Cerebral Cortex Advance Access published August 31, 2012
Cerebral Cortex
doi:10.1093/cercor/bhs277

Dopamine Asymmetries Predict Orienting Bias in Healthy Individuals

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Pseudoneglect is traditionally viewed as reflecting right hemisphere specialization for processing spatial information, resulting in orienting toward the contralateral, left, hemispace. Recent evidence suggests that healthy individuals differ from each other in both direction and magnitude of orienting bias, and moreover, the bias displayed by a person is consistent across time, suggesting that it may represent a trait of the individual. Animal studies reveal consistent orienting bias within an individual, which reflects asymmetry in dopaminergic brain systems. We measured basal D2-like receptor binding using positron emission tomography and the high-affinity ligand [F-18]fallypride, to test the hypothesis that asymmetry in dopaminergic neurotransmission in healthy humans modulates the orienting bias in humans. As predicted, we found that individual differences in the direction and magnitude of the orienting bias were strongly associated with the pattern of asymmetric binding of dopamine (DA) D2 receptors in the striatum, as well as clusters in the frontal and temporal cortex. These findings show for the first time that orienting bias reflects individual differences in the lateralization of DA systems in the healthy human brain.

Keywords: asymmetry, dopamine, individual differences, PET, spatial attention

Introduction

Asymmetrical activation of the 2 hemispheres has been proposed to determine the direction of orienting attention in space, such that relatively greater activation of 1 hemisphere results in orienting toward the contralateral space (Kinsbourne 1970). This model also suggests that the activation imbalance between the hemispheres reflects hemispheric specialization, and it is therefore expected to show the same directionality across individuals, and vary depending on task demands. Thus, the frequently reported tendency of healthy subjects to show small but consistent leftward deviation in horizontal line bisection (termed "pseudoneglect") is considered an example of a behavioral pattern reflecting right hemisphere specialization for processing spatial information. However, recent evidence (Tomer 2008; Nash et al. 2010) suggests that, contrary to the predominant interpretation of the orienting bias reflected by pseudoneglect as a population trait, under similar task demands there is a large variability in both direction and magnitude of orienting bias, and moreover, the bias displayed by an individual is consistent across time, suggesting that it may represent a trait of the individual (Tomer 2008). This latter conclusion is supported by recent findings (Nash et al. 2010) reporting a significant correlation between an index of orienting bias and asymmetric electroencephalography (EEG) alpha power at rest, a measure that has been shown to be stable over time (Davidson 2004).

Individual differences in the direction and magnitude of orienting asymmetry have also been documented in animals such that individual animals display varying degrees of lateral bias, and this lateral bias is consistent across testing sessions (Zimmerberg et al. 1974; Andrade et al. 2001), supporting the idea that the orienting bias indexes an individual trait. This bias has been shown to reflect asymmetric dopamine (DA) neurotransmission, such that animals habitually orient contralaterally to the striatum with higher DA activity (Glick et al. 1977; Castellano et al. 1989). Thus, DA may modulate the orienting bias. A role for DA in modulating spatial orienting in humans has been suggested by the improvement of hemispatial neglect in patients treated with a DA agonist (Fleet et al. 1987; Geminiani et al. 1998). Clark et al. (1989) reported changes in orienting attention among healthy individuals following pharmacological manipulation of central dopaminergic transmission, further supporting the role of DA in orienting attention. We have recently reported that orienting bias is significantly correlated with spontaneous eye blink rate, an index of striatal dopaminergic activity, thus providing more indirect support for the association between orienting bias and DA neurotransmission (Slagter et al. 2010). However, to our knowledge, the relationship between DA asymmetry and orienting bias has not been examined directly in healthy individuals.

The aim of this study was to test the hypothesis that asymmetry in dopaminergic neurotransmission in healthy humans modulates the orienting bias. Specifically, we examined whether individual differences in the direction and magnitude of orienting bias can be predicted by asymmetric DA signaling. To this end, we measured basal D2-like receptor binding using positron emission tomography (PET) and the high-affinity ligand [F-18]fallypride. Tonic DA levels represent the constant low-level background DA neuron firing which is sufficient to tonically stimulate D2 receptors, and such tonic stimulation modulates a large variety of behavior-related changes in postsynaptic striatal and prefrontal neurons (Schultz 2007). Quantitative variation in baseline tonic DA levels could therefore account for individual differences in DA-related behaviors (Hauber 2010). Therefore, asymmetries in baseline D2 receptor binding may serve as an index of asymmetric tonic DA activity that modulates orienting bias. Mukherjee et al. (2002) reported very small baseline test-retest

variability in D2 receptor binding in striatal and extrastriatal brain regions in healthy volunteers over a period of 4–6 weeks, suggesting that individual differences, to the extent that they exist, are reliable, and, therefore, asymmetries in baseline D2 receptor binding may serve as an index of individual differences in tonic DA asymmetry in healthy humans. Our main prediction was that individual differences in orienting bias in healthy individuals will be associated with asymmetric binding of DA D2 receptors, and in particular with striatal binding asymmetry.

Materials and Methods

Subjects

Fourteen undergraduate students (9 women, age range: 19–29 years, average age: 20.2 ± 2.9 years, all right-handed) took part in this study. Only healthy participants without history of developmental disorders, head trauma, psychiatric disorders, or neurological diseases were included. Potential participants who reported having used psychoactive drugs in the past 5 years were excluded. All participants had normal or corrected-to-normal visual acuity. Subjects were compensated for participation and the study was approved by the institute's ethics committee.

Experimental Design and Procedure

This study was carried out at the Waisman Laboratory for Brain Imaging and Behavior, University of Wisconsin, Madison. Data were collected in 3 sessions, separated by 1–4 weeks: Behavioral data were collected in the first session, PET imaging was conducted in the second session, and a magnetic resonance imaging (MRI) scan for anatomical localization purposes was obtained in a third session.

Orienting Bias

Orienting bias was assessed using the computerized version of the grayscales task, a validated measure of orienting bias in healthy individuals (Nicholls et al. 1999), as described by Tomer (2008) and Slagter et al. (2010). Briefly, this task requires participants to judge which of 2 brightness gradients (grayscales) appears darker overall. Each stimulus pair includes one grayscale shaded from black on the left to white on the right and one grayscale shaded in the reverse direction. The horizontal midlines of the stimuli are aligned with the center of the display screen, and the stimuli are aligned vertically (one above the other) such that choices (top vs. bottom) are orthogonal to the direction of the gradients, reducing the potential influence of response biases. Each pair of stimuli is presented on the screen until a response is made and maximally for 4 s. Following a practice block of 12 trials, a "test" block of 72 trials is presented, in which one stimulus is only slightly darker than the other. Without any notice or break, they then continue to complete a "bias" block of 72 trials in which the grayscales within a pair are identical in overall luminance, but left–right mirror reversed. Participants are asked to align their midlines with the center of the screen, and to press the up or down arrow key to indicate the top or bottom rectangle, respectively. Accuracy of response was stressed as important rather than speed, but participants were told to respond while the stimuli were present on the screen. Responses were categorized as either "left" or "right" according to whether participants selected the rectangle that was dark on its left or right side, respectively. Based on the behavioral data from the "bias" block, an asymmetry index (AI) was calculated for each subject: AI = (number of right responses-number of left responses)/total. The values of this index can vary between −1.0 and +1.0, with negative scores indicating a leftward bias and positive scores indicating a rightward bias.

Imaging Data Acquisition and Analysis

MRI Acquisition

Anatomical brain images were acquired on a 3T GE Signa scanner, which is equipped with high-speed gradients and a whole-head transmit–receive quadrature birdcage head coil (GE Medical Systems). Anatomical scans consisted of a high resolution 3D T_1-weighted inversion recovery fast gradient echo image (inversion time = 600 ms, 256 × 256 in-plane resolution, 240-mm field of view (FOV), 124 × 1.1 mm axial slices) and a T_2-weighted fast spin echo image (256 × 256 in-plane resolution, 240-mm FOV, 81 × 2-mm sagittal slices).

Radiochemical Synthesis

The synthesis of [F-18]fallypride was carried out using previously reported methods (Mukherjee et al. 1995). The final sterile 0.9% saline solution of [F-18]fallypride was produced with radiochemical purity >95% and specific activity of 227 ± 140 GBq/umol.

PET Acquisition

The PET data were acquired using a Siemens HR+ PET scanner in 3D mode (septa retracted). Subjects were asked to abstain from smoking, eating, or drinking coffee for at least 4 h prior to scanning. They were positioned head first, supine with the canthomeatal line parallel to the in-plane field of view. The head rested in the scanner head holder and was held in place by surgical tape placed firmly across the subject's forehead. A 5-min transmission scan was then acquired to correct for the attenuation of the gamma rays within the tissue. The acquisition of the dynamic [F-18]fallypride PET scan was initiated with the injection of radioligand (237 ± 43 MBq). A 150-min dynamic acquisition was acquired, initiating with the 30-s bolus infusion of radiotracer. The time series were binned into 6 1-min frames and 48 3-min frames. Following the acquisition of the PET data, the subject was removed from the PET scanner.

Data Processing

The PET data were reconstructed using a filtered backprojection algorithm with sinogram trimming, axial, and inplane smoothing (4 mm Gaussian filter) to a voxel size of 1.84 × 1.84 × 2.43 mm and corrected for random events, attenuation of annihilation radiation, deadtime, scanner normalization, and scatter radiation. The reconstructed PET time series was then inspected and corrected for head motion during the acquisition of the scan using the SPM2 coregistration (Wellcome Trust Centre for Neuroimaging, http://www.fil.ion.ucl.ac.uk/spm) algorithm based on frame-to-frame coregistration to an early integrated reference image. The cerebellar time–activity curve was extracted from the PET data based on a region of interest drawn on the cerebellar lobes of the early PET data. Parametric images of distribution volume ratios (DVR) were generated using the cerebellar time course to represent the behavior of the radiotracer in brain regions with negligible binding (Mukherjee et al. 2002). The DVR parameter represents an index that is proportional to the concentration of D2/D3 binding sites (B_{max}), given by the relationship: DVR = (B_{max}/K_D) $f_{ND} + 1$ where K_D is the apparent (in vivo) equilibrium dissociation constant, and f_{ND} is the free fraction of radiotracer in the brain tissue (Innis et al. 2007). A multilinear approach was used to generate the DVR estimates using the data starting at 39 min (t^*) until the end of the acquisition (Logan et al. 1996; Ichise et al. 2002). The DVR parametric images were spatially coregistered to the same subject's T_1-weighted MRI images using the FMRIB Software Library (FSL) linear registration tool (Jenkinson and Smith 2001).

In order to compare both DA binding and the relative asymmetry of DA binding across subjects, we used a novel strategy for spatial normalization. T_1-weighted MRI images were manually masked to exclude nonbrain tissues. These "skull-stripped" T_1-weighteted MRI images for each subject were coregistered to the Montreal Neurological Institute (MNI)-152 template packaged with FSL twice, once using the default options and once enforcing a left/right flip during the transformation. The resulting standard space skull-stripped T_1-weigted MRI images were averaged to create single-subject templates in standard space. Small differences in brain asymmetry were

accounted for by performing a nonlinear warp using FSL's nonlinear registration tool (http://www.fmrib.ox.ac.uk/analysis/techrep/tr07ja2/tr07ja2.pdf) to align each subject's flipped and nonflipped standard space skull-stripped T_1-weighted MRI images to their single-subject template. These transformations were then combined with the DVR to T_1-weighted MRI transforms, and applied to the DVR images to create both absolute amount and relative asymmetric DA images. In order to compute a measure of relative asymmetry in binding, DA asymmetric images were created by subtracting the x-flipped template-space images from the nonflipped template-space images. Because differences observed in across subjects analyses might result from individual differences in brain anatomy, rather than true differences in DA binding, we assessed the probability of gray matter at each voxel in each subject's brain. Estimates of gray-matter probability (GMP) were assessed based on the skull-stripped standard-space T_1-weighted MRIs using FSL's automated segmentation tool (Zhang et al. 2001). Similar to the DA asymmetric images, GMP asymmetric images were computed by subtracting the x-flipped GMP images from the nonflipped GMP images. Prior to statistical analyses, all images were blurred using an 8-mm full-width at half-maximum Gaussian filter in order to account for potential across subject differences in anatomy.

Statistical analyses examining the relationship between orienting bias and asymmetry in DA binding in the brain were performed across subjects using Spearman's rank correlations tests (see below). In all analyses, we accounted for individual differences in the probability of gray matter at each voxel in the brain (Oakes et al. 2004). Thus, analyses examining the effect of the grayscales bias AI on the DA asymmetric images were performed while controlling for GMP asymmetry at each voxel of the brain. Only voxels with an average DA binding value of 1.2 or greater (i.e., >1.2 times the binding rate in the cerebellum, the reference area), were included in any analysis.

Our main prediction was that asymmetries in DA binding in the striatum would be predictive of individual differences in orienting bias. To examine this prediction, we correlated individual differences in receptor binding asymmetry with individual differences in the grayscales bias AI, while controlling for GMP at each voxel. To correct for multiple comparisons, we carried out significance testing via a 2-stage permutation testing (Nichols and Holmes 2002). At the first stage (voxel level), gray matter probability was regressed out of D2 receptor binding. Then, subject identity was randomly shuffled, and the Spearman's correlation between the grayscales AI and the residualized binding values was computed again at each voxel. This was repeated 1000 times, generating a distribution of correlation coefficients at each voxel under the null hypothesis of no relationship between grayscales AI and D2-like receptor binding. Statistical Z values were taken as the normalized distance of the real correlation coefficient compared with the null distribution. Voxels with a Z value >2.6 ($P < 0.005$) were retained as being significant at the voxel level. In the second stage (cluster level), Z values were computed based on 1 of the 1000 random permutation iterations, and the statistical map was thresholded again. This time, the number of voxels in the largest suprathreshold cluster was stored. This was repeated 500 times, generating a distribution of maximum cluster sizes under the null hypothesis. The cluster threshold was defined as the standardized distance from the mean of the maximum cluster distribution corresponding to $P < 0.005$ (19 contiguous voxels). To interrogate the relationship between absolute DA binding and grayscales bias AI, the above procedure was repeated with absolute DA binding values instead of DA binding asymmetric values.

Results

Behavior

The pattern of performance on the grayscales task was similar to previously reported findings in larger samples of young healthy individuals (Tomer 2008; Slagter et al. 2010): Although there was a modest leftward bias for the group as a whole (mean AI = −0.16 ± 0.52), variability among subjects was large, and individual AI values ranged from −0.94 to +0.58, with 9 subjects showing leftward bias and 5 showing rightward preference. As may be expected from this variability, despite the overall left bias, the AI of the entire sample did not differ significantly from zero ($t[13] = 1.151$, ns). However, the magnitude of asymmetry, regardless of direction (reflected in the absolute value of the AI) was significantly different from zero (mean ± standard deviation: 0.46 ± 0.25, $t[13] = 6.967$, $P = 0.000$), and the magnitude of asymmetry did not differ between left and right biased subjects (absolute AI: 0.48 ± 0.29 and 0.43 ± 0.15, respectively, $t[12] = 0.403$, ns). There was no difference in AI between males and females ($t[12] = 1.06$, n.s.). Examination of errors made in the "test" condition revealed that subjects tended to err in the direction of their preferred orienting during the "bias" condition such that those with leftward orienting bias made more errors of choosing left when right was the correct response, and the opposite was true for subjects with rightward orienting preference. Mean AI for the errors ([right errors − left errors]/total number of errors) was −0.16 (±0.54), and the correlation between bias AI and error AI was $r[12] = 0.939$, $P = 0.000$, suggesting that the orienting bias of each individual was strong enough to overcome the difference in the physical properties of the stimuli in the "test" block.

Orienting Bias and D2 Receptor Binding Asymmetry

As predicted, examination of the whole brain voxelwise correlation analysis between D2 binding asymmetry and orienting asymmetry revealed clusters in the putamen (*xyz* peak coordinates: −24, −2, 8; $z_{max}[12] = 3.1$, $P < 0.005$), and the caudate (*xyz* peak coordinates: −12,12,−2; $z_{max}[12] = 3.1$, $P < 0.005$), where higher binding in the left relative to the right hemisphere was associated with stronger rightward orienting bias whereas the opposite binding asymmetry was associated with

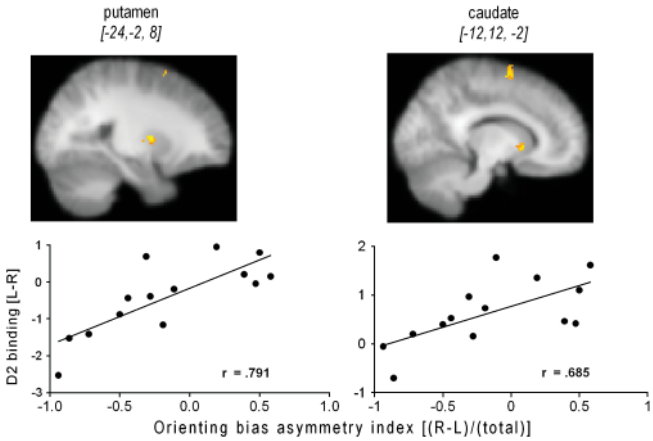

Figure 1. Association between asymmetric D2 receptor binding in the striatum and orienting bias asymmetry index. Positive orienting bias score denotes rightward bias whereas negative bias score indicates leftward bias. Positive D2 binding values indicate relatively higher binding in the left hemisphere, compared with the corresponding cluster in the right hemisphere. Top panel: Clusters (MNI coordinates of peak voxel) in the left hemisphere, where higher D2 binding was associated with rightward orienting bias. Bottom panel: Scatter plots showing the cross-subject correlation between D2 binding asymmetry and orienting bias asymmetry score, separately for the putamen and caudate clusters. Binding asymmetry values are based on the peak voxel within each cluster. For illustrative purposes, the correlation is shown using the nonranked data.

leftward orienting (Putamen: $r[12] = 0.791$, $P = 0.001$; caudate: $r[12] = 0.685$, $P = 0.007$, Fig. 1).

This finding supports the hypothesis that striatal DA asymmetry predicts orienting bias in healthy human subjects. Interestingly, orienting bias was also associated with D2 binding asymmetry in several cortical brain regions (Table 1), which have previously been shown to subserve attentional orienting (Perry and Zeki 2000; Himmelbach et al. 2006). As Figure 2 shows, relatively higher D2 binding in one hemisphere was significantly correlated with contralateral orienting bias (middle frontal gyrus: $r[12] = 0.610$, $P = 0.02$ and middle temporal gyrus: $r[12] = 0.784$, $P = 0.001$). It should be emphasized that orienting AI was not predicted by absolute values of D2 receptor binding in any brain region in either the left or the right hemisphere; rather, it was the relative level of binding in the 2 hemispheres that was associated with the asymmetric orienting.

Discussion

The current study examined the hypothesis that asymmetry in dopaminergic neurotransmission underlies the orienting bias, using PET and the high-affinity radioligand [F-18] fallypride. As predicted, individual differences in the direction and magnitude of the orienting bias were strongly associated with the pattern of asymmetric binding of DA D2 receptors in the striatum, such that orienting was directed contralaterally to the hemisphere with higher D2 receptor binding. Moreover, similar association between binding asymmetry and orienting bias was found for clusters in the frontal and temporal cortex, and significant positive correlations were noted between the measures of direction and magnitude of DA binding asymmetry in the striatal and cortical clusters (Table 2). These findings show for the first time that orienting bias reflects individual differences in the lateralization of DA systems in the healthy human brain.

Tonic stimulation of D2 receptors modulates a large variety of behaviors by affecting postsynaptic striatal and prefrontal neurons (Schultz 2007). An extensive body of literature suggests that DA neurons transmit an alerting signal that triggers orienting reactions (see Bromberg-Martin et al. 2010 for a recent review) and that DA receptor activity in the striatum plays an important role in modulating orienting behavior (Midgley and Tees 1986). Animal studies have repeatedly shown that, following unilateral DA depletion induced by 6-OHDA, rats display neglect of the hemispace contralateral to the lesion (Glick and Shapiro 1985). Marmoset monkeys with unilateral 6-OHDA lesions of nigrostriatal DA projections also exhibit an acute unilateral syndrome, which resembles contralesional spatial neglect resulting from an experimentally induced middle cerebral artery stroke (Milton et al. 2004). Of further relevance, as described in the Introduction, an orienting bias in varying degrees is well documented at the level of the individual in animals with an intact brain, and has been shown to reflect asymmetries in dopaminergic brain circuits (Glick and Shapiro 1985). Research in humans also supports the idea that DA plays an important role in spatial orienting. Thus, orienting bias toward the side of the lesion is common following unilateral brain damage in humans (Heilman et al. 1983), and improvement of neglect behavior has been reported in patients treated with a DA agonist (Fleet et al. 1987; Geminiani et al. 1998). Moreover, Ebersbach et al. (1996) reported that Parkinson's disease patients with greater DA deficit in the right striatum showed a rightward bias in early spontaneous orientation. However, to our knowledge, the current study is the first to show a similar relationship between DA asymmetry and orienting bias in healthy individuals.

Individual orienting bias was predicted by D2-like receptor binding asymmetry in striatal areas and several regions in frontal and temporal cortex. These regions have been previously shown to be part of a neural network of orienting and directed attention, in neuroimaging studies of healthy subjects (Perry and Zeki 2000; Himmelbach et al. 2006; Fairhall et al. 2009; Shulman et al. 2009). The observation that spatial neglect is most often associated with right hemisphere lesions

Table 1
MNI coordinates for clusters showing significant correlations between DRD2 asymmetry and orienting bias scores

Brain region	MNI coordinates			*Z*	Cluster size (mm^3)
	x	*y*	*z*		
Frontal cortex					98
SFG	−10	2	72	3.1	
MFG	−28	10	62	3.0	
Frontal pole	32	60	18	3.4	27
Operculum	−54	−24	18	3.1	41
Middle temporal gyrus	−50	−4	−26	3.1	104
Striatum					72
Putamen	−24	−2	8	3.1	
Caudate	−12	12	−2	3.1	

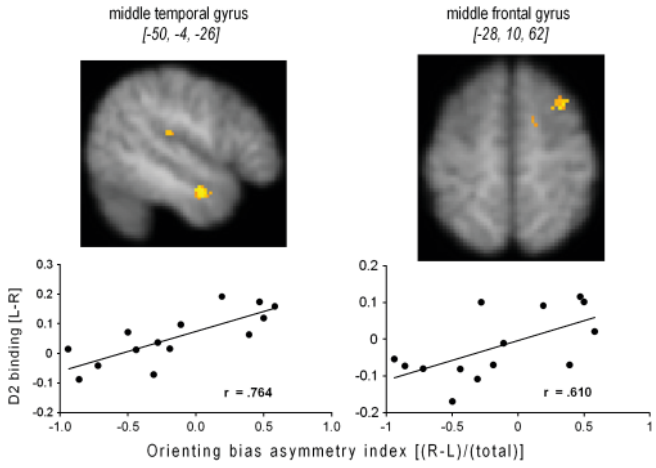

Figure 2. Association between asymmetric D2 binding in frontal and temporal cortical regions, and orienting bias. See Figure 1 for details.

Table 2
Correlations and *P* values between D2 binding asymmetries in the striatal and cortical clusters

Clusters	Putamen	Caudate	Midtemporal	Midfrontal
Putamen		**0.487** *0.039*	**0.531** *0.025*	**0.462** *0.048*
Caudate			**0.697** *0.003*	**0.545** *0.022*
Midtemporal				**0.662** *0.005*
Midfrontal				

Bold numbers indicate *r* values; significance level (*P* values) are in italics.

(Adair and Barrett 2008) is often interpreted as suggesting that the neural network for orienting and alerting is strongly lateralized to the right. According to this model, all healthy individuals should display a leftward orienting bias. However, in the current study we observed large individual differences in the direction of orienting bias, suggesting that orienting preference reflects individual differences in asymmetric hemispheric activity rather than consistent population lateralization. Corbetta and Shulman (2011) have recently argued that the brain regions controlling spatial attention are largely symmetrically organized with each hemisphere predominantly representing the contralateral side of space, and the lateralized impairment seen in neglect patients results from impaired arousal, a right lateralized nonspatial function. This is in agreement with Kinsbourne's model (Kinsbourne 1970) which suggests that attentional bias reflects asymmetrical activation of the 2 hemispheres. Nash et al. (2010) have recently reported that a behavioral measure of attentional bias in healthy individuals was significantly associated with asymmetric alpha EEG power, an index of activation level, further supporting the idea that the orienting bias which characterizes an individual results from asymmetric baseline activation of the 2 hemispheres. Reliable individual differences in resting measures of asymmetrical frontal EEG activity are well established, suggesting that frontal EEG asymmetry may be regarded as a trait of an individual (Davidson 2004). The developmental origins of frontal EEG asymmetry are not well understood. However, Trevarthen (1996) proposed that the development of cortical asymmetries is regulated by input from asymmetric subcortical neurochemical systems that regulate motor initiatives, exploration, and attention. The significant correlations between asymmetric DA signaling and orienting bias observed in the current study, are consistent with Trevarthen's model.

Our findings suggest that asymmetric activity of tonic DA in healthy humans contributes to asymmetric activation of the 2 hemispheres, resulting in orienting bias. Haber and Knutson (2010) described nigrocortical DA projections to the frontal, temporal, and parietal cortex, in addition to the massive DA projections to the striatum, and a large-scale PET study conducted by Ito et al. (2008) recently documented D2 receptors in the normal human brain in extensive subcortical and cortical brain regions, including the putamen, posterior cingulate, frontal base and frontal convexity, and the lateral temporal cortex. Draganski et al. (2008) provided a detailed analysis of the cortical and subcortical connectivity patterns of human basal ganglia, demonstrating the coexistence of both topographical segregation and a high degree of overlap between projections from specific areas. Thus, the caudate and putamen are connected not only with premotor and motor cortical areas (as suggested by the segregated loops described by Alexander et al. 1986) but also with the dorsolateral and medial prefrontal cortex, providing the anatomical substrate for the modulation of cortical activation by subcortical dopaminergic neurotransmission. Asymmetric tonic firing of midbrain DA neurons may thus result in asymmetric stimulation of D2 receptors in this neural network.

In conclusion, our findings suggest that asymmetries in dopaminergic system contribute to the asymmetric pattern of hemispheric activation. The direction and magnitude of tonic asymmetric DA signaling may represent a trait of the individual, which is behaviorally manifested in orienting bias.

Funding

This work was supported by the National Institute of Mental Health (grant numbers MH43454 and P50-MH084051) and the Fetzer Institute to R.J.D. and core support from P30-HD003352 (M. Seltzer, PI).

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