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ORIGINAL CONTRIBUTION

Beneath the surface: hyper-connectivity between caudate and salience regions in ADHD fMRI at rest

Stefano Damiani[1] · Livio Tarchi[1] · Andrea Scalabrini[2] · Simone Marini[3] · Umberto Provenzani[1] · Matteo Rocchetti[1] · Francesco Oliva[4] · Pierluigi Politi[1]

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Abstract

Attention-Deficit/Hyperactivity Disorder (ADHD) comprises disturbances in attention, emotional regulation, and reward-related processes. In spite of the active efforts in researching neurofunctional correlates of these symptoms, how the activity of subcortical regions—such as basal ganglia—is related to ADHD has yet to be clarified. More specifically, how age may influence the critical changes observed in functional dynamics from childhood to adulthood remains relatively unexplored. We hence selected five core subcortical regions (amygdala, caudate, putamen, pallidum and hippocampus) as regions of interest from the previous literature, measuring their whole-brain voxel-wise rsFC in a sample of 95 ADHD and 90 neurotypical children and adolescents aged from 7 to 18. The only subcortical structure showing significant differences in rsFC was the caudate nucleus. Specifically, we measured increased rsFC with anterior cingulate and right insula, two mesolimbic regions pertaining to the Salience Network. The degree of hyper-rsFC positively correlated with ADHD symptomatology, and showed different patterns of evolution in ADHD vs neurotypical subjects. Finally, the rsFC scores allowed a fair discrimination of the ADHD group (Area Under the Curve ≥ 0.7). These findings shed further light on the fundamental role covered by subcortical structures in ADHD pathogenesis and neurodevelopment, providing new evidence to fill the gap between neurofunctional and clinical expressions of ADHD.

Keywords Attention deficit hyperactivity disorder · fMRI · Caudate nucleus · Salience network · Reward

Abbreviations

ADHD	Attention deficit hyperactivity disorder
AFNI	Analysis of Functional NeuroImages
AUC	Area under the curve
Bcaud	Bilateral caudate
DVARS	Spatial standard deviation from volume N to volume N + 1
FDR	False Discovery Rate
fMRI	Functional magnetic resonance imaging
GSR	Global Signal Regression
rsFC	Resting-state functional connectivity
FSIQ	Estimates of Full-Scale Intelligent Quotient
MNI	Montreal Neurological Institute
rACC	Right Anterior Cingulate Gyrus
rINS	Right anterior insula
ROI	Region/regions of interest
SN	Salience network
TYP	Neurotypicals
vmPFC	Ventro-medial Pre-Frontal Cortex

Stefano Damiani and Livio Tarchi have contributed equally to the work.

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✉ Livio Tarchi
livio.tarchi01@universitadipavia.it

[1] Department of Brain and Behavioral Sciences, University of Pavia, Via Bassi 21, 27100 Pavia, PV, Italy

[2] Department of Psychological, Health and Territorial Sciences (DiSPuTer), G. D'Annunzio University of Chieti-Pescara, Via dei Vestini 33, 66100 Chieti, CH, Italy

[3] Department of Epidemiology, University of Florida, 2004 Mowry Road, Gainesville, FL 32610, USA

[4] Department of Clinical and Biological Sciences, University of Turin, Regione Gonzole 10, 10043 Orbassano, TO, Italy

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Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is a common condition affecting approximately 5% of school-aged children and 2.5% of adults [1]. It is clinically characterized by a reduced ability to focus or sustain attention and excessive motor and emotional activity, which in turn leads to impulsivity and disorganization [1].

Structural imaging suggests a central role of subcortical regions such as caudate and amygdala in ADHD (see "The role of subcortical structures in ADHD pathogenesis"). In recent years, functional alterations in subcortical structures started to be explored [2]. However, these studies often yielded inconsistent findings that require further corroborations [3].

The role of subcortical structures in ADHD pathogenesis

Basal ganglia dimensions were found generally reduced or altered in shape in ADHD [4, 5].

The caudate nucleus is a core subcortical, bilateral structure regulating not only motor but also emotional, cognitive and perceptual functions [6]. Caudate serves as entry point to both the basal ganglia and the dopaminergic reward systems. In ADHD, caudate's architecture shows volumetric reductions and increased asymmetry [7]. Together with putamen and nucleus accumbens, caudate forms the striatum nucleus, which connections have been demonstrated to be altered in ADHD. An altered cortico-striatal connectivity has been linked to behavioral features characterizing ADHD, such as the inability to tolerate delays in receiving a reward (delay-discounting, see Patros et al. [8]).

Recently, mesolimbic structures such as amygdala also started to be considered among the key regions laying at the core of ADHD pathophysiology. The presence of structural changes in the amygdala of ADHD subjects has been confirmed by an increasing number of findings [9]. Intriguingly, these alterations share a strong bond with the individual behavioral phenotype: it has been demonstrated how volumetric reductions in amygdala have been connected to higher hyperactivity [10] and impulsivity [11] scores. If on one hand the involvement of deep subcortical structures in ADHD is strongly supported by the morphological evidences, on the other the studies trying to describe their role from a functional perspective often showed mixed results.

fMRI correlates of subcortical spontaneous activity in ADHD

In functional neuroimaging, current scientific literature suggests the presence of major alterations in motor, cognitive, and emotional tasks for ADHD [12, 13]. A second line of research focused instead on the spontaneous activity of the brain (also known as resting state, see references for a systematic review [2]). The degree of co-activation between different regions at rest (resting-state functional connectivity, or rsFC) may deeply influence stimuli-processing through complex and yet unclear dynamics [14–17]. Yang et al. [18] measured both hyper- and hypo-rsFC between dorsal-caudate and several brain regions in subjects between the age of 7 and 13. Rosch and colleagues [19] found that dorso-lateral prefrontal cortex showed increased rsFC with striatum and decreased hypo-rsFC with the amygdala and hippocampus in children between the age of 8 and 12. Hulvershon et al. [20] focused on amygdala rsFC in relation with the emotional liability of the subject, finding a positive correlation between emotional liability and amygdala-anterior cingulate rsFC and a negative correlation between emotional liability and amygdala-insula rsFC. In a smaller sample, Cao et al. [21] narrowed their analyses on the putamen nucleus, finding altered rsFC patterns without any association to clinical symptoms. Another study showed increased rsFC between thalamus and putamen/caudate [22]. Oldehinkel et al. considered the rsFC of the reward system in adolescents and young adults, which showed no differences between ADHD and controls [23], but a positive relationship between symptoms and the increase of rsFC for caudate and putamen [24]. Altogether, the studies on ADHD subcortical structures' rsFC have often conducted region-based analyses, leaving open questions about the rsFC dynamics between subcortical structures and the whole-brain. In addition, the crucial diachronic component of age has been overlooked and a characterization of the maturational processes of the brain on observed results requires further exploration. As Zhou et al. [25] highlighted, not considering the age of the subject fMRI when measuring rsFC differences may lead to controversial results.

Brain maturation in ADHD

The discrepancies in basal ganglia morphology in ADHD tend to progressively reduce through adolescence [5].

As it has been shown morphologically for caudate, the functional relationship between amygdala and cortical structures also goes through important changes during the maturational processes of the individual [26]. In a similar way, ADHD's local connectivity appears to be altered in several areas (including subcortical regions [27]), and its topology changes from childhood to adolescence and adult age. Recent findings in healthy individuals showed that cortico-striatal rsFC progressively decreased through age, and a persistent hyper-rsFC was related to the presence of ADHD-like symptoms among others [28].

According to the aforementioned evidences, we may hypothesize that changes in rsFC are age-dependent and that these different developmental pathways on the neuronal side may subtend to clinical manifestations of ADHD.

Aims

We explored the rsFC of five subcortical regions (caudate, amygdala, putamen, pallidum and hippocampus), choosing them for their anatomical adjacency and their plausible involvement in the pathogenesis of ADHD (see "The role of subcortical structures in ADHD pathogenesis" and "fMRI correlates of subcortical spontaneous activity in ADHD"). The primary endpoint of the present study was to determine the presence of altered rsFC in ADHD when compared to neurotypical control subjects (TYP), expecting to find increased cortico-striatal rsFC and altered rsFC in amygdala. Specifically, we evaluated whether the strength of the functional connections between subcortical regions is differently influenced by age in these two groups. We predicted to find a delayed maturational process in ADHD with respect to the TYP trajectory according to the structural and preliminary functional evidence.

The secondary endpoints aim to explore (1) the relationship between the rsFC of subcortical structures and ADHD symptoms, possibly confirming previous literature and (2) the possibility to detect the presence of the disorder based on the fMRI findings.

Materials and methods

Sample

Our sample was obtained from the New York University dataset of the ADHD200 repository, specifically from the International Neuroimaging Data-Sharing Initiative. Scanning and sample characteristics are reported in Tables 1 and 2.

All the recordings were collected in accordance with the Declaration of Helsinki.

Estimates of Full-Scale Intelligent Quotient (FSIQ) above 80, right-handedness and absence of other chronic medical or psychiatric conditions were required for all subjects. A quality check for each subject was present in the phenotypic key provided with the dataset, and those subjects that did not pass were discarded preventively. Additional information can be found on the website (https://fcon_1000.projects.nitrc.org/indi/adhd200/).

Procedures

fMRI data preprocessing steps were implemented in AFNI (https://afni.nimh.nih.gov/afni, Cox 1996). First, the structural volume was corrected for signal intensity bias using AFNI's 3dUnifize at standard settings. The structural and functional reference images were then co-registered [29].

Table 1 Image acquisition

Sample	MR characteristics		Functional imaging				
	Scanner/software	Anatomical resolution	Scan duration	TR (ms)	TE (ms)	Flip angle	Resolution
ADHD200	Siemens Magnetom Allegra syngo MR 2004A	1.3 × 1.0 × 1.3 [mm]	360 s	2000	15	90	3.0 × 3.0 × 4.0 [mm]

Table 2 Sample data

Sample	Subj (*n*)	Subj (*n*) after motion correction	Mean age (years ± 1 SD)	Sex (M/F)	Medications
ADHD200	ADHD: 123	ADHD: 95	ADHD: 11.42 ± 2.74	ADHD: 72♂/23♀ 76% males	ADHD: 23 naïve 20 medicated 52 unknown
	TYP: 99	TYP: 90	TYP: 12.38 ± 3.12	TYP: 44♂/46♀ 49% males	TYP: 90 naïve

SD standard deviation

The first three frames of each fMRI run were removed to discard the transient effects in amplitude observed until magnetization achieves steady state [30]. Slice timing correction [31] and despike methods [32] were applied. Rigid-body alignment of the structural and functional image was performed. The anatomical image was then warped using the Montreal Neurological Institute standard space (MNI152_T1_2009c) template provided with the AFNI binaries. Volume registration was then used to align the functional data to the base volume, warping it to the stereotactic space of choice. Spatial blurring was performed, with a kernel of full width at half maximum of 6 mm. Bandpass (0.01–0.25 Hz) was performed [33], to include the low-frequency bands from slow-5 to slow-2 [34]. Each of the voxel time series was then scaled to have a mean of 100. To control for non-neural noise, regression based on the six rigid body motion parameters and their derivates was applied, as well as mean time series from white matter and cerebro-spinal fluid masks [35] eroded by one voxel [36]. Whether preprocessing should include or not Global Signal Regression (GSR) is controversial [37]: to account for possible artifacts due to the exclusion of GSR, results were computed with and without the additional regression of the grey matter averaged timeseries. To further improve motion correction, censoring/scrubbing such as DVARS of two [38] and Framewise Displacement of 0.5 mm was applied [39] to the timeseries: two subjects (one ADHD—one TYP) were excluded from the fMRI analysis, as they exceeded the cut-off of 5% censored timepoints.

Primary aim

Resting-state functional connectivity—voxel-wise analysis

Based on previous literature (see "The role of subcortical structures in ADHD pathogenesis" to "Aims"), we selected caudate, amygdala, hippocampus, pallidum and putamen as seeds from the MNI atlas provided with the AFNI binaries. We extracted Left and Right regions from the atlas and combined them in a single bilateral region. An illustration of the ROIs used in this study can be found in the Supplementary Materials as Figure S1. Voxel-wise rsFC analysis was performed to investigate the differences between neurotypicals and ADHD patients during resting state. Individual rsFC maps were generated by calculating the Pearson's correlation coefficients between the mean time series of the seed and the time series of each voxel in the whole brain. In the *t* test between TYP and ADHD FC, clusters with more than 30 voxels at the threshold of $p = 0.05$ (corrected for False Discovery Rate, or FDR) were considered significant [40].

Resting-state functional connectivity—region-based analysis

To quantify the results' magnitude, single region significant voxel-wise masks were obtained and defined as regions of interest (ROIs). Mean values of correlations in those regions were extracted and compared between ADHD and TYP subjects. Statistical analyses included *t* test for the measure of rsFC mean value differences between ADHD subjects and neurotypicals. Pearson's coefficient was used to measure correlations/anticorrelations of the rsFC mean value with clinical scales. R-3.6.1 and R Studio-1.2.1335 were used to plot correlation figures.

Subsequently, age was used as a covariate and its effect estimated through an ANCOVA analysis on voxel-wise results. Mean values of correlations, mentioned above, were also averaged through groups and age classes, then plotted to follow their evolution in time. Two polynomial fits, each for diagnostic class, were used to represent the differences observed through age. The "ggplot2" library, in R/R-Studio, was used to graphically represent 95% confidence intervals of the polynomial fits.

Secondary aims

1. Total ADHD, Hyperactivity and Inattention scores were collected using the Conners' Parent Rating Scale-Revised, Long Version [41] for all the available subjects (93 ADHD and 88 TYP, 2 missing observations for each class). Those scores were correlated with the above-mentioned ROIs to test whether the presence of an altered rsFC may be related or not to the phenomenological level.
2. ROC curves were built based on components obtained from the significant ROI's rsFC values, and the diagnostic power of AUC was evaluated. To do so, the software MATLAB 2019b (version 9.7.01190202) and its app "Classification Learner" were used. Two logistic regressions were fit using either rACC or rINS results in order to classify TYP and ADHD samples. A fivefold cross-validation was used to estimate the test error rate. For this kind of test, the sample was split into five subgroups (20% of the sample each). Each group was taken as a test set versus the remaining groups, which were considered as the training set. The model was thus fit on the training set and subsequently evaluated on the test set. Finally, the skill of the model was computed using the summarized evaluation scores of the five models [42].

Confirmatory and control analyses

The present study included the following control analyses:

1. Motion during scan was evaluated through measurements of Framewise Displacement (FD). Mean values of FD were averaged per subject, then its distribution evaluated for diagnostic class. The "ggplot2" library was used to graphically illustrate mean Framewise Displacement values through a histogram plot and density curves, divided by diagnostic class.
2. To account for possible artifacts due to the exclusion of Global Signal Regression (GSR), results were computed with the additional regression of the grey matter averaged timeseries.
3. Some ADHD subjects were not medication free, with type and dose of the medication not known (see Table 2). For all these subjects though, psychostimulant drugs were withheld at least 24 h before scanning. A *t* test was performed to compare the medicated and non-medicated population in ADHD patients, to exclude confounding effects given by the pharmacological status.
4. ADHD patients were not homogenous for diagnostic criteria applied, different sub-groups of ADHD diagnosis from DSM-5 were used for the inclusion criteria. *T* tests were conducted on the two significant FC-ROI to investigate the possible differences between clinical ADHD sub-groups. Hyperactive subjects were excluded from this confirmatory analysis as only one patient was present in our sample.
5. As the distribution of males and females was unequal between the two populations (see Table 2 for exact percentages), a control analysis for rsFC differences possibly due to gender was necessary. Hence, we performed four ROI-based *t* tests between TYP and ADHD computing: (1) Bcaud-rACC rsFC for male subjects. (2) Bcaud-rACC rsFC for female subjects. (3) Bcaud-rINS rsFC for male subjects. (4) Bcaud-rINS rsFC for female subjects.
6. To confirm the specificity of our findings, we performed whole brain, voxel-wise rsFC analyses using the result regions from rACC and rINS. Masks obtained from result regions were used as seeds.

Results

Primary aim—voxel-wise analysis

No statistically significant difference was observed in rsFC between TYP and ADHD for bilateral amygdala, hippocampus, pallidum and putamen (Table 3). Conversely, when bilateral caudate (Bcaud) was considered as a seed, two significant ROI with increased rsFC in ADHD were found—right anterior cingulate cortex (rACC) and right anterior insula (rINS). Results are shown in Fig. 1 and Table 3; overlaps with the MNI coordinates are reported in Supplementary Materials (Table S1).

Primary aim—region-based analysis

rACC and rINS masks were generated. Average values of correlation between Bcaud and statistically significant ROIs (rACC and rINS) were calculated and subsequently used for confirmatory analyses. Mean rsFC values between the regions are shown in Table 4.

When rsFC values of significant ROI were extracted, a strong difference for developmental trends was observed between ADHD and TYP, especially in the range between 9- and 12-years old (Fig. 2). The trendline of this difference was better represented by a second-order polynomial (i.e., U-shaped curve, $r^2 = 0.7788$) rather than by a linear relationship ($r^2 = 0.0527$), with a peak at the age between 11 and 13 and a progressive reduction after that time window. Similar trends were observed for rINS, though with a smaller age effect than in rACC. Again, the distribution of differences better fitted to a second-order polynomial than to a linear trend. Mean differences per year of age are reported

Table 3 Whole brain, voxel-wise functional connectivity *t* test between TYP and ADHD

Seed (bilateral)	Smallest FDR *p*	Significant ROI*	Voxels forming the cluster (*n*)	Center of mass MNI coordinates (x,y,z. RAI)
Caudate	0.003	rACC	183	−10.5, −40.5, +19.5
		rINS	38	−34.5, −16.5, −4.5
Amygdala	0.354	–	–	–
Hippocampus	0.331	–	–	–
Pallidum	0.228	–	–	–
Putamen	0.209	–	–	–

FDR False Discovery Rate correction

*at FDR $p = 0.05$

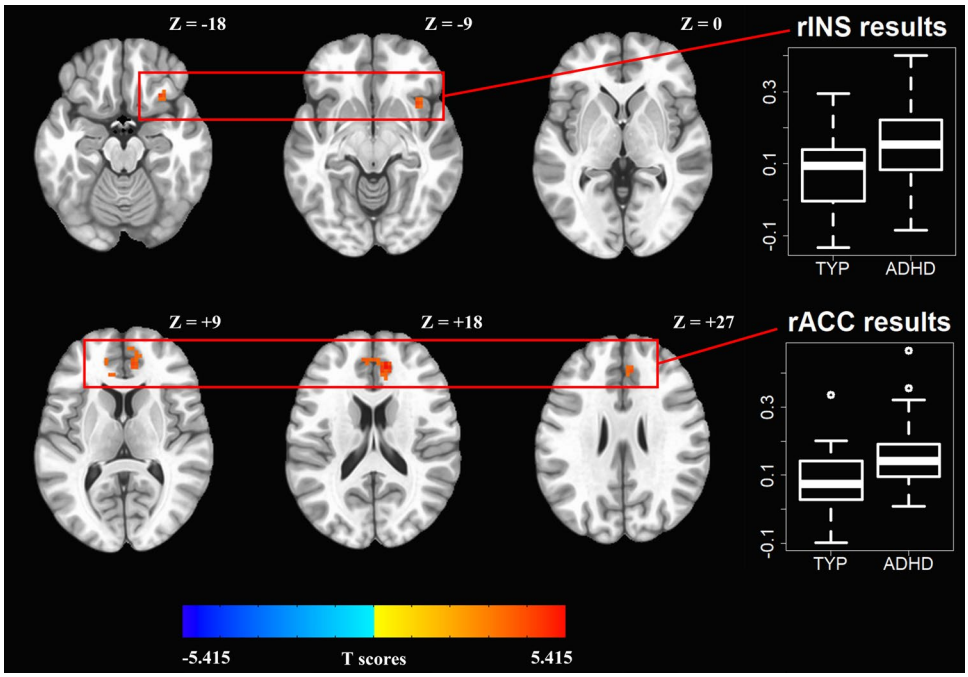

Fig. 1 Graphical representation of the voxel-wise, resting-state functional connectivity of the bilateral caudate (t map, *t* test between neurotypical and ADHD groups; significant clusters at FDR corrected *p* value = 0.05). Red indicates increased functional connectivity in ADHD. The first row represents the result region identified as right Insula, the second row the result region of the right Anterior Cingulate Cortex. *rINS* right Insula, *rACC* right Anterior Cingulate Cortex

Table 4 Region-based analysis, comparison of Bcaud rsFC mean values between TYP and ADHD

	Mean (variance)		*t* stat	*p* value
	TYP	*ADHD*		
rACC	0.079286 (0.005897)	0.153021 (0.006271)	−642.927	1.08E-09
rINS	0.07335 (0.010524)	0.149825 (0.010429)	−507.903	9.34E-07

rACC right anterior cingulate, *rINS* right insula

for both samples in Table 5. 95% confidence intervals for polynomial fitted curves were plotted, to evaluate tail distributions, and can be found as Supplementary Figure S2. 95% confidence intervals did not overlap for the 9–15 years old groups, both for rACC and rINS results, whereas results for the < 9 and > 15 years old showed a convergence of the confidence intervals. To confirm statistical significance of the age effect, a series of *t* tests for mean differences in measured values between age sub-classes (< 9, 9–15, > 15) was calculated and can be found as Table S2a and b. Statistical significance was reached only for the 9–15 years old group, both for rACC and rINS results.

Secondary aims

A low to moderate, significant association of the Bcaud/rACC and Bcaud/rINS rsFC with (1) the main ADHD index; (2) Inattentive score; (3) Hyperimpulsive score of the Connor Parents Rating Scale has been reported for the whole sample. The relationship of the rsFC values with symptoms and clinical scales, the correlations matrices and the significance levels are shown in Fig. 3. An overview of the correlations measured not by the whole sample, but within the diagnostic class, can be found in the Supplementary Materials as Table S3a and b.

RsFC values between the Bcaud seed and rACC/rINS were used to build predictive models, to estimate their diagnostic value in ADHD. Estimates of predictive performances were obtained after fivefold cross validation. ROC curves were plotted, reporting their AUC values (see Fig. 4). The logistic regression model built on Bcaud-rACC rsFC findings showed accuracy of 67%, sensitivity of 64% and specificity of 71%. The logistic regression model built on Bcaud-rINS showed an accuracy of 64.3%, sensitivity of 62% and specificity of 64%.

Confirmatory and control analyses

Motion during the scan is one of the fundamental drawbacks in fMRI studies [43]. As our sample is particularly vulnerable to such an effect, the degree of motion during the scan was evaluated through mean individual FD values. A *t* test of mean FD value per subject between TYP and ADHD patients was calculated and did not show a statistically significant difference (mean FD for TYP: 0.105 ± 0.003; mean FD for ADHD = 0.117 ± 0.004; *p* value for independent samples *t* test = 0.197, see Table S4). The distribution of mean FD values per subject, per diagnostic class, was plotted and can be found as Supplementary Figure S3.

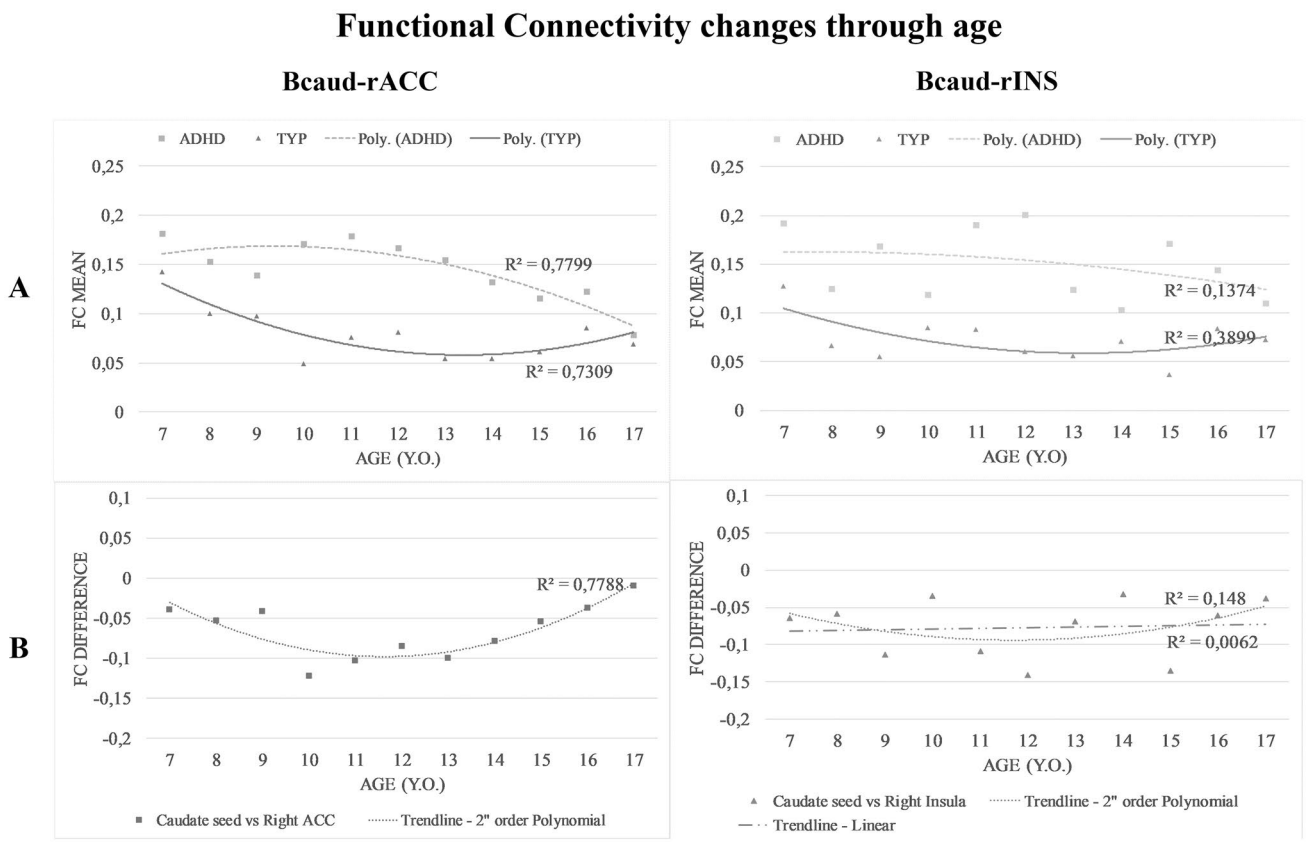

Fig. 2 Functional connectivity (rsFC) differences between neurotypicals and ADHD patients ordered by subjects' age. **a** *rsFC* mean value per age class, ADHD and TYP. **b** Differences and trendlines for rsFC mean values and age class (TYP-ADHD). The trendline shows a better fit of the subjects' distribution to a U-shaped polynomial rather than to a linear trend

Table 5 Average rsFC values per age class

Age	rACC			rINS		
	TYP	ADHD	Difference	TYP	ADHD	Difference
7	0.143	0.182	−0.039	0.127	0.192	−0.065
8	0.100	0.153	−0.053	0.066	0.125	−0.058
9	0.098	0.140	−0.042	0.055	0.169	−0.113
10	0.050	0.172	−0.122	0.085	0.119	−0.034
11	0.076	0.179	−0.103	0.083	0.191	−0.108
12	0.082	0.167	−0.085	0.061	0.201	−0.141
13	0.054	0.155	−0.100	0.056	0.124	−0.068
14	0.054	0.133	−0.078	0.071	0.103	−0.033
15	0.061	0.116	−0.055	0.036	0.171	−0.135
16	0.086	0.123	−0.037	0.084	0.144	−0.061
17	0.069	0.079	−0.010	0.072	0.110	−0.038

Results obtained including GSR showed high concordance when the analyses were repeated non including GSR, confirming significant rsFC differences in the two regions of interests (see Figure S4 and Table S5 in Supplementary Materials for Bcaud rsFC maps).

No statistically significant difference was found between medicated and non-medicated ADHD patients, nor when the sub-type of ADHD diagnosis was considered. An overview of the minimal FDR-adjusted *p* value associated with this control analyses can be found in the Supplementary Materials as Table S6.

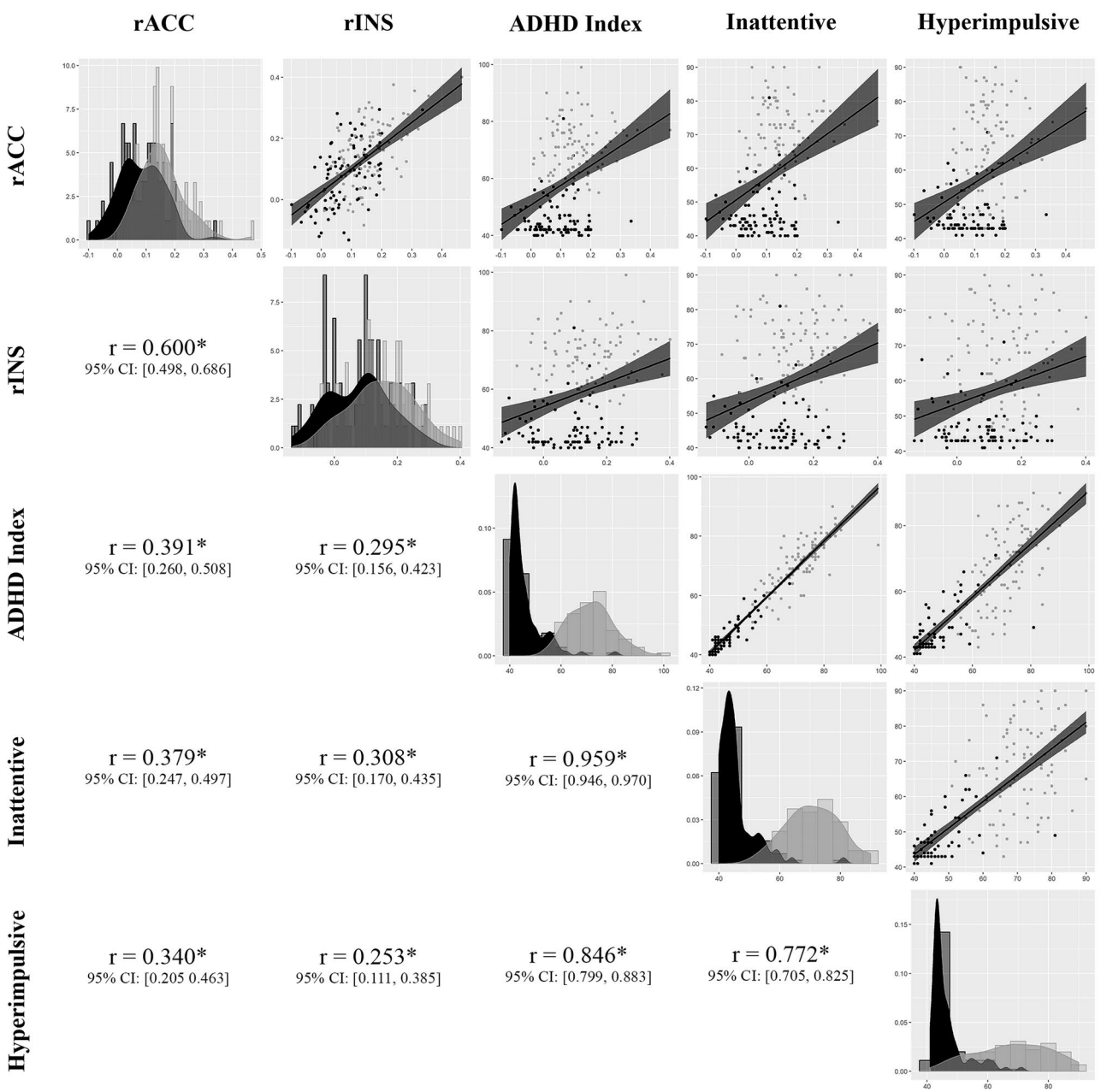

Fig. 3 Correlation matrices between fMRI findings and clinical scales. All the subjects (TYP and ADHD) are considered in the analysis. *$p < 0.01$ (Bonferroni corrected). ADHD patients are represented by the color black in the distribution curves and scatter plots. TYP patients are in light gray

Statistically significant differences between-groups of rsFC values were maintained when considering only males or only females, in all the four *t* tests performed. A detailed overview of the control analyses for sex can be found in the Supplementary Materials as Table S7, with a report of means, standard deviations and standard errors.

Taking rACC and rINS as seeds, higher rsFC observed in ADHD remained specific for the caudate, as no other region emerged from the voxel-wise analysis (see Figures S5 and S6 in the Supplementary Materials).

Discussion

The present study finds a significantly higher rsFC in ADHD subjects between Bcaud, rACC and rINS, which are part of the so-called salience network (SN). The rsFC evolutional pattern shows age-dependent dynamics and is mildly linked to core ADHD clinical constructs such as hyperactivity-impulsivity and inattention. Finally, when rsFC between caudate and mesolimbic areas of the SN is taken as a single

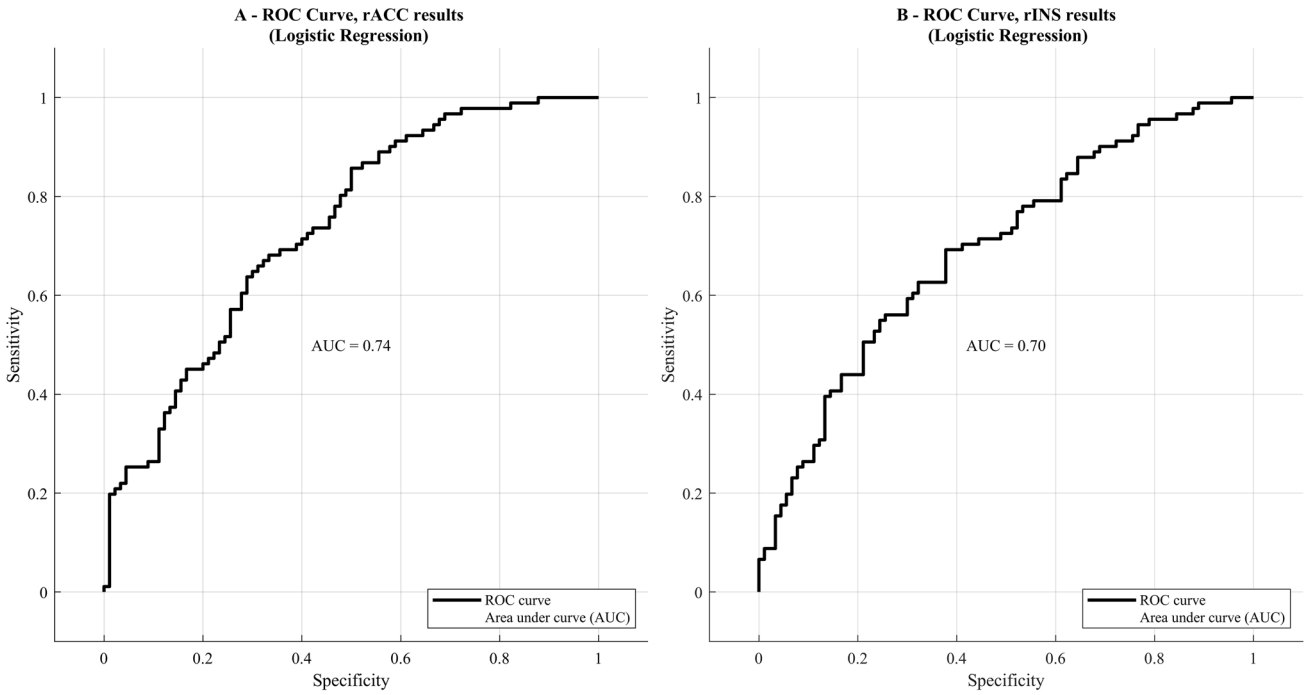

Fig. 4 *AUC* Area Under the Curve. Values above 0.700 are suggestive of a fair diagnostic discrimination between TYP and ADHD. **a** ROC curve for the logistic regression model built on rACC results. **b** ROC curve for the logistic regression model built on rINS results

parameter to differentiate ADHD from TYP, a fair diagnostic discrimination is reached.

Connectivity topography and ADHD functioning

The caudate nucleus shares an increased rsFC (Fig. 1) with rACC and rINS. These regions pertain to the SN, a well-studied functional network playing a pivotal role in attentional switches, internal–external integration, and tolerance to reward delays [44]. The possibility of a stimulus to emerge with respect to the other ones is directly connected with the attentional valence attributed to it by the brain throughout a *phasic* process [45]. Clinically, alterations in this process such as heightened phasic attention at the expenses of the tonic/sustained one reflect ADHD distractibility [46]. Neuronally, our study shows a positive correlation (i.e., increased interdependence) of the rsFC strength between the caudate and SN region with impulsivity and inattention scores. A strengthened bond between subcortical and mesolimbic salience regions may thus relate clinical and neurobiological findings to a fundamental alteration of salience processes in ADHD. More specifically, dACC and rINS are crucial regions for attentional switching such as the one between rest-oriented versus task-oriented modalities [47]. The rsFC differences we observed in both of them may thus be related to the attentional lapses and increased reaction-time variability that may be due to an impaired switching in ADHD [48]. The involvement of rINS in both attentive and emotional processes [49] highlights the deep intertwinement between salience and emotion: the appetitive-aversive (emotional) quality attributed to a stimulus is directly connected to its strength, i.e., its possibility to emerge from the "environmental noise" [50].

The evaluation of a stimulus' emotional quality appears to be quantitative and given by the level of its appetitive-aversive strength registered by deep structures of the brain such as caudate [51]. Other structures such as SN subregions are then recruited to actively bestow a refined qualitative and cognitive valence to the emotional content [52]. An increased interdependence between subcortical and limbic-cognitive areas may characterize ADHD as a disorder of emotional salience regulation. The hyper-connection between caudate and SN regions showed by our findings, coherently with existing literature, might allow us to consider ADHD as a disorder of emotional salience attribution.

Salience and brain maturation

We showed how caudate rsFC is characterized by an increased and reciprocal influence with the meso-limbic districts. Additionally, we characterized distinct progressions through the age in TYP vs ADHD subjects according to the areas that are considered. Furthermore, the between-groups rsFC shows the maximum difference

around the age of 10. After this peak, discrepancies between TYP and ADHD tend to regress, a process similar to the one observed in structural caudate related findings. Behaviorally, the rsFC in TYP vs ADHD may indicate: (1) a delay in brain maturation [53]; (2) an excessive interdependence between reward/emotional and salience/attentional processes in ADHD, resulting in a reduced ability to involve cognition as a mediator for a more fine-grained processing of information and decision making (which is instead characteristic of the adult neurotypical brain). Of note, our findings are in line with the ones from Szekely et al. [54] suggesting an age-dependent corticalization of the inhibition-related disfunctions in ADHD: while they are predominantly related to caudate's activity during childhood, this link is not evident in adults, where modulations of other areas such as vmPFC and precuneus are instead shown.

Reward and salience: two sides of a coin?

Caudate contributes to initiate and shape complex human behaviors which comprise not only emotion and attention [6] but also the evaluation of appropriate goal-directed behaviors, including motivation and cognition [55]. Reward and salience are in fact reciprocally modulating processes [56]. Cortico-striatal connections hence deeply relate constructs such as reward, emotion and salience [57], all of which show a certain degree of impairment in ADHD [58].

From fMRI findings further support this hypothesis: being caudate and insula neural determinants of human habitual action control and avoidance motivation [59], their activity shows major differences in ADHD and is related to the severity of impulsivity [60]. The high correspondence of salience and reward networks [61] in ADHD is coherent with the association of the caudate-SN hyper-connectivity to both inattentive and hyper-impulsive scores. While inattention and impulsivity pertain to two different neurobiological domains (salience and reward respectively), these domains are closely interacting through dopaminergic pathways involving especially in caudate, insula, and anterior cingulate [62, 63]. An increased rsFC may thus be a common neural phenomenon reflecting the expression of both symptoms.

Diagnostic prediction of rsFC scores

Both Bcaud/rACC and Bcaud/rINS rsFC were useful to discriminate ADHD and TYP subjects with a fair rate of success (AUC $\geq$ 0.7). These results are promising as although they use a single parameter, they achieve similar predictive scores when compared with more complex and integrated models [64, 65]. Such a measure is experimental and needs further validation, as a larger cohort with replication samples can increase the model precision or disconfirm it. A cohort including adults as well as adolescents may also help to differentiate the patterns related to each life stage, possibly helping to integrate the clinical observations throughout the diagnostic process.

Limitations

(1) Even though the findings are solid, follow-ups of the same subject across different time-points should strongly improve the accuracy when measuring the developmental evolution in brain rsFC, possibly locating neuroimaging as a useful diagnostic tool for ADHD.
(2) The increased caudate/salience rsFC does not explain per se the persistency of ADHD symptoms in adulthood, as the difference between TYP and ADHD subjects progressively reduces through age. Nevertheless, our functional findings are in line with the progressive reduction of the structural discrepancies observed for caudate in ADHD subjects.
(3) Our findings are only partially consistent with previous studies such as Yang et al. [18], which firstly explored caudate FC. These differences may be due to the different age range of the sample studied and to methodological differences (in Yang et al. [18] age was not regressed as a possible factor influencing caudate rsFC, scrubbing of the fMRI signal was not performed and only dorsal caudate was considered, using one voxel masks).
(4) The lack of effect of medication on the results, which contradicts most of the literature available, is most likely due to the fact that drugs were suspended at least 24 h before the scan was performed, and although medicated, most patients retained high levels of clinical severity.
(5) rsFC is an effect determined by the combined action of factors not analyzed by this study, as they pertain to structural and biochemical domains going beyond the purpose of our work. Hence, our work does not allow to suppose causative effects of the subcortical functioning over the mesolimbic one or vice versa. Parallelly, the present findings encourage future research combining structural, functional and biochemical data to further qualify and quantify the contribution of subcortical structures to both ADHD symptomatology and the overall brain activity.

Conclusions

In our paper, we confirmed how in ADHD subcortical-mesolimbic rsFC is markedly increased and involves specific areas pertaining to the SN. Caudate, which structurally and functionally pertains to circuits involved in salience and reward, has specific areas of increased rsFC associated with the SN, confirming the involvement of key pathways theorized by previous authors. Therefore, our results allow to contextualize neuronal, biological, and behavioral findings into an enriched framework in line with ADHD literature adding new conceptual and clinical implications.

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Compliance with ethical standards

Conflict of interest The authors declare they have no conflict of interest.

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