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Lateral Prefrontal Cortex is Organized into Parallel Dorsal and Ventral Streams Along the Rostro-Caudal Axis

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Anatomical connectivity differences between the dorsal and ventral lateral prefrontal cortex (PFC) of the non-human primate strongly suggests that these regions support different functions. However, after years of study, it remains unclear whether these regions are functionally distinct. In contrast, there has been a groundswell of recent studies providing evidence for a rostro-caudal functional organization, along the lateral as well as dorsomedial frontal cortex. Thus, it is not known whether dorsal and ventral regions of lateral PFC form distinct functional networks and how to reconcile any dorso-ventral organization with the medio-lateral and rostro-caudal axes. Here, we used resting-state connectivity data to identify parallel dorsolateral and ventrolateral streams of intrinsic connectivity with the dorsomedial frontal cortex. Moreover, we show that this connectivity follows a rostro-caudal gradient. Our results provide evidence for a novel framework for the intrinsic organization of the frontal cortex that incorporates connections between medio-lateral, dorso-ventral, and rostro-caudal axes.

Keywords: cognitive control, connectivity, dorsolateral, intrinsic, prefrontal cortex, resting state, ventrolateral

Introduction

Cognitive control refers to the ability to flexibly select, maintain, update, or transform information in service of an active goal. The prefrontal cortex (PFC) implements processes critical for cognitive control (Miller and Cohen 2001). Anatomical studies in non-human primates make the distinction between dorsolateral PFC (DLPFC) subregions (BA 9, 46, 9/46) and ventrolateral PFC (VLPFC) subregions (BA 44, 45, 47/12) based on differences in cytoarchitecture and connectivity to the rest of the brain (Petrides and Pandya 1999, 2002). These anatomical differences strongly suggest the presence of functional differences, and there has been an extensive amount of research attempting to elucidate the function of these subregions. Functional neuroimaging, a method that is well suited to reveal fine distinctions in function, has characterized the roles of DLPFC and VLPFC in cognitive control. For instance, studies have revealed that VLPFC subregions demonstrate enhanced activity during various forms of first-order cognitive control processing such as selection, maintenance, and retrieval of goal-relevant information, and both VLPFC and DLPFC demonstrate enhanced activity during second-order cognitive control processes such as manipulation, monitoring, or relational processing of goal-relevant information (D'Esposito et al. 1999; Petrides 2000; Blumenfeld and Ranganath 2006; Amiez and Petrides 2007; Hampshire et al. 2007; Blumenfeld et al. 2011; for review, see Blumenfeld and Ranganath 2007). However, studies rarely find evidence for a complete dissociation of function, and often, results are complicated by task difficulty confounds. Thus, after more than 15 years of neuroimaging studies of the frontal lobes, the functional organization of the dorso-ventral axis of PFC still remains underspecified.

In contrast, a groundswell of recent functional magnetic resonance imaging (fMRI) studies has found evidence for rostro-caudal gradients of function in regions of the lateral frontal cortex. For instance, Koechlin et al. (1999, 2003), Koechlin and Hyafil (2007), Badre and D'Esposito (2007), and Badre et al. (2009) found that within dorsal regions of the lateral frontal cortex, progressively more rostral regions implement control at progressively higher levels of abstraction. There is further evidence that a rostro-caudal functional organization may exist in ventral frontal regions as well (Poldrack et al. 1999; Badre et al. 2005). For example, Race et al. (2009) find that priming of progressively more abstract item features leads to repetition suppression of progressively more rostral areas of ventral frontal cortex.

Evidence has emerged that a rostro-caudal organization may also exist across dorsomedial frontal cortex. Studies by Kouneiher et al. (2009) and Venkatraman et al. (2009) find that progressively more rostral regions of dorsomedial frontal cortex, from pre-supplementary motor area (pre-SMA) to an anterior aspect of the superior frontal gyrus, implement motivational processes or resolve uncertainty at progressively higher levels of abstraction. Moreover, studies have demonstrated point-to-point functional connectivity between the dorsomedial and lateral rostro-caudal gradients (Kouneiher et al. 2009; Taren et al. 2011). This finding provides strong evidence for dorsomedial and dorsolateral frontal rostro-caudal gradients, which may interact in a rostral-to-caudal fashion.

The observation that a rostro-caudal organization may exist either in dorsal or in ventral lateral frontal cortex provides some, albeit indirect, evidence for a dorso-ventral PFC organization. Our hypothesis is that dorsolateral and ventrolateral PFC subregions form parallel rostro-caudally organized networks and that these networks are functionally connected to the dorsomedial frontal cortex in a rostral-to-caudal manner. Thus, the aim of this study is to test an anatomical framework in which the frontal cortex is composed of parallel dorsolateral, ventrolateral, and dorsomedial rostro-caudal processing networks. We devised a novel multistep method for testing our hypothesis that is based on functional connectivity in resting-state fMRI data. Results from such data are consistent with findings from anatomical tracer studies (Young et al. 2003; Greicius et al. 2009; Margulies et al. 2009; van den Heuvel et al. 2009; Kelly et al. 2010; Hutchison et al. 2011) and have been shown to reflect, in large part, neuroanatomical structure. Resting connectivity methods have been

particularly useful in elucidating the anatomical organization of frontal networks (Dosenbach et al. 2007; Vincent et al. 2008; Margulies et al. 2009; Kelly et al. 2010; Meunier et al. 2010) and the methods employed here bear important similarities to tract-tracer methods, in that they are unbiased, data driven with built-in replication steps.

Materials and Methods

Participants

Forty-four participants were enrolled in this experiment (26 females, mean age 22 ± 2.2). Participants gave informed consent and were paid for their participation. The data from 24 participants were used in the map-wise analysis, and all other analyses were carried out on the remaining 20 participants' data.

Scanning Protocol

Magnetic resonance images were collected on a whole-body 3 T Siemens MAGNETOM Trio scanner using a 12-channel head coil. High-resolution structural images were acquired using an axial MP-RAGE 3D T_1-weighted sequence (repetition time [TR] = 2000 ms, echo time [TE] = 2.98 ms, 1 × 1 × 1 mm voxels). T_2-weighted echo planar images (EPI) were acquired in an axial orientation (TR = 1370 ms, TE = 26 ms, 24, 3.85-mm thick slices). Five minutes of EPI data was analyzed (219 time points). During EPI scanning, participants were instructed to stay awake with their eyes open.

Preprocessing

Image preprocessing was performed using AFNI (Cox 1996). EPI data were slice-time corrected and non-brain structures were masked out. Spatial smoothing using a 6-mm Gaussian kernel was applied to the EPI data. Signal from movement parameters, white matter, and ventricles were considered nuisance variables and regressed out (Fox et al. 2005). The high-resolution structural image was coregistered to the mean functional image, and for the construction of nuisance masks, the high-resolution image was segmented using SPM5 (Wellcome Department of Cognitive Neurology, London, United Kingdom). The template used for segmentation was derived from 152 normal subjects (MNI152 atlas, Montreal Neurological Institute, Montreal, Quebec, Canada). Segmentation produced transformation parameters to the MNI152 template and from the MNI152 template to native space for each subject. Functional connectivity analyses were performed in the native space. Regions of interest (ROIs) derived from normalized data were reverse-normalized into native space. In addition, although functional connectivity statistical maps were computed in native space, the results were normalized for the construction and visualization of the group statistical map.

Map-Wise Analysis

This analysis, performed with 24 participants, examined functional connectivity between ROIs arranged along the rostro-caudal axis of dorsomedial frontal cortex and lateral PFC. Five dorsomedial frontal cortex ROIs (DM1–5), as defined by Taren et al. (2011), were delineated in normalized space (3 mm spheres; for coordinates, see Table 1a) and reverse-normalized into native space. For each ROI, voxel time-series were averaged and bandpass filtered (0.009–0.08 Hz) to remove physiological noise. For each participant and for each DM ROI, functional connectivity was assessed by correlating the average time-series from the DM ROI with time-series from individual voxels within the entire lateral frontal cortex; however, we were most interested in voxels along lateral PFC (voxels inspected to be rostral to the precentral sulcus). The resultant statistical maps were Fisher transformed and spatially normalized. The Fisher z-transformation increases the normality of cross-correlations and is commonly applied in resting fMRI correlational datasets (He et al. 2007; Van Dijk et al. 2010). Group statistical maps were created for each DM ROI. These 5 group maps were thresholded at a Fisher value of 0.50. This group threshold was based on the minimum value necessary to produce at least one center of mass in VLPFC and one in DLPFC for all of the map-wise tests (DM1–5).

Unlike standard map-wise analyses that are aimed at detecting "if" there are super-threshold voxels (and therefore must stringently protect against Type I error), our analyses were designed to identify ROIs that could subsequently be utilized for ROI-to-ROI connectivity analyses. With these analyses, lower statistical thresholds, if anything, will lead to a bias against finding a discernable rostro-caudal pattern of connectivity because lowering thresholds will increase the potential for including "noisy" voxels in the ROI or increase the overlap between the centers of mass. We used the minimum threshold possible to detect 5 dorsolateral and 5 ventrolateral frontal clusters, and thus, this analysis presents a strict test of our hypothesis. For each group map (i.e. DM1–5), multiple clusters were present on the lateral surface. We labeled each cluster for each DM seed as either dorsocaudal/pre-motor cortex, DLPFC, VLPFC, or parietal. Each DM seed yielded only one DLPFC and one VLPFC cluster. The (x,y,z)

Table 1
Regions of interest

	x	*y*	*z*	
(a) DM ROIs				
DM1	−4	10	50	Superior frontal gyrus, medial segment/cingulate sulcus (BA 6, 32)
DM2	−4	16	45	Superior frontal gyrus, medial segment/cingulate sulcus (BA 8)
DM3	−6	23	39	Superior frontal gyrus, medial segment/cingulate sulcus (BA 8)
DM4	−4	30	37	Superior frontal gyrus, medial segment/cingulate sulcus (BA 8)
DM5	−6	35	34	Superior frontal gyrus, medial segment/cingulate sulcus (BA 9, 32)
(b) Lateral ROIs defined by resting-state correlations				
DL1	−34	42	30	Middle frontal gyrus (BA 46)
DL2	−34	47	27	Middle frontal gyrus (BA 46)
DL3	−32	52	22	Middle frontal gyrus (BA 46)
DL4	−32	56	13	Middle frontal gyrus (BA 46/10)
DL5	−30	59	9	Middle frontal gyrus (BA 46/10)
VL1	−45	13	2	Inferior frontal gyrus, pars opercularis/triangularis (BA 44/45)
VL2	−43	15	1	Inferior frontal gyrus, pars triangularis/insula (BA 45)
VL3	−41	19	0	Inferior frontal gyrus, pars triangularis (BA 45)
VL4	−41	22	−6	Inferior frontal gyrus, pars orbitalis/insula (BA 47/12)
VL5	−46	27	−11	Inferior frontal gyrus, pars orbitalis (BA 47/12)
(c) VLa ROIs defined by a cognitive control task				
VLa1	−39	0	39	Precentral gyrus (~BA 6)
VLa2	−45	15	24	Inferior frontal gyrus, pars opercularis (BA 44)
VLa3	−51	36	12	Inferior frontal gyrus, pars triangularis (BA 45)
VLa4	−42	33	−3	Inferior frontal gyrus, pars orbitalis (BA 47/12)

coordinates from all suprathreshold DLPFC and VLPFC centers-of-mass were noted.

Replication and Testing for Rostro-Caudal Organization

An independent dataset ($n = 20$) with a different sample of participants was used for this set of analyses. The aims of these analyses were to 1) replicate map-wise results in an independent sample and 2) quantitatively test for the rostro-caudal organization of the dorsolateral and ventrolateral connectivity to dorsomedial PFC.

Region of Interest Analyses

To address the first aim, we correlated the resting-state functional connectivity between the DM ROIs (DM1–5) previously used and a set of lateral PFC ROIs constructed based on the center-of-mass of lateral PFC regions implicated in the first map-wise analysis. Specifically, normalized ROIs (3 mm^3) centered around the 5 DLPFC (DL1–5) centers-of-mass and the 5 VLPFC (VL1–5) centers-of-mass defined in the map-wise analysis were constructed. For each participant and for each ROI, a mean time-series was constructed by averaging across voxels in each ROI. These mean time-series were used to perform 3 separate ROI-to-ROI correlation analyses. In the first analysis, we computed the correlations between every DLPFC and DM ROI (i.e. 25 correlations computed); in the second analysis, we correlated time-series of every VLPFC and DM ROIs; and in the third analysis, we correlated time-series of DLPFC and VLPFC ROIs. The resulting correlation values were Fisher transformed.

Regression Analyses

We employed 2 ordinary least squares (OLS; Jones et al. 2001; http://www.scipy.org/Cookbook/OLS) regression analyses to examine the rostro-caudal organization of the DLPFC and VLPFC connectivity to dorsomedial frontal cortex. For the first regression analysis, examining DLPFC to dorsomedial frontal cortex connectivity, the correlation between each DLPFC and each DM ROI for each participant was entered as an observation (i.e. 25 observations for each participant). These correlations were entered into the OLS model as dependent variables. The rostro-caudal position of the DLPFC ROI served as the first independent variable (DL) and the rostro-caudal position of the DM ROI served as the second independent variable (DM). An interaction term (DL × DM) was entered into the model. The interaction tested whether the DLPFC–DM correlation varies as a function of the rostro-caudal positions of both DLPFC and DM ROI. The second OLS regression used a similar procedure to the first regression but instead used VLPFC–DM correlations. The correlation between each VLPFC and each DM region for each participant was entered as an observation of the dependent variable. The rostro-caudal position of the VLPFC ROI was the first independent variable (VL), the rostro-caudal position of the DM ROI was the second independent variable (DM) and an interaction term (VL × DM) was entered.

Testing for Statistically Independent Streams of Connectivity

In this analysis, we performed a set of partial correlation analyses to examine the extent to which these streams of functional connectivity are statistically independent from one another. A partial correlation removes the effect of a third variable from the relationship between 2 variables. In the first analysis, at each rostro-caudal position (1–5), we computed the correlation between the DLPFC and DM ROI after partialling out the time series of the VLPFC ROI at the same rostro-caudal position (e.g. partial out the effect of VL1 from the correlation between DM1 and DL1). Similarly, in the second analysis, at each rostro-caudal position, we computed correlations between DM and VLPFC ROI pairs after partialling out the DLPFC time-series at the same rostro-caudal position. This allowed us to test whether the 2 streams of lateral–medial functional connectivity are statistically independent. A final analysis was performed to test whether DLPFC–VLPFC connectivity would persist after removing the contribution of the dorsomedial frontal cortex. For this analysis, at each rostro-caudal position, we computed correlations between DLPFC and VLPFC ROI pairs after partialling out the DM time-series at the same rostro-caudal position.

Examining Connectivity Between DM and Lateral Frontal Regions Associated with Cognitive Control

To address whether VLPFC regions previously linked with cognitive control functions along the rostro-caudal frontal axis functionally connect to dorsomedial frontal cortex along the rostro-caudal axis, we performed a set of ROI × ROI correlations and a regression analysis. Our methods were similar to those listed above, but instead of using VLPFC ROIs derived from the map-wise analysis, for this analysis, we used 4 ROIs based on coordinates given in a study examining a rostro-caudal gradient in VLPFC (Race et al. 2009; Table 1c). Normalized ROIs (3 mm^3) centered around these 4 VLPFC ROIs (VL1a—4a) were constructed. Similarly, for the regression analysis, an OLS model was constructed and tested in a similar manner to the method used in the main analysis above; however, the time-series from VL1a to VL4a were used.

Results

The aim of this experiment was to test whether there exist separable streams of rostro-caudally organized connectivity between dorsolateral, ventrolateral, and dorsomedial frontal cortex. To this end, we performed several analyses examining resting-state functional connectivity (resting-state time-series correlation; Fox et al. 2005) between the lateral and dorsomedial frontal cortex. In the first set of analyses, we performed map-wise analyses to test whether regions along the rostro-caudal axis of the dorsomedial frontal cortex form intrinsic connections along the rostro-caudal axis of both DLPFC and VLPFC. In the second set of analyses, using an independent dataset, we performed ROI × ROI correlation analyses and regression analyses aimed at replicating our map-wise results and determining whether the functional connectivity between the DLPFC and the dorsomedial frontal cortex or between the VLPFC and the dorsomedial frontal cortex are both organized in a rostro-caudal fashion. In the third set of analyses, also using the independent dataset, we performed a partial correlation analysis aimed at testing whether the dorsolateral-dorsomedial, ventrolateral-dorsomedial, and dorsolateral-ventrolateral frontal streams of functional connectivity are statistically independent and therefore parallel. These 3 sets of analyses tested lateral regions identified solely in a data-driven manner. In the fourth set of analyses, we examined dorsomedial-lateral connectivity using a set of lateral ROIs from a previously published study of cognitive control (Race et al. 2009). This allowed us to test whether lateral regions associated with rostro-caudally organized cognitive control processes also exhibit connectivity with the dorsomedial frontal cortex along a rostro-caudal gradient.

Map-Wise Analysis

In this analysis, we examined functional connectivity between set of 5 ROIs arranged along the rostro-caudal axis in the dorsomedial frontal cortex (DM1–5) that have been implicated in hierarchical executive functions (Kouneiher et al. 2009; Venkatraman et al. 2009; Taren et al. 2011) and voxels within the lateral frontal cortex. For each DM ROI, we thresholded the voxel-wise connectivity maps to the lateral frontal cortex at the Fisher value (z) = 0.50 and extracted a center-of-mass coordinate from each resultant cluster. Thus, 5 correlation maps (one for each DM seed) were constructed. Strikingly, 2 distinct centers of connectivity appeared in each of these 5 maps; one along the middle frontal gyrus in DLPFC and another along the inferior frontal gyrus/anterior insula in VLPFC (Fig. 1*b*).

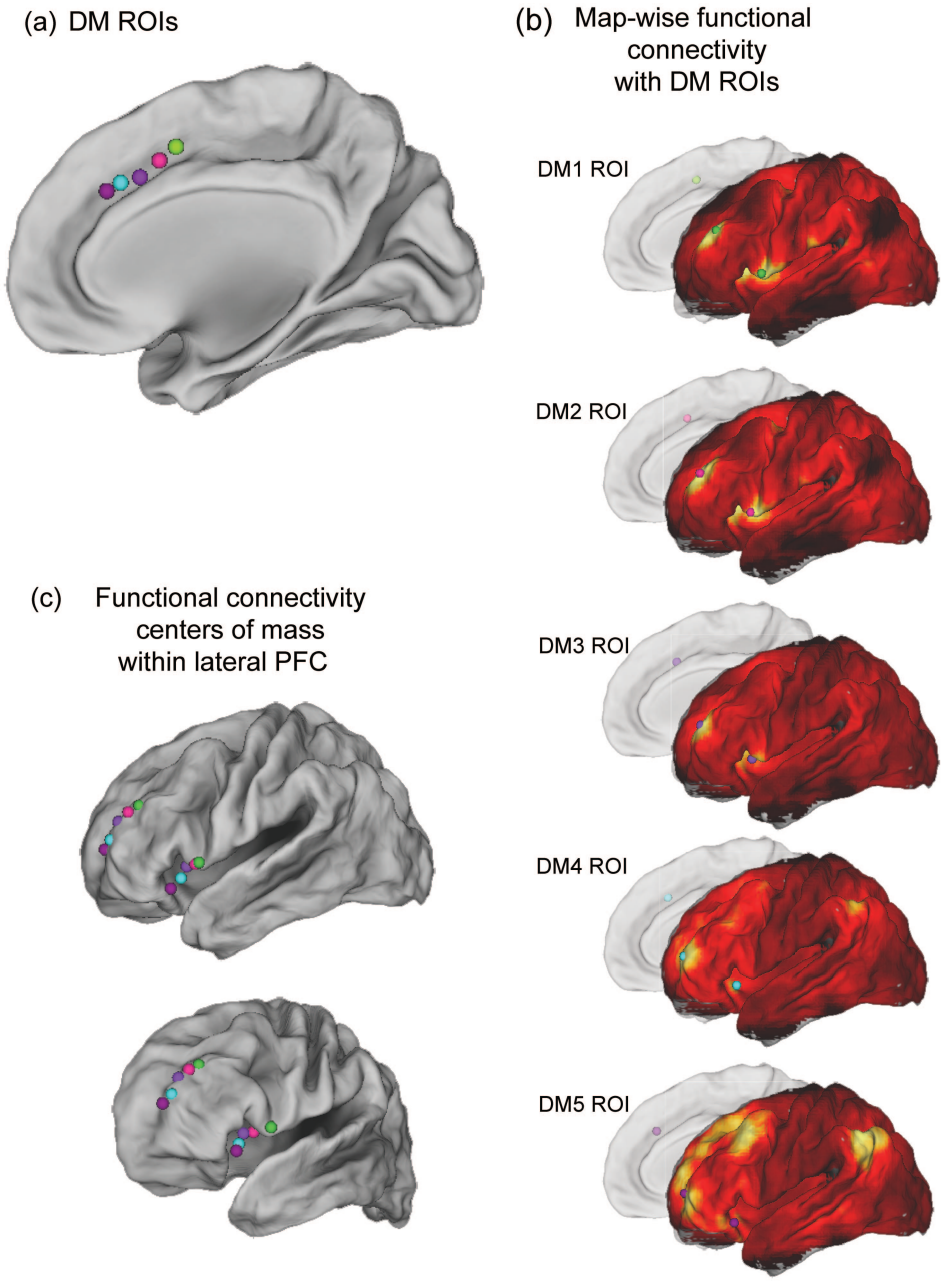

Figure 1. Results from map-wise analysis examining functional connectivity between 5 ROIs positioned along the rostro-caudal axis of the dorsomedial frontal cortex and voxels along lateral PFC. (*a*) Depicts the coordinates of the 5 dorsomedial frontal cortex ROIs (DM1–5). (*b*) Resting-state functional connectivity between DM1–5 and the lateral surface. No threshold has been applied. Note that centers of mass (depicted as colored spheres) appear in both DLPFC and VLPFC in all 5 statistical maps. Note also the rostral progression of connectivity along both DLPFC and VLPFC as the DM ROI progresses rostrally. (*c*) Depicts the coordinates of the resulting DLPFC and VLPFC centers-of-mass projected onto the lateral surface. The bottom brain figure illustrates these coordinates not projected. Note that DM1–5 are projected onto the right hemisphere for ease of visualization; however, left lateralized DM1–5 ROIs were used in all analyses.

Most notably, the activity in each of these centers progressed rostrally as a function of increasing the rostral position of DM ROI. Thus, separate DLPFC and VLPFC streams of rostro-caudal functional connectivity emerged with the dorsomedial frontal cortex (Fig. 1*b* and Table 1b). We extracted 3 mm^3 spheres at the location of each DLPFC and VLPFC center of mass (Fig. 1*c*).

Replication and Testing for Rostro-Caudal Organization

In this set of analyses, using an independent dataset, we first aimed to replicate the map-wise findings and then to quantitatively test whether the DLPFC and VLPFC streams of connectivity with the dorsomedial frontal cortex are both rostro-caudally organized. To replicate the map-wise analyses, we computed the correlations between the lateral PFC ROIs defined by the centers-of-mass from the map-wise analyses and the DM ROIs, defined above and by previous work (Taren et al. 2011) in resting-state data from a new set of participants. These ROI × ROI correlations, depicted in Figure 2, indicate that functional connectivity between the lateral PFC and the DM ROIs varies systematically as a function of rostro-caudal position. In particular, Figure 2*a*,*b* depicts that caudal

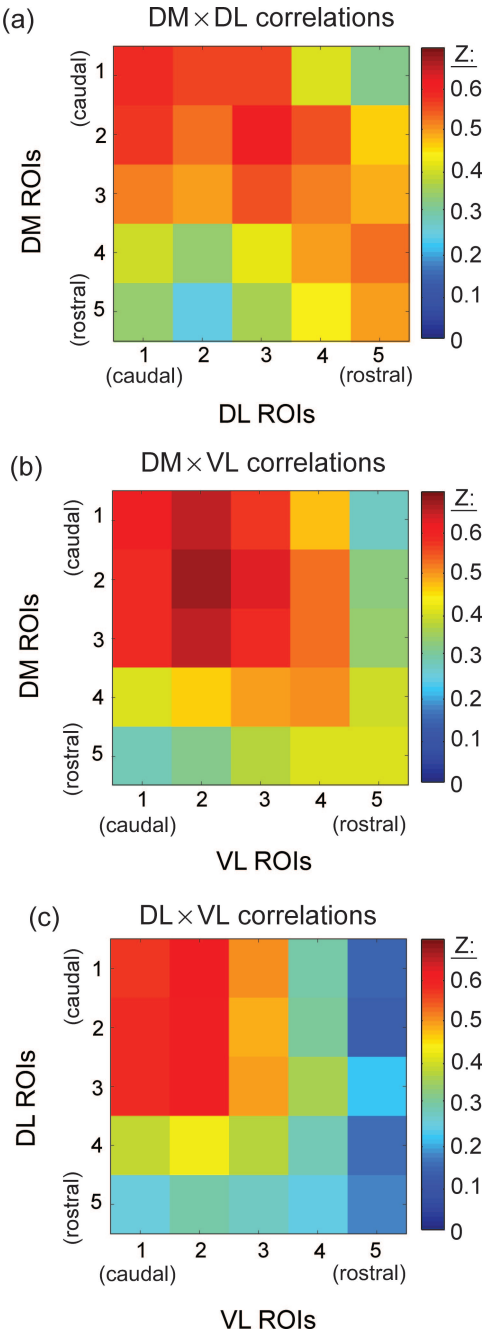

Figure 2. Results from ROI × ROI correlations from an independent dataset. In each of these panels, each cell represents the group averaged Fisher-transformed correlation value (*z*-score) (He et al. 2007; Van Dijk et al. 2010) for a given ROI pair. All 3 panels demonstrate a rostro-caudal organization. This can be observed in each panel by noting that the maximal correlations fall along or near the diagonal line. All correlations depicted in all 3 plots, included those along the diagonal, are statistically significant ($P < 0.05$, corrected). (*a*) Correlation matrix from the DM × DL ROI analysis. Caudal DM ROIs correlate most highly with caudal DL ROIs and rostral DM ROIs correlate most highly with rostral DL ROIs. (*b*) Correlation matrix from the DM × VL ROI analysis. Caudal DM ROIs correlate most highly with caudal DL ROIs, and despite lower overall correlations between rostral ROIs, rostral DM ROIs correlate most highly with rostral DL ROIs. (*c*) Correlation matrix from the DL × VL analysis. Caudal DL ROIs correlate most with caudal VL ROIs and rostral ROIs are less highly correlated.

DM ROIs correlate most highly with caudal lateral PFC ROIs and rostral DM ROIs correlate most highly with rostral lateral PFC ROIs. These correlation plots further show that correlations are maximal along the diagonal, indicating that the strongest correlations are between seeds at matched rostro-caudal positions. This finding replicates our first-stage results in an independent dataset. It should be noted that the correlations in the rostral portion of Figure 2*b* appear lower overall compared with the caudal portion of Figure 2*b*. Despite this overall difference, the rostral DM and VL ROIs are maximally correlated. Moreover, all the correlations that fall along the diagonal in Figure 2*a*,*b* are statistically significant ($P < 0.05$, corrected). In Figure 2*c*, despite evidence that VLPFC and DLPFC ROIs at similar rostro-caudal positions are most strongly correlated, caudal regions of VLPFC and DLPFC appear relatively more correlated than rostral regions of VLPFC and DLPFC.

Next, to explicitly test whether functional connectivity between the dorsomedial frontal cortex and lateral PFC ROIs varies with the rostro-caudal position, we performed 2 regression analyses (see the Materials and Methods section). In the first regression, the correlations between DM and DLPFC ROIs were entered as dependent variables. The predictors were the DM ROI's position (5 levels), DLPFC ROI's position (5 levels), and the interaction between the DM and DLPFC's position. In the second regression, the correlations between DM and VLPFC ROIs were entered as dependent variables. The predictors were the DM ROI's position (5 levels), VLPFC ROI's position (5 levels), and the interaction between the DM and VLPFC position. Of interest in each of these regressions is the interaction term which tests whether the correlation between DM and the lateral region depends on the position of both DM and the lateral PFC ROIs. Both of these regressions produced highly significant interactions (Table 2). All the other independent variables were also significant.

Testing for Statistical Independence of Streams of Connectivity

The analyses performed thus far have determined that 2 parallel streams of rostro-caudal functional connectivity exist between the dorsomedial frontal cortex and the lateral PFC. In this next analysis, we computed partial correlations to examine the extent to which these streams of functional connectivity are statistically independent from one another. For each rostro-caudal position, we computed the correlations between the time-series of DM and DLPFC ROIs after partialling out the contribution of the VLPFC time series at the corresponding position (i.e. correlation between DM1–DL1 partialling VL1 time-series) and we computed the correlations between the time-series of DM and VLPFC ROIs after partialling out the contribution of the DLPFC time-series at the corresponding position.

Table 2
Regression results from resting-state-based ROIs

Variable	β	*P*-value
Intercept	0.505	$<1.0 \times 10^{-6}$
DM	−0.054	1.0×10^{-6}
DL	−0.053	2.0×10^{-6}
VL	−0.049	1.3×10^{-5}
DM × DL	0.255	$<1.0 \times 10^{-6}$
DM × VL	0.279	$<1.0 \times 10^{-6}$
DL × VL	0.191	$<1.0 \times 10^{-6}$

We found that the correlations between each DLPFC–DM ROI pair and each VLPFC–DM ROI pair remained significant after partialling (lowest $t(19) = 5.72$, all P's < 0.05 Bonferroni corrected; Fig. 3*a*,*b*). This provides additional evidence that the DLPFC–DM frontal and VLPFC–DM frontal streams of connectivity are parallel. We performed a third partial correlation analysis to examine whether the functional connectivity between DLPFC and VLPFC ROIs are statistically independent of the dorsomedial frontal cortex (Fig. 3*c*). At each rostro-caudal position, we computed the correlations between the time-series of DLPFC and VLPFC ROIs after partialling out the contribution of the DM time series at the corresponding position. All correlations did not remain significant after removing the contribution of the DM ROIs; more caudal regions (positions 1–3) remained (DL1–VL1: $t(19) = 6.43$, DL2–VL2: $t(19) = 6.76$, DL3–VL3: $t(19) = 3.71$, all P's < 0.05 Bonferroni corrected), but correlations between more rostral regions DL4–VL4 and DL5–VL5 did not (DL4–VL4: $t(19) = 1.68$, DL5–VL5: $t(19) = 0.02$, P's > 0.05 Bonferroni corrected).

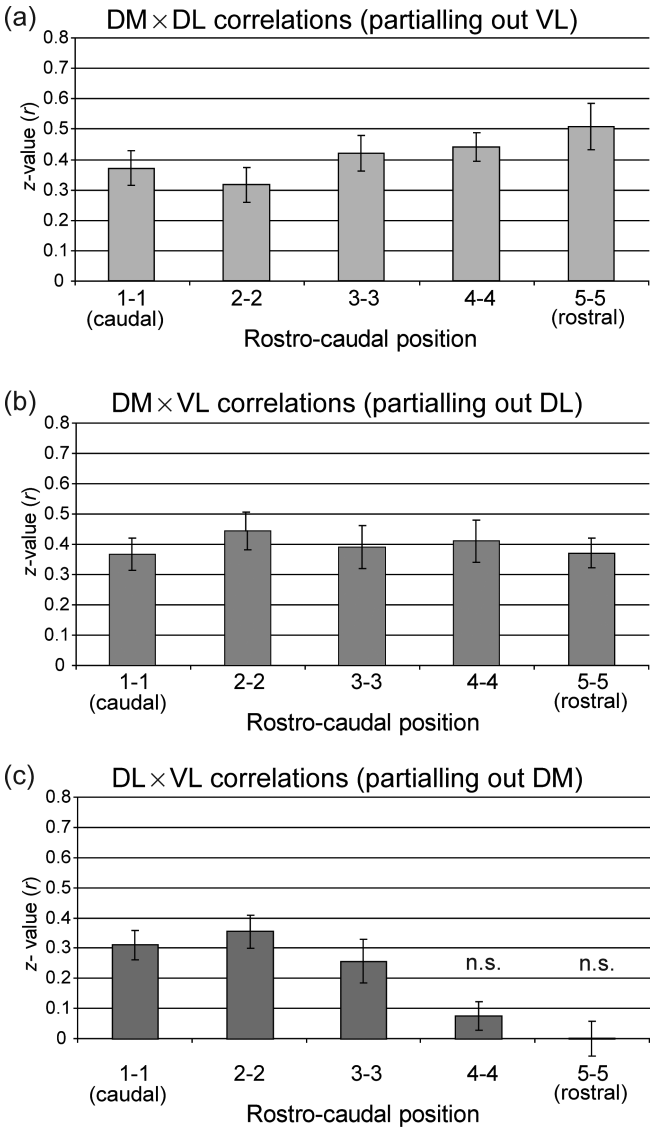

Figure 3. Results from partial correlation analyses. Demonstrates that connections between the dorsomedial frontal cortex and DLPFC and between the dorsomedial frontal cortex and VLPFC along the rostro-caudal axis are statistically independent and parallel. (*a*) Group-averaged correlations between matched DM ROIs and DL ROIs after partialling out the time series of the corresponding VL ROI. For instance, the leftmost bar in this panel is the value of the correlation between DM1 × DL1 (most caudal position) after partialling out VL1. (*b*) Group-averaged correlations between matched DM ROIs and VL ROIs after partialling out the time series of the corresponding DL ROI. Partial correlations are in Fisher-transformed *r*-values (*z*-scores). All correlations are statistically significant ($P < 0.05$) after Bonferroni correction except were noted by "n.s."

Examining Connectivity Between DM and Lateral Frontal Regions Associated with Cognitive Control

Thus far, we have demonstrated that the dorsomedial frontal cortex forms parallel functional connections with VLPFC and DLPFC along a rostro-caudal gradient. However, the VLPFC and DLPFC regions used in these analyses were identified solely using resting data and not all of the ROIs that we identified overlap with the regions previously found to be linked to cognitive control functions subserved by the rostro-caudal frontal axis. In this fourth set of analyses, we examined connectivity between the DM and lateral frontal ROIs that have been explicitly implicated in rostro-caudally organized cognitive control functions. This allowed us to test whether regions linked to cognitive control demonstrate a pattern of rostro-caudal connectivity with DM similar to our findings above. Toward this aim, we selected the 4 ventrolateral ROIs (VL1a–4a) defined from a recent study by Race et al. (2009). These ROIs were all clearly within the ventrolateral frontal cortex; thus, these ROIs allowed us to test whether task-relevant VLPFC regions are functionally connected to the dorsomedial frontal cortex along a rostro-caudal axis. At present, there is no single fMRI study of cognitive control that has demonstrated a rostral–caudal gradient in which all activated regions are solely within DLPFC. ROIs from such studies either contain a mixture of dorsal and ventral ROIs (Koechlin et al. 2003; Kouneiher et al. 2009) or contain ROIs that are ambiguous (i.e. along the inferior frontal sulcus; Badre and D'Esposito 2007).

In this analysis, we performed ROI × ROI time series correlations and an OLS regression analyses using the DM ROIs defined above and the VLa ROIs defined from Race et al. (2009) (Table 1c). The ROI × ROI time-series analyses demonstrated that correlations between the DM frontal cortex and VLa ROIs vary systematically with the rostro-caudal position (see Supplementary Fig. 1). Specifically, caudal DM ROIs correlate most highly with caudal VLa ROIs and rostral DM ROIs correlate most highly with rostral VLa ROIs. The regression analysis, which quantitatively tested this rostro-caudal gradient, produced a highly significant interaction term (Table 3).

Discussion

The PFC is composed of distinct subregions along its medio-lateral, dorso-ventral, and rostro-caudal axes, and there has

Table 3
Regression results from task-based cognitive control ROIs

Variable	β	*t*-value
Intercept	0.335	$<1.0 \times 10^{-6}$
DM	−0.059	6.21×10^{-4}
VLa	−0.033	0.03
DM × VLa	0.1	1.5×10^{-5}

been much investigation examining the role of these subregions in cognitive control. Most studies tend to consider each of these axes independently, and in doing so, they fail to consider the important anatomical and functional interactions that occur between frontal axes that likely shape the function of any particular frontal subregion (Petrides 2005; Yeterian et al. 2011). The aim of this study was to examine the intrinsic connectivity between these frontal cortex axes in order to identify a framework for how the dorsomedial and lateral frontal cortex interact. Using resting fMRI connectivity data, we demonstrated that the dorsomedial frontal cortex forms parallel connections with the rostro-caudal axes of dorsolateral and ventrolateral PFC (see Fig. 4 for a graphical summary). The existence of these parallel streams of functional connectivity highlights that dorsomedial, dorsolateral, and dorso-ventral frontal regions do not operate in isolation; rather, our results suggest a systematic interaction between these regions along their rostro-caudal axes. Thus, these findings provide a novel framework for understanding the intrinsic organization of the frontal cortex that incorporates the connections between the medio-lateral, dorso-ventral, and the rostro-caudal axes.

Our results add to the growing literature supporting a rostro-caudal organization of function by providing evidence for parallel dorsolateral and ventrolateral PFC rostro-caudal gradients. Recent neuroimaging studies have identified rostro-caudal patterns of activity in PFC using a variety of complex tasks that vary demands for different types of control processing. For example, studies have demonstrated that activity progresses along the rostro-caudal axis in lateral PFC as control processing becomes increasingly abstract (Koechlin et al. 1999, 2003; Koechlin and Jubault 2006; Badre and D'Esposito 2007; Koechlin and Hyafil 2007; Race et al. 2009). Interestingly, careful inspection of these studies reveals some evidence for dorsal–ventral distinctions. For example, studies that have manipulated the abstractness of action plans by increasing, for example, the number of sequential goals or subgoals that needed to be processed for a decision (Koechlin et al. 1999; Badre and D'Esposito 2007; Koechlin and Hyafil 2007; Kim et al. 2011), have found a caudal to rostral progression of activity in more dorsal areas of lateral PFC near the inferior frontal sulcus/middle frontal gyrus. Studies that manipulated factors related to the abstractness of the stimulus produced rostro-caudal gradients in more ventrolateral PFC regions along the inferior frontal gyrus (Koechlin and Jubault 2006; Race et al. 2009; see also Bookheimer 2002). However, there is a good deal of overlap between the more dorsal and more ventral rostro-caudal gradients (compare Koechlin et al. 2003; Race et al. 2009). Thus, it is not clear from these studies whether separate dorsolateral and ventrolateral PFC rostro-caudal gradients exist.

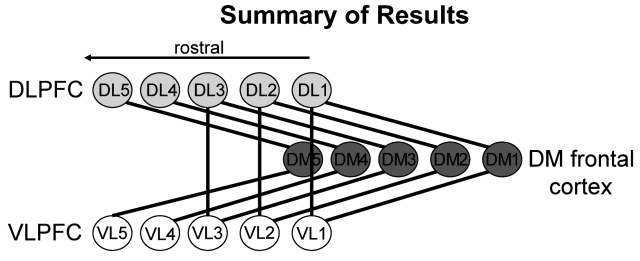

Figure 4. Summary of results and framework for understanding intrinsic organization of the frontal cortex. We identified parallel dorsolateral and ventrolateral streams of connectivity with the dorsomedial frontal cortex using resting-state time-series correlations. VLPFC ROIs (VL1–5) and DLPFC ROIs (DL1–5) were maximally connected with DM ROIs (DM1–5) at similar rostro-caudal positions. The correlations between DL1–5 and DM1–5 and between VL1–5 and DM1–5 remained significant after a partial correlation analysis was performed. However, the correlations between the more rostral VL and DL ROIs no longer remained significant after partialling.

The parallel rostro-caudal streams of connectivity evident in dorsolateral and ventrolateral PFC are consistent with the notion that these regions are structured to support separate functions and interact with each other and with the dorsomedial frontal cortex along their rostro-caudal axes. Most studies converge on the notion that subregions within ventrolateral PFC support various "first-order" processes and subregions within dorsolateral PFC support "higher-order" processes. For instance, the ventrolateral PFC regions implicated in our map-wise analysis, pars triangularis (~BA 45) and pars orbitalis (~BA 47/12), have been linked to working memory maintenance (D'Esposito et al. 1999), selection (Thompson-Schill et al. 1997; Badre et al. 2005; Hampshire et al. 2007), retrieval (Nelson et al. 2003; Badre et al. 2005), and item memory encoding (Blumenfeld and Ranganath 2006; Blumenfeld et al. 2011). In contrast, dorsolateral PFC regions similar to those implicated in the present study (~BA 9 and 46) have been linked to working memory manipulation (D'Esposito et al. 1999), monitoring (Champod and Petrides 2007), global processing (Hampshire et al. 2007), and relational memory encoding (Blumenfeld and Ranganath 2006). Our results highlight that theories must account for how these putative "first-order" and "second-order" processes are organized along the rostro-caudal axis in a manner consistent with their connectivity.

Two recent functional neuroimaging studies have demonstrated a rostro-caudal progression along the dorsomedial frontal cortex (Kouneiher et al. 2009; Venkatraman et al. 2009). These studies manipulated different temporal aspects of reward and decision-making, which had the effect of increasing the temporal abstractness of the strategies or motivation for performing a certain cognitive task. For instance, caudal dorsomedial frontal regions (anterior SMA, pre-SMA, around DM1–2) were recruited during "response-level" conditions where response conflict or motivational incentives were maximal at the individual trial or response. At more abstract levels, where conflict or incentives were maximized across a block of trials or responses ("decision-level") or even across the entire experiment ("strategy-level"), more rostral dorsomedial frontal regions were recruited (anterior pre-SMA, medial area 9). Our results demonstrated that connectivity between these dorsomedial frontal regions and lateral PFC regions are maximal at similar rostro-caudal positions. Our pattern of findings is consistent with a study by Taren et al. (2011) (see also Kouneiher et al. 2009) that demonstrated that the dorsomedial frontal cortex forms point-to-point intrinsic connectivity with the rostro-caudal gradient in lateral PFC identified by Koechlin et al. (1999, 2003). Our study adds to these studies by establishing that the rostro-caudal axes of dorsolateral and ventrolateral PFC are separable and intrinsically connected to the rostro-caudal axis of the dorsomedial frontal cortex in a parallel manner. This intrinsic architecture may allow the dorsomedial frontal cortex to modulate or bias lateral PFC activity, or through feedback, allow lateral PFC to modulate dorsomedial frontal regions that are actively

processing incentive or motivational information (for a similar perspective, see Kouneiher et al. 2009; Taren et al. 2011).

Although the main focus of this study was to examine connectivity between the dorsomedial frontal cortex and the lateral PFC, we additionally measured connectivity between dorsolateral and ventrolateral PFC regions along the rostro-caudal axis. Two findings merit discussion. First, our DLPFC–VLPFC regression analysis produced a significant interaction implying that connectivity between the regions of DLPFC and VLPFC that we identified is maximal at similar rostro-caudal positions. Second, we observed that correlations between rostral DLPFC (~BA 46/10) and VLPFC ROIs (~BA 47/12) were relatively low, and after the time series of the dorsomedial frontal cortex was partialled out, these ROIs were no longer significantly connected. This finding is consistent with an organization of lateral PFC in which DLPFC and VLPFC subregions at similar rostro-caudal positions are biased to interact; yet, more rostral regions may function more autonomously.

Resting-state connectivity methods, like the ones used in the present study, capitalize on the fact that anatomically connected brain regions exhibit coherent fluctuations at rest. Indeed, results from resting-state analyses are largely consistent with white matter connectivity findings in both humans and macaques, particularly in PFC (Damoiseaux and Greicius 2009; Greicius et al. 2009; van den Heuvel et al. 2009; Van Dijk et al. 2010), and strong intrinsic connections have been found between both monosynaptically and non-monosynaptically connected brain regions (Stein et al. 2000; Zhang et al. 2008). However, it must be stressed that the link between resting-state fMRI correlations and anatomical connectivity is complex and multiple methodological and physiological variables such as head motion and respiratory artifacts can confound measurements of correlations from the resting fMRI signal. Moreover, because correlational methods do not remove all the possible indirect sources of influence, it is dubious to infer the existence of direct anatomical connections from these data. Nonetheless, a careful re-examination of prior anatomical findings in the macaque revealed that our imaging results are highly consistent with the known connections of the macaque frontal lobe (Bates and Goldman-Rakic 1993; Luppino et al. 1993; Lu et al. 1994; Cipolloni and Pandya 1999; Petrides and Pandya 1999, 2002, 2006, 2007; Gerbella et al. 2010). That is, in the macaque, mid-DLPFC and mid-VLPFC regions (roughly homologous to or DL1–2 and VL1–2 ROIS) are connected to caudal dorsomedial frontal regions (roughly homologous to DM1–2 ROIs). Similarly, rostral DLPFC and VLPFC in the macaque (roughly homologous to DL3–5 and VL3–5 ROIs) are connected to the rostral dorsomedial frontal cortex (roughly homologous to DM3–5 ROIs). Moreover, examining the connections within lateral PFC is also consistent with our fMRI finding. That is, DLPFC (BA 9, BA 46) and VLPFC (BA 45, BA 8Av) subregions are densely connected; yet, at the rostral extent, relatively fewer monosynaptic connections are apparent between DLPFC (BA 46, 9) and VLPFC (e.g. BA 47/12) (Bates and Goldman-Rakic 1993; Petrides and Pandya 1999, 2002, 2006, 2007; Gerbella et al. 2010). These anatomical findings taken together provide clear evidence for the anatomical basis for our findings. Our results demonstrate that resting-state connectivity analyses can inform our understanding of human neuroanatomy and compliment to traditional tracer studies in the non-human primate for generating anatomical predictions and motivating future tracing studies.

The parallel dorsal and ventral rostro-caudal gradients of connectivity within PFC that we have identified may be understood in terms of the dual origin theory of the cerebral cortex (Sanides 1969; discussed in Barbas and Pandya 1991; and Yeterian et al. 2011). According to this theory, dorsal and ventral PFC regions evolved separately from 2 distinct architectonic trends: The subregions of dorsolateral and dorsomedial PFC evolved from the primordial hippocampal archicortical trend (dorsal line) and the subregions of orbital, ventromedial, and ventrolateral PFC evolved from the primordial paleocortical trend. Interestingly, the subregions within these trends have parallel patterns of lamination along the rostro-caudal axis, with the most caudal regions being the most differentiated, the middle subregions being the least differentiated, and the most rostral having intermediate differentiation. In addition, it has been observed that subregions within each trend are preferentially connected and form connections to both more and less connected regions within their stream. According to the dual-origin theory, these 3 factors: Parallel organization, differences in differentiation across the rostro-caudal axis, and preferential yet mixed connectivity during evolution, have given rise to the ability of PFC subregions to subserve both divergent and integrated processing roles. Although according to this theory, dorsal and ventral trends have divergent connectivity, our results suggest that regions within both of these trends make parallel connections to the dorsomedial frontal cortex.

As mentioned above, resting-state correlations in fMRI data are influenced by head motion (Power et al. 2012; Van Dijk et al. 2012). Specifically, head motion induces spatial autocorrelations over relatively short distances, which can artifactually "increase" the correlation between voxels that are proximal (approximately <25 mm) and "decrease" long-range correlations (>25 mm). For at least 3 reasons, it is unlikely that our pattern of results could be explained by spatial autocorrelations caused by head motion. First, our results concern relatively long-range connections between medial and lateral frontal ROIs, which are situated >25 mm apart. Second, if spatial autocorrelations were alone driving our results, we would expect DL × VL correlations to be the highest (since these ROIs are the closest) but in fact we find the opposite. Third, our sample consisted of healthy young adults that exhibited relatively little movement (<3 mm).

Authors' Contribution

Statement of contribution: R.S.B. and M.D. conceived of experiment; R.S.B., E.M.N., and C.G. conceived of specific analyses; E.M.N and C.G. developed analytic tools; R.S.B. and M.D. wrote the manuscript; all authors discussed the results and implications and commented on the manuscript at all stages.

Supplementary Material

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/.

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Notes

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