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Subregions of DLPFC display graded yet distinct structural and functional connectivity

Abbreviated title: structural and functional connectivity of DLPFC

JeYoung JUNG¹, Matthew A. LAMBON RALPH² & Rebecca L. JACKSON²

¹School of Psychology, University of Nottingham, Nottingham NG7 2RD, UK

²MRC Cognition and Brain Sciences Unit, University of Cambridge, Cambridge CB2 7EF, UK

Corresponding authors:

Dr JeYoung Jung

School of Psychology University of Nottingham, University Park, Nottingham
NG7 2RD UK

Tel: +44(0) 115 846 7241

Email: jeyoung.jung@nottingham.ac.uk

Dr Rebecca L. Jackson

MRC Cognition and Brain Science Unit (CBU), University of Cambridge, Cambridge
CB2 7EF UK

Tel: +44 (0) 1223 769 452

Email: rebecca.jackson@mrc-cbu.cam.ac.uk

Conflict of interest

The authors declare no competing financial interests.

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33 **Abstract**

34 The human dorsolateral prefrontal cortex (DLPFC, approximately corresponding to
 35 Brodmann areas 9 and 46) has demonstrable roles in diverse executive functions
 36 such as working memory, cognitive flexibility, planning, inhibition, and abstract
 37 reasoning. However, it remains unclear whether this is the result of one functionally
 38 homogeneous region or whether there are functional subdivisions within the DLPFC.
 39 Here, we divided the DLPFC into seven areas along rostral-caudal and dorsal-
 40 ventral axes anatomically and explored their respective patterns of structural and
 41 functional connectivity. In vivo probabilistic tractography (11 females and 13 males)
 42 and resting-state functional magnetic resonance imaging (57 females and 21 males)
 43 were employed to map out the patterns of connectivity from each DLPFC subregion.
 44 Structural connectivity demonstrated graded intra-regional connectivity within the
 45 DLPFC. The patterns of structural connectivity between the DLPFC subregions and
 46 other cortical areas revealed that the dorsal-rostral subregions were restricted to
 47 connection to other frontal and limbic areas, whereas the ventral-caudal region was
 48 widely connected to frontal, parietal, and limbic cortex. Functional connectivity
 49 analyses demonstrated that subregions of DLPFC were strongly interconnected to
 50 each other. The dorsal subregions were associated with the default mode network
 51 (DMN), while middle dorsal-rostral subregions were linked with the multiple demand
 52 network (MDN), respectively. The ventral-caudal subregion showed increased
 53 functional coupling with both DMN and MDN. Our results suggest that the
 54 connectivity of the DLPFC may be subdivided along a dorsal rostral – ventral caudal
 55 axis with differing (albeit graded) patterns of connectivity reflecting the integrative
 56 executive function of the DLPFC.

57

58 **Keywords**

59 Dorsolateral prefrontal cortex; tractography, resting-state fMRI, structural
 60 connectivity; functional connectivity; executive control

61

62 **Significance Statement**

63 Research has shown that the dorsolateral prefrontal cortex (DLPFC) plays a role in
 64 various executive functions. By dividing the DLPFC into seven areas along rostral-
 65 caudal and dorsal-ventral axes anatomically, we explored their patterns of structural
 66 and functional connectivity. The patterns of connectivity within DLPFC subregions
 67 demonstrated graded intra-regional connectivity. The patterns of connectivity
 68 between the DLPFC subregions and other cortical areas revealed distinctive patterns
 69 of connectivity from dorsal-rostral subregions to ventral-caudal subregions. Divisions
 70 across DLPFC subregions seem to align with their structural and functional
 71 connectivity. Our results suggest that DLPFC may be subdivided by the diagonal
 72 axis of the dorsal-ventral axis and rostral-caudal axis, supporting the framework of a
 73 functional organization along the anterior-posterior axis in the lateral prefrontal cortex.

74 Introduction

75 The dorsolateral prefrontal cortex (DLPFC) approximately corresponds to
 76 Brodmann areas (BA) 9 and 46 and consists of the lateral part of superior frontal
 77 gyrus (SFG) and middle frontal gyrus (MFG) (Brodmann, 1908; Walker, 1940;
 78 Petrides and Pandya, 1999). More recently, Petrides (2005b) designated DLPFC as
 79 BA 9, BA 46, and BA 9/46. Previous anatomical and functional studies have
 80 demonstrated differences in the subparts of lateral prefrontal cortex connectivity
 81 including the DLPFC (For the review, see Petrides, 2005b; Thiebaut de Schotten et
 82 al., 2012; Cieslik et al., 2013). Although the DLPFC can be divided into two or three
 83 subregions cytoarchitectonically, the functional role of each subregion is not clear.

84 DLPFC plays an important role in executive functions, such as working
 85 memory, cognitive flexibility, planning, inhibition, and abstract reasoning (Miller and
 86 Cummings, 2007) and is connected to a variety of brain regions including the
 87 thalamus, basal ganglia, hippocampus, and associative cortex such as posterior
 88 temporal, and parietal areas (Petrides and Pandya, 1984; Morris et al., 1999;
 89 Petrides, 2005b; Yeterian et al., 2012). Anatomical studies have demonstrated that
 90 different areas within the DLPFC receive their input from distinct subparts of the
 91 parietal cortex (Petrides and Pandya, 1984; Thiebaut de Schotten et al., 2012) and
 92 that the functional role of the DLPFC may be partly determined by its anatomical
 93 connections to other brain regions (Morecraft et al., 2004; Hoshi, 2006). Strong
 94 evidence from studies with both human and primates suggests an anterior-posterior
 95 axis of functional organization of the lateral prefrontal cortex (Koechlin et al., 2003;
 96 Petrides, 2005b, a; Thiebaut de Schotten et al., 2012). Lesions in the caudal DLPFC
 97 (BA 46 and 9/46) are associated with a deficit on monitoring of information in working
 98 memory whereas additional caudal lesions to BA6 and 8 impair tasks requiring
 99 selection between alternative choices (Petrides, 1985, 2005a). The rostral mid-lateral
 100 prefrontal regions (BA 10 and 46) play a more abstract role in cognitive control
 101 (Petrides, 2005b; Moayed et al., 2015). In addition to the caudal-rostral axis, there is
 102 a dorsal-ventral axis of organization of the mid-lateral prefrontal cortex (DLPFC: BA
 103 46 and 9/46) (Petrides and Pandya, 1999; Petrides, 2005b). In monkeys, the dorsal
 104 DLPFC (BA9/46d) plays a role in motor planning, multi-tasking, and maintaining
 105 goals whereas the ventral DLPFC (BA9/46v) is preferentially involved in the
 106 visuospatial information of attended signals and cues. These findings suggest a
 107 possibility that some functionally distinct subparts may exist within the DLPFC.

108 Despite the well-documented role of the DLPFC in various executive functions,
 109 it remains unclear whether functional subdivisions are present within the DLPFC.
 110 DLPFC is activated for a range of cognitive demands such as response inhibition,
 111 working memory, and decision making as a key node of the multiple demand
 112 network (MDN) including the inferior frontal gyrus (IFG), frontal eye field, insular, pre-
 113 supplementary motor area (pre-SMA), anterior cingulate cortex (ACC), and
 114 intraparietal sulcus (IPS) (Duncan, 2010). Although numerous fMRI studies report
 115 DLPFC activation, the exact location and extent of activation sites vary according to

tasks used in those studies (Nee et al., 2007; Zheng et al., 2008; Rottschy et al., 2012; Bahlmann et al., 2014; Kohn et al., 2014). One study parcellated the DLPFC using a meta-analysis of task-dependent and task-independent connectivity (Cieslik et al., 2013). They delineated the DLPFC into two regions with different connections: the anterior subregion co-activated with the anterior cingulate cortex (ACC) and the posterior subregion co-activated with the parietal cortex. These findings support functional variation along a rostral-caudal axis in the DLPFC (Petrides, 2005a). In addition, a dorsal-posterior region of DLPFC was associated with the default mode network (DMN), demonstrating functional connections with posterior cingulate cortex, ventromedial prefrontal cortex, and angular gyrus (AG) (Alves et al., 2019). Together, the functional heterogeneity and diversity of anatomical connections in the human DLPFC suggests it may consist of functionally distinct subregions.

Here, we test whether there are connectivity differences across the rostral-caudal and dorsal-ventral axes in the DLPFC that would lead to different functional subregions. We used diffusion weighted imaging (DWI) and resting state fMRI to explore the structural and functional connectivity across the DLPFC in human participants. To improve signal in ventromedial frontal and anterior temporal regions, while maintaining signal across the whole brain, we employed probabilistic tractography of distortion-corrected DWI (Embleton et al., 2010) and seed-based analysis of dual-echo resting state fMRI (Halai et al., 2014). The DLPFC was separated into seven different areas based on the rostral-caudal and dorsal-ventral divisions of the Brodmann regions (BA9, 46, and 9/46) (Petrides, 2005b). For each seed region, we investigated and compared the structural connectivity to sixty-three target regions including left frontal, temporal, parietal, and limbic cortex and the whole brain functional connectivity. We hypothesized that there would be functional subregions of the DLPFC determined by their structural or functional connectivity and that there would be differential patterns of structural and functional connectivity within the DLPFC along the rostral-caudal or dorsal-ventral axis.

Materials and Methods

Subjects and data acquisition

Two different datasets were employed in this study. Dataset 1 included 24 healthy, right-handed subjects (11 females; mean age = 25.9, range 19-47), whereas dataset 2 included 78 healthy right-handed subjects (57 females; mean age = 25.2, range 20-44). Each dataset has been utilized for various investigations: Dataset 1 (Cloutman et al., 2012; Bajada et al., 2016; Bajada et al., 2017; Jung et al., 2017; Jackson et al., 2020). Dataset 2 (Jackson et al., 2016; Jackson et al., 2018; Jung et al., 2018; Jackson et al., 2020). Dataset 1 consisted of distortion-corrected DWI and structural MR imaging. DWI was performed using a pulsed gradient spin echo-planar sequence, with TE = 59ms, TR $\approx$ 11884ms, G = 62 mTm⁻¹, half scan factor = 0.679, 112 x 112 image matrix reconstructed to 128 x 128 using zero padding, reconstructed resolution 1.875 x 1.875 mm, slice thickness 2.1 mm, 60 contiguous

slices, 61 non-collinear diffusion sensitization directions at $b = 1200 \text{ smm}^{-2}$ ($\Delta = 29.8 \text{ ms}$, $\delta = 13.1 \text{ ms}$), 1 at $b = 0$, SENSE acceleration factor = 2.5. Acquisitions were cardiac gated using a peripheral pulse unit positioned over the participants' index finger or an electrocardiograph. For each gradient direction, two separate volumes were obtained with opposite polarity k -space traversal with phase encoding in the left-right/right-left direction to be used in the signal distortion correction procedure (Embleton et al., 2010). A co-localized T2 weighted turbo spin echo scan, with in-plane resolution of $0.94 \times 0.94 \text{ mm}$ and slice thickness 2.1 mm , was obtained as a structural reference scan to provide a qualitative indication of distortion correction accuracy. A high resolution T1-weighted 3D turbo field echo inversion recovery image ($TR \approx 2000 \text{ ms}$, $TE = 3.9 \text{ ms}$, $TI = 1150 \text{ ms}$, flip angle 8° , 256×205 matrix reconstructed to 256×256 , reconstructed resolution $0.938 \times 0.938 \text{ mm}$, slice thickness 0.9 mm , 160 slices, SENSE factor = 2.5) was used.

Dataset 2 included resting-state fMRI and structural MR imaging. To cover the whole brain without signal dropout around the rostral temporal and inferior frontal cortices, a dual-echo fMRI protocol was performed (Poser et al., 2006; Halai et al., 2014). This involves parallel acquisition at a short echo (12ms) leading to less signal loss in areas of high magnetic susceptibility and a standard long echo (35ms) to maintain high contrast sensitivity throughout the brain. The results from the two echoes were combined using linear summation, previously shown to be optimal. The fMRI parameters included 42 slices, 80×80 matrix, $240 \times 240 \times 126 \text{ mm}$ FOV, in-plane resolution 3×3 , slice thickness 4 mm . 130 volumes were collected over 6.25 minutes. T1-weighted structural images were acquired using a 3D MPRAGE pulse sequence with 200 slices, in-planed resolution $0.94 \times 0.94 \text{ mm}$ slice thickness 1.2 mm , $TR = 8.4 \text{ ms}$, $TE = 3.9 \text{ ms}$. During resting-state fMRI, all subjects were instructed to keep their eyes open and look at the fixation cross. Imaging data were acquired on a 3T Philips Achieva scanner (Philips Medical System, Best Netherlands). The study was approved by the local ethics committee and all participants provided written informed consent forms.

Definition of seed regions and target masks

In order to divide the DLPFC (BA 9 and BA46) on the rostral-caudal dimension and to explore differences in DLPFC connectivity, seven anatomically defined regions of interest (ROIs) were defined in the left hemisphere (Fig.1A): two located on BA 9 (anterior: 9a, posterior: 9p), two placed in dorsal-middle frontal gyrus (anterior: 9/46da, posterior: 9/46dp), one was on BA 46 (46), and two placed in ventral-middle frontal gyrus (anterior: 9/46va, posterior: 9/46vp). The seeds regions were identified as a sphere with 6 mm radius in the MNI template brain based on topographic description and defined carefully without overlapping each other. 63 target regions covering frontal, temporal, parietal, and limbic cortex were defined using WFU Pick Atlas (Maldjian et al., 2003) and SPM Anatomy toolbox (Eickhoff et al., 2005). It should be noted that the occipital lobe was not included in this study

because there was no direct white matter pathways connecting the DLPFC and occipital lobe (Petrides and Pandya, 1984; Morris et al., 1999; Petrides, 2005b; Yeterian et al., 2012). The frontal lobe regions included BA 10 (frontal pole: FP), BA 44 (pars opercularis), BA 45 (pars triangularis), BA47 (pars orbitalis), medial orbitofrontal cortex (medOFC), lateral OFC (latOFC), supplementary motor area (SMA), and primary motor cortex (M1). The parietal lobe had 7 regions in superior parietal cortex (SPC: 5L, 5M, 5Ci, 7A, 7PC, 7M, 7P), 3 regions in intraparietal sulcus (IPS: IPS1, IPS2, IPS3), and 7 regions in inferior parietal cortex (IPC: PFop, PFt, PF, PFm, PFcm, PGa, PGp). The temporal lobe had 20 ROIs covering superior temporal gyrus (STG), middle temporal gyrus (MTG), inferior temporal gyrus (ITG), fusiform gyrus (FG), parahippocampal gyrus (PhG) (please, see the detailed location of the temporal ROIs for Jung et al., 2017; Jung et al., 2018). The limbic lobe included insular, amygdala, hippocampus, caudate, putamen, pallidum, thalamus, and 3 regions of cingulate cortex (anterior cingulate cortex; ACC, middle CC; MCC, posterior CC; PCC). The DARTEL (diffeomorphic anatomical registration through an exponentiated lie algebra) toolbox (Ashburner, 2007) was used to transform the seeds and masks from the MNI space into each individual's native diffusion space. The transform was estimated using each subject's T1-weighted image coregistered to their diffusion weighted images. The accuracy of the transformation of ROIs into native space was inspected using the anatomical images. For resting-state functional connectivity analysis, ROIs without DARTEL transformations were used, as analysis was performed in MNI space.

Probabilistic tractography

Unconstrained probabilistic tractography was performed using the PICO software package (Parker and Alexander, 2005), sampling the orientation of probability density functions (PDFs) which was generated using constrained spherical deconvolution (Tournier et al., 2008) and model-based residual bootstrapping (Haroon et al., 2009; Jeurissen et al., 2011). 20,000 Monte Carlo streamlines were initiated from each voxel in the DLPFC seed regions. Step size was set to 0.5 mm. Stopping criteria for the streamlines included terminating if the pathway curvature over a voxel was greater than 180°, or the streamline reached a physical path limit of 500 mm. A single whole-brain probabilistic map was generated for each of the 7 seed ROIs for each participant. Probability maps were masked with each ROI and the maximum connectivity value (ranging from 0 to 20,000) between the seeds and each mask was extracted. The resultant connectivity matrices were subjected to a double threshold to ensure that only connections with high probability in the majority of participants were considered. For the first-level individual threshold, following the approach described by Cloutman et al. (2012), the λ -value of the Poisson distribution identified was used to determine a threshold value at $p = 0.025$. For the second-level group threshold, we used two criteria for consistency (over 75%

of participants, i.e., at least 18/24 participants and over 50% of participants, i.e., at least 12/24 participants).

Resting-state fMRI data analysis

Pre-processing was performed using SPM 8 and the data processing assistant for Resting State fMRI (DPARSF Advanced Edition, V2.3) toolbox. The first two volumes were discarded to allow for magnetic saturation effects. The images were slice-time corrected, realigned, and coregistered to the individual's structural image using SPM 8. Censoring was applied using a threshold of greater than 3mm of translation or 1 degree of rotation, which resulted in the exclusion of 6 participants from further analysis. Within DPARSF nuisance covariates were regressed out and the images were normalised using DARTEL, smoothed with an 8mm full-width half maximum (FWHM) Gaussian kernel. The results were filtered at .01 - .08 Hz. Nuisance covariates were regressed out including 24 motion parameters calculated from the 6 original motion parameters using Volterra expansion (Friston et al., 1996), which was shown to improve motion correction compared to the 6 parameters alone (Yan et al., 2013; Power et al., 2014). Additional covariates were included for outlier time points with a z-score greater than 2.5 from the mean global power or more than 1mm translation as identified using the ARTifact detection Tools software package (ART; www.nitrc.org/projects/artifact_detect). These were entered as covariates with white matter, cerebrospinal fluid (CSF) and global tissue signal. Then, linear detrending was performed. Seed-based functional connectivity analyses were performed using DPARSF. Functional connectivity maps from the seeds were z-score normalised. One sample t-tests were used to detect areas with significant connectivity to the seed regions. The resultant images were thresholded at $p < 0.001$, FWE-corrected at the cluster level. Comparisons between the functional connectivity maps of different seed regions were conducted using paired t-tests.

Similarity analysis

To provide formal spatial inference on the both the comparisons between subregions of DLPFC, we computed similarity of the connectivity patterns of DLPFC subregions. Using the connectivity patterns of DLPFC subregions, we constructed a similarity matrix for the structural and functional connectivity by conducting correlation analyses between each DLPFC subregion's connectivity patterns. In the similarity matrix, the patterns of connectivity between each DLPFC subregion and other brain areas were similar - similarity '1', whereas that of the DLPFC subregions was dissimilar - similarity '0'. Then, we performed one-sample t-test for similarity matrix to determine a significant similarity between DLPFC subregions.

Results

Structural connectivity patterns across the DLPFC

Using probabilistic tractography, the structural connectivity for each DLPFC seed was identified, see Table 1 and Fig. 1. The full pattern of connectivity across the brain may be seen in Fig. 2. There was strong intra-DLPFC connectivity on the dorsal-ventral axis (along the gyri). Additionally, the mid-DLPFC regions (9/46da and 9/46dp) showed the strongest intra-DLPFC connectivity, with connections to more dorsal and ventral areas (Fig. 1B). Across the DLPFC, there was a high level of connectivity with limbic regions, especially the insular and basal ganglia (caudate, putamen, and pallidum) (Fig. 1C). The ventral-caudal seeds (9/46dp, 9/46va, and 9/46vp) showed structural connections with the thalamus. Only 9/46vp had a connection to hippocampus. However, no direct connection was identified between any seed regions and the amygdala. Fig. 1D shows the pattern of connectivity between the DLPFC seed regions and other lateral associative cortices. Most DLPFC seed regions showed strong connectivity with the frontal pole (FP) and inferior frontal gyrus (IFG: BA44 and BA45) but not the most ventral aspects of the prefrontal cortex, including pars orbitalis (BA47) and the OFC. Only the ventral-caudal seeds (9/46va and 9/46vp) had strong evidence of connections to primary and supplementary motor regions. Additionally, only the 9/46vp seed connects to somatosensory and dorsal parietal regions (7PC and IPS). It should be noted that the DLPFC seed regions did not show any connection with the temporal and inferior parietal cortices. Overall, all DLPFC seeds showed strong connectivity with the FP, IFG, and the limbic system. The tractography results suggest a single axis of changing connectivity from ventral-caudal to dorsal-rostral regions, with the key differences being between the most ventral-caudal regions and elsewhere. Specifically, the ventral-caudal seeds (9/46va and 9/46vp) show widespread structural connectivity to frontal, limbic, sensorimotor, and superior parietal cortex.

		9a	9p	9/46da	9/46dp	46	9/46va	9/46vp
DLPFC	9a	100	88	21	8	8	8	0
	9p		100	67	58	33	38	0
	9/46da			100	100	100	67	4
	9/46dp				100	96	96	8
	46					100	96	13
	9/46va						100	75
	9/46vp							100
Frontal lobe	FP	92	96	96	96	96	88	25
	BA44	0	17	4	25	21	88	100
	BA45	17	67	17	63	75	96	92

	latOFC	4	0	0	0	0	0	0
	medOFC	0	0	0	0	0	0	0
	BA47	17	33	8	25	33	38	46
	SMA	0	8	0	17	0	54	79
	M1	0	4	0	13	4	79	96
Temporal lobe	STG	0	4	0	0	0	4	4
	LAT	0	4	0	0	0	4	0
	MED	0	0	0	0	0	0	0
	aSTG	0	0	0	0	0	0	4
	aMTG	0	0	0	0	0	0	0
	aITG	0	0	0	0	0	0	0
	aFG	0	0	0	0	0	0	0
	aPhG	0	0	0	0	0	0	0
	HG	0	0	0	0	0	0	0
	mSTG	0	0	0	0	0	0	4
	mMTG	0	4	0	0	0	0	13
	mITG	0	0	0	0	0	0	0
	mFG	0	0	0	0	0	0	0
	mPHG	0	0	0	0	0	0	0
	pSTG	0	0	0	0	0	4	8
	pMTG	0	0	0	0	0	8	25
	pITG	0	0	0	0	0	4	21
	pFG	0	0	0	0	0	0	0
	LG1	0	0	0	0	0	0	0
	LG2	4	4	4	4	4	0	0
Parietal lobe	S1	0	0	0	0	0	13	63
	5Ci	0	0	0	0	0	0	4
	5M	0	0	0	0	0	0	0
	5L	0	0	0	0	0	0	0
	7PC	0	0	0	0	0	0	50
	7A	0	0	0	0	0	0	4

	7P	0	0	0	0	0	0	0
	7M	0	0	0	0	0	0	0
	IPS1	0	0	0	0	0	0	50
	IPS2	0	0	0	0	0	0	50
	IPS3	0	4	4	4	4	4	33
	PFo	0	0	0	0	0	0	8
	PFt	0	0	0	0	0	0	17
	PF	0	0	0	0	0	0	25
	PFm	0	0	0	0	0	0	17
	PFcm	0	0	0	0	4	0	46
	PGa	0	0	0	0	0	0	25
	PGp	0	0	0	0	0	0	13
Limbic lobe	ACC	4	33	17	33	25	25	0
	MCC	0	0	0	0	0	4	4
	PCC	0	4	0	4	0	4	0
	Insular	92	100	71	96	79	100	92
	caudate	75	92	67	79	79	92	58
	putamen	54	88	46	88	50	92	88
	pallidum	42	83	38	67	42	88	88
	thalamus	17	46	29	54	38	79	75
	amygdala	0	0	0	0	0	0	0
	hippocampus	13	13	4	4	4	29	63

308 Table 1 Structural connectivity results for each DLPFC region. Bold font indicates
 309 that the connection probability was over 50% (12/24) for group analysis.

310 FP = frontal pole; BA = Brodmann's areas; medOFC = medial orbitofrontal cortex;
 311 latOFC= lateral orbitofrontal cortex; SMA=supplementary motor area; M1 = primary
 312 motor cortex; S1 = primary somatosensory cortex; IPS =intraparietal sulcus; 5Ci, 5M,
 313 5L = BA 5 (superior parietal cortex); 7PC, 7A, 7P, 7M = BA 7 (superior parietal
 314 cortex); PFop, PFt, PF, PFcm, PFm = supramarginal gyrus; PGa, PGp = angular
 315 gyrus; STG = superior temporal gyrus; LAT = lateral temporal pole; MED = medial
 316 temporal pole; MTG = middle temporal gyrus; ITG = inferior temporal gyrus; FG =
 317 fusiform gyrus; PhG = parahippocampal gyrus; HG = Heschl's gyrus; LG1 = lingual
 318 gyrus next to fusiform gyrus; LG2 = medial lingual gyrus; ACC = anterior cingulate
 319 cortex; MCC= middle cingulate cortex; PCC = posterior cingulate cortex

320

321 Figure 1. (A) The location of the seven DLPFC areas used as seed regions for the
 322 connectivity analyses. Red arrow indicates the anterior-posterior axis of the lateral
 323 prefrontal cortex. Black arrows represent each axis of the subregions of DLPFC.
 324 Brodmann area: BA; 9a: the anterior seed of BA9; 9p: the posterior seed of BA9;
 325 9/46da: the dorsal-anterior seed of BA9/46; 9/46dp: the dorsal-posterior seed of
 326 BA9/46; 46: BA46, 9/46va: the ventral-anterior seed of BA9/46; 9/46vp: the ventral-

327 posterior seed of BA9/46. (B) Intra-DLPFC structural connectivity. (C) The structural
328 connectivity between DLPFC seed regions and the limbic regions. (D) The structural
329 connectivity between DLPFC seed regions and the frontal and parietal regions. Each
330 DLPFC seed is represented by a circle. Lines connecting ROIs are displayed if the
331 probabilistic tractography exceed the minimum probability threshold in either 50%
332 (thin line) or 75% (thick line) of the participants.

333 FP = frontal pole; medOFC = medial orbitofrontal cortex; latOFC = lateral
334 orbitofrontal cortex; SMA = supplementary motor area; M1 = primary motor cortex;
335 S1 = primary somatosensory cortex; 7PC = BA 7 (superior parietal cortex); IPS =
336 inferior parietal sulcus; PFop, PFt, PF, PFcm, PFm = supramarginal gyrus; PGa =
337 angular gyrus.

338

339

340 Figure 2. Structural connectivity patterns of the DLPFC seed regions.

341 Brodmann area: BA, 9a: the anterior seed of BA9, 9p: the posterior seed of BA9,
342 9/46da: the dorsal-anterior seed of BA9/46, 9/46da: the dorsal-posterior seed of
343 BA9/46, 46: BA46, 9/46va: the ventral-anterior seed of BA9/46, 9/46vp: the ventral-
344 posterior seed of BA9/46.

345

Functional connectivity patterns across the DLPFC

The whole-brain resting-state functional connectivity (rsFC) map of each DLPFC seed region is displayed in Fig. 3. Overall, the seven ROIs showed involvement in two distinct networks with gradedly different rsFC patterns suggesting a transition between these networks. The two BA 9 seeds (9a and 9p) were primarily correlated with the regions of the default mode network (DMN) including medial prefrontal cortex (mPFC), OFC, IPC (particularly angular gyrus), precuneus, PCC, anterior/middle temporal regions, and hippocampus (Raichle et al., 2001; Buckner et al., 2008). All other seed regions were strongly correlated with brain regions of the multiple demand network (MDN) including IFG, SMA, ACC/MCC, SPC, IPS, supramarginal gyrus, and pMTG (Duncan and Owen, 2000; Seeley et al., 2007; Woolgar et al., 2011; Spreng et al., 2013). However, area 9/46vp showed connectivity with both the MDN and the DMN. All DLPFC seed regions were strongly functionally connected to the insular and basal ganglia regions. The results appear to vary along the dorsal-ventral axis such that the dorsal parts of the DLPFC are connected with the DMN, whereas the ventral parts of DLPFC are associated with the MDN. Similar to the structural connectivity results, the most ventral-caudal seed (9/46vp) shows widespread functional connectivity across both of the DMN and MDN.

Figure 3. Functional connectivity patterns of the DLPFC seed regions. Brodmann area: BA, 9a: the anterior seed of BA9, 9p: the posterior seed of BA9, 9/46da: the dorsal-anterior seed of BA9/46, 9/46da: the dorsal-posterior seed of BA9/46, 46: BA46, 9/46va: the ventral-anterior seed of BA9/46, 9/46vp: the ventral-posterior seed of BA9/46.

To quantify the differences in rsFC across the DLPFC and visualise the shifting connectivity across the critical axes, the rsFC maps were compared between pairs of DLPFC seed regions varying along the rostral-caudal axis. Fig. 4 shows the result of comparisons within each gyrus, along the rostral-caudal axis. 9a revealed

stronger rsFC with the insula and IPL than 9p, whereas 9p showed higher rsFC with mPFC, angular gyrus, and precuneus than 9a. 9/46da showed higher rsFC with the IFG, insula, M1/S1, MCC, SPC, IPC, ITG, and visual cortex, yet lower rsFC with IPC, precuneus, PCC, and lateral temporal cortex than 9/46dp. The comparisons between the more rostral and caudal ventral seed regions exhibited prominent differences in similar regions. Relatively rostral regions showed higher rsFC with regions of the MDN including the IFG, SMA, M1/S1, supramarginal gyrus, ACC/MCC and visual cortex, yet lower rsFC with DMN regions, such as the mPFC, OFC, angular gyrus, precuneus, PCC, and lateral temporal cortex, than more caudal regions.

386

387 Figure 4. Comparison of the rsFC along the rostral-caudal axis. Circles indicate the
 388 DLPFC seed regions. Warm colours indicate the comparison from the rostral to the
 389 caudal regions. Cold colours indicate the comparison from the caudal to the rostral
 390 regions. Brodmann area: BA, 9a: the anterior seed of BA9, 9p: the posterior seed of
 391 BA9, 9/46da: the dorsal-anterior seed of BA9/46, 9/46dp: the dorsal-posterior seed
 392 of BA9/46, 46: BA46, 9/46va: the ventral-anterior seed of BA9/46, 9/46vp: the
 393 ventral-posterior seed of BA9/46.

394

395 In order to compute the differences between seed regions along the dorsal-
 396 ventral axis, we combined the each set of seed regions on the rostral-caudal axis.
 397 Fig. 5 shows the result of comparisons along the dorsal-ventral axis. Dorsal regions
 398 (9a and 9p) had significantly higher rsFC with the regions in the DMN and lower
 399 rsFC with the parts of the MDN than the middle regions (9/46da and 9/46dp). The
 400 middle regions showed higher rsFC with the MDN, yet lower rsFC with the DMN than
 401 ventral regions (46, 9/46va, and 9/46vp). The ventral regions had significantly higher
 402 rsFC with the MDN, yet lower rsFC with the DMN than the dorsal regions. Overall,
 403 the dorsal parts of the DLPFC had strong connectivity with the DMN, whereas the
 404 ventral DLPFC regions were strongly connected with the MDN.

405

406

407 Figure 5. Comparison of the rsFC along the dorsal-ventral axis. Circles indicate the
 408 location of the DLPFC seed regions.

409

410 *Structural and functional connectivity profiles of DLPFC seed regions*

411 The connectivity profile of the DLPFC seed regions is displayed in Fig. 6A.
 412 Overall, the seed regions showed more widespread connections to target regions
 413 functionally than structurally (although the structural connectivity of 9/46vp was quite
 414 extensive), with structural connectivity mainly limited to the frontal and limbic cortex.
 415 With a more liberal threshold in structural connectivity (25% of the participants), the
 416 dorsal- caudal seeds (9p and 9/46dp) and the ventral-rostral seed (46) showed a
 417 connection with the ACC and the most ventral-caudal seed (9/46vp) had a

418 connection to the posterior MTG and angular gyrus (PGa) (Fig. 3 & Fig. 6A).
 419 Functional profiles of the DLPFC revealed the distinctive connectivity patterns of the
 420 BA 9 region was strongly coupled with the DMN (medial frontal lobe: latOFC &
 421 medOFC; anterior temporal lobe: STG, LAT, MED, aSTG, & aMTG; angular gyrus:
 422 PGa & PGp) and that of the BA 9/46vp was connected to the DMN (angular gyrus)
 423 as well as MDN (pMTG, pITG, & IPS) (Fig. 6A). The other regions in middle and
 424 ventral DLPFC (BA 9/46da, 9/46dp, 46, and 9/46va) have strong functional
 425 connectivity with region in the MDN.

426 To compare the connectivity patterns of DLPFC regions, we used our ROIs
 427 and computed similarity of connectivity patterns according to each DLPFC region.
 428 The similarity matrix for structural and functional connectivity was constructed by
 429 computing the patterns of similarity (Pearson's correlation) (Fig. 6B). Then, we
 430 compared the similarity matrix between the DLPFC seed regions. The similarity
 431 results of structural connectivity revealed that most DLPFC subregions had similar
 432 patterns of connectivity such that the dorsal regions of DLPFC showed strong
 433 similarity to the ventral-anterior part of DLPFC (9/46va) and neighbouring regions
 434 along the rostral-caudal axis also revealed the very similar patterns of connectivity.
 435 However, 9/46vp did not showed such similarity with 9a, 9/46da, and 46. (Fig. 6C
 436 left). It demonstrated the distinctive patterns of structural connectivity between the
 437 most ventral-caudal region from dorsal-caudal regions (9a, 9/46da, and 46).
 438 Functional similarity of DLPFC subregions showed that (1) neighbouring regions
 439 showed similar patterns of connectivity and (2) the dorsal regions (9a and 9p) did not
 440 have functional similarity with the ventral regions (46 and 9/46va) (Fig. 6C right).
 441 Importantly, the ventral-caudal region showed the similar pattern of functional
 442 connectivity with all other DLPFC subregions, which is supported by its widespread
 443 structural connectivity.

Figure 6. (A) The results of the structural (top) and functional (bottom) connectivity profiles of the DLPFC seed regions. The colour scale of structural connectivity indicates connection probability and that of functional connectivity indicates correlation coefficient. Negative correlations are not shown. (B) Similarity analysis. An example of structural and functional connectivity matrix from 7 DLPFC subregions. We computed the similarity for the patterns of connectivity of the DLPFC subregions. (C) The results of similarity analysis. *** p Bonferroni-corrected < 0.05 ($p < 0.00023$).

453 FP = frontal pole; BA = Brodmann's areas; medOFC = medial orbitofrontal cortex;
 454 latOFC= lateral orbitofrontal cortex; SMA=supplementary motor area; M1 = primary
 455 motor cortex; S1 = primary somatosensory cortex; 5Ci, 5M, 5L = BA 5 (superior
 456 parietal cortex); 7PC, 7A, 7P, 7M = BA 7 (superior parietal cortex); IPS = inferior
 457 parietal sulcus; PPop, PFt, PF, PFcm, PFm = supramarginal gyrus; PGa, PGp =
 458 angular gyrus; STG = superior temporal gyrus; LAT = lateral temporal pole; MED =
 459 medial temporal pole; MTG = middle temporal gyrus; ITG = inferior temporal gyrus;
 460 FG = fusiform gyrus; PhG = parahippocampal gyrus; HG = Heschl's gyrus; LG1 =
 461 lingual gyrus next to fusiform gyrus; LG2 = medial lingual gyrus; ACC = anterior
 462 cingulate cortex; MCC= middle cingulate cortex; PCC = posterior cingulate cortex;
 463 INS = insula; CdN = caudate nucleus; PT = putamen; PL = pallidum; THA =
 464 thalamus; AMG = amygdala; HCP = hippocampus

465

466 Discussion

467 We investigated the patterns of connectivity in subregions of DLPFC along the
 468 rostral-caudal and dorsal-ventral axes. We showed that subregions of DLPFC had
 469 differential structural and functional connectivity. Divisions across DLPFC subregions
 470 seem to align with their structural and functional connectivity. Structural connectivity
 471 analyses demonstrated graded intra-regional connectivity within the DLPFC. The
 472 patterns of connectivity between the DLPFC subregions and other cortical areas
 473 revealed a separation of dorsal-rostral subregions from the most ventral-caudal
 474 subregion. The dorsal-rostral subregions were restricted to link other frontal and
 475 limbic areas, whereas the ventral-caudal region was widely connected to frontal,
 476 temporal, parietal, and limbic cortex. The patterns of functional connectivity revealed
 477 that subregions of DLPFC were strongly interconnected to each other within the
 478 whole frontal cortex and coupled with two functional brain networks: MDN and DMN.
 479 The dorsal subregions were associated with the DMN, while middle dorsal-rostral
 480 subregions were linked with the MDN, respectively. Similar to the results of structural
 481 connectivity, the most ventral-caudal subregion showed increased functional
 482 coupling with both DMN and MDN. Our results suggest that DLPFC may be
 483 subdivided by the diagonal axis of the dorsal-ventral axis and rostral-caudal axis.
 484 Our findings support the framework of a functional organization along the anterior-
 485 posterior axis in the lateral prefrontal cortex (Petrides and Pandya, 1999; Koechlin et
 486 al., 2003).

487 The Cascade model proposes that executive control is implemented across
 488 the lateral prefrontal cortex along a posterior-to-anterior hierarchy, from simple to
 489 more abstract cognitive control processing (Koechlin et al., 2003). For example,
 490 posterior DLPFC supports action selection based on sensory input and anterior
 491 DLPFC provides episodic control for action selection, taking into account the ongoing
 492 context. The frontopolar cortex supports branching control for action selection based
 493 on a holding temporal context. Our structural connectivity results support this
 494 progressive posterior to anterior hierarchy within the DLPFC subregions, showing

highly interconnected subregions within each gyri via short U-fibres, as well as DLPFC connections with the FP, IFG and motor regions via short frontal tracks (Catani et al., 2012; Yeterian et al., 2012). Specifically, the dorsal-rostral subregions connected to the FP via the frontal aslant tract, while the ventral-caudal subregions connect to sensory motor regions through the frontal longitudinal tracts. Similarly, our functional connectivity results demonstrated that subregions of DLPFC had strong coupling with other frontal regions including the FP, IFG, OFC, and motor cortex. The results of the intra-DLPFC connectivity were strong (especially between the neighbouring regions) and graded presumably reflecting local U-shaped fibres with few sharp divisions (9a was not structurally connected with other DLPFC seeds). The graded intra-DLPFC connectivity is consistent with primarily similar local computations, such that the region as a whole has the properties of mass action (Farah and McClelland, 1991). Furthermore, these patterns of connectivity within the DLPFC, along with connection to other frontal areas, suggest there is a graded and integrative organization of the whole frontal lobe (Petrides and Pandya, 1999; Petrides, 2005b).

We observed that the dorsal-rostral subregions (anterior parts of the DLPFC) were linked to the frontopolar regions with increased functional connectivity with the DMN. The frontopolar cortex is a supramodal area involved in various higher order functions such as self-directed thought, rational integration - the simultaneous consideration of multiple relations, and cognitive branching – holding goals while exploring secondary goals, planning, and reasoning (Ramnani and Owen, 2004). With co-activation of the frontopolar cortex, it has reported that the DMN could be activated for self-generated thought (Christoff et al., 2016) or increased cognitive reasoning complexity (Sormaz et al., 2018). These studies support our findings that dorsal-rostral subregions of the DLPFC connected with the FP, were strongly coupled with the DMN. In line with the anterior-posterior gradient in the prefrontal cortex, our connectivity analysis suggests that the anterior parts of the DLPFC would be involved in more challenging cognitive control, such as complex cognitive reasoning and cognitive branching.

In contrast, the middle-ventral subregions (middle-posterior parts) were connected to the IFG (BA 44 and 45) with strong coupling with the MDN and the ventral-caudal region (the most posterior part) had anatomical connections with temporal and parietal areas with increased functional connectivity with both DMN and MDN. Several cortico-cortical association pathways link the prefrontal cortex and other cortical regions (Petrides and Pandya, 1984; Petrides, 2005b; Catani et al., 2012; Thiebaut de Schotten et al., 2012; Yeterian et al., 2012). The superior longitudinal fasciculus (SLF) links the PFC and parietal cortex. SLF has three distinct branches: SLF I connecting the superior frontal area (BA 8, 9, 32) to SPC, SLF II connecting the SFG/MFG to IPS/AG, SLF III connecting IFG to IPS. The arcuate fasciculus (AF) connects the posterior regions of the frontal lobe and temporal lobe (Parker et al., 2005). The inferior fronto-occipital fasciculus (IFOF) connects occipital cortex, temporal areas, ventrolateral frontal cortex and inferior parietal regions

(Schmahmann et al., 2007; Martino et al., 2010). As a part of the MDN, the IFG is involved in cognitive control and language processing (Brass et al., 2005; Camilleri et al., 2018). As the IPS shows anatomical connection with the DLPFC via SLF I/SLF II (Petrides and Pandya, 1984; Petrides, 2005a; Thiebaut de Schotten et al., 2012), the IPS acts as a multifaceted behavioural integrator, binding task-relevant information from the sensory, motor, and cognitive domains, mediated by the top-down control of DLPFC (Gottlieb, 2007). These findings suggest that the middle-posterior parts of the DLPFC would be associated with the core processes of cognitive control, supporting the anterior-to-posterior functional organization of the DLPFC.

In our results, the middle-ventral subregions did not show anatomical connections with the IPS but they were functionally coupled with the MDN. One explanation of this discrepancy is that a weak anatomical connection between two regions may still hold a high functional significance via indirect connections of shared brain regions (Friston, 2002; Damoiseaux and Greicius, 2009). Functional connectivity does not necessarily require direct, physical connections and several studies have reported functional connections between regions without anatomical connectivity (Damoiseaux and Greicius, 2009). Therefore, the functional connectivity without physical connections potentially results from indirect anatomical connections via shared brain areas.

The DLPFC is functionally and structurally connected with subcortical areas including the insular and ACC (Catani et al., 2012; Cieslik et al., 2013). As core areas of the MDN, insular and ACC play a role in cognitively demanding tasks, responding to uncertainty and emotional salience (Seeley et al., 2007; Menon and Uddin, 2010; Camilleri et al., 2018). A meta-analysis study demonstrated strong functional connectivity between DLPFC and insular/ACC (Cieslik et al., 2013). We also showed significant functional connectivity between insular/ACC and the DLPFC. However, our tractography analyses showed structural connections between the DLPFC and insular only, not the ACC. With a lower threshold, we found some evidence of a connection between the DLPFC regions and ACC (25% of participants). In addition, we showed that the corticostriatum projections directly link all DLPFC subregions to the basal ganglia and thalamus (Alexander et al., 1986; Jarbo and Verstynen, 2015). In particular, the anatomical connections between the basal ganglia and DLPFC form a neural circuit involved in several aspects of goal directed behaviours (for a review, see Haber, 2003), which supports a role for the DLPFC in action control (Petrides, 2005b; Cieslik et al., 2013). Furthermore, the extensive connections from the basal ganglia to the cerebral cortex potentially account for the discrepancy between the structural and functional connectivity in the DLPFC subregions.

Although most studies investigating the MDN have focused on the context of goal-directed tasks, it has been shown to play an important role in regulating self-generated thoughts, autobiographical memory, social and emotional information,

which are thought to be associated with the DMN (Spreng and Grady, 2010). In particular, DLPFC may be a key region to play a crucial role in modulating them (Spreng et al., 2018; Turnbull et al., 2019). Emerging evidence suggest that the executive and default network coupling is associated with self-regulation, memory, planning, cognitive control, and creative thinking (Spreng et al., 2010; Andrews-Hanna et al., 2014; Gerlach et al., 2014; Spreng et al., 2014; Beaty et al., 2015). Consistent with these studies, our results demonstrated that DLPFC was coupled with both DMN and MD, showing differential connectivity with subregions of DLPFC. Our findings support the default–executive coupling hypothesis that default and control networks can cooperate to facilitate goal-directed cognition (Andrews-Hanna et al., 2014).

In the current study, we explored the structural and functional connectivity across the subregions of DLPFC using probabilistic tractography and rsfMRI approaches. The key limitations of probabilistic tractography are the issues of distance effect and thresholding (Jones, 2008; Morris et al., 2008). A degree of uncertainty in fibre orientation exists at each step in the propagation of a pathway. This accumulation of uncertainty from voxel to voxel as the streamline is advanced causes a decrease in probability with increasing path length and a progressive dispersion of the streamlines with the distance from the seed (Morris et al., 2008). Therefore, it is difficult to determine a threshold value which will identify true positives while simultaneously minimising the rate of both Type I errors in regions close to the seed and Type II errors in distant regions. Although our procedure most likely produced a conservative cut-off value for longer pathways (Binney et al., 2012; Cloutman et al., 2012), there may be long-range connections left undetected.

Author contribution

J.J: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing - original draft, Writing - review & editing, Visualization.

M.A.L.R: Methodology, Investigation, Writing - review & editing.

R.L.J: Methodology, Writing - original draft, Writing - review & editing.

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