Eat2beNICE

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Abstract

In the current research programme, we investigated the role of physical activity as an intervention for ADHD. More specifically, we aimed to predict whether brain imaging based biomarkers would predict for which patients this physical therapy would lead to an improvement in ADHD symptoms. Current clinical / behavioral measures overall poorly predict treatment outcome in ADHD. To our knowledge, this is the first study to examine neuroimaging-based treatment prediction in ADHD in a large clinical trial for a treatment based on a physical activity intervention.

Objective: To measure brain activation in patients with ADHD as a biomarker to predict subsequent therapeutic response to a physical activity intervention over a long follow-up period in general health, depression or ADHD symptoms.

Design: Functional magnetic resonance imaging (fMRI) data were collected prior to the intervention (T2) intervention and at the end of the clinical trial (T4). Changes in clinical status (GHQ, ADHD, IDS-C30) were regressed on brain responses and tested for selectivity for the reward system.

Intervention: Patients were treated with protocol-based bright light therapy (BLT), aerobic exercise therapy (AEI) or treatment as usual (TAU) as part of a mHealth-based intervention, the so-called PROUD trial in Frankfurt (WP6), department of child and adolescent psychiatry and department of psychiatry, psychosomatics and psychotherapy.

Patients: Twenty-three stable ADHD patients meeting DSM-IV criteria.

Brain imaging measures: Brain responses in a monetary incentive delay task (MID), a delay discounting task (DD) and a resting-state connectivity (rs-fMRI) scan were examined with fMRI prior to initiation of the PROUD clinical trial.

Main outcome measures: Whole-brain regression analyses with differential fMRI responses for rs-fMRI (nucleus accumbens connectivity), MID, and DD in the General Health Questionnaire (GHQ), the IDS-C30 (Depression) and the ADHD scale score as the treatment outcome measure.

Results: No pretreatment responses in the MID or the DD significantly predicted subsequent treatment outcome. However, pretreatment responses of the nucleus-accumbens connectivity significantly predicted subsequent treatment outcome of patients in regions of the precuneus or posterior cingulate gyrus. A decrease in the GHQ was paralleled by an increase of connectivity between accumbens and posterior cingulate gyrus in a subset (n=21) of patients.

Conclusions: The results suggest that rs-fMRI brain imaging of the reward system (accumbens seed) can provide biomarkers that substantially improve predictions for the success of physical therapy intervention over a long time-period (3-5 months from baseline scan) and more generally suggest that such biomarkers may offer evidence-based, personalized medicine approaches for optimally selecting among treatment options.

Introduction

ADHD, one of the most common psychiatric disorders worldwide, is associated with significant impairment, reduced quality of life, and psychiatric comorbidity (Thapar and Cooper 2016). The gold standards of treatment for ADHD to date have been cognitive behavioral therapy and pharmacotherapy with stimulants. However, non-pharmacological treatment approaches have been only moderately effective to date. There is no reliable predictor for the response to treatment for any treatment approach, let alone an identification of patients who would preferentially be considered for a certain treatment (personalized medicine).

It is possible that the main reason for the large interindividual differences in response to treatment is the variability within current psychiatric disease categories that exists at all levels (genetic, neurobiological, and clinical phenotype). This fundamental variability is not well understood but is likely to be essential for understanding the etiology and improving the treatment of these disorders. Noninvasive neuroimaging measures may provide important indices of patient variation (biomarkers or neuromarkers) because psychiatric illnesses can be conceptualized as brain disorders, and brain structure and function reflect both genetic and environmental influences on current behavior.

Some studies using neuromarkers have yielded promising results that are likely to capture meaningful variation among individuals sharing a diagnosis and could improve prognosis in patients with a range of behavioral disorders. In schizophrenia, for example, neuromarkers have been used to identify individuals at high risk for the disease, predict onset of psychosis in high-risk individuals, and predict treatment outcome (Li et al. 2020). In depression, neuromarkers have predicted recovery from the illness eight months later and response to CBT or drug treatment (Siegle, Carter and Thase 2006). In addition, neuromarkers have been used to predict the likelihood of relapse in drug addiction (Paulus, Tapert and Schuckit 2005). Finally, neuromarkers have been used successfully to predict treatment response in social anxiety disorder (Whitfield-Gabrieli et al. 2016).

Given the high prevalence of ADHD, surprisingly few studies to date have correlated neuroimaging with treatment outcome. Therefore, in the present study, we asked whether fMRI can better predict the treatment outcome of an mHealth intervention (PROUD trial) for ADHD better than current clinical measures alone. To this end, thirty patients with ADHD underwent an fMRI session at baseline and after completion of therapy in the PROUD trial. The reward system was examined using three well-validated procedures: A monetary-incentive-delay task (reward anticipation), a delay-discounting paradigm, and functional connectivity between the brain and a central hub of the reward system, the ventral striatum, were used.

Based on previous findings with appetitive or rewarding stimuli in patients with ADHD (Grimm, Rooij, et al. 2021), we hypothesized that patients' reward system would show weaker activation of the reward system at baseline, so-called blunted response of the reward system. This should improve over the course of treatment and be associated with treatment response in clinical scales.

Specifically, we expected that brain regions identified as dysfunctional in previous neuroimaging studies of ADHD might provide predictors of treatment response. These brain regions include the striatum, particularly the ventral striatum, the orbitofrontal cortex, the anterior insula, and generally portions of the limbic system.

Patients participated in a 10-week mHealth intervention using light therapy, fitness therapy, or standard treatment (PRO**U**D clinical trial) (Mayer et al. 2018). Reward system measures (MID, DD & rs-fMRI) taken before and after the intervention to assess treatment-related changes were correlated with GHQ, IDS-C30 and ADHD clinical scales collected before and after treatment. Based on the results of previous studies comparing ADHD patients with control subjects, we hypothesized that dysregulation of various aspects of the reward system might predict treatment response over a 3-5 month period (Grimm, Rooij, et al. 2021).

In summary, to our knowledge, we report the first data on neuromarkers of ADHD treatment response with different treatment approaches in a large sample of patients with ADHD. Based on the hypothesis that brain activation may be a more sensitive measure for revealing interindividual variability in ADHD pathology relevant to treatment response, we expected that fMRI-based characterization of the reward system would both predict treatment response and provide insight into relevant neural circuitry.

Methods

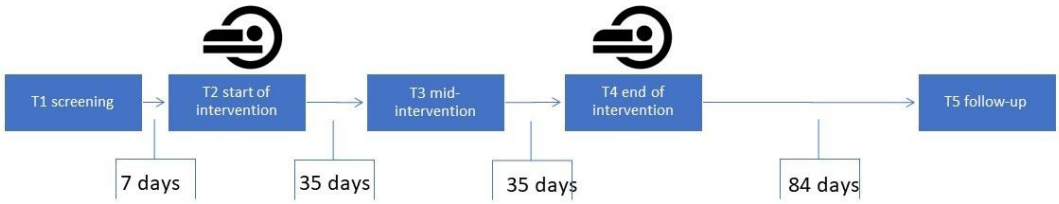


Figure 1 Schematic work-flow of fMRI scanning during the PROUD trial with schematic depiction of the fMRI scan's timepoint

Participants

The study includes n=28 subjects with ADHD who took part in the PROUD trial. Recruitment took place at the Goethe University Frankfurt am Main (GUF).

Inclusion criteria were age between 18 and 45 years. Exclusion criteria were acute severe mental illness, serious acute or chronic physical diseases, pregnancy, as well as exclusion criteria of the MRI examination. Participants were examined by a registered psychiatrist in Frankfurt.

The project was carried out in accordance with the provisions of the Declaration of Helsinki (World Medical Association 2013) and the European guidelines on Good Clinical Practice and was approved by the Ethics Committee of the Medical Faculty of the J.W. Goethe University Frankfurt am Main (reg.no. 256/16).

The study was registered in the German register of clinical studies since on 16/11/2016 with the study ID DRKS00011248, indexed in the WHO clinical trial search platform (https://apps.who.int/trialsearch/). Subjects gave written informed consent. The subjects received 10€ per hour for participation. In addition, the monetary gain of the Monetary Incentive Delay Task of all three measurement dates was paid out to the volunteers.

Clinical variables

We extracted from the CRF of the PROUD trial the clinical ratings of the IDS-C30 interview, a structured clinical interview for depression, the ADHD DSM-V rating scale, which assigns a value of 0-4 to each of the 18 ADHD criteria (interview) and the self-rating questionnaire on general health (General Health Questionnaire GHQ). This was extracted for the time point before (T2) and after the study intervention (T4 and T5). Therapeutic response was calculated as the difference between T4 and T2 or T5 and T2.

Monetary incentive delay fMRI-paradigm

We used a MID-task in combination with fMRI measurement (see **Figure 3**). A modified version of this MID-task has been evaluated extensively before and leads to a valid and reliable signal in the striatum during anticipation. The task was validated in previous studies (Francois et al. 2016; Grimm, Nägele, et al. 2021). Volunteers were shown 30 “smileys” as well as 30 neutral, scrambled “control smileys” on a screen in the MRI in an unpredictable order, to which they had to react as quickly as possible with the push of a button after a flashlight occurred. After presentation of the smileys (or conditioned stimuli), the participants earned a monetary feedback of 50 cents if they reacted quickly. To prevent habituation, participants were unexpectedly rewarded with a booster prize (max. four times) of 2 € in between. If the reaction time was too slow, the participant did not win money. The smiley represents the winning condition (b). In a control condition (a) the test persons were shown a scrambled smiley, a yellow circle (see figure 2). In the control condition only a written positive or negative feedback was provided. The money won, as well as the current account balance, was displayed on the screen after each run (e.g. "You win 50 cents, the account balance is 10 euros").

After each trial, the reaction time was adapted depending on success (tougher next trial, reaction time +10%) or miss (easier next trial, reaction time + 5%). In order to increase the expectation of rewards, the participants were informed beforehand that money won in the MID task will be paid out in cash directly after the measurement.

Delay Discounting Task

A validated inter-temporal choice paradigm (McClure, Laibson, Loewenstein, & Cohen, 2004) comprising a total of 40 inter-temporal choice trials was used (see **Figure 4**). During each trial subjects had to choose between two monetary reward options which differed in amount and delay-to-delivery. During each trial two yellow triangles underneath the two money/time pairs indicated that a choice could be made. Responses were made by pressing one of two response buttons corresponding to the location of the options on the screen. Once the subjects made their choice, the associated yellow triangle turned red for 2 s signaling that the selection was successfully recorded.

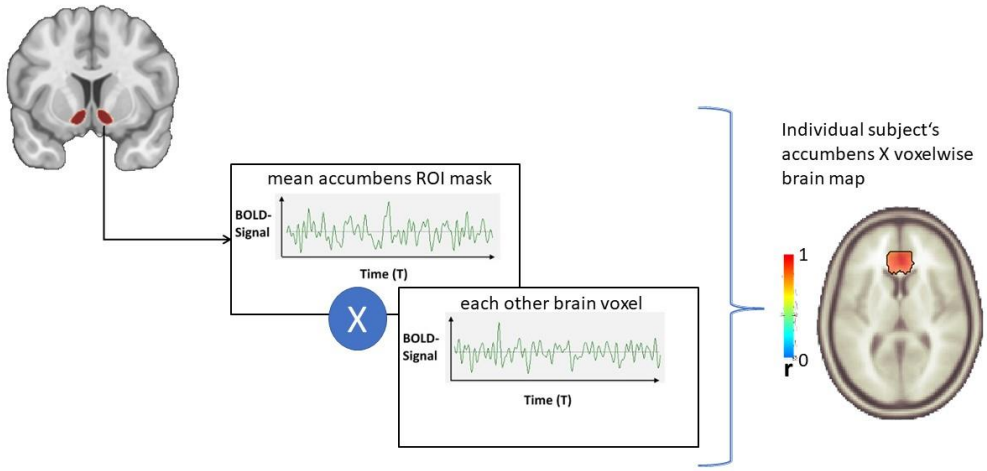


Figure 2: Resting-state functional connectivity: Generating BOLD-response time series for specific brain regions (ROIs). The time series were correlated to BOLD-responses from the rest of the brain. Here a brain region in the occipital cortex is given as an example for "other brain regions". A significant overlap in BOLD-responses indicates functional connectivity between the compared brain regions as measured by a z-normalized correlation coefficient.

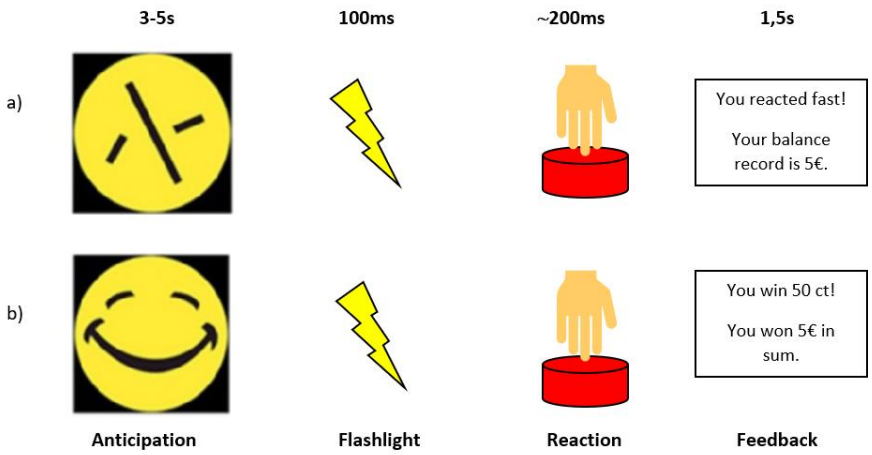


Figure 3: Monetary incentive delay (MID) task: event-related functional magnetic resonance imaging (MRI): 30 control conditions (a) and 30 winning conditions (b). In sum 60 trials. A circle (a) or a smiley (b) is displayed in the anticipation phase. Then a flashlight appears and the participant has to react as fast as possible by pressing a button. After the reaction a feedback is shown: control condition (a): feedback about the success of the reaction and winning condition (b): feedback about winning money - 50 cents or a booster of 2€.

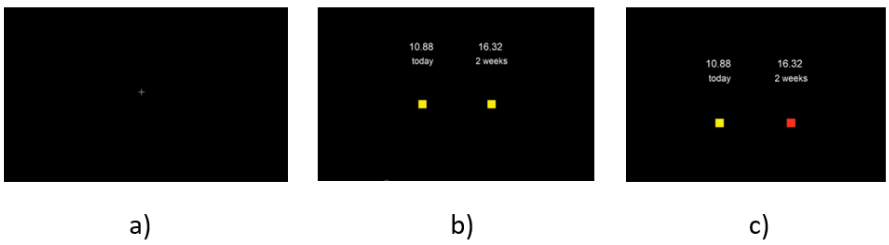


Figure 4: Delay Discounting Paradigm (DD): fMRI task: First the cross hairs (a) are presented for 12 seconds. There are 40 trials with choices between smaller-but-sooner (e.g 10.88€ today) and later-but- larger rewards (16.32€ in 2 weeks) (b). Then the participant has to press a button to choose one of the presented options (c). There are different kinds of choices as immediate/today, early (2 or 4 weeks) or later (6 weeks). The participant can win this sum of money at the corresponding time point. The cross hairs are presented after each trial for 12 seconds.

Data analysis: fMRI preprocessing

Images from participants were realigned, slice-time corrected, spatially normalized to standard stereotactic space (Montreal Neurological Institute [MNI] template), resampled to 3mm isotropic voxels, and smoothed with 8mm full-width at half maximum Gaussian kernel. A band-pass filtering was used in the frequency band frequency bands to 0.01–0.1Hz to get rid of non-neural signals for the resting-state data. Further noise correction was done by regressing out motion parameters derived from the realignment procedure, the 1st order derivative of movement parameters. Data analysis was done with SPM12 in addition to CONN-toolbox for preprocessing of resting-state data: A band-pass filter reduced frequency bands to 0.01–0.1 Hz, additional noise correction of rs-fMRI was done by regressing out motion parameters (from rigid-body transformation), their 1st order derivative and correcting for cerebrospinal-fluid signal and white-matter-signal (so called aCompCor-strategy) (Whitfield-Gabrieli and Nieto-Castanon 2014).

Accumbens seed connectivity

For seed-voxel connectivity, we used the region of interest (ROI) mask of the nucleus accumbens from the high-resolution probabilistic in vivo atlas of human subcortical brain nuclei (CIT168) (Pauli et al., 2018). Data processing was done with CONN v1.8 toolbox with SPM12. For a schematic outline of the workflow, see **Figure 2**.

Data analysis: group statistics

First-level correlation maps were calculated by extracting the residual BOLD-time course from the seed ROIs and correlating these with the other voxels within the brain. These correlation coefficient maps were then converted via a normally distributed z-score (Fisher transformation). Transformed correlation maps were used for directed paired t-tests on the second-level stage. For correction of multiple testing during second-level statistics we used cluster-wise whole-brain analysis with topological FDR correction pFDR<0.05 (cluster defining voxel threshold $p < 0.001$) (Chumbley et al. 2010).

Results

An overview of behavioral data and demographics is given below:

Table 1: Demographic overview with behavioral measures of task

Number of participants	N=28
Resting state	27
MID task	22
DD task	25
Number of fMRI scans	
One scan	7
Two scans	21
Age	28.18 (4.86)

Sex	
Female	14
Male	14
Weight (kg)	75.38 (17.78)
Height (m)	1.72 (0.09)
Clinical specification	
ADHD subtype	
Combined	18
Inattentive	8
Hyperactive	2
Comorbid disorders	
Overweight (BMI>25)	11
Depression	18
Substance addiction	11
Movement parameters	
Median position change (mm)	
Resting state	0.2 (0.09)
MID task	0.186 (0.08)
DD task	0.17 (0.07)
Mean position change (mm)	
Resting state	0.22 (0.11)
MID task	0.22 (0.11)
DD task	0.22 (0.11)
Behavioral data	
Mean response time in MID task (ms)	
Winning condition	191.51 (27.17)
Control condition	198.25 (28.18)
Mean number of no responses MID task (ms)	
Winning condition	0.77 (1.17)
Control condition	0.82 (1.77)

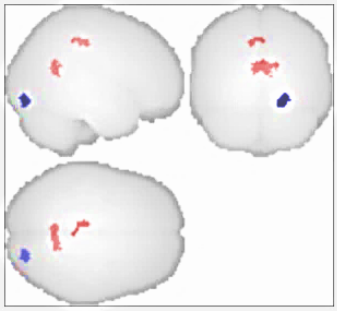
Choices DD	
immediate choice early	7.8 (4.47)
immediate choice late	8.04 (4.7)
delayed choice early	11.2 (6.54)
delayed choice late	12.12 (6.54)
Mean reaction time DD (ms)	
immediate RT	2875.73 (1492.8)
delayed RT	3231.43 (1731.9)

Neither the MID task, not the DD task were able to predict changes in GHQ (T5-T1), ADHD symptoms (T4-T2) or IDS-C30 (T4-T2). In addition, no changes between participants with two time points were found.

In contrast to this, seed functional connectivity in the resting-state fMRI indicated that the nucleus accumbens seed ROI demonstrated changed connectivity when predicting therapeutic changes. Change in Ncl Accumbens connectivity to the precuneus and the posterior cingulate gyrus predicted a decrease in the general health questionnaire score (GHQ T5-T1) between the timepoints T1 and T5, indicating a timespan of about 5 month. Time changes in ADHD and IDS-C30-scores were not predicted by baseline NAc-connectivity (see **Figure 5**).

How does the brain change between the treatment timespan? In a smaller subset of patients (n=21), we compared the time difference between T2 and T4 for a change in ADHD, GHQ and IDS-C30-scores. A change in NAcc-PGC-connectivity paralleled a decline in the depression score (see **Figure 6**) as well as the GHQ-score (see **Figure 7**).

Results



Clusters (x,y,z)	size	size p-FWE	size p-FDR	size p-unc	peak p-FWE	peak p-unc
-04 -56 +16	152	0.001158	0.000715	0.000026	0.977438	0.000036
+26 -84 -14	86	0.031829	0.009987	0.000740	0.425884	0.000003
-08 -26 +44	59	0.148234	0.033024	0.003669	0.989283	0.000045

153 voxels covering 3% of atlas.Precuneous (Precuneous Cortex)
73 voxels covering 8% of atlas.OFusG r (Occipital Fusiform Gyrus Right)
42 voxels covering 2% of atlas.PC (Cingulate Gyrus, posterior division)
14 voxels covering 0% of atlas.PreCG l (Precentral Gyrus Left)
5 voxels covering 0% of atlas.Cereb1 r (Cerebelum Crus1 Right)
3 voxels covering 0% of atlas.OP r (Occipital Pole Right)

Figure 5: Significant cluster show connectivity change from Nucleus Accumbens Seed. Red cluster show a

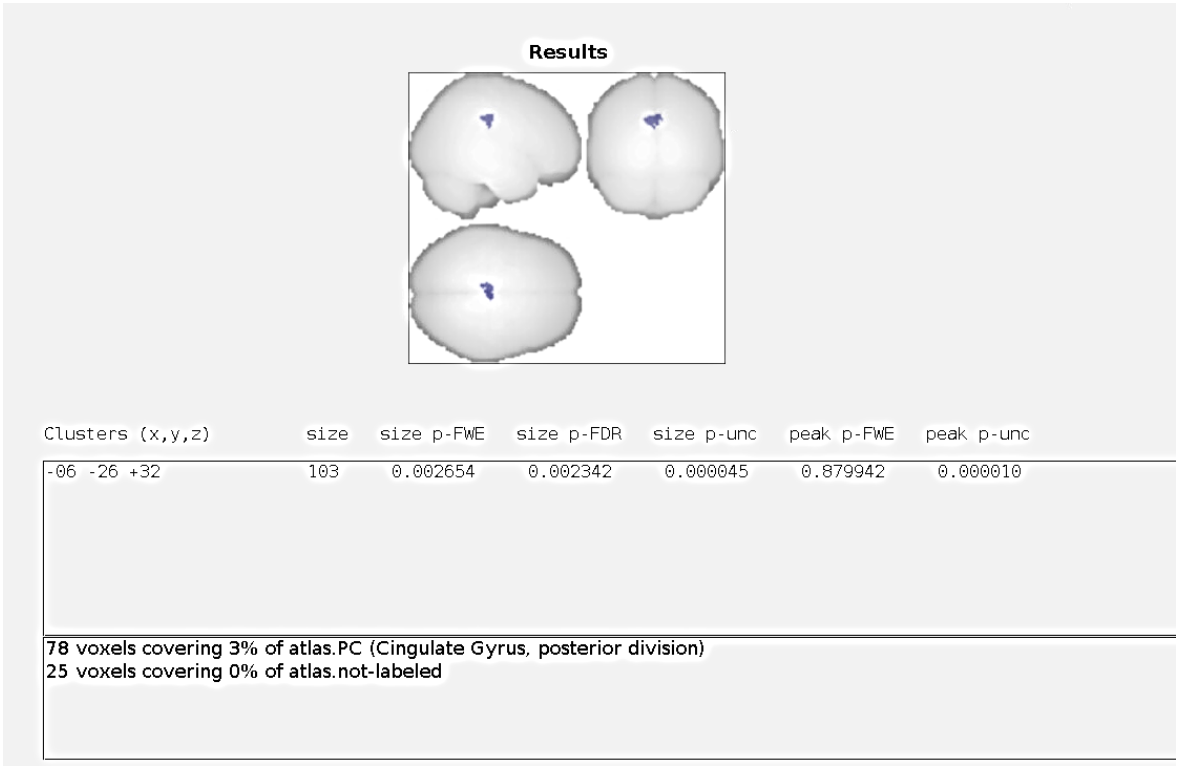


Figure 6: NAcc-connectivity to the posterior cingulate gyrus is inversely correlated with decrease of depression scores between T4 and T2 in the IDS-C30.

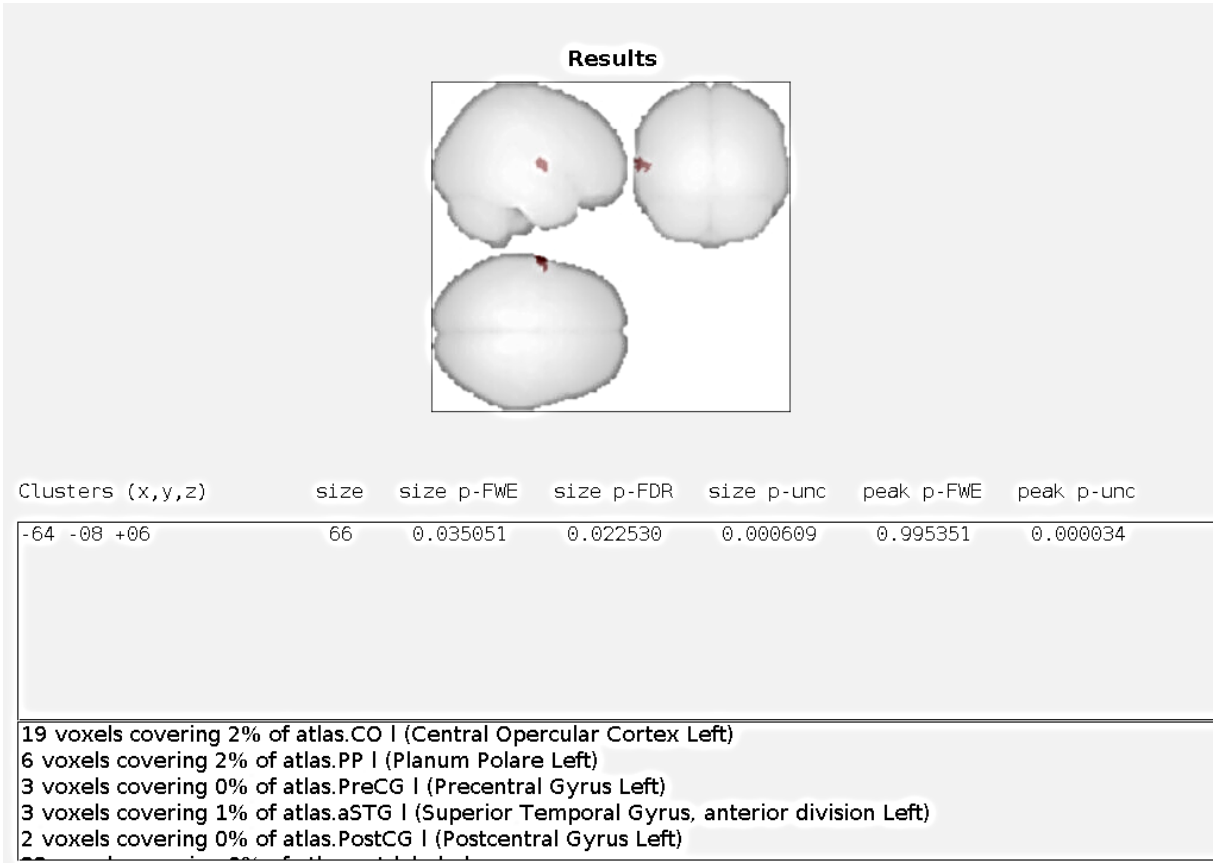


Figure 7: Increase of connectivity between T2 and T4 between NAcc and the Central Opercular Cortex/Insula correlates with decrease of General Health Questionnaire (GHQ).

Discussion:

To our knowledge, this is the first study looking at a neuromarker for prediction of therapeutic response in a non-pharmacological trial in ADHD patients. We not only studied the predictive power of fMRI but studied the brain changes in relation to therapeutic response in a smaller subset of patients who had scans at baseline and in addition at the end of the intervention.

Our study investigated a subset of the PROUD study (Mayer et al. 2018). This trial was a prospective, pilot phase-IIa, parallel-group RCT with three arms (two add-on treatment groups [BLT, AEI] and one treatment as usual [TAU] control group). The primary outcome variable, a change in the Inventory of Depressive Symptomatology total score between baseline and ten weeks of intervention, did not meet statistical significance.

We detected changes in connectivity between mainly the PCG and the NAc in predicting therapeutic changes as well as changes in neural patterns paralleling therapeutic response. Thus, the PCC is anatomically suited to contribute to appraisal and decision-making processes. Imaging studies in humans revealed that the PCC is activated by changes in subjective motivational state. For example, Small and colleagues tested human participants before and after they were fed chocolate to satiety, which resulted in increased BOLD signal in the PCC (Small et al. 2001). This correlated with subjective ratings, i.e., how pleasant the chocolate was. Kable and Glimcher demonstrated that PCC activation varied systematically with temporally decreased value in an intertemporal decision task (Kable and Glimcher 2007). Interestingly, we did not confirm this in our reward delay discounting paradigm. Taken together, this suggests a role for the PCC in evaluating motivationally significant events and actions and their subjective value in guiding future behavior.

Neuroimaging studies of ADHD and other comorbid psychiatric disorders have identified differences in the brain, but these observations have had limited clinical impact (Grimm, Rooij, et al. 2021). Neuromarkers could become a practical clinical tool to guide the selection of optimal treatments for individual patients. However, several limitations of the present study would need to be addressed in further studies before such a practical application is possible. First, we are limited by the small sample size available for the current study. Ideally, a follow up study would allow a model to be derived from a specific group and subsequently applied to a completely independent group. This would be allow us to determine the true generalizability of the model, as well as greatly increase the statistical power of the analysis In particular, the use of machine-learning models would lend itself to this, e.g., the applicability of an ML model from a big-data dataset to a smaller, clinically relevant sample. Second, although statistically it did not seem to make a difference whether patients in the PROUD study were in the TAU, BLT, or AEI condition, it would be interesting in a larger study to treat patients uniformly. In the present study, because of the small sample, all patients were treated the same regardless of treatment group. Third, it is unknown why the two fMRI paradigms, which are at least partially evaluated neuromarkers. did not give more significant differences, but one fMRI connectivity marker gave significant differences. The reward system is not an uniform entity. Fourth, a direct comparison of participants with ADHD and healthy controls over time would be useful to determine the typical activation pattern in these predictive brain areas to make specific statements about pathophysiological mechanisms. Fifth, it will be important to conduct studies that contrast alternative treatments to determine whether neuromarkers can differentially predict which treatment is optimal for a patient. However, the positive finding that a NAcc connectivity marker can significantly predict treatment outcome provides evidence that treatment selection for a patient with ADHD can move toward evidence-based neurobiological approaches that can lead to optimal, individualized clinical benefit.

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