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An integrated analysis across separate task domains reveals a lack of common processing in the ADHD brain

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Short/running title

Lack of common processing in the ADHD brain

Keywords

Integration, resting state, tasks, ADHD, siblings, common processing

Abstract

Background

Multiple cognitive theories have been proposed to explain the cognitive impairments observed in Attention-deficit/Hyperactivity Disorder (ADHD). Functional imaging studies building on these theories reveal a heterogeneous pattern of neuronal dysfunction and fail to provide an overarching perspective on the pathophysiology of ADHD. Going beyond single task analyses, we here apply a biotyping strategy that integrates results across multiple task domains and assess common neuronal alteration.

Method

We integrated across multiple functional magnetic resonance imaging acquisitions: resting-state, and working memory, monetary incentive delay, and stop signal tasks collected in 96 participants with ADHD, 78 unaffected siblings, and 156 controls (total N=330, age range=8-27 years). We indexed whether connections were modulated away from the resting-state baseline, across all tasks or specific to individual task paradigms and we then assessed their group membership.

Results

Participants with ADHD and unaffected siblings exhibited a reduced number of connections that were modulated regardless of task, compared to control, but an increased number of task-specific connections. However, siblings over-modulated connections also modulated by the other groups, while participants with ADHD relied on over-modulating task-specific patterns of connectivity. Finally, task common connections were reproducible in controls, yet highly variable in both ADHD and siblings.

Conclusions

Participants with ADHD and unaffected siblings exhibit a similar neurobiological profile characterized by a lack of across task connections and an increase in task-tailored connections. Although showing a similar functional brain fingerprint, siblings might compensate through increasing the amount of modulation. The absence of common connections is a potential predictive biomarker of an at-risk ADHD profile.

Introduction

Attention-deficit/Hyperactivity Disorder (ADHD) is an early onset neurodevelopmental disorder characterised by symptoms of inattention and/or hyperactivity-impulsivity that result in impairments in multiple functional domains[1]. Different cognitive theories have been proposed to explain the disorder, including a dysfunction in state and arousal regulation[2], deficient response inhibition[3], a broader deficit in executive functioning[4], a motivational dysfunction[38], and/or delay aversion[4]. Functional imaging studies building on these cognitive explanations have investigated the neural underpinnings of ADHD, but have revealed a heterogeneous pattern of neuronal dysfunction spread across the brain[1,5,6,37]. This fragmented pattern of findings asks for new approaches that allow providing an overarching perspective on the functional architecture of the ADHD brain.

Here, we aim to provide such a perspective by applying an approach that entails integrating findings of cognitive tasks across multiple cognitive domains to assess the role of task-dependent localised effects[7]. We thereby capitalize on the idea that regional task-induced activity builds on the brain's functional connectivity architecture as revealed by resting-state MRI analyses[8,9,10], resulting in an imaging phenotype across task paradigms in terms of the locality and strength of task-induced connectivity modulations[7]. Indexing potency across tasks then allows disentangling modulations that are shared across multiple cognitive functions, thus forming a cognitive core[11,12,13], from those that are unique to a single task.

Accordingly, using this approach allows examining overarching cognitive theories about ADHD by studying the relationship between tasks that probe key cognitive dysfunctions. For example, suppose that a comparison of probes for working memory, response inhibition, and reward shows a core alteration across tasks that mainly relates to inhibition networks. This would then provide support for theories that claim a prominent role for poor response inhibition in ADHD[3]. Alternatively, theories suggesting inefficient management of resources would be supported by

observing a pattern of overall more 'expensive' modulation in ADHD compared to typically developing controls in an otherwise similar functional architecture[14,15]. Both types of theories are not antinomic as alterations could be overcome in a suboptimal way, impacting the efficiency of the the whole system. In light of these possibilities we hypothesized that alterations in how the brain's functional core interacts with more specialized modulations would result in inefficient use of the brain's resources in ADHD.

To test our hypothesis, we applied the task-potency paradigm to a large cohort of participants with ADHD, their unaffected siblings (to assess the impact of their genetic vulnerability[30]), and healthy controls (N=330) and describe functional connectivity patterns across response inhibition[14], WM[390], and reward processing[15]. This allowed assessing the impact of ADHD on the brain's functional architecture in terms of commonality versus task-specificity as well as in terms of the strength of the observed modulations.

Methods

Participants and (f)MRI acquisitions

We selected participants with ADHD, unaffected siblings of individuals with ADHD (but not related to the participants with ADHD included in this study), and typically developing controls (unrelated to any participant) from the NeuroIMAGE sample[16]. All selected participants completed an anatomical MRI scan, a resting state fMRI scan (RS), and at least one of the following task fMRI scans: a spatial working memory task (WM), a monetary-incentive-delay reward task (REWARD), and/or a stop signal response inhibition task (STOP) (see Table S2). Table 1 summarizes the demographics of the 96 participants with ADHD, 78 unaffected siblings, and 156 controls included in the current analyses. A full description of the selection criteria, task paradigms, and MRI acquisition parameters is provided in ST3 and SA.

Insert Table 1 here

Task potency calculation

Our task potency approach is described in detail in Chauvin et al. 2019[7]. In brief, for each participant and each pre-processed RS, WM, REWARD, and STOP fMRI acquisition (see eMethod for pre-processing procedures) we defined functional connectivity matrices using 179 regions from a hierarchical whole-brain atlas[17] (see Figure S2). We calculated connectivity as the normalized Fisher-Z partial correlation between the timeseries of each pair of regions in the atlas (see Supplement Method). To isolate connectivity changes induced by task modulation (WM, REWARD, STOP) from changes in the brain's baseline architecture (RS), we standardized each individual-level pair-wise

correlation obtained during task acquisition by subtracting the corresponding pair-wise correlation value calculated for the RS scan of that participant. This effectively allows comparing each connection in the task connectivity matrices in terms of its magnitude of deviation from that participant's resting baseline[7]. We refer to this deviation as 'task potency'.

For each task, we created group-level task potency matrices by averaging the individual-level potency matrices across all participants in each diagnostic group. Within these group-level matrices we aimed to select those connections that were *sensitive* to task modulation. Using the values within each potency matrix, we used a mixture modelling approach featuring a Gaussian curve to model the main (noise) distribution of the potency values and two gamma distributions to model the left and right (signal) tails[18]. We subsequently defined a limit for each signal tail and selected potency values exceeding this limit as being sensitive to task modulation. To integrate results across task-paradigms, we further subdivided these sensitive connections depending on their modulation by one or more of the tasks. In particular, we refer to connections that were modulated by one task only as *task-specific*, to connections that were modulated by more than one but not all tasks as *task-unspecific,* and to connections that were modulated regardless of task as *common*.

Group differences in task connection type

To assess whether ADHD was associated with a deviant distribution of task-induced modulations across the brain and across tasks, we compared the distribution of task-sensitive, task-specific, common, and task-unspecific connections across the three diagnostic groups. We compared the amount of sensitive connections between groups by indexing the percentage of connections included for each group relative to the total number of sensitive connections. We assessed between-group differences in the specificity of connections by obtaining for each group the percentage of connections per type relative to the total number of sensitive connections for that group. Finally, we assessed the ratio of connections uniquely modulated by each diagnostic group (unique connections) versus those connections that were also modulated by one or both of the other groups (shared

connections). To allow statistical inference, we calculated group-level distributions for each of these percentages through bootstrapping, using 10000 repetitions each including 80% of participants (see Supplement Method). Using the variance across these bootstraps, we conducted pair-wise group comparisons for each percentage.

To further define whether differences in the selection of connections were associated with different strategies of modulation, we extracted the group-level average task potency for selected connections and tested for between-group differences in task-potency amplitude by computing a p-value across the 10000 bootstraps. P-values were assessed for significance using FDR correction at $p<0.05$. Replication of the analyses in light of possible confounder effects (medication, gender, scanner of acquisition, and comorbidity) are presented in Figure S4.

Finally, we assessed the reproducibility of the selection of connections to estimate the stability versus the heterogeneity of task connection types in the different groups. To this end, we computed across bootstraps each connection's selection rate at the group level and its associated shared selection rate between two groups. We computed these rates for sensitive, common, task-specific, and task-unspecific selections. These group-level selection rates index how specific a selected connection is to one particular group by computing the difference in selection rate at the connection level between groups. We can then display the *uniqueness* versus the *sharedness* of each connection. By comparing both rates, we can estimate which connections are uniquely and reproducibly selected in one group only, potentially representing idiosyncratic strategies to solve the task, making them ideally suited as candidate bio-markers.

Results

Establishing an ADHD biotype

Starting from the set of connections that yielded significant connectivity modulations across all participants, we compared the diagnostic groups in terms of the sensitivity and specificity of their

connectome to task modulations. Figure 1 shows that a significantly higher percentage of sensitive connections was modulated by controls (61.9%, sd=7.9) compared to participants with ADHD (38.9%, sd=8.2, $p<0.006$) and siblings (30.9%, sd=6.9, $p<0.0005$). Within their respective sets of sensitive connections, siblings exhibited a larger percentage of shared connections (i.e., connections also modulated by another group; 58.2%, sd=7.5) compared to controls (39.7%, sd=5.1, $p<0.01$) and participants with ADHD (44.9%, sd=7.6, $p=0.058$ after FDR correction). This illustrates that the control and ADHD groups exhibited a higher rate of connections that only they modulated, compared to siblings whose modulations displayed greater overlap with both other groups.

Illustrating the task-specific nature of the sensitive connections, the bottom part of Figure 1 displays the proportion of selected connections that were common across tasks or specific to one task only (full results including task-unspecific edges are available in Figure S4). Controls modulated more than 20% of their sensitive connections regardless of task, i.e. common connections. This was significantly higher compared to the siblings (13%, $p<0.005$) and the ADHD group (10%, $p<0.001$). In addition, about 70% of the controls' common connections were unique to this group, compared to only 20% unique connections observed for the siblings (21%, $p<0.005$) and the ADHD group (22%, $p<0.02$). Accordingly, the common connections observed for ADHD and siblings are mostly connections that controls also modulated. Conversely, the set of common connections that controls used across tasks were mostly unique to them and not modulated by either ADHD participants or siblings.

In contrast to the lower number of common connections, both the ADHD and sibling groups exhibited a significantly higher percentage of task-specific connections compared to controls (see Figure 1). We observed no between-group differences in the uniqueness of the task-specific connections, with on average 80% of the task-specific connections being unique to each diagnostic group.

Establishing Predictive Value

To examine the bio-marker potential of our findings we assessed the variability of task connection types across participants within groups. Figure 2 shows that sensitive connections displayed a distribution shifted toward controls when comparing their selectivity to siblings or ADHD (Figure 2 top row). This indicates that task connection types observed for controls were more stable across bootstraps and thus less heterogeneous across participants. Moreover, the common connections in particular displayed strong homogeneity across control participants. This demonstrates that controls reliably selected connections across tasks that were not present in other groups, further validating the results presented in Figure 1. Consequently, as common connections are highly reproducible in controls yet missing in ADHD and siblings, they could potentially be used to optimally differentiate controls. In contrast, the task-specific connections observed in ADHD and siblings (see Figure 1) were variable and heterogeneous across participants, as illustrated by an absence of a shift in the distributions shown in Figure 2 towards the ADHD and sibling groups (see also Figure S5).

Compensation Mechanisms

As a proxy for compensatory mechanisms we assessed whether the group differences in specificity were associated with group differences in the potency (i.e., amplitude) of the modulations (see Figure 3; Table S4 provides statistical details). Figure 3 shows that we observed a siblings > controls > ADHD effect on task-potency in the common connections that groups shared with each other, illustrating that siblings overmodulated these connections. In addition, we observed that controls exhibited significantly *lower* modulation compared to both the siblings ($p<0.05$) and ADHD groups ($p<0.01$) for task-specific connections that were uniquely modulated by each group, suggesting that the ADHD and sibling groups placed more emphasis on those specific connections.

Discussion

In this study, we used a novel framework that allows integrating across task domains to infer the efficiency of the underlying cognitive infrastructure observed via connectivity modulations in ADHD under working memory, reward processing, and response inhibition task demands. Our biotyping method reveals that participants with ADHD and unaffected siblings both used significantly fewer connections compared to controls to complete each task. Furthermore, the functional architecture of participants with ADHD and siblings was characterised by a low percentage of common connections that allow sharing resources across tasks. Instead, both groups relied more strongly on unique sets of task-specific connections requiring more independent resources and potentially inducing high switching costs. Participants with ADHD under-modulated the 'efficient' common connections, while siblings strongly over-modulated these connections, suggesting a potential compensatory mechanism.

Collectively our results suggest that participants with ADHD lack a common core of modulations that can be efficiently used regardless of task, and try to overcome this deficit through implementing task-tailored patterns of connectivity. These observations may be interpreted as a neural inflexibility of participants with ADHD[20,36], as using task-tailored connectivity patterns makes switching more demanding, more expensive and inefficient, making task performance more challenging. As such, this connectivity profile provides support for the cognitive-energetic model[2]. In this model, the limitations in arousal observed in ADHD could be a consequence of a higher level of energy required to perform cognitive tasks; potentially related to having to micro-manage task-specific patterns instead of keeping a general processing core ready to perform.

Fitting with the hypothesis of inefficient processing is the observation that participants with ADHD typically do not demonstrate a striking inability to perform tasks but rather exhibit large variability in the way they perform tasks[14,21,22]. Some studies have reported an inefficient use of

resources for specific networks or functions in ADHD including the attention network[22,23], executive functioning[245], or cognitive control[22,25]. However, as these studies focus on specific cognitive aspects, they do not allow identifying a potential common underlying deficit, as demonstrated in the present study. Alternative approaches to investigating the efficiency of the brain's organization have used graph theory and shown that the functional architecture of the ADHD brain is associated with differences in the balance of local and global efficiency[6,26-28]. However, these graph theory metrics provide no information on localized effects affecting specific cognitive functions. In contrast, our integrated approach provides a bridge between cognitive tasks and the functional architecture of the brain to understand the interaction between neural systems.

Unaffected siblings of individuals with ADHD share on average 50% of their genetic make-up with the ADHD probands. Accordingly, they are hypothesized to share part of the ADHD endophenotype, i.e. biological deficits underpinning the ADHD phenotype, yet without crossing the diagnostic threshold, thereby exhibiting a behavioural pattern intermediate between ADHD and controls[29-31]. Here, siblings displayed a similar task connectivity profile as ADHD participants. However, siblings exhibited increased modulation of common and shared connectivity, suggestive of a potential compensatory mechanism that enables successful task performance (see Table S6). Previous research suggests that ADHD participants could compensate by using higher order executive systems or by relying on lower-order visual, spatial, and motoric processing[32-35]. Our results suggest that siblings are potentially still able to recruit more efficient connections, yet they require extra modulation.

The results shown in Figure 2 highlight that task-specific connections can be used to investigate such compensatory mechanisms at the level of individual participants, as task-specific connections are highly variable across participants, which is also described in previous work on task potency[7]. For instance, using longitudinal designs and models of compensatory strategies[35], we can focus on those connections that are subject-specific and highly reproducible at the individual level to

investigate a progressive specialization of individual compensatory mechanisms. In contrast to the high variability of task-specific connections, the absence of common connections was highly reproducible across ADHD and siblings compared to controls (Figure 2). As such, an absence of common connections has potential as a biomarker of an "at risk profile", where participants exhibiting a connectivity profile that includes these common connectivity modulations are unlikely to be related to the ADHD phenotype.

Brain areas involved in the common edges and the associated differences between ADHD and controls are shown in Figure S6. At the brain regional level, participants with ADHD mainly missed modulations that connect regions within the executive control, reward and salience pathways, including cerebellum, striatal, cingulum and cortical areas during task performance[26]. As shown in Figure S6, participants with ADHD preserved only few common connections, interestingly involving striatal regions known to be involved in reward processing. Note that these results do not contradict typical findings of aberrant brain activity in reward-related regions in participants with ADHD[38] as we showed that participants with ADHD used these connections with greater inconsistency and decreased modulation compared to controls. Knowing that ADHD participants make less efficient use of common pathways among multiple cognitive functions, will inform next studies aimed at understanding task response variability in ADHD.

In conclusion, we integrated task-specific connectivity modulations across three tasks and demonstrated that individuals with ADHD had a more specific and variable pattern of connectivity in response to each task compared to controls who displayed more commonly potentiated connections across all tasks. Our work provides an important stepping stone towards new integrative theories explaining how multiple neural alterations interact and result into multiple cognitive impairments in ADHD.

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Disclosures

Jan K Buitelaar has been in the past 3 years a consultant to / member of advisory board of / and/or speaker for Shire, Roche, Medice, and Servier. He is not an employee of any of these companies, and not a stock shareholder of any of these companies. He has no other financial or material support, including expert testimony, patents, royalties. Barbara Franke has received educational speaking fees from Medice and Shire. Roselyne J. Chauvin, Marianne Oldehinkel, Catharina Hartman, Dirk J. Heslenfeld, Pieter J. Hoekstra, Jaap Oosterlaan, Christian F. Beckmann, Maarten Mennes reported no biomedical financial interests or potential conflicts of interest.

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Tables

	N used in final analyses	Age min - max	Age mean (std)	% female	Site[2]	Inattention[1] (std)	Hyperactivity[1] (std)	IQ (std)
Healthy control participants								
RS	156	8.6 - 27	17 (3.4)	52.0%	59%	0.8 (1.7)	0.6 (1.3)	104.2 (14.7)
STOP	87	8.6 - 27	17.1 (3.6)	50.6%	44%	0.6 (1.5)	0.5 (1.0)	104.1 (15.2)
REWARD	92	9.1 - 23.9	17.1 (3.1)	57.6%	60%	0.8 (1.7)	0.6 (1.3)	103.8 (15.1)
WM	102	8.6 - 27	16.7 (3.3)	49.0%	73%	0.8 (1.8)	0.5 (1.2)	104.5 (13.4)
Unaffected Siblings								
RS	78	8.6 - 27	17 (3.7)	53.8%	51%	0.6 (1.3)	0.6 (1.1)	102.1 (15.8)
STOP	46	8.6 - 27	17.4 (4)	52.2%	39%	0.7 (1.5)	0.8 (1.3)	103.2 (17.1)
REWARD	47	9.1 - 23.9	17.3 (3.4)	57.4%	55%	0.5 (0.9)	0.5 (1.06)	100.4 (16.3)
WM	37	8.6 - 27	16.3 (3.7)	54.1%	62%	0.6 (1.4)	0.35 (0.7)	103.1 (14.4)
ADHD participants								
RS	96	8.5 – 26.7	17.6 (3.4)	29.1%	39%	6.8 (1.9)	5.6 (2.4)	94.9 (13.9)
STOP	44	11.1 – 27.5	17.6 (3.4)	18.1%	40%	7.3 (1.5)	5.5 (2.3)	94.7 (15.5)
REWARD	57	11.4 - 26.7	17.8 (3.4)	36.8%	33%	6.5 (2.0)	5.9 (2.1)	97.6 (14.2)
WM	57	11.1 – 26.7	17.8 (3.3)	31.6%	44%	7.0 (1.7)	5.6 (2.2)	94.6 (12.4)

Table 1: Participant information: descriptive, clinical variables, and distribution of scan modalities, for each group sample and tasks: Resting state (RS), stop signal paradigm (STOP), reward processing (REWARD), Working Memory (WM). 1 combined symptoms from KSADS and Conners. 2 ratio of Amsterdam/Nijmegen scan localisation. For participant exclusion, see Table S1. For more detail on age and gender representation, see Figure S1.

Figures

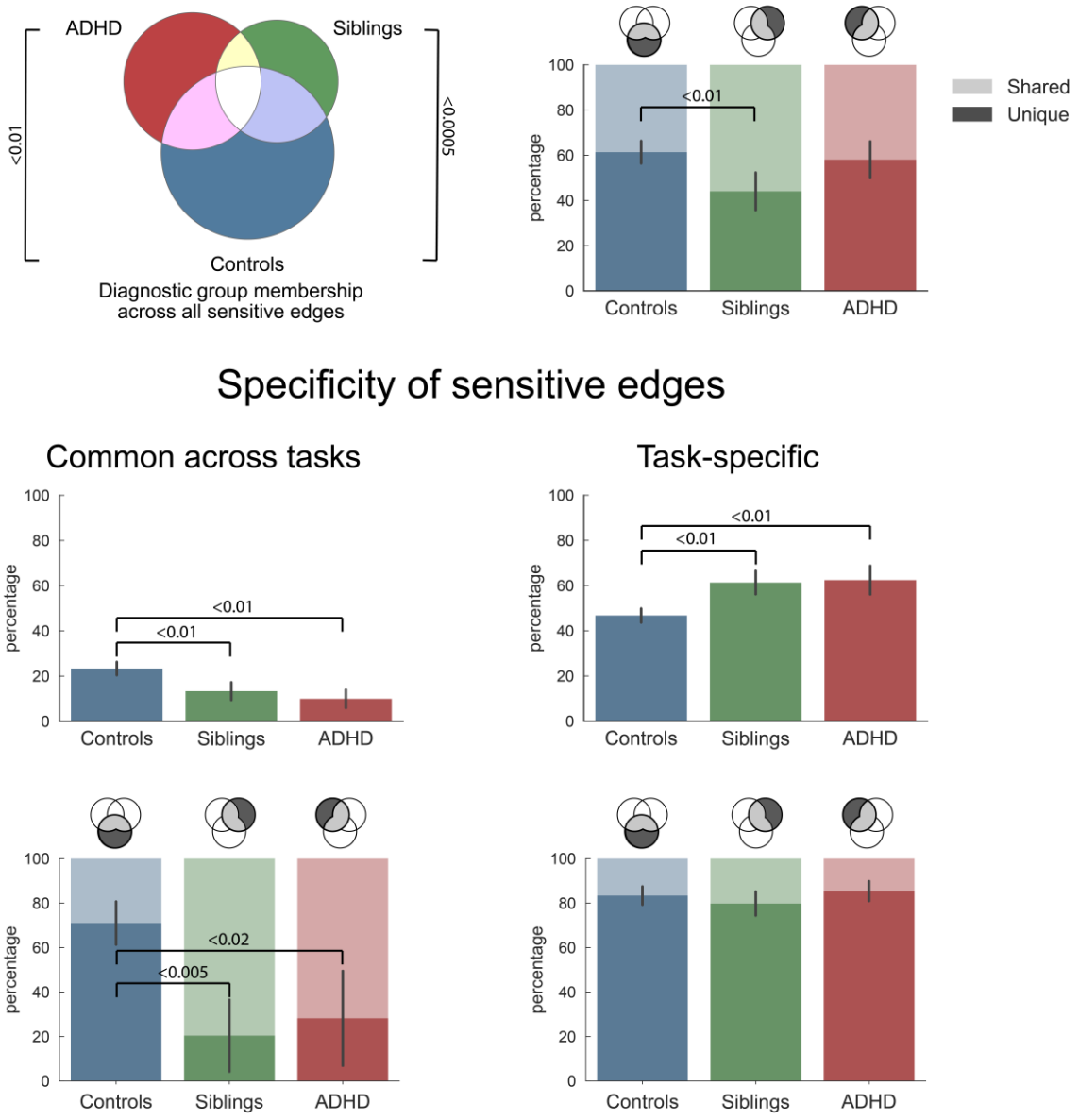


Figure 1: Sensitivity to task modulation. Description of connectivity modulations across the three tasks and diagnostic groups (ADHD, siblings, controls). The first row shows for each group the percentage of connections they modulated across the three tasks (sensitive connections) and within these selected connections, the percentage of connections unique to one group or shared across groups. We further split the selected connections of each group into task-specific, and common connections, corresponding to connections modulated in only one, or all three tasks, respectively.

The second row of this figure quantifies the relative percentage of each connection type within the sensitive connections of each group. For the connections described in the second row, the third row then quantifies whether these connections were unique to that group or shared across groups. Replication of these findings across possible confounding effects (scanner, gender, medication, comorbidity) is available in Figure S7.

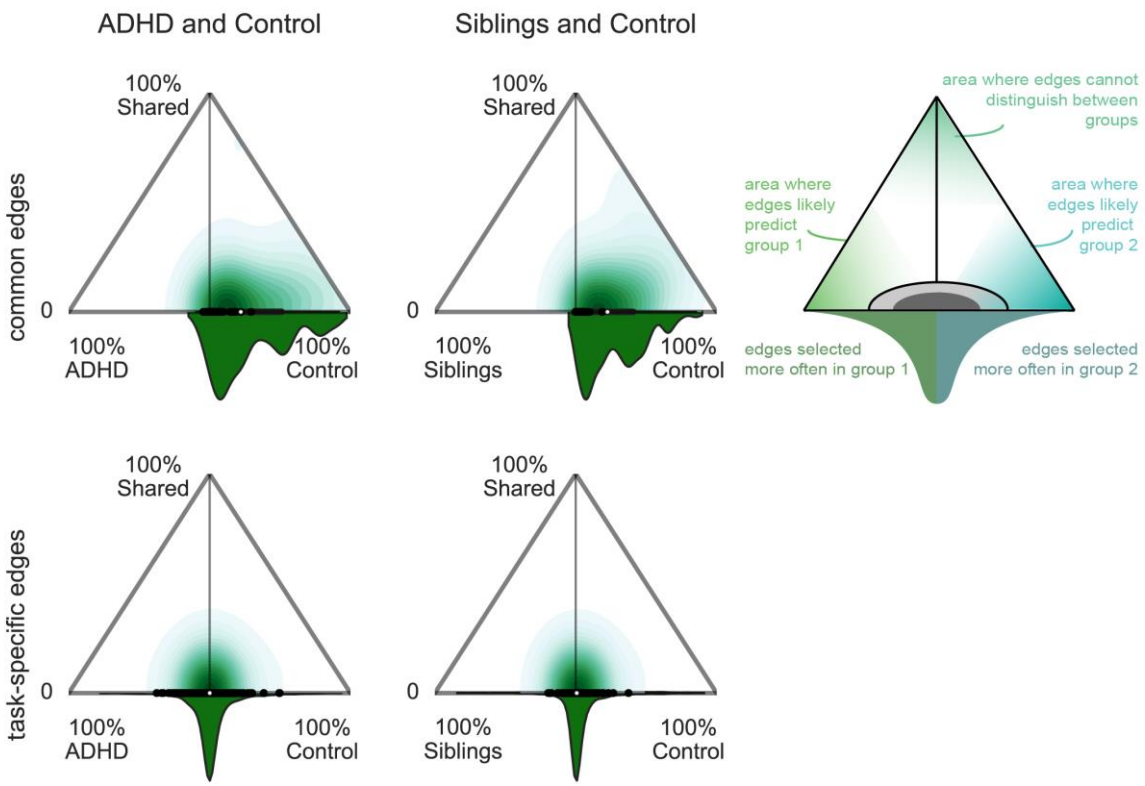


Figure 2: Comparison of selection reliability across bootstraps. By investigating the reproducibility of the selection of connections across bootstraps we inferred on the uniqueness (x-axis) and shareability (y-axis) of each connection between two groups. A connection that was always selected in both groups, shown at the top corner of each triangle, would represent a connection that cannot be used to differentiate between those two groups. A connection that was always selected in one group only, located in the lower corners of the triangles, would be unique to a group and could be used to predict the group. Connections that would be heterogeneously selected in the population

would have a low uniqueness (around 0 on the x-axis) and a low shareability (bottom of y-axis). The distribution at the basis of the triangle informs about the density of connections represented in the triangle, i.e. the spread of the distribution indicates whether only a small subset or a larger representation of connections are most often selected in one group relatively to the total amount of selected connections.

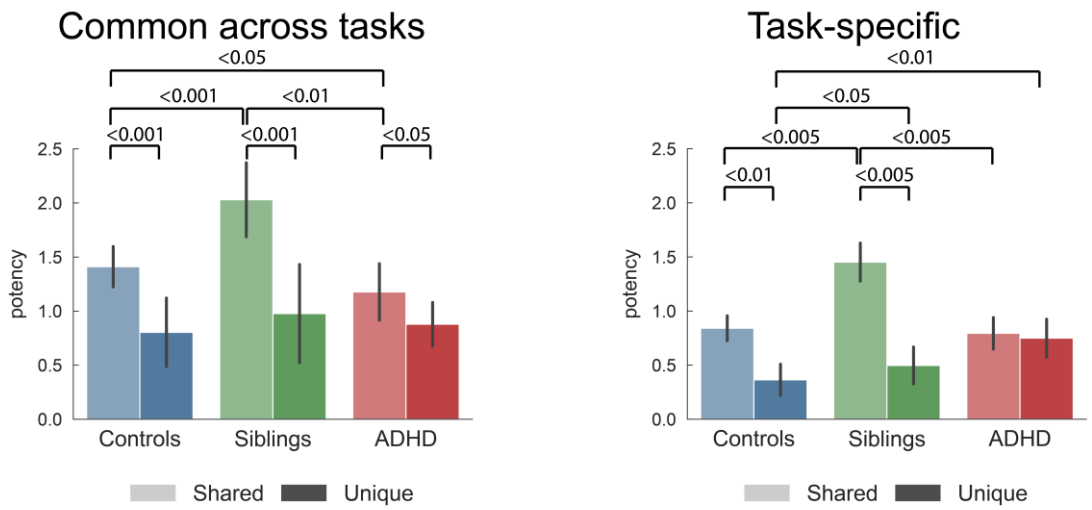
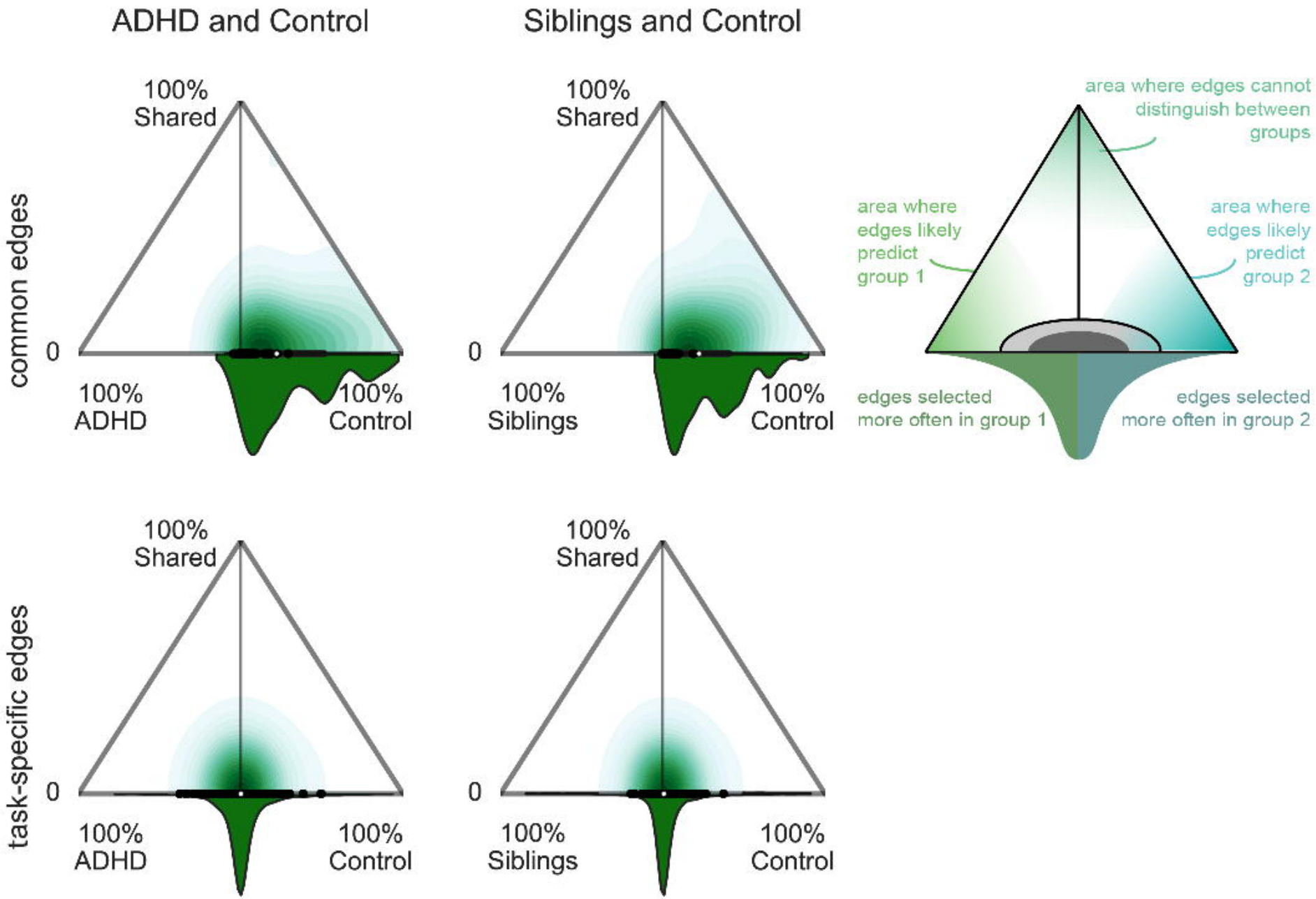
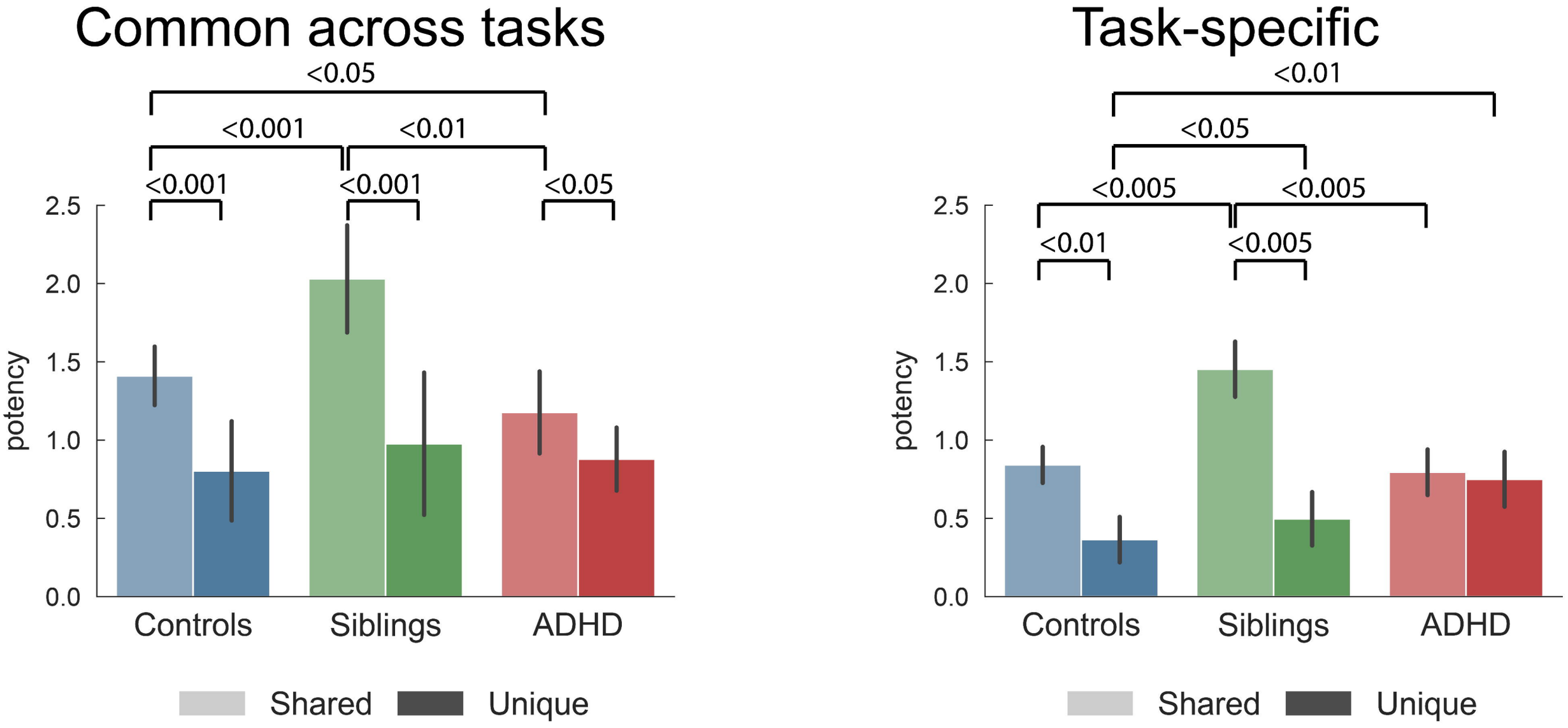
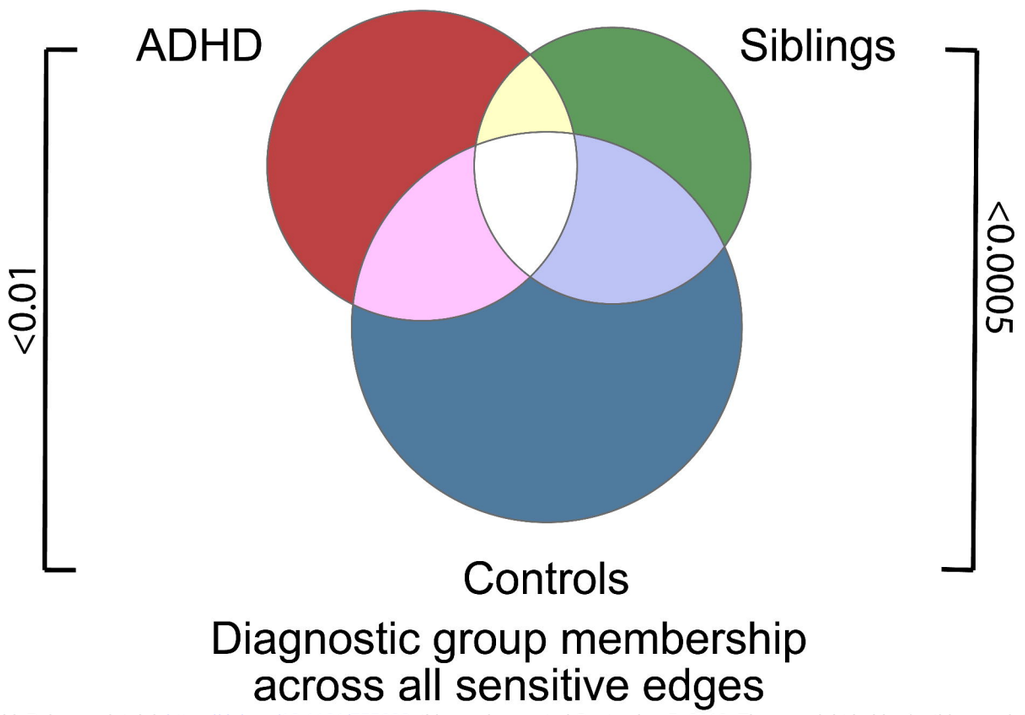


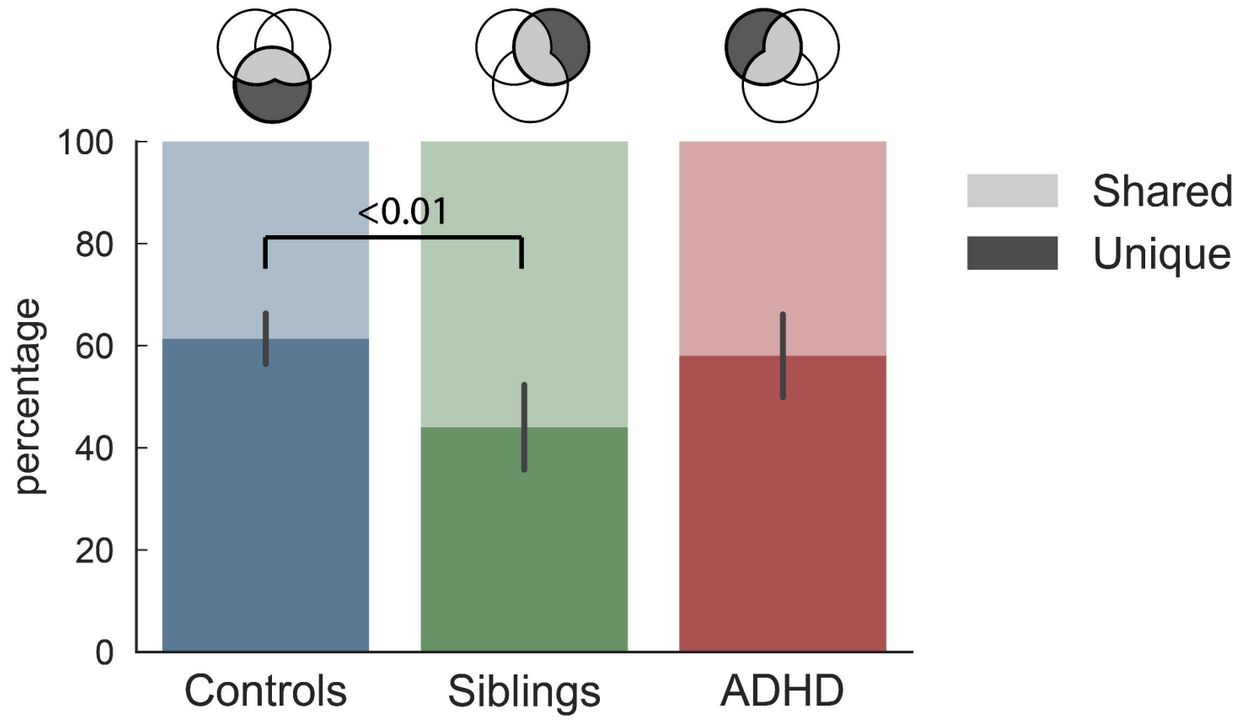
Figure 3: Modulation of edges. The graphs quantify the average task potency across unique or shared connections for each group and connection type. All reported values show the average and standard deviation across 10000 independent bootstraps. Indicated p-values show significant differences after FDR correction. Full ANOVA results are available in Tables S4-5. Replication of these findings in light of possible confounding effects (scanner, gender, medication, comorbidity) is available in Figure S7.


ADHD and Control
Siblings and Control
common edges
task-specific edges
100%
Shared
0
100%
ADHD
100%
Control
100%
Siblings
area where edges cannot distinguish between groups
area where edges likely predict group 1
area where edges likely predict group 2
edges selected more often in group 1
edges selected more often in group 2


Common across tasks
<0.05
<0.001
<0.01
<0.001
<0.001
<0.05
2.5
2.0
1.5
1.0
0.5
0.0
potency
Controls
Siblings
ADHD
Shared
Unique
Task-specific
<0.01
<0.05
<0.005
<0.005
<0.01
<0.005
2.5
2.0
1.5
1.0
0.5
0.0
potency
Controls
Siblings
ADHD
Shared
Unique

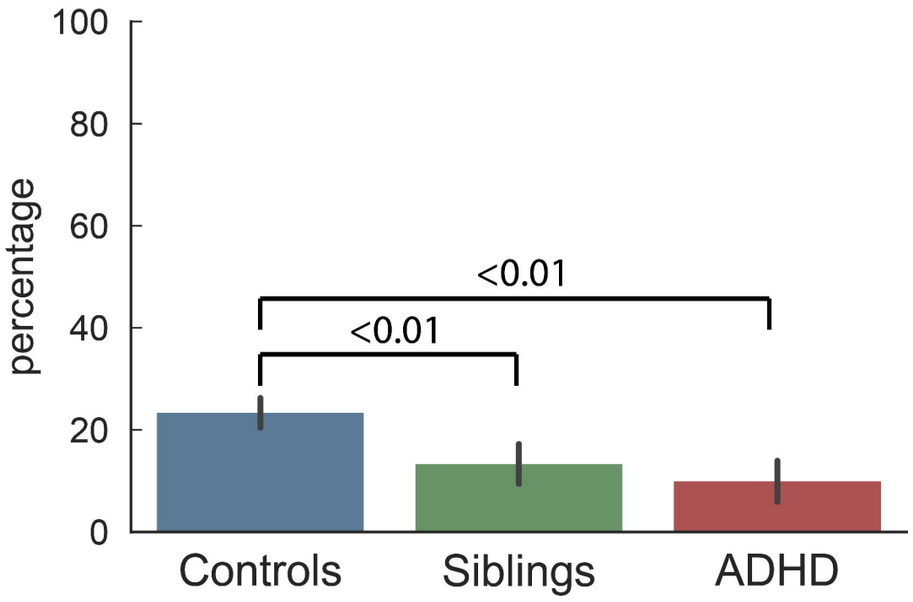


Diagnostic group membership
across all sensitive edges



Specificity of sensitive edges

Common across tasks



Task-specific