Euclidean distance as a measure of ventral and dorsal white matter connectivity

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Abstract

Fiber tractography based on diffusion tensor imaging (DTI) has become an important in-vivo tool for investigating the anatomical connectivity between brain regions. Combining DTI with functional magnetic resonance imaging (fMRI) allows for the mapping of the structural and functional architecture of large-scale networks for cognitive processing. This line of research has shown that ventral and dorsal fiber pathways subserve different aspects of stimulus- and task-dependent processing in the brain.

Here we investigate the feasibility and usefulness of Euclidean distance (ED) as a simple geometric measure to differentiate ventral and dorsal long-range white matter fiber pathways between parietal and inferior frontal cortex in a body of studies that used probabilistic tractography.

We show that ventral pathways between parietal and inferior cortex, on average have a significantly longer ED in 3D-coordinate space than dorsal pathways. This finding needs to be further validated in analyzing studies that used different fiber tracking methods for detecting ventral/dorsal pathways between other brain regions. Thus, it could provide a simple measure and potentially a boundary value to assess patterns of connectivity in the large body of fMRI studies in the absence of DTI data. This would allow for a much broader assessment of general patterns of ventral and dorsal large-scale connectivity for different cognitive operations.

Introduction

In recent years, fiber tracking based on diffusion tensor imaging (DTI) and functional magnetic resonance imaging (fMRI) have allowed for the anatomically constrained investigation of large-scale white matter pathways for cognitive processing in different domains[1–3]. This approach has highlighted the important distinction between ventral and dorsal fiber systems that subserve different aspects of cognitive processing in a variety of domains like vision, attention, language and the motor system. In the context of language processing, this research has demonstrated that, in addition to the classic dorsal fiber pathway (via the arcuate fascicle and superior longitudinal fascicle fiber system), a ventral white matter pathway via the middle longitudinal fascicle and the extreme capsule fiber system connects parietal and posterior temporal areas for speech perception, comprehension and phonological processing with inferior frontal areas for articulation[4–7]. Overall, this research has produced considerable insight into the structural white matter architecture, patterns of large-scale connectivity and the neuronal implementation of different cognitive systems in the brain. Recently, this has lead to an international effort to map the entire human fiber system termed "connectome"[8–10].

In-vivo mapping of human fiber pathways depends on DTI measurements, which have only become widely available for cognitive neuroscience research about a decade ago. From before the advent of DTI, however, we have a large body of functional imaging studies in which the patterns of structural connectivity between the brain regions identified with fMRI (or PET) remain unexplored. Thus, it would be useful if the information on the human fiber system from DTI-based fiber tracking we have now could be harvested to retroactively infer patterns of connectivity between brain coordinates in the absence of DTI data. This would allow for much larger meta-analyses on patterns of large-scale connectivity across a variety of cognitive domains. This, in turn, would increase the aggregated evidence on large-scale networks for cognitive processing based on functional neuroimaging.

To this end, we explore systematic differences in Euclidean distance (ED) as a geometric measure to distinguish between ventral and dorsal fiber pathways in studies that have used DTI-based probabilistic fiber tracking. Our aim is to investigate, whether the anatomical segregation into ventral and dorsal fiber pathways, demonstrated by probabilistic fiber tracking, can be captured by a simple measure of spatial distance. Differentiating ventral and dorsal connectivity between brain coordinates by Euclidean distance would provide a simple tool for assessing patterns of connectivity in the brain even in the absence of DTI data.

Euclidean distance has been previously shown to relate to functional connectivity between brain regions in resting state fMRI in the context of psychiatric disorders. In one study in patients with childhood-onset schizophrenia, the differences between subjects in the topology of functional networks in the resting-state was reflected by variation in ED between connected regions[11]. Another study which compared resting-state fMRI between elderly patients with depression and controls showed increased ED between connected brain regions in the depressed group[12]. With respect to long-range anatomical connectivity via white matter fiber pathways in the brain, however, no geometrical relationships, power laws or allometric principles based on in-vivo DTI imaging data is available so far to our knowledge.

Here we analyzed Euclidean distances between coordinates in parietal and inferior frontal brain regions for which the pattern of ventral or dorsal connectivity has been demonstrated previously by DTI-based probabilistic fiber tracking. We chose probabilistic fiber tracking because we have substantial experience in developing and applying this fiber tracking method[13,14]. In this previous work, probabilistic fiber-tracking investigated ventral and dorsal fronto-parietal fiber pathways in the context of language processing[1,14], motor imagery[2,15], attention[3,16] and mental arithmetic[17] we observed that ventral fronto-parietal fiber pathways seem to travel much longer distances in the brain than dorsal fronto-parietal pathways. However, experiments on perception show that visual estimation of geometric distance between two points often results in an overestimation of the distance, with relative errors increasing with the length of curvilinear paths (that were used as visual cues, called the “detour effect”)[18]. Based on our observation from these tractography studies, we hypothesize that the ventral pathway connecting parietal and inferior frontal cortex is on average longer than the dorsal pathway. To test this hypothesis, we analyze systematic geometric differences in ventral and dorsal connectivity between parietal and inferior frontal regions quantitatively by measuring Euclidean distance in 3D coordinate space in these studies.

Methods

To test this approach, we confined the analysis to two well characterized regions in terms of fiber connectivity, the parietal lobe and the inferior frontal gyrus (opercular and triangular parts). As we have studied white matter fiber connectivity using probabilistic fiber-tracking in variety of contexts and have a good understanding of the methodology of these measurements, we confined this investigation to studies using probabilistic fiber tracking[2,3,7,16].

Identification of coordinates

For the list of studies that were used for identifying the coordinates and their respective connectivity pattern from the fiber tracking see Table 1. All studies that were included in the analysis reported brain coordinates in Montreal Neurological Institute (MNI) space.

Measuring geometrical distance

We used Euclidean distance (ED) $d = \sqrt{(x_2 - x_1)^2 + (y_2 - y_1)^2 + (z_2 - z_1)^2}$ · to measure the distance between two coordinates, located in the inferior parietal and inferior frontal cortex respectively, in three-dimensional MNI space.

We measured ED between two coordinates for which connectivity has been demonstrated previously by DTI-based probabilistic fiber tracking. Fiber pathways from the tracking results were either classified as dorsal or ventral in accordance with the classification from the respective studies (**Fig. 1**).

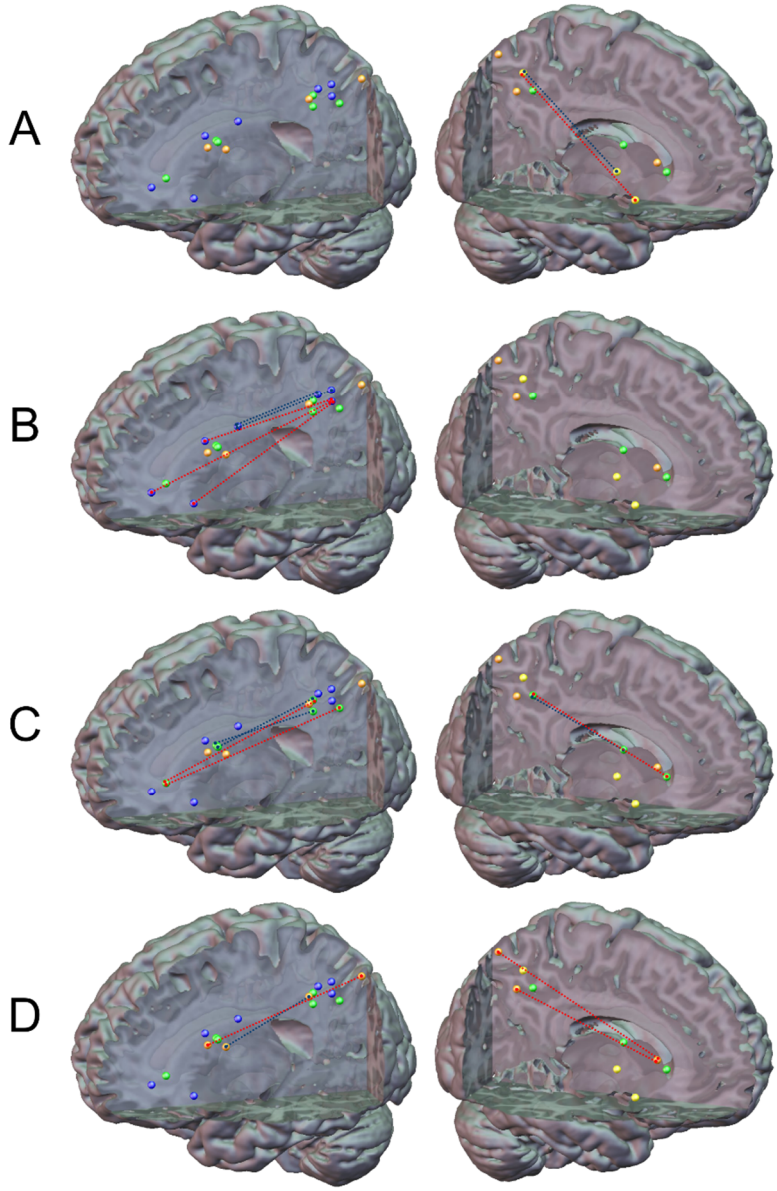

Figure 1 Patterns of dorsal and ventral connectivity from the studies used for measuring Euclidean distance: Panels (A)-(D) show the different Studies with each panel including the seeds from all studies. (A) Umarova et al. 2009 (yellow spheres), (B) Vry et al. 2012 (blue spheres), (C) Kellmeyer et al. 2013 (green spheres), (D) Klein et al. 2013 (orange spheres). Blue dotted line = dorsal pathway; red dotted line = ventral pathway. For MNI coordinates, see Table 1.

Comparing mean Euclidean distance between dorsal and ventral connections

The study's principal null-hypothesis, that Euclidean distance between dorsal and ventral pathways connecting parietal and inferior frontal cortex does not significantly differ, was addressed in a two-sample t-test comparing the mean ED between pathways classified as dorsal or ventral by DTI-based probabilistic fiber tracking.

Results

Euclidean distance between ventral and dorsal fronto-parietal pathways

Table 1 shows the frontal and parietal MNI coordinates (x,y,z) from the 4 studies that were used in our analysis and the respective Euclidean distance between them.

Paper	Parietal region	Parietal MNI coordinates			Frontal region	Frontal MNI coordinates			Euclidean distance	Ventral / dorsal
Umarova et al. 2009	R IPS	27	-51	51	R IFGpo	54	12	12	78.86	dorsal
	R IPS	27	-51	51	R IFG pt	51	21	-3	93.15	ventral
Vry et al. 2012	LIPSa/hIP2	-48	-42	51	L PMv	-54	3	39	58.56	dorsal
	L PSm/hIP2	-42	-51	51	L PMv	-54	3	39	56.60	dorsal
	L IPSp/hIP1	-33	-54	42	L IFG pt	-45	24	-3	90.85	ventral
	L IPSp/hIP1	-33	-54	42	L IFG pt	-39	45	3	106.57	ventral
Kellmeyer et al. 2013	L IPLm	-39	-42	39	L IFG po	-45	12	27	55.64	dorsal
	L IPLa	-39	-42	45	L IFG po	-48	12	27	57.63	dorsal
	R IPLa	36	-42	45	R IFG po	45	12	24	58.63	dorsal
	L IPLp	-27	-60	36	L IFG po	-48	12	27	75.54	dorsal
	R IPLa	36	-42	45	R IFG pt	45	36	12	85.17	ventral
	L IPLa	-39	-42	45	L IFG pt	-45	39	9	88.84	ventral
	L IPLp	-27	-60	36	L IFG pt	-45	39	9	104.18	ventral
Klein et al. 2013	L IPSa	-45	-38	45	L IFG po	-49	11	26	52.71	dorsal
	L IPSp	-30	-71	49	L IFG pt	-53	19	26	95.70	ventral
	R IPSp	41	-49	45	R IFG pt	53	34	19	87.80	ventral
	R SPLp	19	-68	57	R IFG pt	53	34	19	114.04	ventral

Table 1 Studies using DTI-based probabilistic fiber tracking with coordinates in parietal and inferior frontal cortex
Abbr.: L=left hemisphere. R=right hemisphere; a=anterior. p=posterior. m=medial; IPS=intraparietal suclcus; hIP=intraparietal sulcus (1.2.3); IPL=inferior parietal lobule; PMv=ventral premotor cortex; IFG=inferior frontal gyrus. po=pars opercularis. pt=pars triangularis.

The two-sample t-test comparing median Euclidean distance (ED) between brain coordinates in parietal and inferior frontal cortex showed that ED for coordinates connected by ventral pathways (*N*=9, mean 96.26, standard deviation 9.84, standard error 3.28) are significantly ($p<0.0001$) longer than for dorsal pathways (*N*=8, mean 61.77, standard deviation 9.75, standard error 2.43) (Figure 2).

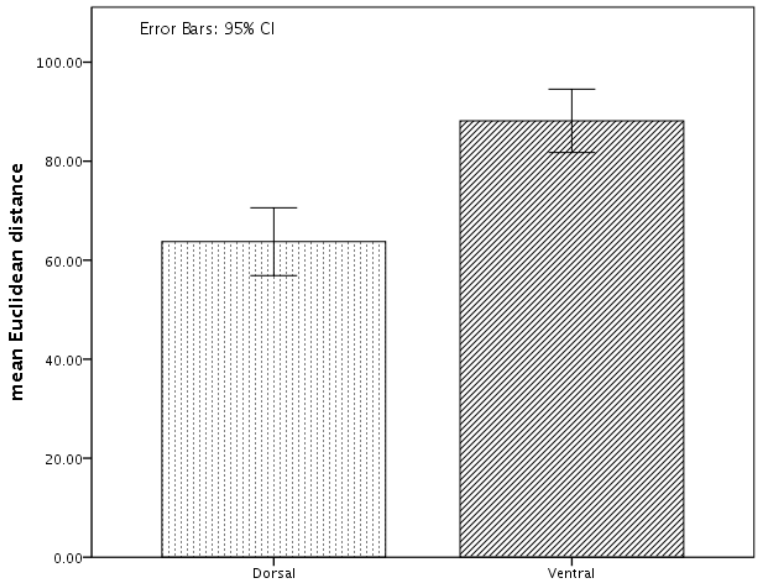

Figure 2 Graph showing mean Euclidean distance for dorsal and ventral pathways between the parietal and inferior frontal coordinates from Table 1.

Discussion

In this sample of DTI-based studies using probabilistic fiber tracking between inferior frontal and parietal regions, we found a significant difference for Euclidean distance to distinguish ventral from dorsal pathways.

If the results can be replicated in future studies, we would propose to use a measure based on Euclidean distance (for example: minus one standard deviation of the mean ED of ventral connections) to distinguish ventral from dorsal connectivity. In the example of our study this would mean, that any given pair of parietal and inferior frontal coordinates that has an ED > 83 (mean ED for ventral connections – 1 STD: 91.84-8.956 = 82.89) is connected via a ventral pathway with high probability (95%).

One explanation for this pattern could be that ventral parieto-frontal connections tend to connect to more anterior-inferior subregions in IFG (pars triangularis, pars orbitalis), whereas dorsal pathways tend to connect to more anterior-superior (pars opercularis). This raises the question, whether there is an anatomical divide within IFG that determines ventral or dorsal connectivity to posterior brain regions (like parietal and temporal cortex)?

To replicate and validate the findings here and to address this question, we propose the following steps for further analyses: First, a voxel-by-voxel connectivity analysis between

defined volumes in parietal cortex (comprising, for example, inferior and superior parietal lobule) and inferior frontal cortex (comprising inferior frontal gyrus, pars opercularis triangularis and orbitalis) could be performed to map the complete ventral/dorsal connectome between these two volumes.

Previous research with such a DTI-related connectivity-based parcellation[19] approach has already shown the pattern of connectivity for inferior frontal cortex[20], orbitofrontal cortex[21] (using fMRI) and inferior parietal cortex[22] separately. However, no voxel-to-voxel whole connectome between parieto-frontal regions is available thus far. If such a whole region-to-region connectome was available, the ED between all coordinates for which either ventral and/or dorsal connectivity was found by the fiber tracking could be measured. Then the mean ED could be compared between ventral and dorsal pathways and the boundary ED value that reliably (>95% of cases) distinguishes between ventral and dorsal connectivity could be computed. In addition, this data could then be used to delineate the anatomical divide at which fronto-parietal connectivity segregates between ventral and dorsal pathways.

This measure would be a particularly useful tool for large-scale meta-analysis of fMRI studies where no DTI data is available. In such a meta-analysis, one could address the question whether the network involved in particular cognitive operations, say speech repetition based on semantic versus phonological features, can be assigned to different pathways according to the MNI coordinates that were identified in fMRI studies on the topic. Information on the structural connectivity of "active" brain regions in neuroimaging studies is of interest for both cognitive and clinical neuroscientists.

For cognitive operations within widely distributed perisylvian networks connected via dorsal and ventral fiber tracks, the fiber length can indeed make a difference with respect to computational efficiency. It has been shown, for example, that the average conduction delay in axonal transmission scales with the average length of long-range connections and average axon diameter[23]. In the healthy brain, it has been shown that differences in domain-independent cognitive processing speed correspond to the length of white matter pathways connecting regions involved in the tasks used[24]. Synthesizing findings from functional and structural imaging studies, dorsal and ventral pathways seem to subserve different functions. In the case of language, for example, the ventral temporo- and parieto-frontal pathways subserve "higher-order" aspects of language like syntactic or lexical-semantic processing[14,25,26]. The same seems to be the case for higher-order cognitive aspects of the motor system like imitation of gestures and pantomime[2,15]. More generally, it has been proposed that the ventral pathway might

subserve processing that is time-independent and related to semantic aspects and that the dorsal pathway is involved in sequential processing in a time-sensitive manner for rapid sensorimotor integration[15,25–27].

From a clinical perspective, whether a particular pathway is significantly longer than another pathway and/or may traverse regions that are more prone to damage (e.g. due to differences in territorial vascular supply) may also entail differences in neurological vulnerability. These differences in vulnerability between ventral and dorsal pathways, in turn, may partly explain different clinical phenotypes of cognitive deficits after brain injury, for example the different aphasia syndromes[28].

More generally, it might be interesting to investigate how geometric measures of connectivity, whether Euclidean distance or other measures, are useful metrics to differentiate patterns of fiber connectivity in other mammalian species, for example non-human primates for which neuroanatomical data in 3D coordinate space is available[29]. This may give further insight into cross-species principles of white matter formation in nervous systems, particularly links between global principles like minimal wiring and more local organizing principles of neuronal circuitry and topographical maps[30,31]. Such information would also be important to link the global geometry of the white matter fiber system to the hierarchical organization of multimodal cortical areas[32].

Importantly, the precise relationship between ED and actual fiber length cannot be inferred from the analysis presented here. It may well be the case, for example, that the given pathways are optimal in terms of their distance under the given physical and anatomical constraints on the actual brain's global shape, local curvature, folding and gyration, Furthermore, as the pathways are not necessarily monosynaptic connections, the ventral pathway is relayed in insular cortex for instance, we do not know how ED relates to whether a particular pathway is mono- or polysynaptic. In this respect, it could be of interest to investigate whether the relationship between Euclidean distance and patterns of ventral and dorsal connectivity may reflect some kind of underlying allometric scaling law for governing principles of long-range white matter fiber connectivity[23,32–35]. For example, it may be the case that the need for long-range connections follows from the fact, that the volume of white matter increases at 4/3 power of the volume of gray matter[32].

It would also be interesting to explore other geometric measures based on manually or automatedly retracing the course of fiber pathways in the raw data of the individuals' DTI. We

speculate that this would most likely result in a non-euclidean, curvilinear measure of geometric distance between given coordinates[36]. In terms of the underlying geometrical principles that may best describe long-range fiber connectivity, algorithms for DTI analysis based on Riemannian and geodesic distance measures have been used that could have advantages over the currently used voxel-based analyses[37–39].

Further studies should also address, whether differences in Euclidean distance related to ventral and dorsal connectivity can also be found in connections between other brain regions (for instance fronto-temporal, occipito-temporal etc.). DTI-based connectivity studies that use different tracking methods such as deterministic fiber tracking should also be examined in order to facilitate large-scale meta-analyses on the structure and function of dorso-ventral pathway systems based on fMRI studies.

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