect of integrative brain-behavior relationship such as the sleep-wake cycle needs to be included.

Sleep disturbances are common for children with ADHD (Brown & McMullen 2001; Corkum 2001; Kirov et al. 2004; Kostanecka-Endress et al. 2000). The great impact of sleep-wake problems in ADHD is evidenced by more than 15 original and 7 review articles related to this topic that were published during the period of 2003–2004 in Medline. Sleep disturbances, including motor restlessness in sleep, not only have clinical importance but may be closely related to the appearance of ADHD symptoms during the day (Lewin & Di Pinto 2004). With this background, the question is whether and how Sagvolden et al.'s behaviorally oriented theory can explain or even predict the sleep-wake changes in ADHD.

So far, a direct answer cannot be derived from the data and explanations given in the target article. However, the authors support the hypothesis that hypofunctioning mesolimbic, mesocortical, and nigrostriatal dopamine branches play a pivotal role for the core symptoms of ADHD. Yet, dopamine has recently been suggested to be functionally involved in sleep-wake regulation. Some psychiatric disorders with dopamine alterations do manifest sleep variations and a number of dopaminergic agents can pharmacologically induce sleep-wake changes (Crochet & Sakai 2003; Mignot et al. 2002; Rye & Jankovic 2002). Therefore, we would like to focus on the neurobiological mechanisms of sleep and ADHD and their clinical implications.

In particular, mesolimbic and mesocortical dopamine circuits are thought to be critical for modulating the quality, quantity, and timing of rapid eye movement (REM) sleep (Keating & Rye 2003; Reid et al. 1996). Hence, a specific sleep pattern in ADHD may be characterized mainly by changes in REM sleep. In support of this suggestion, recent studies have found changes in the amount and timing of REM sleep in children with ADHD (Crabtree et al. 2003; Golan et al. 2004; Kirov et al. 2004; O'Brien et al. 2003a; 2003b; 2003c). Furthermore, periodic leg movements in sleep (PLMS) and restless leg syndrome (RLS) can be successfully treated with dopaminergic agonists (Hening et al. 2004; Stiasny et al. 2002), and both motor disturbances are associated with ADHD (Chervin et al. 2002; Picchietti et al. 1999). Also, alterations in the nigrostriatal dopamine branch are shown to cause PLMS and RLS (Michaud et al. 2002). It appears, therefore, quite possible that the hypofunctioning mesolimbic, mesocortical, and nigrostriatal dopamine branches which Sagvolden et al. consider to be essential for ADHD symptoms, may be associated with the sleep disturbances in patients with ADHD by modulating cortico-subcortical interactions.

Changes in brain dopamine may affect the sleep-wake cycle also by modulating the balance between cortical inhibition and facilitation, which is recognized as important for the sleep-wake regulation (De Gennaro et al. 2004; Gottesmann 1999; Muzur et al. 2002). There are animal-driven data showing that dopamine has a double inhibitory influence at cortical level, either directly or by favoring gamma-amino butyric acid release from interneurons (Grobin & Deutch 1998; Pirot et al. 1992; Retaux et al. 1991; Zhou & Hablitz 1999). Hence, dopamine hypofunctioning may lead to insufficient cortical inhibition. Importantly, studies with transcranial magnetic stimulation have convincingly evidenced that ADHD children display a decreased intracortical inhibition (Buchmann et al. 2003; Moll et al. 2000a; 2001), and the dopaminergic drug methylphenidate significantly improves this deficit (Moll et al. 2000a). Taken together, these results imply that sleep disturbances in ADHD may be associated not only with modified cortico-subcortical interactions following dopamine deficit but also with a related alteration in cortical excitability.

In conclusion, the neurobiological mechanisms of ADHD psychopathology and sleep-wake regulation may have much in common. Therefore, it may be suggested that specific sleep-wake patterns may characterize ADHD phenotypes resulting from variations of an impaired cortico-subcortical interplay. This aspect may certainly be addressed in a model for ADHD. However, sleep problems in ADHD can hardly be explained by Sagvolden et al.'s dynamic developmental theory, since specific sleep-wake patterns are less likely to be determined only by reinforcement/extinction mechanisms.

RED: ADHD under the "micro-scope" of the rat model

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Abstract: Derived from a rat model, the theory of Sagvolden et al. offers an all-explanatory model of attention-deficit/hyperactivity disorder (ADHD) anatomy, behaviour, and cognition as being caused predominantly by a hypo-dopaminergic mesolimbic (affecting the mesocortical and nigrostriatal) system, leading to abnormal reward and extinction processes. This model suffers from oversimplification and reductionism, reflecting the limitations of the use of animal models to explain higher mental disorders.

The target theory is interesting and potentially useful to explain specific reward related aspects of human attention-deficit/hyperactivity disorder (ADHD) behaviour. Rodent models of human disorders can be of use if they try to explain lower level functions that are shared by humans and animals, such as specific motor or limbic dysfunctions. To explain higher complex cognitive dysfunctions via rat behaviour and anatomy is, in my opinion, problematic, considering the nearly inexistent frontal lobes and reduced number of complex neural networks in rodents. No wonder then, that no animal model is fully comparable to clinical ADHD (Davids et al. 2003). The theory of Sagvolden et al. suffers from precisely this attempt to stretch an animal explanatory model of a relatively limited aspect of dopamine-mediated reward behaviour to explain all possible features of the highly complex cognitive disorder that is ADHD. ADHD behaviour (including hyperactivity, impulsivity, and inattention), and ADHD cognition (such as inhibition deficits, delay aversion, and response variability) are partly being redefined, and reduced to dopamine mediated abnormalities in reinforcement and extinction processes. Likewise, brain abnormalities in ADHD are being reduced to three dysfunctional fronto-striatal dopamine pathways insufficiently fed by reduced dopamine in the ventral tegmental area. Uni-causal explanations of complex problems, as much as they appeal to the reductionistic human brain, have shown to rarely match reality. There is evidence to doubt that

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