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ADHD patients with DIRAS2 risk allele need more thalamic activation during emotional face-voice recognition

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1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a psychiatric disorder of multifactorial causation and with a broad variety of symptoms and functional impairments (Faraone et al., 2015). For instance, ADHD patients show deficits in social interaction (Nijmeijer et al., 2008) and emotion recognition (Rapport et al., 2002). Impaired ability of emotion recognition has previously been shown for the auditory, visual and audiovisual modalities (Bisch et al., 2016; Kis et al., 2017; Schönenberg et al., 2019).

DIRAS2 was described as risk gene for ADHD and belongs to the GTP-binding Ras-like protein 2. In humans its expression is almost limited to the brain and is highest in the hippocampus, the cerebral cortex, and the cerebellum (Grünewald et al., 2018). A role of DIRAS2 in cognitive processes has been suggested in a genome-wide association study (Seshadri et al., 2007). The association with ADHD is attributable to the promoter SNP rs1412005 within DIRAS2. Risk allele carriers include individuals with TT and GT genotypes, whereas individuals with a GG genotype are considered non-risk allele carriers (Grünewald et al., 2016).

ADHD has been shown to impact brain activation in a variety of cognitive tasks (Cortese et al., 2012). A recent study showed that poor performance in an audiovisual emotion recognition task related to lower activation in relevant areas of emotion processing (Zuberer et al., 2020). In order to investigate a possible link between emotion recognition deficits, gene-status, and neural activation, data from the forenamed study have been reanalyzed. We hypothesized that DIRAS2 risk allele carriers with or without clinical ADHD diagnosis show lower activation in key areas for audiovisual processing accompanied with poorer performance in audiovisual emotion recognition tasks.

2. Material and methods

Participants including ADHD patients and HC underwent an audiovisual emotion recognition task during three fMRI sessions containing 20 auditory, visual, and audiovisual stimuli. Stimuli were created in cooperation with professional actors presenting German words in five different emotions – neutral, happy, seductive, angry, and disgusted – with corresponding facial expression and tone of voice. Responses were given by choosing from a 5-point scale containing the German words for the mentioned emotions (for detailed imaging and task information, see Zuberer et.al (Zuberer et al., 2020)).

Genomic DNA was extracted from ethylenediaminetetraacetic acid (EDTA) anti-coagulated venous blood using the QIAamp DNA Blood Maxi-Kit (Qiagen; Hilden; Germany). DIRAS2 rs1412005 was genotyped on a StepOne system using TaqMan® SNP Genotyping Assay C__3069317_10 (Thermo Fisher Scientific, Waltham, U.S.). Accuracy was assessed by replicating 18,2% of the original sample, and reproducibility was 100%. The group with ADHD patients (n=44) comprised 19, while HC (n=43) contained 12 GT risk allele carriers.

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Table 1
p values in two sample t-tests comparing differences in fMRI response shown as in figure 1.

Group comparison	AV (p values)	V (p values)	A (p values)
ADHD (GG) vs HC (GG)	0.003	0.006	0.003
ADHD (GG) vs HC (GT)	0.011	0.068	0.053
ADHD (GG) vs ADHD (GT)	< 0.001	0.001	0.010
ADHD (GT) vs HC (GG)	0.079	0.205	0.498
ADHD (GT) vs HC (GT)	0.123	0.418	0.478
HC (GG) vs HC (GT)	0.488	0.399	0.475

Regions of interest (ROI) included right and left superior temporal sulcus, right posterior thalamus, superior frontal gyrus, both amygdalae, parietal cortex and gyrus rectus have been analysed for significant differences concerning DIRAS2 allele status via mixed analysis of variance (ANOVA). Also, the behavioural performance during the emotion recognition task has been analysed using arcsine transformed unbiased hit rates. If a significant interaction was identified, unpaired t-tests were performed to investigate differences in regional activation between GG and GT DIRAS2 allele carriers.

3. Results

The right thalamus showed a significant main effect in activation concerning DIRAS2 allele status $F(1,80)=4.75$, $p=.032$, partial $\eta^2=.056$. Activation of the right thalamus also showed an interaction between DIRAS2 allele status and ADHD diagnosis $F(1,80)=5.007$, $p=.028$, partial $\eta^2=.059$. Whilst taking DIRAS2 status into account, all other ROI showed no significant activation ($p>.05$). DIRAS2 showed no significant main effect on behavioural performance during the emotion face-voice recognition task $F(1,80)=.103$, $p=.749$, partial $\eta^2=.001$.

The fMRI signal of the right thalamus in ADHD patients with DIRAS2 risk alleles was significantly higher in all modalities than in ADHD patients without DIRAS2 risk alleles. ADHD patients without DIRAS2 risk alleles had lower activation than non-risk allele HC in all modalities. Compared to HC with DIRAS2 risk alleles this difference was only significant for the audiovisual modality. There was no significant difference in activation of DIRAS2 risk allele carriers with ADHD diagnosis compared to HC with or without DIRAS2 risk alleles. DIRAS2 status within the HC group also showed no significant difference in activation of the right thalamus (see figure and Table 1).

4. Discussion

Thalamic abnormalities have been reported before in ADHD patients (Xia et al., 2012). Zuberer and colleagues found a significantly lower activation in the right thalamus during an emotion recognition task, but it did not correlate with performance. Our results show that this effect seems to be driven by ADHD patients homozygous for the DIRAS2 GG allele, as ADHD patients carrying a risk allele show similar or even higher activation of the right thalamus compared with HC independent of genotype (see Fig. 1). This is surprising, as it seems more natural that a known risk-allele of ADHD would be associated with a known deficit in activation. But rather the opposite is what we observed: Considering that performance in the emotion recognition task showed no significant differences, higher activation in ADHD patients with DIRAS2 risk allele could reflect a compensatory mechanism, as it has been suggested for altered connectivity in ADHD patients before (Bailey and Joyce, 2015). Given its central role in neural networks, higher activation of the thalamus could also be compensatory for DIRAS2-driven deficits in other regions, that are unknown so far. This theory is also supported by the finding, that DIRAS2 risk allele carriers with no ADHD diagnosis show no increase in thalamic activation and no difference in emotion recognition performance. In summary, compensatory mechanisms within neural networks could lead to these rather surprising findings.

5. Conclusion

Higher activation in the right thalamus of DIRAS2 risk allele ADHD patients was observed during an emotion recognition task, potentially due to compensatory mechanisms within dysfunctional neural networks.

CRediT authorship contribution statement

Bastian Hillmann: Formal analysis, Writing – original draft, Visualization. **Agnieszka Zuberer:** Writing – review & editing. **Lena Obermeyer:** Investigation. **Michael Erb:** Software, Investigation. **Klaus Scheffler:** Resources, Writing – review & editing. **Vanessa Nieratschker:** Formal analysis, Writing – review & editing. **Thomas Ethofer:** Conceptualization, Methodology, Formal analysis, Project administration, Writing – review & editing, Funding acquisition, Supervision.

Declaration of Competing Interest

There are no financial or personal interests or beliefs that could affect

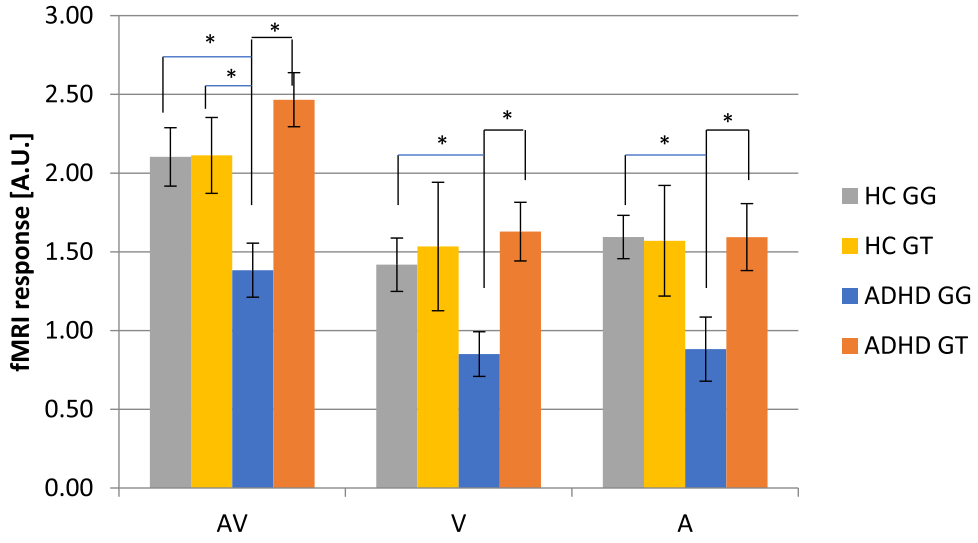

Fig. 1. p values in two sample t-tests comparing differences in fMRI response shown as in figure 1..*=p<0.05

the objectivity in this work.

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