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Neuroanatomical Abnormalities in Adolescents with Attention-Deficit Hyperactivity Disorder

Amy Garrett, PhD., Lauren Penniman, Jeffery N. Epstein, PhD, BJ Casey, PhD, Stephen P. Hinshaw, PhD, Gary Glover, PhD., Simon Tonev, PhD., Alan Vitolo, PhD., Matt Davidson, PhD, Julie Spicer, BA, Larry Greenhill, MD., and Allan L. Reiss, MD.

Drs. Garrett and Reiss, and Ms. Penniman, are with Center for Interdisciplinary Brain Sciences Research, Department of Psychiatry, Stanford University, Palo Alto, CA; Dr. Epstein is with Department of Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, OH; Dr. Casey and Ms. Spicer are with Sackler Institute and Neuroscience Program, Weill Medical College of Cornell University, New York, NY; Drs. Hinshaw and Vitolo are with the Department of Psychology, University of California, Berkeley, CA; Dr. Glover is with the Department of Radiology, Stanford University, Palo Alto, CA; Dr. Tonev is with the Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC; Dr. Davidson is with the Department of Psychology, University of Massachusetts, Amherst, MA; and Dr. Greenhill is with the Division of Child Psychiatry, Columbia University Medical Center/New York State Psychiatric Institute, New York, NY

Abstract

Objective—Several neuroanatomic abnormalities have been reported in individuals with ADHD. However, findings are not always consistent, perhaps because of heterogeneous subject samples. Studying youths with documented familial ADHD provides an opportunity to examine a more homogeneous population.

Method—N=24 youths with a confirmed history of familial ADHD and 10 control youths underwent high-resolution structural Magnetic Resonance Imaging (MRI) examinations. Archived MRI scan data from 12 control youths were included in the analysis to increase statistical power. Individually drawn Region of Interest (ROI) methods were used to examine the frontal lobe gyri and caudate.

Results—Cerebral total tissue was similar between groups. The volumes of the right caudate and right inferior frontal lobe were larger in the ADHD youth compared to the control youth. Data from a subgroup of the ADHD youth suggest that increasing left caudate volume is associated with decreasing functional activation of this region.

Conclusions—Because previous studies have focused primarily on younger subjects or used an extended age range, the present results may reflect neurodevelopmental changes specific to late adolescence in familial ADHD.

Introduction

ADHD has been suggested to be a lifetime condition that is associated with significant comorbidity, including mood and anxiety disorders, conduct disorders, and substance dependence^{1, 2}. The disorder is also associated with academic and interpersonal relationship problems during adolescence³⁻⁵, and adulthood⁶. A refined understanding of the neural basis

Correspondence to Amy Garrett, Ph.D., Department of Psychiatry, 401 Quarry Road, Stanford, CA, 94305-5795. Phone: 650-736-1874; fax: 650-724-4794.

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of ADHD during development may lead to improved treatment that could reduce the deleterious effects of this disorder on the lives of the 3% to 7% affected school-aged children in the U.S.⁷.

A significant body of research suggests that alterations in brain structure occur in association with ADHD. A recent meta-analysis of structural imaging research⁸, indicated that the regions most frequently differentiating healthy controls and individuals with ADHD were total cerebral volume, the caudate nucleus, the splenium of the corpus callosum, and the cerebellum. Many studies have also found abnormalities in frontal lobe regions⁹⁻¹⁵. The majority of these studies have shown decreased frontal volumes in ADHD, although one reported increased area compared to controls¹⁶. Abnormalities in other brain regions have also been reported, including the posterior cingulate gyrus, temporal and parietal cortices, and hippocampus^{11, 13-15}.

Disparate findings between studies might be attributable to differences in subject selection. ADHD undoubtedly results from a wide variety of etiologies (reviews include^{7, 17-19}), producing variations in the neural manifestations of this behaviorally defined condition. A study including a more homogeneous sample with well-documented familial etiology would contribute to our understanding of the neural correlates of inherited forms of the disorder, as distinguished from other forms of ADHD. Such an approach could lead to specific hypotheses about the brain regions that are critical to the disorder.

The current study was conducted to investigate whether a well-characterized sample of participants with familial ADHD may yield additional information about the neural substrates of this disorder. Our study included adolescents with a documented history of familial ADHD in order to focus on heritable forms of ADHD. The subjects who participated in the Multimodal Treatment Study of ADHD (MTA) are a well-characterized group of youths with a documented history of ADHD symptoms that have persisted over time. The current subsample includes those with a family history of ADHD²⁰. By imaging these youths and comparing them to a matched comparison group, we can index brain morphology in ADHD that is related to a familial and well-documented form of the disorder.

An important lack of information in the literature is the functional significance of decreased versus increased regional brain volumes in disorders such as ADHD. For example, increased regional brain volume could be secondary to increased activity and thus indicative of enhanced function, or, alternately, due to impairment of normal regressive neurodevelopmental changes (e.g., pruning), and thus associated diminished function. Thus, the current study also sought to collect preliminary information about the functional consequences of increased or decreased regional volumes in ADHD.

This study is one of 3 conducted using this population: Epstein and colleagues²¹ used functional MRI to investigate brain activation during a Go/NoGo task, and found that youths with ADHD showed attenuated fronto-striatal activation compared to controls. Casey and colleagues²² used Diffusion Tensor Imaging (DTI) to investigate the integrity of frontostriatal white matter tracts related to cognitive control in this group, showing that increasing white matter integrity in frontostriatal regions was associated with improving performance on the Go-NoGo task. Because both of these investigations, as well as previous structural neuroimaging studies, have shown abnormalities in the frontal-striatal regions in ADHD, we focused our investigation on the caudate nucleus and the frontal gyri, hypothesizing that youths with familial ADHD would show aberrant volume in these structures.

Method

Subjects

A sample of 24 youths with familial ADHD were recruited from those who had participated in the Multimodal Treatment of Attention-Deficit Disorder (MTA) study. Only those youths who currently met criteria for ADHD and who also had parents with ADHD were chosen from the MTA study sample. All youths in the MTA study had received a diagnosis of ADHD, combined type, at the time of study recruitment when they were 7 to 9 years old. Upon entry into the current study (6 to 10 years later) youths were required to meet DSM-IV ADHD diagnostic criteria for any ADHD subtype based on scores on the Diagnostic Interview Schedule for Children, Parent Report (DISC-P, 23. In addition, biological parents were required to meet DSM-IV ADHD criteria using the Conners Adult ADHD Diagnostic Interview for DSM-IV (CAADID; 24, 25. Three of the 7 geographical recruiting sites from the MTA study were used (including Duke University Medical Center, University of California, Berkeley, and New York State Psychiatric Institute). Neuroimaging was performed at Duke (12 ADHD and 6 controls), Stanford (10 ADHD and 2 controls), and Cornell (2 ADHD and 2 controls) Universities. A multi-site design was chosen in order to maximize participation of subjects from the multi-site MTA study, while also limiting the number of neuroimaging sites to those possessing a GE scanner.

Ten healthy control dyads were matched, within site, to the ADHD youth's age and sex. These youths were recruited from the Local Normative Comparison Group that was part of the MTA study. Control youths were required to have fewer than 3 ADHD symptoms within each DSM-IV ADHD symptom domain as assessed by the DISC parent report.

All subjects had a minimum IQ of 80, no history of head trauma or neurological disease, and no diagnosis of bipolar disorder, psychosis, or pervasive developmental disorder. IQ was measured in youths using the abbreviated versions of the Wechsler Intelligence Scale for Children (WISC; 26). Written informed consent was obtained for all subjects, and the study was approved by the Institutional Review Boards at each participating site.

Archived data from healthy control youths were added to the database to increase the size of the control subject pool and the power of the analyses. These subjects were chosen to be group-matched on age and gender to the ADHD youths. Data from 12 subjects (4 female) who had previously been scanned at Stanford University using the same 1.5T scanner as the current study, and using the same imaging protocol were selected. For these subjects, IQ had been measured using the WISC, but one of the subjects had IQ measured using the WASI (Wechsler Abbreviated Scale of Intelligence) and 3 using the WAIS (Wechsler Adult Intelligence Scale).

MRI Scan Acquisition

Images were acquired on General Electric (Milwaukee, Wisconsin) 1.5 Tesla scanners at Duke University (n=18), Stanford University (n=25 including 12 archived controls) and Cornell University Medical College (n=4). To ensure cross-site comparability, all sites used identical scanners, software, and pulse sequences for imaging acquisition. To confirm cross-site reliability of scan data before the study began, two additional subjects were scanned at each site, and the resulting measurements of signal-to-noise ratio were compared and found to be similar. The volume of the caudate was measured on each of the scans, and comparisons showed that there was less than a 5% difference between sites. In addition, all sites scanned identical phantoms monthly to check signal drift.

Coronal images were acquired with a 3-dimensional volumetric spoiled gradient echo pulse sequence (SPGR) using the following scans parameters: TR=35 ms, TE=0 ms, flip angle=45

degrees, NEX=1; matrix size = 256×192, field of view=24 cm, slice thickness=1.5 mm, 124 contiguous slices.

Image processing

All image processing was completed at Stanford University. Scans were imported into *BrainImage* software (Stanford University, Stanford, CA) for semi-automated whole brain segmentation and quantification in the coronal plane using previously described and validated methods²⁷. This method gives grey matter, white matter, cerebrospinal fluid, and total tissue volume measures for the whole brain and cerebrum. Previous work in our laboratory has demonstrated that this protocol provides consistent results across scanners of the same magnetic field strength when similar pulse sequences are used and scans are acquired in the same orientation²⁸.

Volumes of the caudate and the superior, middle, and inferior gyri of the prefrontal cortex were obtained manually as described below. Trained research staff followed detailed protocols and achieved a within and between rater reliability of at least .90, determined by intraclass correlation coefficient. Raters were blind to group membership of each image.

Defining the Caudate ROI

Caudate nuclei were drawn on coronal images, in an anterior to posterior direction. The onset of the caudate coincides roughly with the appearance of the lateral ventricles. The caudate was traced on alternating slices, and the intermediate slices were interpolated. The lateral boundary of the caudate was the internal capsule, and the medial boundary was the lateral ventricle. The nucleus accumbens region was excluded. All tissue in the caudate, including head, body, and tail, were included.

Defining the Frontal Gyri ROIs

Sulcal demarcations of the frontal gyri were initially traced on 3-dimensional renderings of the cortical surface, then refined on multi-planar displays.

Superior Frontal Gyrus (SFG)

The medial aspect of the SFG extends from the pre-central sulcus to the frontal pole, and is further delineated by the cingulate and inferior rostral sulci. The sagittal view is consulted while drawing the SFG. The anterior SFG begins at the tip of the frontal pole, with the orbital gyri and middle frontal gyrus (MFG) soon appearing on the same plane, and the internal loops of the frontomarginal sulcus easily notable. When the frontomarginal sulcus disappears, the tips of the cingulate and superior frontal sulci are connected. The bilateral cingulate sulci are usually aligned and symmetrical. The appearance of the cingulate gyrus marks the end of the most inferior medial portion of the SFG. Noting the double gyri of the cingulate cortex, the deepest sulcus is used to delineate cingulate gyrus from SFG. As the posterior extreme of the SFG approaches, the lateral extent narrows, until it ends at the precentral gyrus.

Middle Frontal Gyrus

The anterior MFG is located between the SFG and the lateral orbital gyrus. The MFG is separated from the SFG by the supramarginal gyrus, and is continuous with the lateral orbital gyrus until the inferior frontal gyrus (IFG) appears. As the IFG takes shape, the MFG is situated between the SFG and IFG. Shallow sulci often split the MFG into multiple gyri as you move in the posterior direction. The posterior MFG ends at the pre-central gyrus.

Inferior Frontal Gyrus

The anterior IFG lies between the MFG and the lateral orbital gyrus. The IFG then becomes continuous with the lateral orbital gyrus. By referring to previous and upcoming slices, the IFG is separated from the lateral orbital gyrus. The IFG separates from neighboring gyri as it continues in the posterior direction. Deep sulci are used to help define the IFG. The extreme posterior IFG blends into the pre-central gyrus at the posterior boundary.

Statistical Analyses

Analyses were performed using SPSS software (version 16.0). Data distributions for each ROI were examined to confirm that the data met the assumptions of parametric statistics. MANOVA was used to test for group differences related to diagnosis. For the initial analyses, right and left hemisphere volumes of each ROI were combined, thus dependent variables included the total caudate, total SFG, total MFG, and total IFG volumes. Cerebral total tissue volume was used as a covariate. Follow-up ANOVAs using individual right and left hemisphere region of interest (ROI) volumes were conducted if the omnibus Wilks' Lambda F was significant for the MANOVA ($p < .05$, two-tailed).

Correlations between Volume and Function

In order to better understand the meaning of alterations in brain volume in ADHD youth, we performed correlations between volume and functional activation. Functional MRI activation was measured in a companion study (see 21 for details) during performance of a response inhibition (Go-NoGo) task. Results showed significantly decreased activation in ADHD youths in 4 regions relevant to the results of the current study: the left and right caudate, and two regions of the right IFG (Brodmann's areas 47 and 45). Additional regions showed significant differences between groups and are reported in ²¹. Beta values from the comparison of successful inhibition trials to successful non-inhibition trials (No-Go versus Go) were used as a measure of activation. A Pearson's correlation analysis, including all subjects who had completed both the structural and functional scans ($n=17$ youth, including 9 ADHD and 8 control), was used to assess the association between volume of the left and right caudate and IFG, and activation measures in these regions ($p < .05$).

Results

Demographic characteristics

The demographic and clinical characteristics of the ADHD and control groups are given in Table 1. There were no group differences in age (p values $> .3$) or ethnic distribution between groups. The ADHD and control groups both contained 2 left hand dominant individuals. Gender was similar between groups (18 male and 6 female subjects in the ADHD group; 16 male and 6 female subjects in the control group).

IQ was also similar for ADHD and control groups (including archived controls; $t < 1$), and was therefore not included as a covariate in subsequent analyses. Comparable IQ measures were not available for 8 of the archived control sample, as these subjects had either no IQ test ($n=4$) or had a WASI ($n=1$) or WAIS ($n=3$) test. If these WASI and WAIS scores were included in the sample, there was still no significant difference in IQ between ADHD and combined control groups ($t < 1$). IQ also was not included as a covariate in ROI analyses, as using IQ as a covariate would have removed 4 subjects from the analysis, thereby reducing statistical power in this small sample.

Regions of Interest

Visual inspection of the distribution of ROI data revealed that addition of the archived control sample did not increase the variability of the total control sample, and did not contain outliers that might bias between-group comparisons. Scatterplots of caudate and IFG data points are shown in Figures 1 and 2, respectively.

ROI data were submitted to a MANOVA analysis, as described above. The omnibus Wilks' Lambda for the model was significant ($F=3.34$, $p=.019$, two-tailed). Therefore, ANOVA was used to compare left and right hemispheres of each ROI between diagnostic groups. Regions found to differ significantly between groups were the right inferior frontal gyrus ($F(1,45)=4.29$, $p=.044$) and the right caudate nucleus ($F(1,45)=7.15$, $p=.011$). For both structures, the ADHD youth had larger volumes compared to the control youth. The left ROI for these structures also were somewhat larger in ADHD youth relative to controls (left caudate: $F(1,45)=3.31$, $p=.076$; left IFG: $F(1,45)=1.80$, $p=.19$), but these differences did not reach statistical significance. To determine whether these results were attributable to the inclusion of the archived control sample, analyses of the right caudate and IFG were repeated while excluding the archived control subjects. Results showed that the right caudate nucleus volume was significantly larger in the ADHD youth compared to control youth ($F(1,33)=7.73$, $p=.010$), but there was no difference in the right IFG ($F(1,33)=1.77$, $p=.19$). However, this is likely due to decreased power, as the effect size for the right IFG was comparable with and without the archived controls (Cohen's $d = .54$). See Table 2.

Correlation between volume and function

The volume of the left caudate was negatively correlated with activation in the left caudate ($r=-.54$, $p=.025$), when including both ADHD and control youths (Figure 3). Thus, larger left caudate volume was associated with decreased left caudate functional activation during a Go-NoGo task. Also, larger volumes of the left caudate ($r=-.50$, $p=.04$) and the right caudate ($r=-.54$, $p=.02$) were correlated with decreasing activation in the right IFG (Brodmann's area 45). The volume of the left and right IFG were not significantly correlated with activation in any region.

Discussion

We found that youths in late adolescence, ages 15 to 19, with a well-documented history of familial ADHD, show larger volumes of the right caudate and right inferior frontal gyrus than do controls. In a subset of ADHD and control subjects for whom data were available from a companion study, increased left caudate volume was associated with decreased left caudate functional activation. These data suggest that a larger volume of the caudate and inferior frontal gyrus are seen in ADHD in late adolescence.

At first glance, these findings appear to contradict results from previous studies that reported smaller, rather than larger, caudate volumes in ADHD. However, because of the unique characteristics of the subjects included in our study, the findings reported here actually build on the existing literature. For example, this study is unique by including only subjects with familial ADHD. This was designed to increase the homogeneity of the sample, but also created a sample somewhat different from those in the existing literature. The age of our subjects might also account, in part, for our finding of larger rather than smaller volumes of the caudate and IFG in the ADHD youth sample. A number of previous studies have shown decreased volume of the caudate in ADHD 10, 12, 16, 29-36. Also, several studies have shown decreased volume of the frontal lobe in this disorder 9-15. However, all of these studies examined youth samples spanning a wide age range. For example, children, (ages 5 to 10), are often combined with those in early adolescence (ages 11 to 14) and those in late adolescence (ages 15 to 19). These

studies are extremely valuable, but they do not typically reveal age-specific abnormalities. Castellanos and colleagues³³ suggested that the volume of the caudate nucleus, relative to controls, changes over time, such that individuals with ADHD have smaller caudate in childhood and early adolescence that may normalize at approximately age 16. The volume of the caudate in control subjects appears to gradually decrease over time, whereas the ADHD caudate does not, leading to the appearance of grossly normal caudate volume during adolescence³³. In fact, previous studies that report smaller caudate volume across a wide age range in ADHD, also suggest a slightly (but nonsignificantly) *larger* right and left caudate in the 14.7 to 19.5 year old subgroup (see Table 2 of³²). Furthermore, the only other study reporting significantly larger caudate size in ADHD¹⁶ included subjects in a similar age range as the current study. However, it is important to note that this study measured caudate *area*, rather than volume, using a single slice in non-reoriented brain images.

These studies of caudate morphology suggest that aberrant brain structure and/or function may manifest differently at various ages. Further supporting this hypothesis, the few studies that have examined adults with ADHD did not find differences in caudate nucleus volume, but rather smaller frontal lobe regions, including the dorsolateral prefrontal cortex, anterior cingulate cortex³⁷ and orbitofrontal cortex¹¹. Age specific changes in particular brain regions have been noted in other psychiatric groups, for example, children with PTSD have larger hippocampal volumes than controls, while adults show smaller hippocampal volumes.³⁸

Few studies have investigated the relationship between brain structure and function, so the meaning of increased caudate volume in ADHD is unknown. However, the significant negative correlation between left caudate volume and functional activation (measured during a Go-NoGo task in the companion study) sheds light on the possible implications of our finding, that is, larger caudate in ADHD youth may indicate a functionally deficient brain region, or an aberrant brain region resulting from compromised circuitry. This interpretation is consistent with several previous fMRI studies showing decreased caudate activation in youth with ADHD³⁹⁻⁴². The larger caudate in ADHD could be a result of incomplete synaptic pruning during the late part of adolescent brain development, as control children show a decrease in caudate volume with age³³. Furthermore, results from a previous study also show that increased caudate size is associated with decreased function as measured by neuropsychological tests of attention¹⁶.

Although the correlation of right caudate volume and activation was not significant, we found that right caudate volume was negatively correlated with right IFG activation. This finding suggests that abnormally large caudates may compromise function of fronto-striatal circuits, particularly those associated with response inhibition⁴³⁻⁴⁷. It is important to note that this data analysis is preliminary: it included only a portion of the sample who had both fMRI and sMRI data available (9 ADHD and 8 control youth).

Limitations of the current study include the small sample size. Participants were selected from the MTA sample, only including youths who had parents with ADHD and who continued to show symptoms of ADHD in adolescence. It is also worth noting that all subjects had been previously treated with stimulant medication. Therefore our sample was small but more homogeneous than any previous study. The sample nonetheless had enough power to detect differences compared to the control sample. However, it should be noted that significant group differences could be attributable to Type I error in this small sample. Larger groups of subjects with familial ADHD will be needed to replicate these findings.

The use of archived control subjects as a comparison group for the youth sample is also a limitation of this study. However, the archived control sample did not increase the variability

of the total control sample, and did not contain outliers that might have biased between-group comparisons.

In summary, similar to previous studies, we have demonstrated abnormalities in the volume of the caudate nucleus and inferior frontal gyrus. These differences were seen in the opposite direction from those of several previous studies, as we showed evidence for larger rather than smaller volume. Our finding could be related to the fact that we studied youth in late adolescence, whereas previous studies often include a wider age range. Thus, aberrant volume in these regions may manifest differently in different age ranges, and in certain cases may resemble normal volume in adulthood.

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Figure 1.

Figure 2.

Figure 3.

Table 1
Demographic Variables: No significant differences in gender, ethnic distribution, age, IQ, or handedness between ADHD and control groups.

	ADHD Youth (N=24)	Control Youth (N=10)	Archived Control Youth (N=12)
Gender:			
Male	18	8	8
Female	6	2	4
Ethnic Group:			
White	20	8	7
African American	2	0	0
Other	2	2	5
Age:			
Mean (SD)	16.9(1.1)	17.1(1.1)	16.7(1.4)
Range	15.0-19.0	15.4-18.3	14.1-18.8
IQ			
Mean (SD)	106.0 (11.4)	104.2 (16.5)	120.1 (6.6) (N=8) ^a
Range	80 - 129	80 - 129	107-128
Control + Archived control IQ= 111.3 (15.1)			
Handedness:			
Right	22	8	12
Left	2	2	0
ADHD Subtype:			
Inattentive	14 ^b	0	0
Hyperactive	2	0	0
Combined	7	0	0
Comorbid Disorders			
Eating Disorder	0	0	NA
Agoraphobia	0	0	NA
Depression ^c	2	0	NA
Hypomania	0	0	NA
OCD	0	0	NA
Panic	0	0	NA
PTSD	0	0	NA
Social Phobia	0	0	NA
Specific Phobia	3	0	NA
ODD	1	0	NA

	ADHD Youth (N=24)	Control Youth (N=10)	Archived Control Youth (N=12)
CD	1	0	NA
Alcohol Use Dis	2	0	NA
Marijuana Use Dis	0	1	NA

OCD=Obsessive Compulsive Disorder; PTSD=Posttraumatic Stress Disorder; ODD=Oppositional Defiant Disorder; CD=Conduct Disorder.

^a IQ scores include WISC for the ADHD and control subjects from the MTA sample. However, the archived control sample includes 1 WASI and 3 WAIS scores, as well as 4 missing IQ scores.

^b One of the youths with ADHD did not meet full diagnostic symptom criteria for ADHD. The youth had 4 Inattentive symptoms and 0 Hyperactive/Impulsive symptoms.

^c Assessment of depression included both current and past symptoms; While 8 subjects reported past symptoms, only 2 subjects had current symptoms of depression.

Table 2

A priori regions of interest and results of ANOVA

Region	ADHD Youth (N=24) Mean (std dev)	Control Youth (N=22) Mean (std dev)	ANOVA P (effect size, Cohen's d)
Caudate			
Left	4.19 (.43)	3.99 (.57)	P=.076 (0.40)
Right	4.23 (.42)	3.93 (.52)	P=.011 (0.63)*
IFG			
Left	20.33 (3.98)	19.33 (3.07)	P=.186 (0.28)
Right	18.86 (3.82)	17.26 (3.48)	P=.044 (0.44)*
MFG			
Left	27.15 (3.60)	28.98 (4.04)	P=.122 (0.48)
Right	28.59 (4.42)	27.75 (3.59)	P=.328 (0.21)
SFG			
Left	55.41 (8.36)	53.97 (6.05)	P=.348 (0.20)
Right	54.25 (8.03)	54.04 (7.19)	P=.647 (.03)
Cerebrum Total	1125.95 (107.86)	1138.74 (98.19)	P=.68 (0.12)

Std dev = standard deviation; IFG=inferior frontal gyrus, MFG=middle frontal gyrus, SFG=superior frontal gyrus

*
p < .05