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Modifiable Arousal in Attention-Deficit/Hyperactivity Disorder and Its Etiological Association With Fluctuating Reaction Times

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ABSTRACT

BACKGROUND: Cognitive theories of attention-deficit/hyperactivity disorder (ADHD) propose that high within-subject fluctuations of cognitive performance in ADHD, particularly reaction time (RT) variability (RTV), may reflect arousal dysregulation. However, direct evidence of arousal dysregulation and how it may account for fluctuating RTs in ADHD is limited. We used skin conductance (SC) as a measure of peripheral arousal and aimed to investigate its phenotypic and familial association with RTV in a large sample of ADHD and control sibling pairs.

METHODS: Adolescents and young adults ($N = 292$), consisting of 73 participants with ADHD and their 75 siblings, and 72 controls and their 72 siblings, completed the baseline (slow, unrewarded) and fast-incentive conditions of a RT task, while SC was simultaneously recorded.

RESULTS: A significant group-by-condition interaction emerged for SC level (SCL). Participants with ADHD had decreased SCL, compared with controls, in the baseline condition but not the fast-incentive condition. Baseline SCL was negatively associated with RTV, and multivariate model fitting demonstrated that the covariance of SCL with RTV, and of SCL with ADHD, was mostly explained by shared familial effects.

CONCLUSIONS: ADHD is associated with decreased, but modifiable, tonic peripheral arousal. A shared familial cause underlies the relationship between arousal and RTV and between arousal and ADHD. Given the malleability of SCL, if our findings are replicated, it warrants further exploration as a potential treatment target for ADHD.

Keywords: ADHD, Arousal, Familial influences, Reaction time variability, Sibling study, Skin conductance

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Attention-deficit/hyperactivity disorder (ADHD) has long been proposed to link to problems with the arousal system. Cognitive theories of ADHD, such as the state regulation model (1,2) or more recent dual-process models (3–5), propose that the high within-subject fluctuations of cognitive performance in ADHD may reflect problems in regulating arousal. Yet, direct objective evidence of arousal dysregulation and how it may account for fluctuating cognitive performance in ADHD is limited to date.

Measuring skin conductance (SC) provides an objective, reliable measurement of arousal in the peripheral nervous system (6). SC sensitively measures electrical changes in electrodermal activity, which is stimulated by the autonomic sympathetic nervous system, a key system in influencing arousal and alertness (6–8). Two commonly used measurements of SC are skin conductance level (SCL), which represents a tonic level of arousal (averaged over a given time window), and skin conductance response (SCR) amplitude, which represents a phasic (transient) event-related change in SC (9). Increased SCL indexes an increase in peripheral arousal, whereas increased SCR amplitude indicates a stronger, higher intensity arousal response (6). Although early studies of SC in ADHD yielded conflicting findings (10–13), a number of more recent studies, benefiting from advancements in SC technique, report attenuated SCL in children with ADHD at rest and in task conditions, indicating hypoarousal (14–21). However, discrepancies still remain because some studies report no differences in SCL between adults with and without ADHD (22,23).

The aspect of cognitive performance that most strongly fluctuates in people with ADHD is their speed of responding on standard reaction time (RT) tasks, leading to high RT variability (RTV) (24–26). Our previous analyses on a large sample of ADHD and control sibling pairs showed how RTV captured a large proportion of the familial influences underlying ADHD and separated from a second familial cognitive impairment factor that captured executive function impairments, such as response inhibition (27). In twin analyses the genetic association of RTV was observed particularly strongly with inattention symptoms (28). RTV can, however, improve in individuals with ADHD under certain circumstances: a meta-analysis of eight studies of varying designs suggested an overall significant, although small, effect of incentives (24). While most of these studies have rewarded successful inhibition, we have

examined the effects of rewarding specifically on a reduction in RTV and have further combined the effects of rewards with a faster event rate, to maximize potential RTV improvement. Under such conditions, using the Fast task, we have consistently observed ADHD-sensitive improvement in RTV from baseline to a fast-incentive condition (25,29,30).

Applying SC measurement in a study on ADHD, O'Connell *et al.* (31) investigated performance on a sustained attention to response task. SC was measured before and after taking part in either self-alert training, whereby participants learned to modulate their own arousal levels, transiently increasing their arousal at regular intervals with the aim of reducing momentary lapses of attention, or a placebo training condition. Compared with pretraining performance, ADHD and control adult participants with the alertness training had increased SCR, indicating increased transient arousal; had a more consistent RTV over testing sessions; and made fewer commission errors. Contrarily, ADHD participants and controls in the placebo training condition, who were not taught to modulate their arousal levels, had decreased SCR with time, indicating a decrease in stimulus-related arousal, as well as increased RTV, compared with their pretraining performance. Although the investigators did not report correlations between SC and the cognitive performance measures, they note that SC and RTV followed a similar pattern: block-by-block increases in RTV were accompanied by gradual decreases in SCR, indicating a drop in arousal response over time (31).

We aimed to perform a detailed investigation of SC as an objective measure of peripheral arousal, and its potential association with fluctuating RTs in a large sample of ADHD and control sibling pairs. First, we aimed to investigate if people with ADHD differ from controls in SCL and SCR amplitude during baseline (slow, unrewarded) RT performance. Second, we aimed to test if a fast-incentive condition increases SC-indexed arousal, and if it does, whether it increases more in the ADHD group than in the control group. Third, for the SC variables that show group differences, we aimed to investigate their familial association with RTV and ADHD diagnosis, using sibling model fitting analyses, and to consider specific causal models that may explain the relationships that emerge.

METHODS AND MATERIALS

Sample

Participants are members of the Sibling EEG Follow-Up Study (SEFOS) (32–34), which investigates neurophysiological and cognitive measures in a follow-up sample of ADHD and control sibling pairs. ADHD and control participants who had taken part in our previous research (27,35) were invited to take part in this study. ADHD participants were included if they had ADHD in childhood and met DSM-IV criteria for any ADHD subtype at follow-up. Exclusion criteria included IQ < 70, autism, epilepsy, brain disorders, and any genetic or medical disorder associated with externalizing behaviors that might mimic ADHD. The investigation was performed in accordance with the latest version of the Declaration of Helsinki.

From the original follow-up sample of 404 participants, 311 had SC measured (because SC data collection only started after initial participants had already been assessed). We excluded from the analyses 10 ADHD participants [SC equipment failure ($n = 9$), extreme drowsiness ($n = 1$)] and 9 control participants [SC equipment failure ($n = 8$) and met ADHD criteria based on parent report ($n = 1$)]. The final sample consisted of 73 ADHD probands [mean (SD) age, 18.3 (2.9) years; 87% male], 75 siblings of ADHD probands [mean age, 18.3 (2.9) years; 48% male], 72 controls [mean age, 17.48 (1.8) years; 94% male], and 72 control siblings [mean age, 17.11 (2.4) years; 68% male].

For the ADHD control group differences analyses (aims 1 and 2), both members of control sibling pairs formed the control group ($n = 144$); siblings of ADHD probands were excluded unless they had an ADHD diagnosis themselves. For these analyses, the ADHD and control groups did not differ in sex ($\chi^2 = 1.64$, $p < .20$) but did differ in age ($t = 0.54$, $p = .04$) and IQ ($t = 6.01$, $p < .001$). In all these analyses we included age as a covariate, and in additional analyses we added IQ as a second covariate. For the model fitting analyses (aim 3), all participants were included and differed in age ($t = 1.97$, $p = .05$), sex ($\chi^2 = 35.2$, $p < .01$), and IQ ($t = 22.46$, $p < .01$). In these analyses we therefore used age and sex as covariates, with additional analyses also including IQ as a further covariate. All participants were of European Caucasian descent.

Procedure

The Fast task was administered as part of a longer assessment session at the research center. For participants prescribed stimulants, a 48-hour ADHD medication-free period was required. Participants abstained from caffeine, smoking, and alcohol on the day of testing. Face-to-face or telephone clinical interviews were administered to the parent of each ADHD proband shortly before or after the participant's assessment.

Measures

IQ. The vocabulary and block design subtests of the Wechsler Abbreviated Scale of Intelligence (36) were administered to all participants to derive an estimate of IQ.

ADHD Diagnosis. The Diagnostic Interview for ADHD in Adults (DIVA) (37), a semistructured interview based on the DSM-IV criteria, was conducted with the parent for current symptoms only, because in all cases a clinical and research diagnosis of combined type ADHD had already been established (35). The Barkley's Functional Impairment Scale (38) was used to assess functional impairments commonly associated with ADHD in five areas of their everyday life. Each item ranges from 0 (never or rarely) to 3 (very often). Participants were classified as affected, if they scored a yes on six or more items on the Diagnostic Interview for ADHD in Adults for either inattention or hyperactivity-impulsivity based on parent report, and scored ≥ 2 on two or more areas of impairments on the Barkley's Functional Impairment Scale, rated by their parent.

The Fast Task

The slow-unrewarded (baseline) condition consists of 72 trials, which followed a standard warned four-choice RT task. Four empty circles (warning signals, arranged horizontally) first