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White Matter Integrity and Behavioral Activation in Healthy Subjects

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Abstract: Individual differences in behavioral inhibition and behavioral activation may place certain people at greater risk for neuropsychiatric disorders and engagement in risky behaviors. Therefore, studying the neural correlates of behavioral inhibition and activation may help us understand neural mechanisms underlying risk behaviors in both clinical and non-clinical populations. To investigate, we assessed the relationships between white matter integrity and measures of behavioral inhibition and behavioral activation in 51 healthy participants using diffusion tensor imaging (DTI) and the Behavioral Inhibition System/Behavioral Activation System (BIS/BAS) scale. Scores on the Fun-Seeking subscale of the BAS positively correlated with DTI fractional anisotropy in the left corona radiata and adjacent superior longitudinal fasciculus, and with mean diffusivity in the left inferior longitudinal fasciculus and inferior fronto-occipital fasciculus after controlling for age, gender, and education. These findings suggest that the integrity of white matter connecting extensive brain regions implicated in self-control and the processing of rewards and emotions are associated with individual differences in the motivation for seeking and participating in fun and novel experiences. *Hum Brain Mapp 33:994–1002, 2012.*

Key words: behavioral activation; behavioral inhibition; neuroimaging; DTI; self-control; cognitive control

INTRODUCTION

Gray proposed that a behavioral inhibition system (BIS) and a behavioral activation system (BAS) underlie propensities to engage in motivated behaviors [Gray, 1982, 1987]. According to Gray's theory, the BIS is sensitive to cues of loss, punishment, conflict, or novelty, and inhibits behaviors leading to negative results. Its activation is associated with negative affective states (like anxiety), and its neural correlates include amygdala and septo-hippocampal systems [Gray, 1987; Gray and McNaughton, 2000]. The BAS is sensitive to rewarding cues and promotes approach behaviors to potential rewards. Its activation is associated with positive affective states (like happiness), and its neural correlates include the mesolimbic dopaminergic system [Depue and Collins, 1999; Gray, 1987, 1990].

Although the theory proposing separate systems for behavioral inhibition and activation is mainly based on animal research [Fowles, 1987; Gray, 1987], human studies have demonstrated distinct roles for these systems in clinical and nonclinical populations. In addition, it has been demonstrated that high BIS and BAS function may

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predispose individuals to internalizing and externalizing disorders, respectively [Bijttebier et al., 2009; Colder and O'Connor, 2004; Hundt et al., 2008]. For example, increased BIS activation is associated with anxiety and/or depression among community populations [Carver and White, 1994; Hundt et al., 2007; Johnson et al., 2003; Shackman et al., 2006], while increased BAS activation is associated with conduct-related disorders, eating disorders, and alcohol and drug use [Johnson et al., 2003; Knyazev, 2004; Loxton and Dawe, 2006; Quay, 1993]. Further, patients with depression and/or anxiety consistently report higher BIS scores compared to healthy adults, while patients with bipolar, substance use, or attention deficit hyperactivity disorders report higher BAS scores [Alloy et al., 2009; Bijttebier et al., 2009; Franken et al., 2006]. Taken together, these data suggest that BIS and BAS are associated with negative and positive affect, respectively, and with the development of distinct forms of psychopathology.

The neural correlates of BIS and BAS have been examined in structural brain imaging studies. For example, two voxel-based morphometry (VBM) studies assessed the structural correlates of BIS and BAS in 50 male college students using the Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ), [Torrubia et al., 2001]. Consistent with Gray's theory, Sensitivity to Punishment (SP) scores correlated positively with volumes of gray matter (GM) in the amygdala and hippocampal formation [Barros-Loscertales et al., 2006a], and Sensitivity to Reward (SR) scores correlated negatively with GM volumes in the dorsal striatum and right superior frontal gyrus [Barros-Loscertales et al., 2006b]. Another VBM study assessed personality traits of 85 young adults using the Tri-dimensional Personality Questionnaire (TPQ) [Cloninger, 1987]. Scores on harm avoidance, which are thought to reflect BIS function, correlated negatively with GM volumes in the prefrontal, parietal, and occipital cortices, and scores on reward dependence, which are thought to reflect BAS function, correlated negatively with GM volumes in the caudate and frontal rectal gyrus [Gardini et al., 2009]. A separate study assessed the volumes of amygdala and hippocampal formation in 430 community adults using manual tracing on T1 magnetic resonance image (MRI) and correlated these measures with scores on the BIS/BAS scale [Carver and White, 1994] and found that BIS scores correlated positively with hippocampal volume [Cherbuin et al., 2008]. Taken together, these, but not all, studies provide initial evidence indicating that GM volumes in the hippocampus, amygdala, striatum, and PFC may be associated with aspects of BIS and/or BAS function.

Although prior studies have linked BIS/BAS function to GM volumes, the role of white matter (WM) in BIS/BAS function is not clear. The WM may influence BIS/BAS function because WM connections mediate communications between different brain regions and are essential for integrated brain function. Diffusion tensor imaging (DTI) assesses WM integrity by measuring directional water diffusion [Alexander et al., 2007; Assaf and Pasternak, 2008]. Recently, DTI has been used to assess WM integrity as related to brain function and behavior in healthy subjects and those with neuropsychiatric disorders [Agarwal et al., 2010; Sexton et al., 2009]. The commonly used DTI parameters include fractional anisotropy (FA), mean diffusivity (MD), longitudinal eigenvalue (λ_1), and perpendicular eigenvalue (λ_T). FA is a normalized standard deviation of eigenvalues [Pierpaoli et al., 1996], and decreased FA value in the WM is regularly interpreted as reflecting impaired WM integrity. MD is calculated as the mean of all eigenvalues. Increases in tissue water (e.g., edema) and/or in inter-membrane space in the WM can increase MD values [Alexander et al., 2007]. There are data indicating that axonal degeneration is associated with decreased λ_1 values [Concha et al., 2006; Sidaros et al., 2008], while demyelination is associated with increased λ_T value [Song et al., 2002]. However, the cellular mechanisms underlying the changes of either eigenvalues have not been fully revealed, and several other factors, including directions and patterns of crossing fibers, may also influence eigenvalues [Jbabdi et al., 2010; Wheeler-Kingshott and Cercignani, 2009].

To our best knowledge, no published studies have used DTI to assess the relationship between WM integrity and BIS/BAS measures. Given the role of BIS and BAS in affect and in the development of psychopathology, understanding their neural correlates, including WM, may have broad applicability. To investigate, we analyzed the relationships between WM integrity assessed by DTI and scores on the BIS/BAS scales and subscales in 51 healthy adult participants (HPs). We predicted that: (1) poorer integrity of WM interconnecting striatum and PFC would correlate with greater scores on BAS, because previous studies reported negative correlations between measures on BAS and GM volumes in the striatum and PFC [Barros-Loscertales et al., 2006b; Gardini et al., 2009]; and, (2) better integrity of WM connecting limbic regions would correlate with higher scores on BIS, because previous studies reported positive correlations between measures on BIS and GM volumes of hippocampus and amygdala [Barros-Loscertales et al., 2006a; Cherbuin et al., 2008].

METHODS

Participants

We acquired both DTI and self-reported data on the BIS/BAS scale from 56 HPs. Subjects were recruited by media ads and provided written informed consent approved by the Yale Human Investigations Committee. Participants were screened using the Structured Clinical Interview (SCID) [First et al., 1996, 1997] and had urine samples tested for metabolites of cocaine, opioids, amphetamines, marijuana, and benzodiazepines. Participants were excluded if any metabolites of these substances were positive in their urine samples. Handedness was assessed by asking participants which hand they usually use for tasks

like writing or throwing, and left-handed individuals were not invited to participate. Exclusion criteria included pregnancy, color blindness, a current Axis I disorder, or an unstable medical condition. Two independent neuroimaging researchers, who were blind to the identity of DTI images, independently examined the quality of each image in the original space. Images from five participants were rated as excessively noisy by both investigators and were excluded from further analysis. The excessive noise might be due to one or more possible factors including motion, scanner instability, or static interference from electronic equipments in the scanning room. The final sample included 51 HPs with a mean age of 29.6 [standard deviation (SD) = 10.0, range: 18–54] years, and mean education of 15.0 (SD = 2.0, range: 12–20) years. Twenty-one participants were female.

BIS/BAS Assessment

The BIS/BAS scale is a valid and reliable 20-item questionnaire [Carver and White, 1994; Heubeck et al., 1998]. Seven items measure sensitivity to signals of punishment, non-reward, or conflicts, and comprise the BIS scale. The remaining 13 items comprise the BAS scale, measuring sensitivity to signals of reward or non-punishment, with subscales for Drive (BAS-Drive), Fun-Seeking (BAS-Fun), and Reward-Responsiveness (BAS-Reward), which measure the propensities of pursuing goals, seeking out new potentially-rewarding experiences, and reward response tendencies, respectively [Carver and White, 1994; Heubeck et al., 1998]. The correlations between scores on the BIS/BAS subscales were analyzed using SPSS16.

Scanning Procedures

DTI data were acquired with a 3.0T Siemens Trio scanner at the Yale Magnetic Resonance Research Center. Diffusion sensitizing gradients were applied along 32 directions using b values 1,000 s mm^{-2} (TR = 7,400, TE = 115, matrix = 128 × 128, FOV = 256 × 256 mm^2). In addition one image (b_0 image) was acquired using b value of 0. Forty contiguous slices parallel to the AC-PC line were acquired, and each slice was 3.0-mm thick [Xu et al., 2010]. Two repetitions were acquired for averaging. A high-resolution T1 image was routinely acquired and examined by a neuroradiologist to identify any structural anomalies.

Image Processing

The procedure for DTI processing was described recently [Xu et al., 2010]. FMRIB's Diffusion Toolbox (FDT 2.0) and Tract-Based Spatial Statistics [TBSS 1.2, Smith, 2004; Smith et al., 2006, 2007] from FMRIB's Software Library [FSL 4.1.4, Smith et al., 2004; Woolrich et al., 2009, http://www.fmrib.ox.ac.uk/fsl/] were used for image analyses. A set of mean images was created by aligning and averaging the two image sets from each subject and used to construct the diffusion tensor using FDT. FDT typically generates maps of fractional anisotropy (FA), parallel eigenvalue (λ_1), mean diffusivity (MD), lamda_2 (λ_2), and lamda_3 (λ_3). The map of perpendicular eigenvalue (λ_T) was generated by averaging maps of λ_2 and λ_3.

TBSS was used to register the FA map of each subject into the Montreal Neurological Institute (MNI) template space. A mean FA map was created by averaging registered FA images from all subjects, and a mean FA skeleton was created by thinning the mean FA image [Smith 2004; Smith et al., 2006, 2007]. The highest local FA value was projected to the skeleton after searching the local area in the direction perpendicular to each tract. The transformation matrices created for FA map registration were used to register λ_1, λ_T, and MD maps. Skeletons for λ_1, λ_T, and MD were generated using the same procedures for creating the FA skeleton.

We used a voxel-wise whole-brain analytic approach to assess the relationships between scores on the BIS/BAS scale and values of FA, λ_1, λ_T, and MD using correlation analyses with age, gender, and education as covariates. Among adults, aging is associated with decreased WM integrity as expressed by decreased FA values and increased MD values in the WM [Gunning-Dixon et al., 2009; Madden et al., 2009]. Image analyses were executed using the "randomize" program with 5,000 permutations. This program uses permutation-based, nonparametric inferences to perform voxel-wise, cross-subject statistics [Nichols and Holmes, 2002]. Statistical thresholds for all image analyses were voxel-level $t > 2.0$ and cluster $P < 0.05$, FWE-corrected for multiple comparisons in the voxel-wise whole-brain analysis. JHU ICBM-DTI-81 White-Matter Labels and JHU White-Matter Tractography Atlas provided by FSLVIEW 3.1.2 were used to identify the location of significant clusters [Mori et al., 2008, 2009], and the significant clusters were defined as regions of interest (ROI). The function "fslmeants" from FSL was used to extract means of FA, λ_1, λ_T, and MD from these ROIs, and correlations between these extracted values were analyzed using SPSS 16.

RESULTS

Correlations Between BIS/BAS Subscale Scores

Table I presents correlations between scores on each subscale of the BIS/BAS scale. The scores on BAS-Drive, BAS-Fun, and BAS-Reward correlated positively with each other, and with the total scores of BAS scale. The scores on the BIS scale showed a modest but significant correlation with scores on the BAS-Reward subscale.

Correlations Between DTI and BIS/BAS Scores

The correlations between values of DTI parameters and scores on BIS/BAS were assessed after controlling for age, gender, and education. The scores on the BAS scale

TABLE I. Correlations between subscales of BIS/BAS

	Mean (SD)	BAS total	Drive	Fun	Rew	BIS
BAS total	38.0 (6.1)		0.85**	0.87**	0.77**	0.18
Drive	10.5 (2.5)			0.63**	0.48**	−0.01
Fun	11.1 (2.6)				0.50**	0.09
Rew	16.4 (2.2)					0.39**
BIS	18.2 (3.2)					

Abbreviation: BAS: behavioral activation system; BIS: behavioral inhibition system; Rew: reward.
*$P < 0.05$,
**$P < 0.01$.

correlated positively with λ_1 values in one cluster, but not with other DTI parameters (Fig. 1 and Table II). The significant cluster was at the left corona radiata (CR) and superior longitudinal fasciculus (SLF). Scores on the BAS-Fun subscale significantly correlated with FA, λ_1, and MD, but not with λ_T (Table II and Fig. 2). In both FA and λ_1 map, one cluster at the left CR and SLF positively correlated with scores on the BAS-Fun subscale (see Fig. 2). Visual inspection and the data on the sizes of significant clusters and MNI coordinates of peak voxel in each cluster indicated that the significant clusters in the FA and λ_1 maps overlapped with each other in space, and that the cluster in the λ_1 map was almost identical in location, size, and shape to the cluster showing a significant correlation between λ_1 and scores on BAS scale. In the MD map, one cluster at the left inferior fronto-occipital fasciculus (IFOF) and inferior longitudinal fasciculus (ILF) positively correlated with scores on the BAS-Fun subscale (see Fig. 2). Scores on the BAS-Drive and BAS-Reward subscales and the BIS scale did not show significant correlations with any DTI parameters.

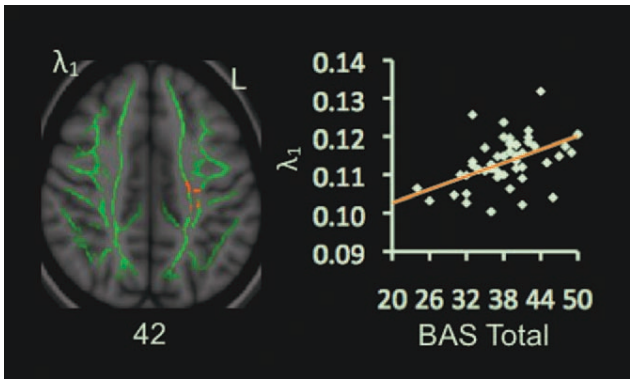

Figure 1.
Correlation between λ_1 values and scores on BAS scale. Red-yellow color on MNI T1 template indicates brain regions exhibiting significant correlations between λ_1 values and scores on the BAS scale. The green color shows the "group mean_FA_skeleton," the number below the brain image indicates *Z* coordinates in MNI space, and only clusters surviving correction for multiple comparisons of voxel-wise whole brain analysis are shown. Scatter-plot demonstrates correlations between mean values of λ_1 (*y*-axis) of each participant and scores on the BAS scale. Mean values of λ_1 were calculated from all voxels in the significant cluster of each participant. Abbreviation: L: left.

ROI Analysis

The cluster showing significant correlation between FA and BAS-Fun scores was defined as a ROI. Partial correlation analyses showed that the correlation between BAS-Fun scores and mean FA values from the ROI was still significant after controlling for either λ_1 ($r = 0.413$, $P = 0.003$) or λ_T ($r = 0.406$, $P = 0.003$), but became nonsignificant ($r = 0.14$, $P = 0.35$) after controlling both λ_1 and λ_T. Correlation analyses showed that mean FA values from the ROI significantly correlated with mean values of λ_1 ($r = 0.67$, $P < 0.001$) and λ_T ($r = -0.85$, $P < 0.001$), but mean values of λ_1 and λ_T did not significantly correlate with each other ($r = -0.18$, $P = 0.21$). The cluster showing a significant correlation between MD values and BAS-Fun scores was defined as another ROI. Partial correlation analyses showed that the correlation between BAS-Fun scores and mean MD values from the ROI became nonsignificant after controlling for either λ_1 ($r = 0.19$, $P = 0.18$) or λ_T ($r = 0.15$,

TABLE II. Positive correlations between DTI and BIS/BAS scale scores

		Size		MNI coordinates		
	L/R	Voxels	*t*-value[a]	*x*	*y*	*z*
BAS Total and λ_1						
CR and SLF	L	363	4.1	−25	−18	44
BAS-Fun and FA						
CR and SLF	L	597	4.26	−22	−22	41
BAS-Fun and λ_1						
CR and SLF	L	438	5.0	−25	−18	44
BAS-Fun and MD						
ILF, IFOF	L	270	4.1	−45	−33	−14

Abbreviations: CR: corona radiata; IFOF: inferior fronto-occipital fasciculus; ILF: inferior longitudinal fasciculus; L: left hemisphere; MNI: Montreal Neurological Institute; SLF: superior longitudinal fasciculus.
[a]*t* value of the peak voxel.

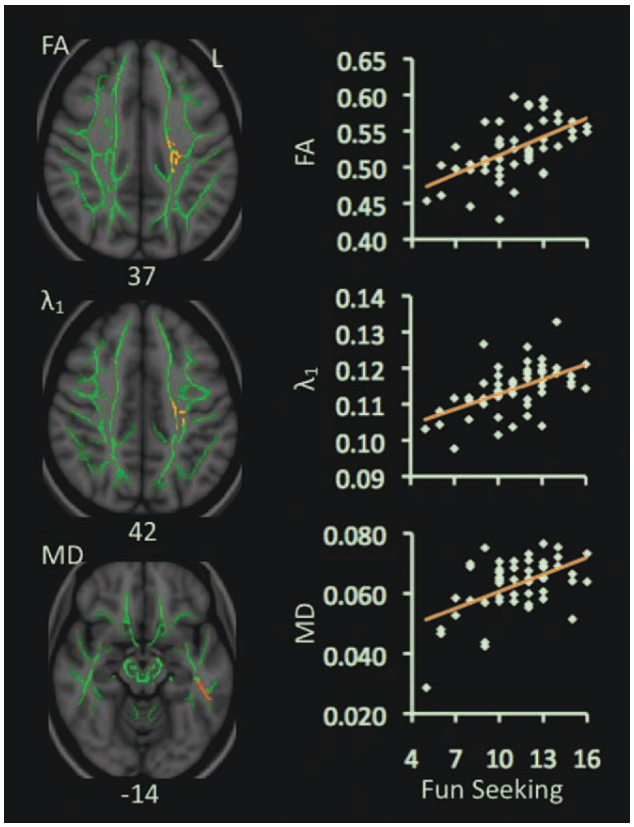

Figure 2.
Correlations between values of FA, λ_1, and MD and scores on BAS Fun Seeking subscale. Red-yellow color on MNI T1 template indicates brain regions exhibiting significant correlations between values of FA, λ_1, and MD and scores on the Fun Seeking subscale. The green color shows the "group mean_FA_skeleton," the numbers below the brain image indicate *Z* coordinates in MNI space, and only clusters surviving correction for multiple comparisons of voxel-wise whole brain analysis are shown. Scatter-plots demonstrate correlations between mean values of FA, λ_1, and MD (*y*-axis) of each participant and scores on the Fun-Seeking subscale. Mean values of FA, λ_1, and MD were calculated from all voxels in the significant cluster of each participant. Abbreviation: L: left.

$P = 0.30$). Correlation analyses showed that mean MD values significantly correlated with mean values of λ_1 ($r = 0.94$, $P < 0.001$) and λ_T ($r = 0.97$, $P < 0.001$), and that mean values of λ_1 and λ_T significantly correlated with each other ($r = 0.84$, $P < 0.001$).

DISCUSSION

This study aimed to assess the relationships between WM integrity and BIS/BAS function in HPs. The most interesting finding is that better WM integrity (i.e., greater FA values) in the left CR and SLF along with worse WM integrity (i.e., greater MD values) in the left IFOF and ILF correlate with higher scores on the BAS-Fun subscale. These findings suggest that specific regions of WM integrity may underlie BAS sensitivity, especially the motivation for seeking and participating in fun and novel situations. In addition to this interesting finding, scores on the BIS/BAS subscales show positive correlations. Implications are discussed below.

Correlations Between BIS/BAS Measures

The scores on the BIS scale and each subscale of BAS reported by HPs in the present study are similar to those reported by HPs in several previous studies [Caseras et al., 2003; Franken et al., 2006; Meda et al., 2009; Miller et al., 2004]. The current findings of significant positive correlations between scores on subscales of the BAS and between scores on the BIS scale and BAS-Reward subscale are consistent with previous findings of significant intercorrelations between these measures [Johnson et al., 2003; Miller et al., 2004; O'Connor et al., 2004; Poythress et al., 2008; Ross et al., 2002]. The consistent findings between current and previous studies suggest that the current HPs are representative of general healthy populations.

Correlations Between WM Integrity and BAS Scores

Scores on the BAS scale and BAS-Fun subscale showed significant correlations with λ_1 at almost identical WM locations (i.e., the left CR and SLF), while scores on the BAS-Drive and BAS-Reward subscales did not show significant correlation with any DTI parameters. Therefore, the significant correlation between scores on BAS scale and λ_1 appears driven by the significant correlation between BAS-Fun subscale scores and λ_1 measures. Furthermore, the scores on the BAS-Fun subscale positively correlated with FA values in a cluster overlapping with the significant cluster in the λ_1 map. These findings suggest that better WM integrity in the CR and SLF is associated with greater scores on BAS-Fun subscale. The SLF connects parietal and frontal cortices, while the CR connects cortical and subcortical structures including the thalamus and midbrain [Schmahmann et al., 2008]. Therefore, better anatomical connections among PFC, parietal cortex, and subcortical structures including thalamus and midbrain appear associated with a greater motivation for seeking and participating in fun and novel experiences. A previous fMRI study reported significant correlation between BAS scores and task-related activity in the lateral PFC, anterior cingulate, and parietal cortex while performing a cognitive control task (i.e., n-back working memory task) [Gray et al., 2005]. The current finding of a significant correlation between BAS-Fun scores and FA values in the CR and SLF suggest that WM integrity may contribute to

the relationships between BAS sensitivity and task-related activity in brain regions involved in cognitive control.

ROI analyses indicated that the correlation between BAS-Fun scores and mean FA values in the significant cluster remained significant after controlling for either λ_1 or λ_T, and only became nonsignificant after controlling for both λ_1 and λ_T. Therefore, both λ_1 and λ_T appear to contribute to the significant correlation between BAS-Fun scores and FA values in the cluster. Furthermore, the mean FA values in the significant cluster correlated positively with mean values of λ_1 but negatively with mean values of λ_T, while the mean values of λ_1 and λ_T did not correlate with each other. These data indicate that either increases in λ_1 values or decreases in λ_T values will increase FA values (i.e., improve WM integrity) in the significant cluster, and that individual differences in λ_1 values are independent of individual differences in λ_T values. Because the cellular mechanisms underlying changes in values of λ_1 and λ_T are different [Concha et al., 2006; Sidaros et al., 2008; Song et al., 2002], at least two different cellular mechanisms may be involved with respect to increasing FA values, one via increasing λ_1 values without affecting λ_T values, and the other via decreasing λ_T values without affecting λ_1 values. Therefore, two or more different cellular mechanisms might contribute to individual differences in FA values in the significant cluster observed in the present study.

The positive correlations between scores on the BAS-Fun subscale and MD in the IFOF and ILF indicate that worse WM integrity in these tracts is associated with greater scores on BAS-Fun subscale. The IFOF connects frontal and occipital lobes, while the ILF connects occipital and temporal lobe structures including the amygdala, hippocampus, and parahippocampus [Catani et al., 2003; Mori et al., 2005; Schmahmann and Pandya, 2007; Schmahmann et al., 2008]. The current findings suggest that worse anatomical connections among the PFC, occipital cortex, and temporal structures including the amygdala, hippocampus, and parahippocampus are associated with a greater motivation for seeking fun and novel experiences. Prior functional imaging studies reported that BAS scores correlated positively with reactivity in the left hippocampus-parahippocampus area and insula while HPs viewed erotic and disgusting pictures, respectively [Reuter et al., 2004]. The present cluster showing a positive correlation between BAS scores and MD values was at the left IFL and IFOF and adjacent to the left insula, and might include fibers connecting to the left insula. Therefore, the increased reactivity to emotional stimuli in the insula and hippocampus-parahippocampus area of HPs with high BAS scores may reflect decreased top-down emotional regulation due to decreased WM integrity and decreased anatomical connection among PFC and occipital and temporal lobes. We should note that the JHU White-Matter Tractography Atlas was used to localize the significant cluster in the left IFOF in the current study. However, the existence of IFOF has been challenged by some investigators [Schmahmann and Pandya, 2007]. Therefore, these findings should be interpreted cautiously and more research should investigate the nature and implications of the current observations.

ROI analyses revealed that the significant correlation between BAS-Fun scores and mean MD values in the significant cluster became non-significant after controlling for either λ_1 or λ_T values. Therefore, both λ_1 and λ_T might contribute to the significant correlation between BAS-Fun scores and MD values. Furthermore, the mean MD values in the significant cluster correlated positively with mean values of both λ_1 and λ_T, and that the mean values of λ_1 and λ_T correlated positively with each other. These data suggest that individual differences in values of λ_1 and λ_T in this significant cluster may be due to the same cellular mechanism, which should be different from the cellular mechanisms underlying individual difference in FA values in the cluster showing significant correlation between BAS-Fun scores and FA values.

It was hypothesized that positive emotion and approach behavioral tendencies have been associated with function of the left hemisphere, while negative emotion and withdrawal behavioral tendencies have been associated with function of the right hemisphere [Davidson, 1992; Davidson et al., 1990]. Data from several (but not all) studies using different methods such as fMRI, VBM, and patients with unilateral brain lesion support this hypothesis [Canli et al., 2002; Davidson and Irwin, 1999; Harmon-Jones, 2003; Harmon-Jones et al., 2006; Omura et al., 2005]. The current finding of a significant correlation between BAS-Fun scores and values on DTI parameters in the left hemisphere provide DTI evidence supporting this hypothesis.

On the basis of the previous findings of negative correlations between BAS-related scores and GM volumes in the dorsal striatum and PFC [Barros-Loscertales et al., 2006b; Gardini et al., 2009], we predicted that poorer integrity of WM interconnecting striatum and PFC would correlate with greater scores on BAS. Though our data showed negative correlations between BAS-Fun scores and WM integrity in the IFOF and ILF, these two fasciculi may not provide direct anatomical connections between PFC and striatum. Furthermore, our data showed positive correlations between BAS-Fun scores and WM integrity in the CR and SLF. Therefore, our data do not support our first prediction, and multiple possibilities exist as to why this might be the case. For example, it is possible that the relationship between GM volumes and integrity of WM is not a linear positive correlation. Future studies should directly test this issue by assessing both GM volumes and WM integrity in the same participants.

On the basis of the previous findings of positive correlations between BIS scores and GM volumes of hippocampus and amygdala [Barros-Loscertales et al., 2006a; Cherbuin et al., 2008], we predicted that better integrity of WM connecting limbic regions would correlate with higher BIS scores. However, our data did not show significant correlations between BIS scores and any DTI

parameters. Furthermore, our data did not show significant correlations between BAS-Reward scores and values of any DTI parameters, even though previous studies reported scores on reward sensitivity negatively correlated with GM values in the striatum and PFC [Barros-Loscertales et al., 2006b; Gardini et al., 2009]. In addition, scores on BAS-Drive did not show significant correlations with values of any DTI parameters. It is currently unclear whether these negative findings reflect truly no relationships between WM integrity and these BIS/BAS measures or are due to methodological issues. The method used in this study analyzed a subset of voxels in the entire WM and employed multiple comparison correction with controlling for family-wise error rate (i.e., FWE-corrected) [Nichols and Holmes, 2002]. The FWE-corrected method may decrease the sensitivity for detecting statistical significance at each voxel. Therefore, the most parsimonious interpretation of our negative findings is that the employed method did not detect significant correlations between scores on these BIS/BAS parameters and values of DTI parameters in this specific sample of HPs.

Limitations and Strengths

The study has several methodological limitations and strengths. The analytic package used to assess WM (TBSS) searches each voxel adjacent to each tract and assigns the local highest value to the skeleton [Smith, 2004; Smith et al., 2006, 2007]. Therefore, TBSS tests only a subset of voxels distributed in the entire WM. Additionally, some of the WM regions identified lie at the border of WM tracts whose function may differ. Therefore, methods with better spatial resolution should be employed in future studies for better localizing significant voxels and implicating specific WM tracts. Study strengths include a large sample size for DTI studies and the use of a whole-brain analytic approach.

CONCLUSIONS

By demonstrating significant correlations between DTI parameters in the CR, SLF, ILF, and IFOF and scores on the BAS-Fun subscale, the present study provides evidence indicating that the integrity of WM in these brain regions may contribute to BAS sensitivity in HPs. This finding expands the existing knowledge of the neural correlates of the BAS acquired from previous fMRI and VBM studies, and lays the groundwork for future investigations of how WM integrity may influence risk-taking and sensation-seeking behaviors in community and clinical samples.

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REFERENCES

Agarwal N, Port JD, Bazzocchi M, Renshaw PF (2010): Update on the use of MR for assessment and diagnosis of psychiatric diseases. Radiology 255:23–41.

Alexander AL, Lee JE, Lazar M, Field AS (2007): Diffusion tensor imaging of the brain. Neurotherapeutics 4:316–329.

Alloy LB, Abramson LY, Urosevic S, Bender RE, Wagner CA (2009): Longitudinal predictors of bipolar spectrum disorders: A behavioral approach system (BAS) perspective. Clin Psychol (New York) 16:206–226.

Assaf Y, Pasternak O (2008): Diffusion tensor imaging (DTI)-based white matter mapping in brain research: A review. J Mol Neurosci 34:51–61.

Barros-Loscertales A, Meseguer V, Sanjuan A, Belloch V, Parcet MA, Torrubia R, Avila C (2006a): Behavioral inhibition system activity is associated with increased amygdala and hippocampal gray matter volume: A voxel-based morphometry study. Neuroimage 33:1011–1015.

Barros-Loscertales A, Meseguer V, Sanjuan A, Belloch V, Parcet MA, Torrubia R, Avila C (2006b): Striatum gray matter reduction in males with an overactive behavioral activation system. Eur J Neurosci 24:2071–2074.

Bhagat YA, Hussain MS, Stobbe RW, Butcher KS, Emery DJ, Shuaib A, Siddiqui MM, Maheshwari P, Al-Hussain F, Beaulieu C (2008): Elevations of diffusion anisotropy are associated with hyper-acute stroke: A serial imaging study. Magn Reson Imaging 26:683–693.

Bijttebier P, Beck I, Claes L, Vandereycken W (2009): Gray's reinforcement sensitivity theory as a framework for research on personality-psychopathology associations. Clin Psychol Rev 29:421–430.

Canli T, Sivers H, Whitfield SL, Gotlib IH, Gabrieli JD (2002): Amygdala response to happy faces as a function of extraversion. Science 296:2191.

Carver CS, White TL (1994): Behavioral inhibition, behavioral activation, and affective responses to impending reward and punishment: The BIS/BAS scales. J Pers Soc Psychol 67:319–333.

Caseras X, Avila C, Torrubia R (2003): The measurement of individual differences in behavioural inhibition and behavioural activation systems: A comparison of personality scales. Pers Indiv Differ 34:999–1013.

Catani M, Jones DK, Donato R, Ffytche DH (2003): Occipito-temporal connections in the human brain. Brain 126:2093–2107.

Cherbuin N, Windsor TD, Anstey KJ, Maller JJ, Meslin C, Sachdev PS (2008): Hippocampal volume is positively associated with behavioural inhibition (BIS) in a large community-based sample of mid-life adults: The PATH through life study. Soc Cogn Affect Neurosci 3:262–269.

Cloninger CR (1987): A systematic method for clinical description and classification of personality variants: A proposal. Arch Gen Psychiatry 44:573.

Colder CR, O'Connor RM (2004): Gray's reinforcement sensitivity model and child psychopathology: Laboratory and questionnaire assessment of the BAS and BIS. J Abnorm Child Psychol 32:435–451.

Concha L, Gross DW, Wheatley BM, Beaulieu C (2006): Diffusion tensor imaging of time-dependent axonal and myelin degradation after corpus callosotomy in epilepsy patients. Neuroimage 32:1090–1099.

Davidson RJ (1992): Anterior cerebral asymmetry and the nature of emotion. Brain Cogn 20:125–151.

Davidson RJ, Irwin W (1999): The functional neuroanatomy of emotion and affective style. Trends Cogn Sci 3:11–21.

Davidson RJ, Ekman P, Saron CD, Senulis JA, Friesen WV (1990): Approach-withdrawal and cerebral asymmetry: Emotional expression and brain physiology. I. J Pers Soc Psychol 58:330–341.

Depue RA, Collins PF (1999): Neurobiology of the structure of personality: Dopamine, facilitation of incentive motivation, and extraversion. Behav Brain Sci 22:491–517; discussion 8–69.

First MB, Spitzer RL, Gibbon M, Williams J (1996): Structured Clinical Interview for DSM-IV Axis I Disorders—Patient Edition (SCID-IP, Version 2.0). New York, NY: Biometrics Research Department, New York State Psychiatric Institute.

First MB, Gibbon M, Spitzer RL, Williams JBW, Benjamin LS (1997): Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II): User's Guide. Washington, DC: American Psychiatric Press.

Fowles DC (1987): Application of a behavioral theory of motivation to the concepts of anxiety and impulsivity. J Res Pers 21:417–435.

Franken IH, Muris P, Georgieva I (2006): Gray's model of personality and addiction. Addict Behav 31:399–403.

Gardini S, Cloninger CR, Venneri A (2009): Individual differences in personality traits reflect structural variance in specific brain regions. Brain Res Bull 79:265–270.

Gray JA (1982): The Neuropsychology of Anxiety: An Enquiry Into the Functions of the Spto-Hippocampal System. New York: Oxford University Press.

Gray JA (1987): The Neuropsychology of Emotion and Personality. In Cognitive Neurochemistry. New York, NY: Oxford University Press. pp171–190.

Gray JA (1990): Brain systems that mediate both emotion and cognition. Cogn Emotion 4:269–288.

Gray JA, McNaughton N (2000): The Neuropsychology of Anxiety, 2nd ed. Oxford: Oxford University Press.

Gray JR, Burgess GC, Schaefer A, Yarkoni T, Larsen RJ, Braver TS (2005): Affective personality differences in neural processing efficiency confirmed using fMRI. Cogn Affect Behav Neurosci 5:182–190.

Gunning-Dixon FM, Brickman AM, Cheng JC, Alexopoulos GS (2009): Aging of cerebral white matter: A review of MRI findings. Int J Geriatr Psychiatry 24:109–117.

Harmon-Jones E (2003): Early Career Award. Clarifying the emotive functions of asymmetrical frontal cortical activity. Psychophysiology 40:838–848.

Harmon-Jones E, Lueck L, Fearn M, Harmon-Jones C (2006): The effect of personal relevance and approach-related action expectation on relative left frontal cortical activity. Psychol Sci 17:434–440.

Heubeck BG, Wilkinson RB, Cologon J (1998): A second look at Carver and White's (1994) BIS/BAS scales. Pers Indiv Differ 25:785–800.

Hundt NE, Nelson-Gray RO, Kimbrel NA, Mitchell JT, Kwapil TR (2007): The interaction of reinforcement sensitivity and life events in the prediction of anhedonic depression and mixed anxiety-depression symptoms. Pers Indiv Differ 43:1001–1012.

Hundt NE, Kimbrel NA, Mitchell JT, Nelson-Gray RO (2008): High BAS, but not low BIS, predicts externalizing symptoms in adults. Pers Indiv Differ 44:565–575.

Jbabdi S, Behrens TE, Smith SM (2010): Crossing fibres in tract-based spatial statistics. Neuroimage 49:249–256.

Johnson SL, Turner RJ, Iwata N (2003): BIS/BAS levels and psychiatric disorder: An epidemiological study. J Psychopathol Behav Assess 25:25–36.

Knyazev GG (2004): Behavioral activation as predictor of substance use: Mediating and moderating role of attitudes and social relationships. Drug Alcohol Depend 75:309–321.

Loxton NJ, Dawe S (2006): Reward and punishment sensitivity in dysfunctional eating and hazardous drinking women: Associations with family risk. Appetite 47:361–371.

Madden DJ, Bennett IJ, Song AW (2009): Cerebral white matter integrity and cognitive aging: Contributions from diffusion tensor imaging. Neuropsychol Rev 19:415–435.

Meda SA, Stevens MC, Potenza MN, Pittman B, Gueorguieva R, Andrews MM, Thomas AD, Muska C, Hylton JL, Pearlson GD (2009): Investigating the behavioral and self-report constructs of impulsivity domains using principal component analysis. Behav Pharmacol 20:390–399.

Miller E, Joseph S, Tudway J (2004): Assessing the component structure of four self-report measures of impulsivity. Pers Indiv Differ 37:349–358.

Moeller FG, Steinberg JL, Lane SD, Buzby M, Swann AC, Hasan KM, Kramer LA, Narayana P (2007): Diffusion tensor imaging in MDMA users and controls: Association with decision making. Am J Drug Alcohol Abuse 33:777–789.

Mori S, Wakana S, Nagae-Poetscher LM, van Zijl PC (2005): MRI Atlas of Human White Matter. Amsterdam: Elsevier.

Mori S, Oishi K, Jiang H, Jiang L, Li X, Akhter K, Hua K, Faria AV, Mahmood A, Woods R, Toga AW, Pike GB, Neto PR, Evans A, Zhang J, Huang H, Miller MI, van Zijl P, Mazziotta J (2008): Stereotaxic white matter atlas based on diffusion tensor imaging in an ICBM template. Neuroimage 40:570–582.

Mori S, Oishi K, Faria AV (2009): White matter atlases based on diffusion tensor imaging. Curr Opin Neurol 22:362–369.

Nichols TE, Holmes AP (2002): Nonparametric permutation tests for functional neuroimaging: a primer with examples. Hum Brain Mapp 15:1–25.

O'Connor RM, Colder CR, Hawk LW Jr (2004): Confirmatory factor analysis of the sensitivity to punishment and sensitivity to reward questionnaire. Pers Indiv Differ 37:985–1002.

Omura K, Todd Constable R, Canli T (2005): Amygdala gray matter concentration is associated with extraversion and neuroticism. Neuroreport 16:1905–1908.

Pierpaoli C, Jezzard P, Basser PJ, Barnett A, Di Chiro G (1996): Diffusion tensor MR imaging of the human brain. Radiology 201:637.

Poythress NG, Skeem JL, Weir J, Lilienfeld SO, Douglas KS, Edens JF, Kennealy PJ (2008): Psychometric properties of Carver and White's (1994) BIS/BAS scales in a large sample of offenders. Pers Indiv Differ 45:732–737.

Quay HC (1993): The psychobiology of undersocialized aggressive conduct disorder: A theoretical perspective. Win-Spr, 1993. Dev Psychopathol 5:165–180.

Reuter M, Stark R, Hennig J, Walter B, Kirsch P, Schienle A, Vaitl D (2004): Personality and emotion: Test of Gray's personality theory by means of an fMRI study. Behav Neurosci 118:462–469.

Ross SR, Millis SR, Bonebright TL, Bailley SE (2002): Confirmatory factor analysis of the behavioral inhibition and activation scales. Pers Indiv Differ 33:861–865.

Schmahmann JD, Pandya DN (2007): The complex history of the fronto-occipital fasciculus. J Hist Neurosci 16:362–377.

Schmahmann JD, Smith EE, Eichler FS, Filley CM (2008): Cerebral white matter: Neuroanatomy, clinical neurology, and neurobehavioral correlates. Ann N Y Acad Sci 1142:266–309.

Shackman AJ, Sarinopoulos I, Maxwell JS, Pizzagalli DA, Lavric A, Davidson RJ (2006): Anxiety selectively disrupts visuospatial working memory. Emotion 6:40–61.

Sexton CE, Mackay CE, Ebmeier KP (2009): A systematic review of diffusion tensor imaging studies in affective disorders. Biol Psychiatry 66:814–823.

Sidaros A, Engberg AW, Sidaros K, Liptrot MG, Herning M, Petersen P, Paulson OB, Jernigan TL, Rostrup E (2008): Diffusion tensor imaging during recovery from severe traumatic brain injury and relation to clinical outcome: A longitudinal study. Brain 131:559–572.

Simon JJ, Walther S, Fiebach CJ, Friederich HC, Stippich C, Weisbrod M, Kaiser S (2010): Neural reward processing is modulated by approach- and avoidance-related personality traits. Neuroimage 49:1868–1874.

Smith SM (2004): Overview of fMRI analysis. Br J Radiol 77: S167–S175.

Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, Bannister PR, De Luca M, Drobnjak I, Flitney DE, Niazy RK, Saunders J, Vickers J, Zhang Y, De Stefano N, Brady JM, Matthews PM (2004): Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage 23(Suppl 1):S208–S219.

Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, Watkins KE, Ciccarelli O, Cader MZ, Matthews PM, Behrens TEJ (2006): Tract-based spatial statistics: Voxelwise analysis of multi-subject diffusion data. Neuroimage 31:1487–1505.

Smith SM, Jenkinson M, Beckmann C, Miller K, Woolrich M (2007): Meaningful design and contrast estimability in FMRI. Neuroimage 34:127–136.

Song SK, Sun SW, Ramsbottom MJ, Chang C, Russell J, Cross AH (2002): Dysmyelination revealed through MRI as increased radial (but unchanged axial) diffusion of water. Neuroimage 17:1429–1436.

Torrubia R, Avila C, Molto J, Caseras X (2001): The sensitivity to punishment and sensitivity to reward questionnaire (SPSRQ) as a measure of Gray's anxiety and impulsivity dimensions. Pers Indiv Differ 31:837–862.

Wheeler-Kingshott CA, Cercignani M (2009): About "axial" and "radial" diffusivities. Magn Reson Med 61:1255–1260.

Woolrich MW, Jbabdi S, Patenaude B, Chappell M, Makni S, Behrens T, Beckmann C, Jenkinson M, Smith SM (2009): Bayesian analysis of neuroimaging data in FSL. Neuroimage 45:S173–S186.

Wozniak JR, Lim KO (2006): Advances in white matter imaging: A review of in vivo magnetic resonance methodologies and their applicability to the study of development and aging. Neurosci Biobehav Rev 30:762–774.

Xu J, DeVito EE, Worhunsky PD, Carroll KM, Rounsaville BJ, Potenza MN (2010): White matter integrity is associated with treatment outcome measures in cocaine dependence. Neuropsychopharmacology 35:1541–1549.