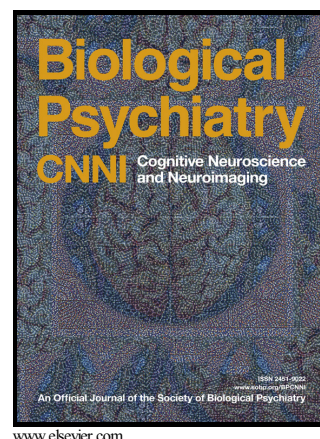


Author's Accepted Manuscript

Modifiable Arousal in ADHD and its Etiological Association with Fluctuating Reaction Times

Sarah-Naomi. James, Celeste H.M. Cheung, Fruhling Rijdsdijk, Philip Asherson, Jonna Kuntsi



PII: S2451-9022(16)30068-4
DOI: <http://dx.doi.org/10.1016/j.bpsc.2016.06.003>
Reference: BPSC61

To appear in: *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*

Received date: 10 May 2016

Accepted date: 14 June 2016

Cite this article as: Sarah-Naomi. James, Celeste H.M. Cheung, Fruhling Rijdsdijk, Philip Asherson and Jonna Kuntsi, Modifiable Arousal in ADHD and its Etiological Association with Fluctuating Reaction Times, *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, <http://dx.doi.org/10.1016/j.bpsc.2016.06.003>

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting galley proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Modifiable arousal in ADHD and its etiological association with fluctuating reaction times***(Short title: Arousal and fluctuating reaction times in ADHD)***

Sarah-Naomi James¹, M.Sc.; Celeste H. M. Cheung^{2,3}, Ph.D.; Fruhling Rijdsdijk¹, PhD.; Philip Asherson¹, M.R.C. Psych., Ph.D.; and Jonna Kuntsi¹, Ph.D.

1. King's College London, MRC Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology and Neuroscience, London, UK
2. King's College London, Department of Psychology, Institute of Psychiatry, Psychology and Neuroscience, London, UK
3. Centre for Brain and Cognitive Development, Department of Psychological Sciences, Birkbeck, University of London, UK

Correspondence to Sarah-Naomi James, King's College London, MRC Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology and Neuroscience, London, UK. Email: sarah.2.james@kcl.ac.uk

Keywords: ADHD; arousal; skin conductance; reaction time variability; familial influences; sibling study

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. Yet, direct evidence of arousal dysregulation and how it may account for fluctuating reaction times 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: 292 adolescents and young adults, consisting of 73 participants with ADHD and their 75 siblings, as well as 72 controls and their 72 siblings, completed the baseline (slow, unrewarded) and fast-incentive conditions of a RT task, whilst SC was simultaneously recorded.

Results: A significant group by condition interaction emerged for SC level (SCL). Participants with ADHD had decreased SCL, compared to controls, in the baseline but not 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 etiology 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.

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). While 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 hypo-arousal (14–21). However, discrepancies still remain, as 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 tasks, leading to high reaction time 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, though 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 maximise 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 (29; 25; 30).

Applying SC measurement in a study on ADHD, O’Connell et al. (2008) investigated performance on a sustained attention to response task (31). SC was measured before and after taking part in either Self-Alert Training, whereby participants learnt 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 to pre-training performance, ADHD and control adult participants with the alertness training had increased SCR indicating increased transient arousal, 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 to their pre-training performance. Although the authors 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 did, whether it increases more in the ADHD than 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.

Accepted manuscript

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 (35; 36) 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 externalising behaviours that might mimic ADHD. The investigation was carried out in accordance with the latest version of the Declaration of Helsinki.

From the original follow up sample of 404 participants, 311 had SC measured, (as SC data collection only started after initial participants had already been assessed). We excluded from the analyses 10 ADHD participants (SC equipment failure (9), extreme drowsiness (1)) and 9 control participants (SC equipment failure (8) and met ADHD criteria based on parent report (1)). The final sample consisted of 73 ADHD probands (mean age: 18.3, SD=2.9, 87% male), 75 siblings of ADHD probands (mean age: 18.3, SD=2.9, 48% male), 72 controls (mean age: 17.48, SD=1.8, 94% male) and 72 control siblings (mean age: 17.11, SD=2.4, 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 gender ($\chi^2=1.64$, $p<0.2$), but did differ in age ($t=0.54$, $p=0.04$) and IQ ($t=6.01$, $p<0.001$). 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 ($t=1.97$, $p=0.05$), gender ($\chi^2=35.2$, $p<0.01$) and IQ ($t=22.46$, $p<0.01$). In these analyses we therefore used age and gender 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 centre. For those 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 (WASI) (37) were administered to all participants to derive an estimate of IQ.

ADHD diagnosis

The Diagnostic Interview for ADHD in Adults (DIVA (38)), a semi-structured 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 (BFIS; (39)) 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 ≥ 6 items on the DIVA for either inattention or hyperactivity-impulsivity based on parent report, and scored ≥ 2 on ≥ 2 areas of impairments on the BFIS, 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 appeared for 8 s, after which one of them (the target) was coloured in. Participants were asked to press the response key that directly corresponded to the position of the target stimulus. Following a response, the stimuli disappeared from the screen and a fixed inter-trial interval of 2.5 s followed. Speed and accuracy were emphasized equally in the task instructions. If the child did not respond within 10 s, the trial terminated. A comparison condition of 80 trials with a fast event rate (fore-period of 1 s) and incentives followed the baseline condition (29). The fast-incentive condition is always administered after the baseline condition. SC measures and cognitive performance measure (RTV) from each condition was included in this analysis. Due to the longer fore-period in the slow condition, the two conditions were not matched on task length, but were matched on the number of trials. We analysed RTV and SC performance on both the full slow condition and between 3 4-minute length-matched segments (supplementary Table S1 and S2) (29).

SC data were measured by attaching a pair of reusable 8mm diameter silver-silver chloride electrodes on the on the palm of the hand (thenar eminence and hypothenar eminence) of participant's non-dominant hand at the start of the testing session. A non-saline gel was used to increase impedance and help establish an electrical signal. A constant imperceptible voltage (0.5 V) was applied.

SC was recorded using PSYCHLAB SC5 24 bit equipment system, which has an absolute accuracy of +/- 0.1 microsiemens (μS) (PSYCHLAB, UK). The SC5 was connected to a computer to run the PSYCHLAB software, where data were monitored, recorded in real time and automatically digitized data. Stimulus onset and participant response events were recorded on a common timeline, which enabled SC activity to be stimulus-locked.

SC data values were calculated using a skin conductance system which is based on a SC sigmoid-exponential model that allows the tonic measure of SC level (SCL) to be disentangled from phasic, stimulus-associated, SC responses (SCR), and further allows the decomposition of overlapping SCRs (40; 41) (6; 9). This system, therefore, is appropriate to use in conditions with long and short inter-stimulus-intervals (42). The statistical model was applied to each condition, as a whole. SCR amplitude (change in SC from the baseline to the highest point of the SCR) was derived from this method, and was calculated on a trial-by-trial basis. The criteria for the smallest SCR were set at 0.02 μS . Means of SC variables (SCL and SCR amplitude) were calculated per participant, across each condition.

Analyses

Covariates

Age was used as a covariate in all analyses. Analyses were initially performed without controlling for IQ, but we subsequently re-ran all analyses with IQ as a covariate to examine IQ effects. Gender was not included as a covariate in the group analyses to avoid controlling for ADHD status (32). Instead, we explored the effect of gender by re-running all analyses with the females (n=15) removed; the pattern of results remained the same (results are available upon request). Analyses were rerun using anxiety and depression scores from the Clinical Interview Schedule-Revised (43) to investigate their confounding effects, but the significance of the results did not change (Supplementary Table S6). All variables were skewed and transformed using the optimized minimal skew (Inskew0) command in Stata version 11.1 (Stata Corporation, College Station, TX). Tests assessing sphericity and equality of variances were performed to ensure assumptions were met.

ADHD-control group comparisons

To test for main effects of group (ADHD vs controls), condition (baseline vs fast-incentive) and interactions for SC variables and RTV, the data were analysed using random intercept models and logistic regression in Stata. The random intercept model is a multilevel regression model that can be used as an alternative to ANCOVA to control for genetic relatedness (where both siblings from a pair are included in analyses) in a repeated-measures design, using a “robust cluster” command to estimate standard errors (32; 44; 45).

Structural Equation Modelling on sibling data

Structural equation modelling in OpenMx (46) was used on sibling-pair data to decompose the variance of traits into etiological factors. Whereas in twin studies, comparison between monozygotic (MZ) and

dizygotic (DZ) twin pairs enables estimation of additive genetic (A), shared environmental (C) and non-shared environmental (E) influences, sibling pairs (all sharing 50% of their alleles and 100% of the environment they grow up in) only enable estimation of the combined effects of A and C (familial, F effects). In addition to familial effects, non-shared effects (NE) are estimated, representing effects due to non-shared environment/genes as well as possible measurement error.

Multivariate modelling on sibling data uses the additional cross-sib cross-trait information to decompose the observed phenotypic correlation between traits into etiological factors. Similar sibling design analyses have been previously performed by our group (see (48) for a more detailed description and rationale of the analysis). In addition, by using the correlations between the F and NE factors, and the standardized estimates, we calculated the extent to which the phenotypic correlation (R_{ph}) between any two variables is due to F (R_{ph-F}) and NE (R_{ph-NE}).

Phenotypic correlations

Before FE modelling (described above), sibling correlations were estimated from a constrained correlation model to give maximum likelihood estimates of correlations between the traits within and across pairs while applying some constraints. Applied constraints reflect the assumptions of the familial model, i.e. that phenotypic correlations across traits within individuals is the same across siblings and that cross-trait cross-sibling correlations are independent of sibling order. Variables used in the sibling model fitting were selected by running phenotypic correlations on variables which showed group differences, and only variable(s) which had a significant relationship with RTV were further analysed.

Phenotypic mediation model

To further investigate a more etiological model that may account for the relationship between SC variable(s) which are associated with both RTV and ADHD, and given the theoretical scope that RTV (an observed behavioural response) may reflect hypo-arousal (an internal physiological process), we hypothesised that RTV may mediate the relationship between SC-indexed arousal and ADHD. A phenotypic mediation model was fitted with SC variable(s) that may be causally associated with both RTV and ADHD. Significant (partial) mediation occurs when a third variable explains some of the association between two other variables (50). The phenotypic mediation model was specified to account for the sibling-structure and selected nature of the data using similar constraints as the correlation model described above. The phenotypic relationship across traits within individuals is specified by means of causal paths, which were constrained to be equal across siblings. The sibling-structure was accounted for by specifying correlational paths across sibling variables.

Ascertainment correction

To account for the selected nature of the sample (selection on ADHD probands), the selection variable (ADHD status) was included in all models with its parameters fixed to population-known values. In the correlation and mediation model this involves fixing the sibling correlation for ADHD status to 0.40 and in the FE models fixing F to .40, representing 80% genetic variance (in case $C=0$). In addition the threshold on ADHD liability was fixed to a z-value of 1.64 to correspond to a population prevalence of 5% (see Rijsdijk et al. 2005 for further explanation and validation of this approach) (51).

ADHD-control group comparisons

For SCL data, a random intercept model indicated a significant main effect of condition ($z=8.95$, $p=0.01$) and group-by-condition interaction ($z=1.89$, $p=0.04$), but no main effect of group ($z=0.19$, $p=0.85$) (Figure 1A). Post-hoc regression analyses revealed that, compared to controls, individuals with ADHD showed significantly lower SCL in the baseline condition ($t=-5.64$, $p<0.001$), but not in the fast-incentive condition ($t=1.1$, $p=0.27$) (Table 1). Both ADHD and control groups had a significant within-group increase from the baseline to fast-incentive condition ($t=7.52$, $p<0.01$, $t=6.44$, $p<0.01$ respectively).

For SCR amplitude data, a random intercept model showed no significant main effects of group ($z=0.46$, $p=0.61$), condition ($z=0.42$, $p=0.28$) or group-by-condition interaction ($z=0.69$, $p=0.51$) (Figure 1B).

All group analyses were re-run with IQ as a covariate, but the significance of results remained unchanged. Analyses were rerun using three length-matched segments from the baseline condition and testing them separately against the fast-incentive condition, but the significance of results did not change (Supplementary Table S1 and S2). Although our sample had a 48-hour medication-free period, to explore the longer-term use of medication, we ran the following additional analyses: (1) SC comparison tests between unmedicated vs medicated participants with ADHD; (2) using current stimulant medication as an additional covariate; (3) analyses in un-medicated children only. The significance of results did not change in any additional analyses (Supplementary Table S3, S4 and S5).

We ran additional phenotypic correlations to examine the SCL-RTV and SCR-RTV relationship in ADHD and control groups separately (supplementary Table S7). In the baseline condition, lower SCL significantly predicted higher RTV in the ADHD group ($r=-0.31$, $p<0.01$), but this correlation did not reach significance in the control group ($r=-0.12$, $p=0.15$) and Fisher's z test indicated that the correlations between the groups differed from one another at a trend level ($z=-1.37$, $p=0.08$). In the fast-incentive condition, the RTV-SCL correlations were not significantly different between the groups ($z=-0.97$, $p=0.16$; $r=-0.29$, $p<0.01$ in the ADHD group and $r=-0.16$, $p=0.06$ in the control group). There were no significant SCR-RTV correlations.

Familial association between SCL, RTV and ADHD

Given that SCL showed a significant group-by-condition interaction, a significant correlation with RTV with large effect sizes and the biggest significant group difference in the baseline condition, we next investigated the phenotypic and etiological overlap between SCL, RTV and ADHD in the baseline condition. The maximum likelihood phenotypic, cross-sibling and cross-sibling-cross-trait correlations across SCL, RTV and ADHD are presented in Table 2.

Sibling-pair multivariate model fitting was performed to decompose variance/covariance of traits into etiological factors F and NE (Figure 2). We calculated the extent to which the phenotypic correlation (R_{ph}) between any two variables is due to F (R_{ph-F}) and NE (R_{ph-NE}) and express these contributions as a percentage (Table 3). Shared familial influences accounted for 55% of the total phenotypic correlation between SCL and ADHD, 94% of the phenotypic correlation between SCL and RTV, and 59% of the phenotypic correlation between ADHD and RTV.

Phenotypic mediation model

Given the significant phenotypic and familial relationship of baseline SCL with RTV, and with ADHD, we tested whether baseline RTV mediated the relationship between baseline SCL and ADHD status. In the mediation model, the causal paths specified were all significant and partial mediation by RTV was indicated (Figure 3). However, model fit statistics demonstrate that the causal mediation model was not a good fit (BIC=2511, RMSEA=0), which is demonstrated by a significant chi-squared statistic ($-\Delta\chi^2=70.09$, $\Delta df=1$, $p<0.01$).

DISCUSSION

In a large sibling study of 292 participants, we show that tonic peripheral arousal, indexed with SCL, is decreased in young people with ADHD during performance on a baseline RT task but normalises in a faster condition with incentives, indicating modifiable arousal dysregulation in ADHD. We further show that a substantial degree of familial sharing accounts for the significant phenotypic associations between SCL and RTV, and between SCL and ADHD.

The SC measure associated with ADHD was SCL. Lower SCL during baseline RT performance indicated a lower tonic level of peripheral arousal in individuals with ADHD, consistent with accounts of hypoarousal (14–16; 21; 52). No group differences emerged for SCR amplitude. Whilst SCL and SCR are commonly used measurements of SC, they are thought to index different processes (47). For example, neuroimaging studies show that the activity of the ventromedial prefrontal cortex and orbitofrontal cortex is associated with SCL (49), whereas anterior prefrontal cortex and limbic regions are associated with SCR (47; 49). Our results, therefore, suggest that while the processes involved in tonic level of peripheral arousal (SCL) are impaired in individuals with ADHD during baseline performance, the processes involved in the phasic, discrete, arousal response elicited by stimulus onset (SCR amplitude),

are not affected. The separation that we observed between SCL and SCR amplitude in their association with ADHD is also supported by studies suggesting that treatment with methylphenidate, an effective medication used to reduce ADHD symptoms, is associated more directly with increased SCL arousal (12; 21; 53).

Tonic peripheral arousal (SCL) normalised in the ADHD group in the fast-incentive condition, as indicated by a significant group by condition interaction and lack of a group difference in the fast-incentive condition. The malleability of SCL is in line with results of modifiable SC-indexed arousal (16; 21; 31) and resembles the pattern observed for RTV (30). The overall pattern of findings is therefore suggestive of an arousal dysregulation, rather than stable hypo-arousal, in individuals with ADHD.

To investigate the familial association between SCL and RTV directly, we focused on the baseline condition that is most sensitive to ADHD. The SCL-RTV correlation was largely (94%) accounted for by shared familial influences, demonstrating that the association of under-arousal with attentional fluctuations is mostly due to overlapping familial effects. Of the familial influences on RTV, half were correlated with those on SCL, indicating that peripheral arousal captures half of the familial influences that contribute to the attentional fluctuations. These findings are in line with theories linking RTV to arousal dysregulation (4; 29; 54–57). However, as half of the familial influences on RTV were not correlated with those on SCL, this implies there are also non-overlapping, distinct, familial influences that contribute to RTV, in line with a multifactorial etiology of increased RTV (54).

We further investigated the familial association between SCL and ADHD, and found that shared familial effects accounted for 59% of the phenotypic correlation between them, providing further support for

an etiological link between under-arousal and ADHD. Of the familial influences on ADHD, a third correlated with those on SCL, demonstrating that peripheral arousal captures a third of the familial influence contributing to ADHD. Yet, two-thirds of the familial influences on ADHD did not correlate with those on SCL, implying that there are also non-overlapping familial influences that contribute separately to ADHD. These findings are in agreement with the view that arousal dysregulation is not the only contributing factor to ADHD, in line with the multifactorial nature of ADHD (3–5; 56–58).

In a novel attempt to investigate the causal pathways that underlie the phenotypic relationship between SCL-indexed arousal, RTV and ADHD, we fitted a model which tests whether there are causal pathways from a) SCL to RTV and b) RTV to ADHD; and c) whether RTV mediates the association between SCL-indexed arousal and ADHD, or whether there is a direct causal pathway from SCL to ADHD. The mediation and causal paths between all variables were significant, suggesting that there are two pathways from SCL-indexed arousal to ADHD: an indirect causal pathway from arousal to RT fluctuations to ADHD, and a direct casual pathway from arousal to ADHD. Overall, our statistical model is consistent with ADHD theories that suggest a role for arousal dysregulation in the etiology of ADHD and the observed lapses of attention (3–5). It is further suggestive of complex relationships between the variables: while the association between under-arousal and ADHD was partially mediated by attentional fluctuations (RTV), under-arousal had additional direct influences on ADHD. However, the causal mediation model did not fit the data very well, and therefore these causal pathway results should be interpreted with caution and further explored in future research.

Since this is the first family study on skin conductance and ADHD, our findings await replication. SC should also be studied in relation to other cognitive tasks, to investigate the generalisability of the findings. In addition, twin studies are required to establish whether the familial influences we identified

reflect largely shared genetic rather than shared environmental influences; as previous research suggests limited role for shared environmental effects for ADHD (59), SC (60; 61) and RTV (62), a strong genetic component seems likely.

In conclusion, we identify SCL as an informative index of underlying, malleable hypo-arousal in ADHD. The demonstration of a link between SCL, RTV and ADHD provides physiological support for the arousal dysregulation accounts (1–5). If our findings are replicated in future research, SCL warrants further exploration as a potential treatment target.

Acknowledgements

This project was supported by generous grants from Action Medical Research and the Peter Sowerby Charitable Foundation (grant GN1777 to J Kuntsi). Initial sample recruitment of the ADHD sample was supported by NIMH Grant R01MH062873 to SV Faraone; the recruitment of the control sample and initial cognitive assessments of ADHD and control groups were supported by UK Medical Research Council grant G0300189 to J Kuntsi. P Asherson is supported by generous grants from the National Institute for Health Research Biomedical Research Centre for Mental Health at King's College London, Institute of Psychiatry, Psychology and Neuroscience and South London and Maudsley National Health Service (NHS) Foundation Trust. S James is supported by a Medical Research Council studentship. We thank all who make this research possible: our participants and their families; Jessica Deadman, Hannah Collyer and Sarah-Jane Gregori. Special thanks to Jeffrey Dalton from the Neuroimaging department for providing the SCanalyse program.

Financial Disclosures

P Asherson, on behalf of King's College London (non-personal pecuniary funds) has served as consultant for Janssen-Cilag, Eli Lilly, Shire, Novartis, Continuum and Alcobra. He has received educational or research grants from or has spoken at sponsored talks from Shire, Novartis, Vifor, Janssen-Cilag, Eli Lilly and QbTech. All other authors report no biomedical financial interests or potential conflicts of interest.

REFERENCES

1. Sergeant JA (2005): Modeling attention-deficit/hyperactivity disorder: a critical appraisal of the cognitive-energetic model. *Biol Psychiatry*. 57: 1248–55.
2. Van der Meere J (2005): State regulation and Attention Deficit Hyperactivity Disorder. In: Gozal D, Molfese DL, editors. *Atten Deficit Hyperact Disord from Genes to Patients*. Totowa, NJ: Humana Press, pp 162–213.
3. O'Connell RG, Dockree PM, Robertson IH, Bellgrove MA, Foxe JJ, Kelly SP (2009): Uncovering the neural signature of lapsing attention: electrophysiological signals predict errors up to 20 s before they occur. *J Neurosci*. 29: 8604–11.
4. Johnson KA, Kelly SP, Bellgrove MA, Barry E, Cox M, Gill M, Robertson IH (2007): Response variability in attention deficit hyperactivity disorder: evidence for neuropsychological heterogeneity. *Neuropsychologia*. 45: 630–8.
5. Halperin JM, Schulz KP (2006): Revisiting the role of the prefrontal cortex in the pathophysiology of attention-deficit/hyperactivity disorder. *Psychol Bull*. 132: 560–81.
6. Boucsein W (2012): *Electrodermal Activity*. Springer Science & Business Media.
7. Van Lang NDJ, Tulen JHM, Kallen VL, Rosbergen B, Dieleman G, Ferdinand RF (2007): Autonomic reactivity in clinically referred children attention-deficit/hyperactivity disorder versus anxiety disorder. *Eur Child Adolesc Psychiatry*. 16: 71–8.
8. Critchley HD (2002): Electrodermal responses: what happens in the brain. *Neuroscientist*. 8: 132–42.

9. Figner B, Murphy R (2011): Using skin conductance in judgment and decision making research. In: Schulte-Mecklenbeck M, Kuehberger A, Ranyard R, editors. *A Handb Process tracing methods Decis Res*. New York: Psychology Press, pp 163–184.
10. Satterfield JH, Dawson ME (1971): Electrodermal correlates of hyperactivity in children. *Psychophysiology*. 8: 191–197.
11. Spring C, Greenberg L, Scott J, Hopwood J (1974): Electrodermal Activity in Hyperactive Boys Who Are Methylphenidate Responders. *Psychophysiology*. 11: 436–442.
12. Zahn TP, Abate F, Little BC, Wender PH (1975): Minimal brain dysfunction, stimulant drugs, and autonomic nervous system activity. *Arch Gen Psychiatry*. 32: 381–7.
13. Satterfield JH (1974): Pathophysiology of the Hyperactive Child Syndrome. *Arch Gen Psychiatry*. 31: 839.
14. Dupuy FE, Clarke AR, Barry RJ, Selikowitz M, McCarthy R (2014): EEG and electrodermal activity in girls with Attention-Deficit/Hyperactivity Disorder. *Clin Neurophysiol*. 125: 491–9.
15. Lazzaro I, Gordon E, Li W, Lim CL, Plahn M, Whitmont S, *et al.* (1999): Simultaneous EEG and EDA measures in adolescent attention deficit hyperactivity disorder. *Int J Psychophysiol*. 34: 123–34.
16. Barry RJ, Clarke AR, McCarthy R, Selikowitz M, MacDonald B, Dupuy FE (2012): Caffeine effects on resting-state electrodermal levels in AD/HD suggest an anomalous arousal mechanism. *Biol Psychol*. 89: 606–8.
17. Mangina C a, Beuzeron-Mangina JH, Grizenko N (2000): Event-related brain potentials, bilateral electrodermal activity and Mangina-Test performance in learning disabled/ADHD pre-adolescents with severe behavioral disorders as compared to age-matched normal controls. *Int J Psychophysiol*. 37: 71–85.
18. Mangeot SD, Miller LJ, McIntosh DN, McGrath-Clarke J, Simon J, Hagerman RJ, Goldson E (2001): Sensory modulation dysfunction in children with attention-deficit-hyperactivity disorder. *Dev Med Child Neurol*. 43: 399–406.
19. O’Connell RG, Bellgrove M a, Dockree PM, Robertson IH (2004): Reduced electrodermal response to errors predicts poor sustained attention performance in attention deficit hyperactivity disorder. *Neuroreport*. 15: 2535–8.
20. Iaboni F, Douglas VI, Ditto B (1997): Psychophysiological response of ADHD children to reward and extinction. *Psychophysiology*. 34: 116–23.
21. Conzelmann A, Gerdes ABM, Mucha RF, Weyers P, Lesch K-P, Bähne CG, *et al.* (2014): Autonomic hypoactivity in boys with attention-deficit/hyperactivity disorder and the influence of methylphenidate. *World J Biol Psychiatry*. 15: 56–65.

22. Mayer K, Wyckoff SN, Strehl U (2015): Underarousal in Adult ADHD: How Are Peripheral and Cortical Arousal Related? *Clin EEG Neurosci.* . doi: 10.1177/1550059415577544.
23. Hermens DF, Williams LM, Lazzaro I, Whitmont S, Melkonian D, Gordon E (2004): Sex differences in adult ADHD: a double dissociation in brain activity and autonomic arousal. *Biol Psychol.* 66: 221–33.
24. Kofler MJ, Rapport MD, Sarver DE, Raiker JS, Orban SA, Friedman LM, Kolomeyer EG (2013): Reaction time variability in ADHD: A meta-analytic review of 319 studies. *Clin Psychol Rev.* 33: 795–811.
25. Kuntsi J, Klein C (2012): Intraindividual variability in ADHD and its implications for research of causal links. *Curr Top Behav Neurosci.* 9: 67–91.
26. Antonini TN, Narad ME, Langberg JM, Epstein JN (2013): Behavioral correlates of reaction time variability in children with and without ADHD. *Neuropsychology.* 27: 201–9.
27. Kuntsi J, Wood AC, Rijdsdijk F, Johnson K a, Andreou P, Albrecht BBB, *et al.* (2010): Separation of cognitive impairments in attention-deficit/hyperactivity disorder into 2 familial factors. *Arch Gen Psychiatry.* 67: 1159–67.
28. Kuntsi J, Pinto R, Price TS, van der Meere JJ, Frazier-Wood AC, Asherson P (2014): The separation of ADHD inattention and hyperactivity-impulsivity symptoms: pathways from genetic effects to cognitive impairments and symptoms. *J Abnorm Child Psychol.* 42: 127–36.
29. Andreou P, Neale BM, Chen W, Christiansen H, Gabriels I, Heise A, *et al.* (2007): Reaction time performance in ADHD: improvement under fast-incentive condition and familial effects. *Psychol Med.* 37: 1703–15.
30. Kuntsi J, Wood AC, Van Der Meere J, Asherson P (2009): Why cognitive performance in ADHD may not reveal true potential: findings from a large population-based sample. *J Int Neuropsychol Soc.* 15: 570–9.
31. O’Connell RG, Bellgrove MA, Dockree PM, Lau A, Fitzgerald M, Robertson IH (2008): Self-Alert Training: volitional modulation of autonomic arousal improves sustained attention. *Neuropsychologia.* 46: 1379–90.
32. Cheung CHM, Rijdsdijk F, McLoughlin G, Brandeis D, Banaschewski T, Asherson P, Kuntsi J (2015): Cognitive and neurophysiological markers of ADHD persistence and remission. *Br J Psychiatry.* bjp.bp.114.145185–.
33. Cheung CHM, Rijdsdijk F, McLoughlin G, Faraone S V., Asherson P, Kuntsi J (2015): Childhood predictors of adolescent and young adult outcome in ADHD. *J Psychiatr Res.* 62: 92–100.
34. Kitsune GL, Cheung CHM, Brandeis D, Banaschewski T, Asherson P, McLoughlin G, Kuntsi J (2015): A Matter of Time: The Influence of Recording Context on EEG Spectral Power in Adolescents and Young Adults with ADHD. *Brain Topogr.* 28: 580–90.

35. Chen W, Zhou K, Sham P, Franke B, Kuntsi J, Campbell D, *et al.* (2008): DSM-IV combined type ADHD shows familial association with sibling trait scores: a sampling strategy for QTL linkage. *Am J Med Genet B Neuropsychiatr Genet.* 147B: 1450–60.
36. Kuntsi J, Wood AC, Rijdsdijk F, Johnson KA, Andreou P, Albrecht B, *et al.* (2010): Separation of cognitive impairments in attention-deficit/hyperactivity disorder into 2 familial factors. *Arch Gen Psychiatry.* 67: 1159–67.
37. Wechsler D (1991): *Wechsler Intelligence Scale for Children*, 3rd ed. London: The Psychological Corporation.
38. Kooij JJS, Francken MH (2007): Diagnostic Interview for ADHD (DIVA) in adults. .
39. Barkley RA, Murphy K (2006): *Attention Deficit Hyperactivity Disorder: A Clinical Workbook.*, 3rd ed. (G. Press, editor). New York.
40. Lim CL, Rennie C, Barry RJ, Bahramali H, Lazzaro I, Manor B, Gordon E (1997): Decomposing skin conductance into tonic and phasic components. *Int J Psychophysiol.* 25: 97–109.
41. Williams LM, Phillips ML, Brammer MJ, Skerrett D, Lagopoulos J, Rennie C, *et al.* (2001): Arousal dissociates amygdala and hippocampal fear responses: evidence from simultaneous fMRI and skin conductance recording. *Neuroimage.* 14: 1070–9.
42. Williams LM, Brammer MJ, Skerrett D, Lagopolous J, Rennie C, Kozek K, *et al.* (2000): The neural correlates of orienting: an integration of fMRI and skin conductance orienting. *Neuroreport.* 11: 3011–5.
43. Lewis G, Pelosi AJ, Araya R, Dunn G (1992): Measuring psychiatric disorder in the community: a standardized assessment for use by lay interviewers. *Psychol Med.* 22: 465–86.
44. Tye C, Rijdsdijk F, Greven CU, Kuntsi J, Asherson P, McLoughlin G (2012): Shared genetic influences on ADHD symptoms and very low-frequency EEG activity: a twin study. *J Child Psychol Psychiatry.* 53: 706–715.
45. Wood AC, Asherson P, Rijdsdijk F, Kuntsi J (2009): Is overactivity a core feature in ADHD? Familial and receiver operating characteristic curve analysis of mechanically assessed activity level. *J Am Acad Child Adolesc Psychiatry.* 48: 1023–30.
46. Boker S, Neale M, Maes H, Wilde M, Spiegel M, Brick T, *et al.* (2011): OpenMx: An Open Source Extended Structural Equation Modeling Framework. *Psychometrika.* 76: 306–317.
47. Zhang S, Hu S, Chao HH, Ide JS, Luo X, Farr OM, Li CR (2014): Ventromedial prefrontal cortex and the regulation of physiological arousal. *Soc Cogn Affect Neurosci.* 9: 900–8.
48. Cheung CHMH, Wood AC, Paloyelis Y, Arias-Vasquez A, Buitelaar JK, Franke B, *et al.* (2012): Aetiology for the covariation between combined type ADHD and reading difficulties in a family study: the role of IQ. *J Child Psychol Psychiatry.* 53: 864–73.

49. Nagai Y, Critchley HD, Featherstone E, Trimble MR, Dolan RJ (2004): Activity in ventromedial prefrontal cortex covaries with sympathetic skin conductance level: a physiological account of a “default mode” of brain function. *Neuroimage*. 22: 243–51.
50. Baron RM, Kenny DA (1986): The moderator-mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. *J Pers Soc Psychol*. 51: 1173–1182.
51. Rijdsdijk F V, van Haren NEM, Picchioni MM, McDonald C, Touloupoulou T, Hulshoff Pol HE, *et al.* (2005): Brain MRI abnormalities in schizophrenia: same genes or same environment? *Psychol Med*. 35: 1399–409.
52. Barry RJ, Clarke AR, Johnstone SJ, McCarthy R, Selikowitz M (2009): Electroencephalogram theta/beta ratio and arousal in attention-deficit/hyperactivity disorder: evidence of independent processes. *Biol Psychiatry*. 66: 398–401.
53. Lawrence CA, Barry RJ, Clarke AR, Johnstone SJ, McCarthy R, Selikowitz M, Broyd SJ (2005): Methylphenidate effects in attention deficit/hyperactivity disorder: electrodermal and ERP measures during a continuous performance task. *Psychopharmacology (Berl)*. 183: 81–91.
54. Tamm L, Narad ME, Antonini TN, O’Brien KM, Hawk LW, Epstein JN (2012): Reaction time variability in ADHD: a review. *Neurotherapeutics*. 9: 500–8.
55. Kuntsi J, Oosterlaan J, Stevenson J (2001): Psychological mechanisms in hyperactivity: I. Response inhibition deficit, working memory impairment, delay aversion, or something else? *J Child Psychol Psychiatry*. 42: 199–210.
56. Sergeant JA, Geurts H, Huijbregts S, Scheres A, Oosterlaan J (2003): The top and the bottom of ADHD: a neuropsychological perspective. *Neurosci Biobehav Rev*. 27: 583–592.
57. Scheres A, Oosterlaan J, Sergeant JA (2001): Response execution and inhibition in children with AD/HD and other disruptive disorders: the role of behavioural activation. *J Child Psychol Psychiatry*. 42: 347–57.
58. O’Connell RG, Dockree PM, Bellgrove MA, Turin A, Ward S, Foxe JJ, Robertson IH (2009): Two types of action error: electrophysiological evidence for separable inhibitory and sustained attention neural mechanisms producing error on go/no-go tasks. *J Cogn Neurosci*. 21: 93–104.
59. Burt SA (2009): Rethinking Environmental Contributions to Child and Adolescent Psychopathology: A Meta-Analysis of Shared Environmental Influences. *Psychol Bull*. 135: 608–637.
60. Tuvblad C, Gao Y, Isen J, Botwick T, Raine A, Baker LA (2012): The heritability of the skin conductance orienting response: a longitudinal twin study. *Biol Psychol*. 89: 47–53.
61. Vaidyanathan U, Isen JD, Malone SM, Miller MB, McGue M, Iacono WG (2014): Heritability and molecular genetic basis of electrodermal activity: a genome-wide association study. *Psychophysiology*. 51: 1259–71.

62. Kuntsi J, Frazier-Wood AC, Banaschewski T, Gill M, Miranda A, Oades RD, *et al.* (2012): Genetic analysis of reaction time variability: room for improvement? *Psychol Med.* 1–11.

Accepted manuscript

Table 1: Descriptive statistics of gender, IQ, age, RTV and SC measures and group comparisons between the control and ADHD group. Age has been controlled for in the analyses on SC and RT variables. Cohen's effect sizes (*d*) are presented without and with IQ as a covariate.

		<i>Control</i>	<i>ADHD probands</i>	<i>Group comparisons</i>		<i>Effect size of group comparison</i>	
		Mean (SD)	Mean (SD)	t/f	p	Cohen's <i>d</i>	Cohen's <i>d</i> : IQ controlled
<i>Demographics</i>							
	Male %	81%	87%	1.64	0.20		
	IQ	109.60 (12.52)	98.60 (14.50)	6.01	<.01		
	Age	17.30 (2.15)	18.30 (2.90)	0.54	0.60		
<i>RTV</i>							
	Baseline	3.80 (0.40)	4.70 (0.80)	6.59	0.001	-1.20	-0.95
	Fast-incentive	3.33 (0.60)	3.70 (0.70)	1.49	0.14	-0.9	-0.9
<i>SCL</i>							
	Baseline	1.84 (0.30)	1.56 (0.30)	-5.64	0.001	0.72	0.67
	Fast-incentive	3.20 (2.00)	3.70 (2.10)	1.10	0.27	-0.17	-0.15
<i>SCR amplitude</i>							
	Baseline	0.41 (0.30)	0.45 (0.60)	1.32	0.20	-0.06	-0.06
	Fast-incentive	0.34 (0.20)	0.32 (0.23)	0.07	0.91	0.05	0.03

Reaction time variability (RTV), skin conductance level (SCL), skin conductance response (SCR) amplitude.

Group means of transformed data and subsequent group comparison tests are listed.

Table 2: Maximum-likelihood phenotypic, cross-sibling and cross-sibling cross-trait correlations across baseline skin conductance level (SCL), reaction time variability (RTV) and ADHD.

<i>Correlations</i>	<i>R</i>	<i>CI</i>
Phenotypic correlations within individual		
SCL-RTV	-0.15*	(-0.23,-0.01)
SCL-ADHD	-0.31*	(-0.42,-0.19)
RTV-ADHD	0.35*	(0.23,0.46)
Cross-sibling correlations		
SCL	0.26*	(0.07,0.40)
RTV	0.26*	(0.10,0.40)
ADHD	FIXED 0.4	
Cross-sibling-cross-trait correlations		
SCL-RTV	-0.15*	(-0.24,-0.01)
SCL-ADHD	-0.14*	(-0.27,-0.02)
RTV-ADHD	0.20*	(0.07,0.30)

* $p < 0.05$. 95% Confidence intervals (CI) are indicated in brackets.

Table 3. Phenotypic correlations (rph) and the phenotypic correlations due to familial effects (rph-F) and non-shared effects (rph-NE) across skin conductance level (SCL), reaction time variability (RTV) and ADHD.

	Phenotypic correlations (rph)	Phenotypic correlation due to F (rph-F)	Phenotypic correlation due to NE (rph-NE)
<i>SCL-</i>	-0.15*	-0.14	-0.01
<i>RTV</i>	(-0.25,-0.02)	(94%)	(6%)
<i>SCL-</i>	-0.31*	-0.17	-0.14
<i>ADHD</i>	(-0.39,-0.16)	(59%)	(41%)
<i>RTV-</i>	0.35*	0.20	0.16
<i>ADHD</i>	(0.23,0.45)	(57%)	(43%)

Figure Captions

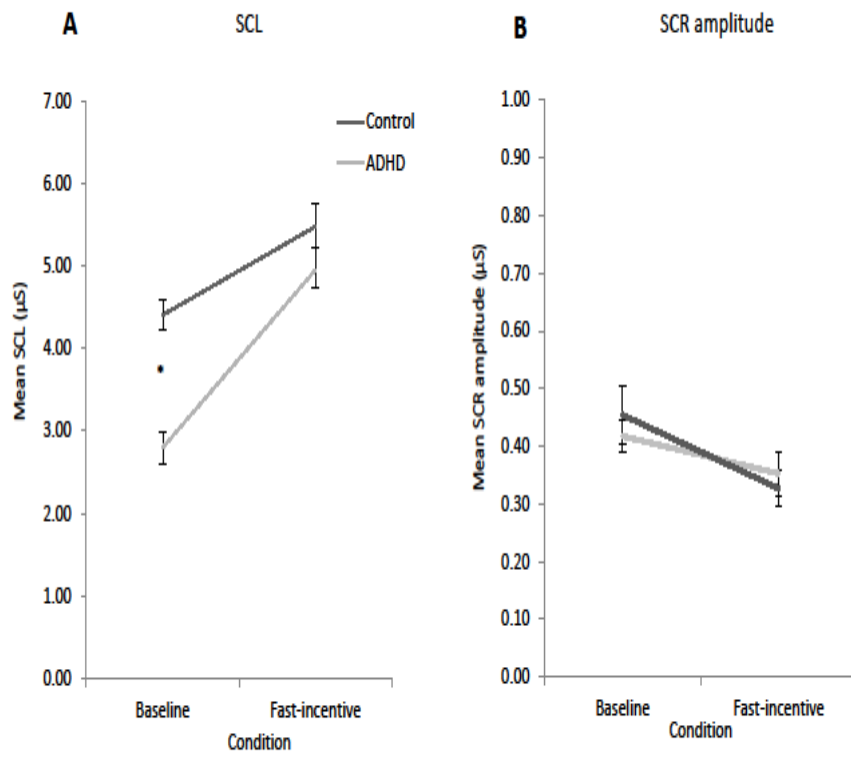
Figure 1: Skin conductance variables measured in control (black) and ADHD (grey) groups during performance on the baseline and fast-incentive conditions of the Fast task.

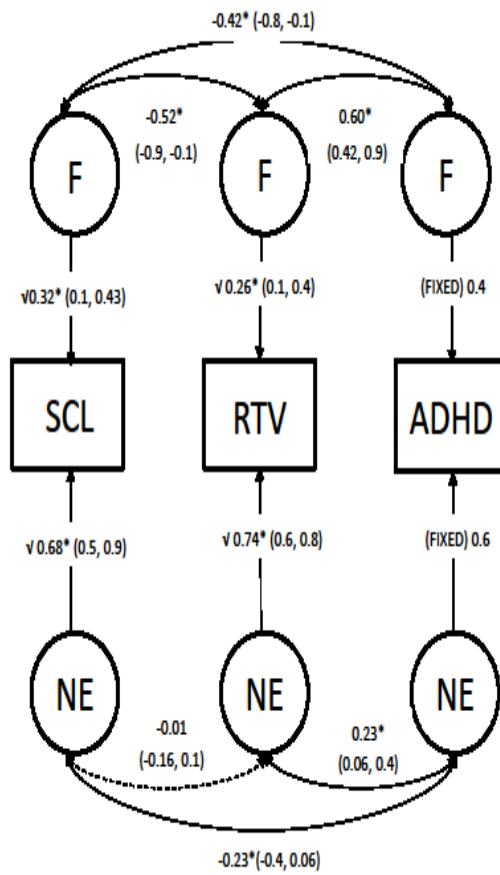
* Indicates $p < 0.05$ significance.

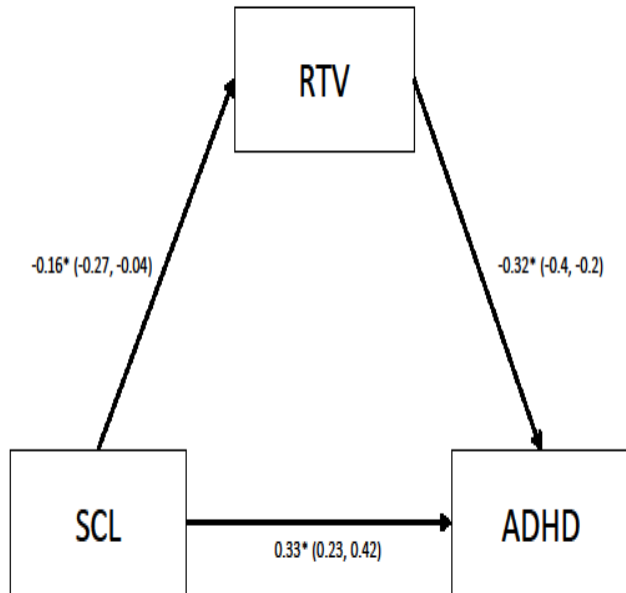
A) skin conductance level (SCL) B) skin conductance response (SCR) amplitude.

Figure 2: Standardised solution of the full correlated factor model across skin conductance level (SCL), reaction time variability (RTV) and ADHD in the baseline condition. Solid lines and * depict significant paths ($p \leq 0.05$) and dotted lines depict non-significant paths ($p > 0.05$). Confidence intervals are indicated in brackets.

Figure 3: Reaction time variability (RTV) as a mediator of skin conductance level (SCL) and ADHD in the baseline condition. Solid lines and * depict significant paths ($p \leq 0.05$) and dotted lines depict non-significant paths ($p > 0.05$). Confidence intervals are indicated in brackets.







cript

Accepted