Hemispheric lateralization of resting-state functional connectivity of the ventral striatum: an exploratory study

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Abstract

Resting-state functional connectivity (rsFC) is widely used to examine cerebral functional organization. The ventral striatum (VS) is critical to motivated behavior, with extant studies suggesting functional hemispheric asymmetry. The current work investigated differences in rsFC between the left (L) and right (R) VS and explored gender differences in the extent of functional lateralization. In 106 adults, we computed a laterality index (fcLI) to query whether a target region shows greater or less connectivity to the L vs R VS. A total of 45 target regions with hemispheric masks were examined from the Automated Anatomic Labeling atlas. One-sample t test was performed to explore significant laterality in the whole sample and in men and women separately. Two-sample t test was performed to examine gender differences in fcLI. At a corrected threshold ($p < 0.05/45 = 0.0011$), the dorsomedial prefrontal cortex (dmPFC) and posterior cingulate cortex (pCC) showed L lateralization and the intraparietal sulcus (IPS) and supramarginal gyrus (SMG) showed R lateralization in VS connectivity. Except for the pCC, these findings were replicated in a different data set ($n = 97$) from the Human Connectome Project. Furthermore, the fcLI of VS—pCC was negatively correlated with a novelty seeking trait in women but not in men. Together, the findings may suggest a more important role of the L VS in linking saliency response to self control and other internally directed processes. Right lateralization of VS connectivity to the SMG and IPS may support attention and action directed to external behavioral contingencies.

Keywords

Ventral striatum; RsFC; Laterality; Hemisphericity; Sex difference

Introduction

There are hemispheric differences in the mesostriatal dopaminergic (DA) system, particularly with respect to the nigrostriatal circuit and its role in motor and spatial behavior (see Molochnikov and Cohen 2014 for a review). For instance, DA agonists elicited greater locomotor hyperactivity when injected into the right than left ventral striatum (VS; Belcheva et al. 1990). Studies also support functional asymmetry in the mesolimbic system. Cortical and hippocampal regulation of DA transmission in the nucleus accumbens appears to be stronger in the left than right hemisphere (Louilot and Le Moal 1994). 6-OHDA lesioning of the right but not left hemispheric mesocortical pathway results in bilateral reduction in DA content and an increase in DA turnover in the striatum (Sullivan and Szechtman 1995). Bilateral lesions of the prefrontal cortex reduced DA content and increased DA turnover only in the right nucleus accumbens (Sullivan and Szechtman 1995). Higher levels of dopamine D1 receptors were reported in the right striatum of female rats (Andersen et al. 2000), as confirmed by a recent study (Murphy and Fryxell 2015).

In humans, theta burst magnetic stimulation of the left but not right hemispheric dorsolateral prefrontal cortex inhibited dopamine release bilaterally in the caudate and unilaterally in the putamen (Ko et al. 2008). Right but not left hemispheric capsulotomy, disrupting cortical-striatal-thalamic circuit functions, has been associated with successful treatment of medication refractory obsessive compulsive disorder (Lippitz et al. 1999), presumably as a result of the modulation of right-hemispheric ventral striatal and amygdalar circuit (Sturm et al. 2003). Although not targeting the VS, other studies provided evidence linking hemispheric organization of the cortical limbic circuit to depression (Downar et al. 2014).

Much work of the VS has focused on its role in reward processing. In particular, numerous studies employed variants of the Monetary Incentive Delay Task to examine how the VS and corticostriatal circuit respond to reward anticipation and prediction. Although the bulk of this work did not distinguish right and left VS responses, a few studies did. For instance, right and left VS each showed a distinct influence of affective control on reward anticipation and prediction error (Staudinger et al. 2009). Gain involved predominantly right VS activation and less activation in major depressive disorder; in contrast, loss involved bilateral VS activation, with left VS activation restored by antidepressants (Stoy et al. 2012). Bilateral VS responded to reward anticipation with slightly greater activation in the left VS during immediate vs delayed reward and, compared to smokers, non-smokers demonstrated greater differences only in the right VS (Luo et al. 2011). Both gain and loss cue elicited greater activation of the right VS activation, in contrast to neutral cue, in control but not in alcoholic participants. Furthermore, right VS activation was negatively correlated with trait impulsivity in alcoholics but not controls (Beck et al. 2009). Reward anticipation elicited bilateral VS activation with ADHD patients showing less activation than controls only in the left VS (Strohle et al. 2008). Together, although it remains unclear how R and L VS differentially influences motivated behavior, these findings suggest potential functional lateralization of the VS and its relevance to a wide range of neuropsychiatric conditions.

We postulate that functional lateralization may be reflected in cerebral connectivity of the VS. Analysis of resting-state fMRI data has proven to be a useful approach to characterizing functional architecture of a brain region. Specifically, low frequency blood oxygenation level dependent (BOLD) signal fluctuations reflect connectivity between functionally related brain regions (Biswal et al. 1995; Fair et al. 2007; Fox and Raichle 2007). Based on correlation in spontaneous BOLD activity, for instance, our recent studies have characterized whole-brain connectivity and the effects of age and medications for many cortical and subcortical areas, including the VS (Farr et al. 2014; Li et al. 2014; Manza et al. 2015; Zhang et al. 2015, 2012; Zhang and Li 2012, 2014). There has also been an accumulating literature to characterize VS rsFC during development (Fareri et al. 2015; Porter et al. 2015) and how VS rsFC is altered in neuropsychiatric illnesses, including depression (Leaver et al. 2015), autism (Rane et al. 2015), Alzheimer's disease (Dennis and Thompson 2014), and Parkinson's disease (Tahmasian et al. 2015).

Here, we examined rsFC of the VS in a cohort of 106 adults, focusing on hemispheric lateralization in cerebral connectivity and gender differences, and attempted to replicate the findings in an independent cohort of 97 adults. Following previous studies, we computed a laterality index (LI) for individual brain regions as identified from the automated anatomical labeling (AAL) atlas (Di et al. 2014; Liu et al. 2009), highlighted those that show a significant lateralization, and examined whether the lateralization in VS connectivity differs between men and women and varies with age and personality traits.

Methods

Data set

Resting-state fMRI scans of 106 healthy controls were obtained on a 3-Tesla Siemens Trio scanner at Yale University (43 men, 19–47 years of age with median = 27, and 63 women, 20–49 years of age with median = 25, and there was no age difference between men and women, $p = 0.1$; one scan per participant; duration: 10 min; TR = 2 s; eye closed). The replication sample comprised the "Beijing_Zang" data set from the Human Connectome Project (18–26 years of age; 31 men; one scan per participant; 8 min, TR = 2 s; eye closed). Individual subjects' images were viewed one by one to ensure that the whole brain was covered. In our data set, 54 subjects were assessed with Cloninger's Tridimensional Personality Questionnaire - Short Form (TPQ-Short). Derived from the 100-item long form of the TPQ (Cloninger 1987), the TPQ-Short demonstrated reliability and validity (Sher et al. 1995). It consists of 44 yes/no questions covering novelty seeking (NS; 13 items), harm avoidance (HA; 22 items) and reward dependence (RD; 9 items). Each personality subscale score was calculated by summing the item scores, reverse scoring where necessary. A higher subscore of each represents a higher level of NS, HA and RD. Because of the role of the VS in reward-related processes, we examined for correlations of lateralization with NS and RD scores across these individuals.

Imaging data processing

Brain imaging data were preprocessed using Statistical Parametric Mapping (SPM 8, Wellcome Department of Imaging Neuroscience, University College London, UK). Images

from the first five TRs at the beginning of each trial were discarded to enable the signal to achieve steady-state equilibrium between RF pulsing and relaxation. Standard image pre-processing was performed. Images of each individual subject were first realigned (motion corrected) and corrected for slice timing. A mean functional image volume was constructed for each subject per run from the realigned image volumes. These mean images were co-registered with the high resolution structural image and then segmented for normalization with affine registration followed by nonlinear transformation (Ashburner and Friston 1999; Friston et al. 1995). The normalization parameters determined for the structure volume were then applied to the corresponding functional image volumes for each subject. Finally, the images were smoothed with a Gaussian kernel of 8 mm at Full Width at Half Maximum.

Additional pre-processing was applied to reduce spurious BOLD variances that were unlikely to reflect neuronal activity (Fair et al. 2007; Fox and Raichle 2007; Fox et al. 2005; Rombouts et al. 2003). The sources of spurious variance were removed through linear regression by including the signal from the ventricular system, white matter, and whole brain, in addition to the six parameters obtained by rigid body head motion correction. First-order derivatives of the whole brain, ventricular and white matter signals were also included in the regression.

Cordes and colleagues suggested that BOLD fluctuations below a frequency of 0.1 Hz contribute to regionally specific BOLD correlations (Cordes et al. 2001). Thus, we applied a temporal bandpass filter (0.009 Hz $< f < 0.08$ Hz) to the time course to obtain low-frequency fluctuations, as in previous studies (Fair et al. 2007; Fox and Raichle 2007; Fox et al. 2005; Lowe et al. 1998).

Head motion

As extensively investigated in Van Dijk et al. (2012), micro head motion (>0.1 mm) is an important source of spurious correlations in resting-state functional connectivity analysis (Van Dijk et al. 2012). Therefore, we applied a "scrubbing" method proposed by Power and colleagues (Power et al. 2012) and successfully applied in previous studies (Power et al. 2012; Smyser et al. 2010; Tomasi and Volkow 2014) to remove time points affected by head motions. Briefly, for every time point t, we computed the frame-wise displacement given by $FD(t) = |d_x(t)| + |d_y(t)| + |d_z(t)| + r|\alpha(t)| + r|\beta(t)| + r|\gamma(t)|$, where (d_x, d_y, d_z) and (α, β, γ) are the translational and rotational movements, respectively, and r (=50 mm) is a constant that approximates the mean distance between center of MNI space and the cortex and transforms rotations into displacements (Power et al. 2012). The second head movement metric was the root mean square variance (DVARS) of the differences in % BOLD intensity $I(t)$ between consecutive time points across brain voxels, computed as follows: $DVARS(t) = \sqrt{\langle |I(t) - I(t-1)|^2 \rangle}$, where the brackets indicate the mean across brain voxels. Finally, to compute each subject's correlation map, we removed every time point that exceeded the head motion limit FD(t) >0.5 mm or DVARS(t) >0.5% (Power et al. 2012; Tomasi and Volkow 2014). On average, 1% of the time points were removed across subjects.

Seed based correlation and group analyses

The left and right VS masks were generated using both cytoarchitectonic and topographical criteria (Fig. 1a; see details in our previous study: Li et al. 2014). The BOLD time courses were averaged spatially over each of the left and right VS seeds. For individual subjects, we computed the correlation coefficient between the averaged time course of each seed region and the time courses of all other brain voxels. To assess and compare the resting-state functional connectivity, we converted these image maps, which were not normally distributed, to z score maps by Fisher's z transform (Berry and Mielke 2000; Jenkins and Watts 1968): $z = 0.5 \log_e[(1 + r)/(1 − r)]$. The Z maps were used in group random effect analyses. We performed one-sample t test each on the Z maps of left and right VS and paired-sample t test comparing the two Z maps.

Functional connectivity laterality index (fcLI)

A few considerations distinguished the computation of functional connectivity laterality index (fcLI) from the laterality index employed conventionally to characterize lateralization of cerebral activations to cognitive challenges: $(L − R)/(L + R)$. First, in the latter, negative connectivity of a brain region to the L (or R) seed cannot be distinguished from positive connectivity to the R (or L) seed in the contribution to laterality. Second, target regions in the same hemisphere of the seed region will always have stronger functional connectivity than their hemispheric counterparts (please see "Results" below). To manage these issues, therefore, we followed previous studies (Di et al. 2014; Liu et al. 2009) to compute the fcLI based on connectivities of paired seed and target regions between the hemispheres. Briefly, the fcLI was computed as follows:

$$fcLI = \frac{(LL−RL)−(RR−LR)}{|LL|+|LR|+|RR|+|RL|}$$

where LL is the functional connectivity between the L seed and L target region; RR is the functional connectivity between the R seed and R target region; RL is the functional connectivity between the R seed and L target region; and LR is the functional connectivity between the L seed and R target region (Fig. 1b). As computed, a positive fcLI indicates left lateralization; i.e., the target region, irrespective of its hemisphericity, is more connected to the L than R seed region. By contrast, a negative fcLI indicates right lateralization. The value of fcLI ranges from −1 (R lateralization) to +1 (L lateralization), with lager value indicating greater lateralization in the connectivity between the seed and target. In the current study, we computed the fcLI with each of the 45 brain regions with both L and R hemispheric masks from the AAL atlas as target regions.

Results

Differences in whole-brain connectivity between right and left VS

Figure 2a, b each shows the whole-brain rsFC of the left and right VS, at $p < 0.05$, corrected for whole-brain voxelwise family-wise error (FWE) of multiple comparisons. In general, the left and right VS each showed greater positive connectivity to cortical and subcortical

regions in the same hemisphere and negative connectivity in the opposite hemisphere. A direct contrast between these maps clearly demonstrated these differences (Fig. 2c).

Therefore, to examine whether the L and R VS shows lateralized cerebral connectivity, one needs to go beyond this intrinsic, "biased" pattern of connectivity. An important question to ask is whether a given brain region is more connected to the L or R VS irrespective of its hemisphericity. To this end, we followed previous studies (Di et al. 2014; Liu et al. 2009) to derive a lateralization index of each of the 45 brain regions with both L and R hemispheric masks from the AAL atlas.

fcLI identified lateralized regional connectivities to the VS

The results showed that, at a corrected threshold ($p < 0.05/45 = 0.0011$), the dorsomedial prefrontal cortex (dmPFC) and the posterior cingulate cortex (pCC) showed L lateralization and the intraparietal sulcus (IPS) and supra-marginal gyrus (SMG) showed R lateralization in VS connectivity (Fig. 3). The following analysis thus focused on these four regions of interest.

So far, the analysis has focused on fcLI as a measure of the lateralization of VS connectivity to the brain regions irrespective of their hemisphericity. For example, the dmPFC "as a whole" is more connected to the L vs R VS. However, the fcLI is computed through VS connectivity to the right- and left-hemispheric dmPFC. It would be of interest to examine whether the lateralization of VS connectivity to dmPFC (and other brain regions) is mediated primarily through greater connectivity of the L VS to L dmPFC and/or less connectivity of the R VS to R dmPFC, etc. To this end, we extracted the connectivity z values for L and R VS to each hemispheric mask for a three-way (L/R VS × L/R target region × gender) ANOVA (Fig. 4). The results showed that, as expected, all regions showed a significant VS × target region interaction (all p's $< 10^{-6}$). However, the three way interactions were not significant for any of the four regions (all p's > 0.26). Thus, we removed the gender factor and conducted a two-way (L/R VS × L/R target region) ANOVA for the 4 target regions of interest. In addition to a significant interaction (all p's $< 10^{-6}$), the results showed a significant main effect for VS hemisphericity for 3 target regions ($p < 0.007$, pCC; $p < 0.000005$, IPS; $p < 0.0005$, SMG) but not for the dmPFC ($p = 0.15$) and a marginally significant main effect of target region hemisphericity for the SMG ($p = 0.05$).

Thus, the lateralization is accounted by a higher connectivity to the hemispheric VS for the pCC, SMG, and IPS. That is, L lateralization of the pCC results from higher connectivity of both L and R target region to the L VS and R lateralization of the IPS and SMG results from higher connectivity of both L and R target region to the R VS. For the SMG, the R lateralization may also result from higher connectivity of the R and L VS to the R SMG.

The effect of age and personality traits on fcLI

We examined whether age influences lateralization of these rsFC, as our earlier work showed age-related changes in cerebral connectivity to the dorsal striatum (Manza et al. 2015). None of these regions demonstrated an fcLI in correlation with age for the entire sample (all p's > 0.27) or when men (all p's > 0.20) and women (all p's > 0.21) were examined separately.

We also examined whether personality traits influence lateralization of these rsFC in a subset of the participants ($n = 54$, 17 males) who were assessed with the Tridimensional Personality Questionnaire (TPQ). We performed 36 correlations—3 TPQ subscores × 3 samples (all, male, female) × 4 regions of interest—and used a p value of 0.0014 (0.05/36) as the threshold of statistical significance. Only the fcLI of pCC appeared to show an overall trend in correlating negatively with novelty seeking ($r = -0.47$, $p = 0.004$).

Findings from the replication sample

In an independent sample of 97 young adults (18–26 years of age; 31 men) scanned under similar conditions, we performed identical analyses to examine the fcLI. The results showed that the dmPFC ($p < 0.0011$, uncorrected) was significantly left-lateralized in VS connectivity, and SMG ($p < 0.006$), and IPL ($p < 0.030$) were significantly right-lateralized in VS connectivity. However, the pCC did not show a significant fcLI ($p = 0.1$).

Results based on different pre-processing approaches

A recently study compared three different pre-processing approaches, where unfiltered spurious variance signals such as head motion estimates are regressed out of time series after voxelwise bandpass filtering (BpReg), with bandpass filtering after regression (RegBp) and simultaneous filtering (Simult), and suggested that the Simult approach is superior (Hallquist et al. 2013). Furthermore, Power et al. (2014) also suggested that motion artifact can influence time points before and after the main component of motion. An additional consideration is the smoothing kernel. Therefore, we reprocessed the data with Simult, 4 mm smoothing kernel, and removal of time points before and after the main component of motion. The results showed that the fcLI findings were largely the same. Under a threshold of $p < 0.05/45 = 0.0011$, SMG and IPL remained significant in lateralization. The pCC ($p = 0.0025$) and dmPFC ($p = 0.0015$) came out slightly short at the threshold.

Discussion

Resting-state functional connectivity (rsFC) of the VS

The patterns of rsFC of the VS are very similar to those shown in earlier reports. For instance, the VS shows positive connectivity to an incentive-based learning and motivation circuit that includes the amygdala, hippocampus, medial prefrontal cortex, and insula, although not every study reported VS connectivity to these structures (Cohen et al. 2009; Delgado et al. 2000; Di Martino et al. 2008; Hare et al. 2008; Knutson et al. 2001, 2005; Leotti and Delgado 2011a, b; Li and Daw 2011; Li et al. 2011; O'Doherty 2004; Wimmer et al. 2012). In contrast, as could be visualized from Fig. 2, the VS exhibited a distributed pattern of negative connectivities with parietal regions commonly associated with spatial and temporal attentional selection and with lateral frontal cortical regions that subserve working memory and cognitive control (Coull et al. 2003; Di Martino et al. 2008; Fernandez-Duque et al. 2000; Lepsien and Nobre 2006; Nobre et al. 2004). These similarities support the general validity of the current findings.

In the below, we discuss the findings in a broad context of functional specialization of the individual brain regions that demonstrated lateralized connectivity to the VS. Note that the

literature specifically on lateralized connectivity of the VS is non-existent. Therefore, our discussion focused on the functions of these individual brain regions to support a role each of the L VS in linking saliency response to self control and other internally directed processes and the R VS in attention and action directed to external behavioral contingencies. Further, in view of the exploratory nature of the study, we referenced widely previous studies of VS connectivity in the context of individual differences and clinical implications.

Hemispheric lateralization of VS rsFC

The dorsomedial prefrontal cortex (dmPFC) is critical to cognitive motor control and the posterior cingulate cortex (pCC) has been implicated in internally directed attention and cognition (Leech and Sharp 2014). In imaging studies, the dmPFC was shown to respond to proactive control, response inhibition, and post-error slowing in the stop signal task (Cai et al. 2014a; Chao et al. 2009; Duann et al. 2009; Hendrick et al. 2010; Hu et al. 2015; Ide and Li 2011). Lesion of the dmPFC in humans led to deficits in control in the presence of response conflicts (Nachev et al. 2007). Direct current stimulation of the pre-supplementary motor area (pre-SMA) facilitated response inhibition (Yu et al. 2015). The pCC is part of the default mode network (DMN). Although the DMN has conventionally been characterized as a "task-negative" network, deactivating to external challenges, it increases activity when attention is internally directed, such as during episodic memory retrieval and planning for the future (Spreng 2012). Thus, the findings of left lateralized VS connectivity to the dmPFC and pCC may suggest a more important role of the L VS in linking saliency response to internally directed processes such as self control.

In contrast, the supramarginal gyrus (SMG) and intra-parietal sulcus (IPS) of the inferior parietal lobule are each part of the ventral and dorsal attention system and positively connected to somatomotor cortical and subcortical structures (Zhang and Li 2014). The SMG responded to sudden onsets in "odd-ball" paradigms across multiple sensory modalities (Huang et al. 2005) and to saccadic eye movements to a visual target (Perry and Zeki 2000), and mediated bottom-up process linking attention to memory retrieval (Burianova et al. 2012; Ciaramelli et al. 2008). A study with concurrent electroencephalography and fMRI highlighted the role of the IPS in biasing task-related visual cortical activation during cued spatial attention (Liu et al. 2014). In task-related regional interaction, cognitive control was associated with increased connectivity of the dorsome-dial prefrontal cortex with the IPS (Harding et al. 2015). Thus, right lateralization of VS connectivity to the inferior parietal cortex may support action priming and externally triggered behavioral contingencies.

Animal studies

Whereas there were no functional connectivity studies, previous work has suggested structural and functional lateralization of the VS in animal models. For instance, nucleus accumbens core volume was larger in the right than left hemisphere across male and female rats (Wong et al. 2016), although findings from humans seemed less than consistent (Ahsan et al. 2007; Mamah et al. 2007; Neto et al. 2008; Tamagaki et al. 2005). Dopamine concentration (Rosen et al. 1984; and Schwarting 2001) and D2 receptor binding with [^{3}H] spiroperidol (Schneider et al. 1982) appeared to be higher on the right mesolimbic striatum

in rats. However, this hemispheric asymmetry may be only true in animals with right paw preference (Budilin et al. 2008; Cabib et al. 1995). VS function is regulated by prefrontal cortical structures. As discussed earlier, 6-OHDA lesioning of the right but not left hemispheric mesocortical pathway results in bilateral reduction in DA content and an increase in DA turnover in the striatum (Sullivan and Szechtman 1995). Bilateral lesions of the prefrontal cortex reduced DA content and increased DA turnover only in the right nucleus accumbens (Sullivan and Szechtman 1995). Another study reported hemispheric effects of prefrontal cortical lesions on VS DA concentration and escape behavior elicited by foot shock (Carlson et al. 1996). Along with these findings, the current results suggest hemispheric asymmetry in subcortical and prefrontal cortical regulation of VS DA and behavior supported by the VS.

Potential clinical implications

Patients with major depressive disorder showed increased VS connectivity to part of the default mode network, including the precuneus and pCC, and electroconvulsive therapy remediated this hyperconnectivity (Leaver et al. 2015). Patients with depression showed reduced activation for wins compared with losses in multiple structures including bilateral VS and the pCC in a monetary reward task (Satterthwaite et al. 2015). Furthermore, rsFC within this network, most notably connectivity strength in the left VS, was also diminished in proportion to depression severity. Hypoconnectivity of the VS to pCC is reported in individuals with high social anhedonia (Wang et al. 2015b) and adolescents with internet addiction disorder (Lin et al. 2015), who frequently showed comorbid depression. VS connectivity to the dmPFC was also implicated in the etiological processes of many neuropsychiatric conditions, including depression (Grimm et al. 2009), anorexia nervosa (Via et al. 2015) and other eating disorders (Dunlop et al. 2015; Val-Laillet et al. 2015) that frequently involve comorbid depression.

In substance use disorders, lateralization of responses to impulsive decision making and drug craving has recently been noted in a meta-analysis (Gordon 2016). Prefrontal regulation of VS activity is implicated in control of craving in cigarette smokers (Kober et al. 2010). Abstinence from smoking was associated with reduced functional connectivity between the left VS and superior frontal gyrus in cigarette smokers (Sweitzer et al. 2016). The right anterior insula plays an important role in monitoring and integrating environmental stimuli (Cai et al. 2014b; Chen et al. 2015). In a study of the effects of a distractor on attention, high vs low reward distractors activated the anterior insula and this effect could be predicted by the changes in functional connectivity between the anterior insula and VS (Wang et al. 2015a). Nicotine-addicted individuals demonstrated decreased urges and craving to smoke following unilateral insula damage, with apparently a stronger effect in the right hemisphere (Naqvi et al. 2007). In another study, cocaine addicts demonstrated increased anticorrelations (more negative rsFC in addicts than in controls) between right VS and pCC, as well as between right VS and IPS (Wilcox et al. 2011). In cocaine addicts methylphenidate reduced connectivity of the right VS with the IPS extending to the angular gyrus and precuneus (Konova et al. 2013). Duration of prescription opioid dependence positively correlated with the functional connectivity between VS and mPFC (Upadhyay et

al. 2010). Overall, these studies suggest the clinical relevance in delineating lateralization of VS connectivity, which is widely implicated in mood disorders and addiction.

The rsFC between the dmPFC and VS was also associated with personality traits such as rejection sensitivity (Powers et al. 2013) and negative urgency (Muhlert and Lawrence 2015). "Type A" behavioral pattern, characterized by competitiveness and hostility, time urgency and impatience, is associated with greater rsFC between the left VS and the left ventromedial prefrontal cortex (Wang et al. 2014). VS-dmPFC connectivity was negatively correlated with impulsivity in individuals with antisocial personality disorder (Kolla et al. 2016). Together, these studies suggest the importance in differentiating hemispheric functional asymmetry in understanding cerebral function and dysfunction (Nielsen et al. 2013).

Conclusions and limitations

The focus of the study is on the ventral striatum (VS) and the lateralization of VS cerebral connectivity. The results showed a predominant pattern of right- and left-hemispheric lateralization each for externally and internally directed processes. These results are to be considered with the hypothesis of prefrontal lateralization of cognitive and affective processing, where right- and left-hemispheric activities are often linked to pleasant stimuli/ approach behavior and unpleasant stimuli/avoidance behavior (Miller et al. 2013; Spielberg et al. 2013). However, our data set do not contain behavioral measures and more research is needed to further explore this hypothesis. Further, because of the exploratory nature of the work, we did not formulate specific hypotheses to test against the datasets. The findings from the current work, however, raised the question whether right- and left-lateralization of rsFC each for externally and internally directed processes would extend to other seed regions. An additional limitation concerns non-replication for VS lateralization in connectivity with the pCC. This issue requires further investigation in a larger data set.

Acknowledgments

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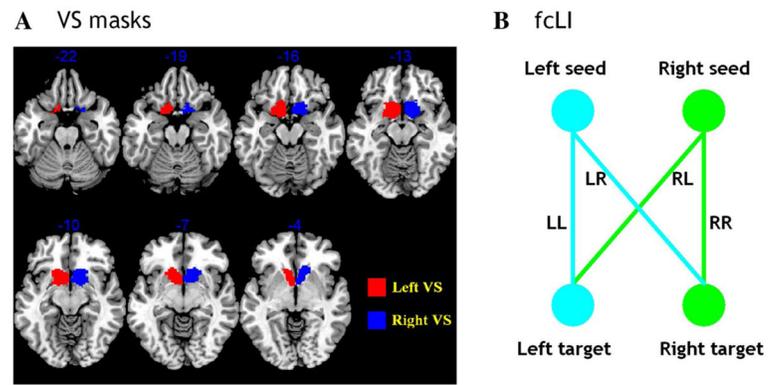
Fig. 1.
a Seed regions: *right* and *left* ventral striatum (VS). **b** A schematic to show how the functional connectivity lateralization index (fcLI) is computed. Please see text for a detailed explanation
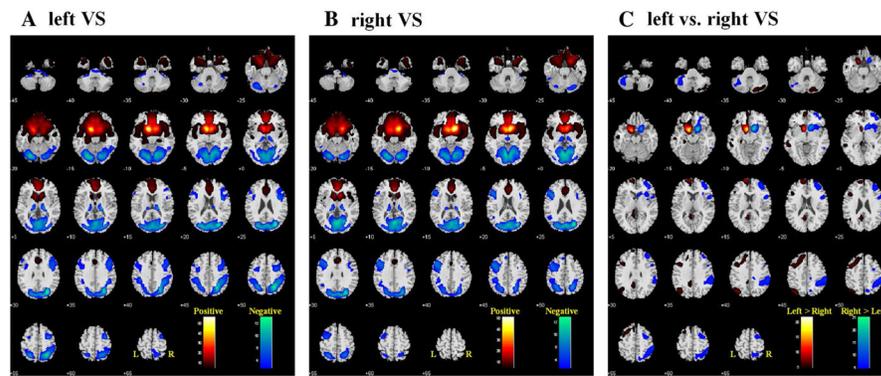
Fig. 2.

Whole brain functional connectivity of the *left* (**a**) and *right* (**b**) ventral striatum (VS), one-sample *t* test, $p < 0.05$, FWE corrected. *Warm color* positive correlation, *cool color* negative correlation. **c** two-sample *t* test: *left* vs *right* VS, $p < 0.05$ FWE corrected. *Warm color* left > right, *cool color* right > left. Neurological orientation: R = right
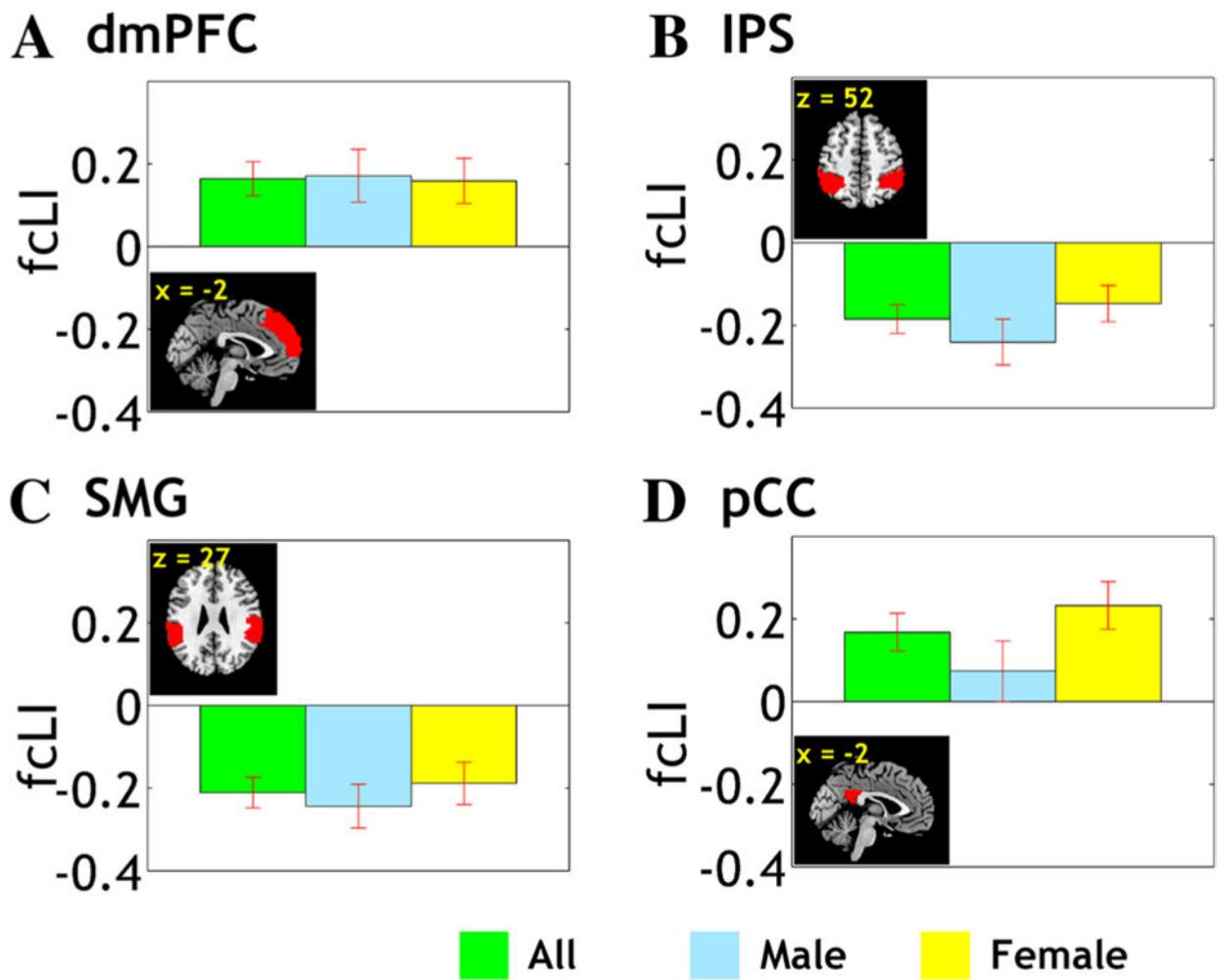
Fig. 3.
fcLI of the dorsomedial prefrontal cortex (dmPFC), intraparietal sulcus (IPS), supramarginal gyrus (SMG), and posterior cingulate cortex (pCC). VS connectivity to the dmPFC and pCC is *left* lateralized (fcLI > 0) whereas connectivity to the IPS and SMG is *right* lateralized (fcLI < 0)
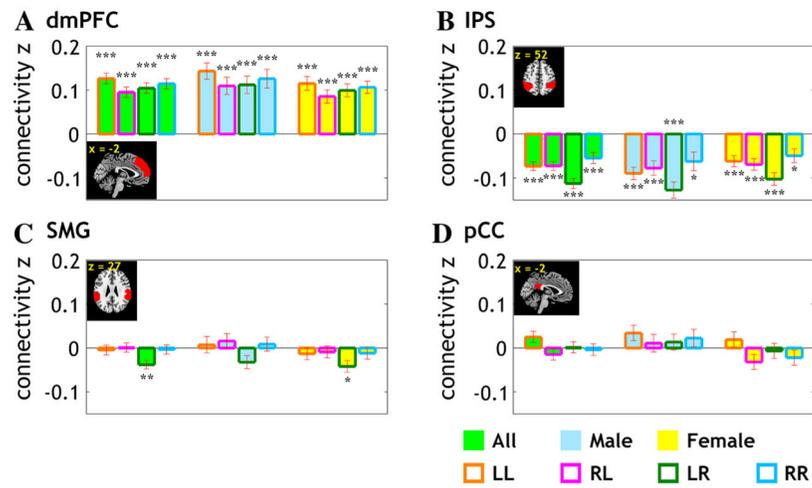
Fig. 4.
Mean ± standard error for the connectivity *z* value for the four target regions that showed a significant lateralization in VS connectivity. The data are broken down according to gender (men vs women), VS (L vs R), and target region (L vs R). Significance of the connectivity were further examined by one-sample *t* test against zero for *z* values and marked with *** for *p* < 0.0001, ** for *p* < 0.001, and * for *p* < 0.01