Deciphering the frontostriatal circuitry through the fiber dissection technique: direct structural evidence on the morphology and axonal connectivity of the fronto-caudate tract

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OBJECTIVE The authors sought to investigate the very existence and map the topography, morphology, and axonal connectivity of a thus far ill-defined subcortical pathway known as the fronto-caudate tract (FCT) since there is a paucity of direct structural evidence regarding this pathway in the relevant literature.

METHODS Twenty normal adult cadaveric formalin-fixed cerebral hemispheres (10 left and 10 right) were explored through the fiber microdissection technique. Lateral to medial and medial to lateral dissections were carried out in a tandem manner in all hemispheres. Attention was focused on the prefrontal area and central core since previous diffusion tensor imaging studies have recorded the tract to reside in this territory.

RESULTS In all cases, the authors readily identified the FCT as a fan-shaped pathway lying in the most medial layer of the corona radiata and traveling across the subependymal plane before terminating on the superolateral margin of the head and anterior part of the body of the caudate nucleus. The FCT could be adequately differentiated from adjacent fiber tracts and was consistently recorded to terminate in Brodmann areas 8, 9, 10, and 11 (anterior pre–supplementary motor area and the dorsolateral, frontopolar, and fronto-orbital prefrontal cortices). The authors were also able to divide the tract into a ventral and a dorsal segment according to the respective topography and connectivity observed. Hemispheric asymmetries were not observed, but instead the authors disclosed asymmetry within the FCT, with the ventral segment always being thicker and bulkier than the dorsal one.

CONCLUSIONS By using the fiber microdissection technique, the authors provide sound structural evidence on the topography, morphology, and connectional anatomy of the FCT as a distinct part of a wider frontostriatal circuitry. The findings are in line with the tract’s putative functional implications in high-order motor and behavioral processes and can potentially inform current surgical practice in the fields of neuro-oncology and functional neurosurgery.

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KEYWORDS fronto-caudate tract; frontostriatal; premotor; prefrontal; anatomy; functional neurosurgery

ABBREVIATIONS ACC = anterior cingulate cortex; ADHD = attention deficit hyperactivity disorder; AF = arcuate fasciculus; ALIC = anterior limb of the internal capsule; ATR = anterior thalamic radiation; BA = Brodmann area; CC = corpus callosum; CR = corona radiata; CRad = callosal radiation; CS = centrum semiovale; DBS = deep brain stimulation; DLPFC = dorsolateral prefrontal cortex; DMPFC = dorsomedial prefrontal cortex; DTI = diffusion tensor imaging; DWI = diffusion-weighted imaging; FAT = frontal aslant tract; FCT = fronto-caudate tract; FCTd = dorsal component of the FCT; FCTv = ventral segment of the FCT; FOC = fronto-orbital cortex; OPPFC = orbitopolar prefrontal cortex; SLF = superior longitudinal fasciculus; SMA = supplementary motor area; VCVS = ventral internal capsule/ventral striatum; VLPFC = ventrolateral prefrontal cortex.
The interest in frontostriatal connectivity is not new. In the 19th century, Meynert et al. used the term “corona radiata of the caudate nucleus” to refer to a system of fibers connecting the frontal lobe with the caudate nucleus in the human brain. Six years later (in 1893), Muratoff was able to trace a homologous bundle in the canine brain. At this time, the term “subcallosal fasciculus” was coined. During the mid-20th century Yakovlev and Locke indicated similar connections between the prefrontal cortex and the caudate nucleus in primates.

Nevertheless, it was not until the late 20th century that significant progress toward a more thorough understanding of corticostriatal connectivity was made. Seminal animal studies by Alexander and Crutcher and Webster offered valuable insights into the fundamental principles regulating the functional and structural interconnections between the frontal cortex and the striatum. The presence of a direct and an indirect pathway was advocated, supporting the theory that the corticostriatal circuit is parcellated into subcomponents according to anatomy and function. Indeed, Alexander was able to trace different frontostriatal loops mediating motor, cognitive, and behavioral processes. This theory of a “parallel functional architecture” remains a cornerstone in our perception of basal ganglia anatomy and function to this day.

The interest in the relationship of structure to function in the frontostriatal pathways has been revived during recent decades, as various clinical entities, ranging from behavioral and psychiatric conditions to movement disorders, have been attributed to alterations in the white matter integrity of this subcortical network. In this context, increased understanding of the anatomy of the corticostriatal connections in the human brain may be valuable in designing novel treatment strategies for various pathologies. Nevertheless, the process of elucidating this anatomy is arduous and challenging, since many of the basic techniques implemented in the study of animal brains cannot be applied in humans. Due to this fact, most of the available data on human frontostriatal connectivity are derived from diffusion tensor imaging (DTI) studies. Yet, the various diffusion-weighted imaging (DWI) protocols, although they can be performed quickly and in vivo, present serious inherent limitations, as proven by relevant studies.

Therefore, the amount as well as the quality of direct structural evidence available regarding the anatomy and connectivity of the frontostriatal pathways is limited. In addition, two further issues complicate the acquisition and dissemination of new anatomical information. First, the terminology used for the fronto-caudate tract (FCT) and other frontostriatal tracts is inconsistent throughout the literature, and second, very few studies have addressed the FCT’s intrinsic anatomy. With these shortcomings in mind, we opted to investigate the topography, morphological, connectional anatomy, and asymmetry of the FCT. We used fiber dissections since they provide direct anatomical evidence of high sensitivity and are used to validate conflicting DTI results. To the best of our knowledge, this is the first focused anatomical study in the English literature addressing this issue.

Methods

Twenty normal adult cadaveric formalin-fixed cerebral hemispheres (10 right and 10 left) were treated with Klinger’s preparation and were explored using the white matter dissection technique and an operating microscope (Carl Zeiss OPMI). Prior to dissection, the surface anatomy of the frontal area was recorded.

Focused lateromedial and mediolateral dissections on the prefrontal/premotor areas were employed in a tandem manner in all specimens to map the FCT and illustrate its spatial relationship with adjacent bundles such as the frontal aslant tract (FAT), anterior limb of the internal capsule (ALIC), anterior thalamic radiations (ATRs), corpus callosum (CC), and callosal radiations (CRads). Since most of these tracts converge tightly toward the central core, we were very diligent in differentiating them by mapping and recording their respective trajectories and termination patterns. To elucidate these crucial details, during the final steps of the dissection we detached the central core from the rest of the hemisphere to clearly delineate the different fiber layers and their exact termination areas on the thalamus and caudate nucleus. In 5 hemispheres, the fibers of the FCT along with their termination zone on the head and body of the caudate nucleus were dissected free from the rest of the hemisphere to illustrate the intrinsic morphology of the tract.

Our dissection tools were variously sized microforceps, microdissectors, and microscissors, which we used because they proved to be more precise in dissecting than wooden spatulas. In each step of the process, we obtained multiple photos from various angles to document and illustrate our findings.

Results

Surface Anatomy

Surface landmarks on the lateral and medial cerebral aspect were recorded to act as reference points for future dissections. Hence, the superior and inferior frontal sulci; the precentral, central, and postcentral sulci; the superior, middle, and inferior frontal gyri; the precentral and postcentral gyri; the cingulate sulcus and gyrus; the medial aspect of the superior frontal gyrus; the CC; and the anterior commissure were all identified.

Stepwise Dissections

Lateral to Medial Dissections

Upon removing the cortical gray matter and the underlying U-fibers, we expose the superior longitudinal fasciculus (SLF)/arcuate fasciculus (AF) complex. Dissecting away the longitudinal fibers of the SLF/AF complex helps to uncover the continuous fibers of the centrum semiovale (CS; running above the level of the ventricular system) and corona radiata (CR; running at the level of the lateral ventricles) (Fig. 1B). In this step, the FAT is also identified as a distinct group of fibers running from the supplementary motor area (SMA) toward the posterior part of the inferior frontal gyrus. In the region of the insula, upon dissecting the fibers of the extreme capsule and claustrum, one encounters the gray substance of the putamen (Fig. 1C).
FIG. 1. Stepwise lateral to medial dissection of a left hemisphere. A: The superficial U-fibers are exposed. The silhouette of the main sulci is superimposed on the specimen for orientation purposes (dotted and dashed lines). FIG. 1. (continued)
The putamen is removed along with the part of the globus pallidus that overlies the thalamus (Fig. 1E). In addition, the projecting fibers of the CS/CR are gradually dissected until their deepest layer that resides in the subventricular zone is reached. At this stage, a meticulous dissection technique is required to preserve the integrity of the very thin white matter that comprises the fronto-caudate and fronto-thalamic projections. At the end of this step, the ventral segment of the FCT (FCTv) is identified and seen to terminate on the head of the caudate nucleus (Fig. 1E). The FCTv exhibits a lazy S-shaped configuration, with its fibers initially observed to travel in a relatively straight direction and then seen to curve to adapt to the silhouette of the head of the caudate nucleus before terminating at this area. While the FCTv is nicely exposed at this stage, the dorsal component of the tract (FCTd) is covered by fibers of the ATR, which are seen to pass slightly lateral to the caudate nucleus in order to terminate to the thalamus (Fig. 1E). These fronto-thalamic fibers are carefully removed during the medial to lateral dissections to reveal the underlying fibers of the FCTd. In the last step, the frontal horn is entered and the spatial relationship of the FCT with the intraventricular structures and the CC is demonstrated. The stepwise lateral to medial dissection process is illustrated in Video 1.

**Video 1.** Dissecting the FCT. Stepwise lateral to medial and medial to lateral dissections. AF = arcuate fasciculus; ALIC = anterior limb of the internal capsule; ATR = anterior thalamic radiation; Caud = caudate nucleus; Cg = claustrum; CR = corona radiata; CS = central sulcus; EC = extreme capsule; FCT = fronto-caudate tract; GPi = internal globus pallidus; IFG = inferior frontal sulcus; MFG = middle frontal gyrus; Pu = putamen; SFG = superior frontal sulcus; SMA = supplementary motor area; Th = thalamus. Copyright Spyridon Komaitis. Used with permission. Figure is available in color online only.

Segmentation and Connectivity Pattern of the FCT

We consistently identified two discrete segments of the FCT. The ventral segment (FCTv) is formed from fibers recorded to originate from the frontal pole (Brodmann area [BA] 10), fronto-orbital region (BA 11), ventrolateral prefrontal cortex (VLPF; BA 47), and ventral part of the anterior cingulate cortex (ACC; BA 32) and terminate on the head of the caudate nucleus (100% of the specimens). The dorsal segment (FCTd) receives fibers from the anterior part of the pre-SMA (BA 6), dorsolateral prefrontal cortex (DLPFC; BA 8), dorsomedial prefrontal cortex (DMPFC; BA 9), and dorsal ACC (BA 32) and then travels medial to the fibers of the ATR and terminates at the body of the caudate nucleus. The transition zone of FCTv to FCTd corresponds to the transition area of the head to the body of the caudate, which is located at the level of the foramen of Monro. Further, the FCTv was consistently seen to be thicker and bulkier than the FCTd. The segmentation and termination pattern of the FCT is summarized in Table 1. Additionally, the tract’s ventral and dorsal connectivity is illustrated in Fig. 3.

Spatial Relationships of the FCT

The FCT is a deep-seated group of fibers that lies in the subventricular zone of the frontal horn, which is located medial with respect to the CS/CR and lateral to the...
FIG. 2. Stepwise medial to lateral dissection of a right hemisphere. **A:** The relevant superficial anatomy is marked with dotted and dashed lines. **B:** The superficial U-fibers are exposed. The silhouette of the main sulci is superimposed on the specimen for orientation purposes. **FIG. 2. (continued)**
FIG. 2. C: The superficial U-fibers of the frontal area are removed. The superior arm of the cingulum is evident. D: The rostrum, genu, and anterior part of the body of the CC as well as the superior arm of the cingulum are dissected away. The intraventricular parts of the caudate nucleus and the CRads are illustrated. E: The ependymal layer covering the caudate nucleus is carefully removed. The CRads are dissected in a superior to inferior direction to reveal the fibers of the FCT and their termination zone on the caudate nucleus. Upper inset: The FCTv and FCTd are highlighted in light blue and dark blue, respectively, with the first terminating on the head of the caudate nucleus and the second on the body of the caudate nucleus. The relevant BAs at which the tracts terminate are highlighted. Middle inset: The silhouette of the FCT superimposed on the surface of the same specimen. Lower inset: Advanced stage of a mediolateral dissection of a right hemisphere. The FCT along with its termination zone on the caudate nucleus and the structures of the limbic lobe and diencephalon are dissected free from the rest of the hemisphere. The morphology of the tract is demonstrated. ac = anterior commissure; BA = Brodmann area; CC = corpus callosum; CCg = genu of the corpus callosum; CCS = splenium of the corpus callosum; Cdb = body of the caudate nucleus; Cdh = head of the caudate nucleus; CF = calcarine fissure; Cg = cingulate gyrus; Cgb = body of the corpus callosum; Cp = choroid plexus; CR = corona radiata; Crad = callosal radiations; Cs = cingulate sulcus; FCT = fronto-caudate tract; FCTd = dorsal component of the fronto-caudate tract; FCTv = ventral component of the fronto-caudate tract; fm = foramen of Monro; Fx = fornix; IC = internal capsule; OC = optic chiasm; POS = parieto-occipital sulcus; Pv = pulvinar; SP = septum pellucidum; SpS = subparietal sulcus; Th = thalamus. Copyright Spyridon Komaitis. Used with permission. Figure is available in color online only.

FIG. 3. Dorsal and ventral connectivity of the FCT. A: Advanced stage of a lateromedial dissection of a right hemisphere. The morphology of the dorsal terminations of the FCT is illustrated. Inset: The fibers of the FCTd (dark blue) arising from the body of the caudate nucleus can be seen radiating toward BA 8 and BA 9 (anterior pre-SMA and DLPFC). The fibers of the FCTv (light blue) arising from the head of the caudate nucleus can be seen terminating toward BA 10 and BA 11. B: Advanced stage of a lateromedial dissection of a left hemisphere. The dorsal connectivity of the FCT is again illustrated. Inset: The FCTd (dark blue) connecting the body of the caudate with the anterior pre-SMA (BA 8) and DLPFC (BA 9) and the FCTv (light blue) radiating from the head of the caudate toward the frontal pole (BA 10) and FOC (BA 11). C: Ventral connectivity of the FCT and its relationship to the ATR. Oblique views of advanced stages of a lateromedial dissection of a left hemisphere. The central core of the hemisphere along with the diencephalic and mesencephalic structures is dissected free from the rest of the hemisphere. The termination fibers of the FCT on the head and body of the caudate have been preserved. At this step, the FCTv is seen to terminate at the head of the caudate nucleus, while the FCTd is covered by the fibers of the ATR that pass laterally to reach the thalamus. Inset: The FCTv and ATR are highlighted with dark blue and red, respectively. D: Ventral connectivity of the FCT. Oblique views of advanced stages of a lateromedial dissection of a left hemisphere. The fibers of the ATR have been removed and the fibers of the FCTd are nicely illustrated to terminate into the body of the caudate nucleus. Lower inset: The FCTv and FCTd are highlighted in dark blue and light blue, respectively. Upper inset: An arbitrary dashed line (1) passing through the anterior border of the anterior perforated substance demarcates the transition between the FCTv and FCTd. A second dashed line (2) passing through the lateral geniculate body defines the posterior limit of the FCTd and thus the posterior limit of the entire FCT. These lines were consistently recorded to delineate the aforementioned boundaries in all studied specimens. FIG. 3. (continued)→
CRads. At the level of the superior frontal gyrus, the fibers of the FCT travel medially in relation to the fibers of the FAT. As mentioned, the FCT is documented to terminate on the superolateral margin of the caudate nucleus at the level of the CR/ALIC transition. Therefore, the differentiation between fibers of FCT and ALIC is accurate and reliable because in contrast to the FCT, the fibers of the anterior limb bypass the basal ganglia and course between the head of the caudate and the globus pallidus. Finally, as already stated, the ATR lies just lateral to the FCTd. The correlative anatomy of the FCT with respect to the adjacent fiber tracts is illustrated in Fig. 4.

Discussion

In the neuroscientific literature, the existence of wide frontostriatal circuitry and its implications in higher motor and cognitive processes have been well appreciated. The caudate nucleus and putamen represent the main input of the basal ganglia and have been proven to exhibit strong connections with the prefrontal area in both animals and humans. Particularly, the head of the caudate constitutes the main target of afferent fibers stemming from both prefrontal and frontopolar cortices. Many animal and human studies have paved the way toward a more comprehensive understanding of this frontostriatal complex and have offered valuable insights into the topography and morphology of its different subcomponents. However, most of the existing data in humans derive from sophisticated DTI protocols, whereas there seems to be a paucity of direct structural evidence that is much needed to shape a more accurate understanding of these pathways. In addition, the nomenclature used to describe the subcomponents of this network is inconstant, thus adding further perplexity.

Indeed, in Table 2 we provide a review of the literature focusing on the structural evidence of the fronto-caudate connectivity. More specifically, in a DTI study, Lehéricy and colleagues aimed to elucidate the SMA and pre-SMA connections to the human striatum. The authors advocate that the caudate nucleus holds strong connectivity with the pre-SMA, while the putamen is functionally relevant to the SMA and motor cortices. This pre-SMA/caudate stream is further implicated by the authors to subserve motor preparation and sequencing. Later, Kamali and colleagues coined the term “prefronto-caudate pathway” to describe a group of fibers seen to arise from the prefrontal cortex and curve around the head of the caudate nucleus before terminating at the thalamus. The authors found the so-called prefronto-caudate tract to travel medially in relation to the ATR and postulated its functional implications in a broad spectrum of disorders, including schizophrenia, Parkinson disease, and Huntington disease. One of the very few studies providing direct structural evidence was that by Rigoard and colleagues. These authors employed focused fiber dissections to explore the anatomy of the human accumbofrontal fasciculus and proposed three types of connections between the fronto-orbital cortex (FOC) and the striatum: the accumbofrontal fasciculus connecting the medial FOC with the nucleus accumbens and the intermediate and lateral fasciculi connecting the medial and lateral FOC, respectively, with the head of the caudate nucleus. In an elegant study, Kinoshita and colleagues combined evidence from DTI and awake subcortical mapping and provided useful insights on the structural morphology, connectivity, and function of the pre-SMA/caudate pathway. The term “frontostriatal tract” was used to describe a group of fibers seen to lie medial to the FAT and to connect the pre-SMA with the anterior part of the caudate nucleus. The authors further advocated the view of this pathway as an integral part of a wider “negative motor network,” because its stimulation elicited inhibition of motor initiation in both hemispheres and verbal fluency deficits in the dominant hemisphere. The topography of

<p>| TABLE 1. Connectivity and segmentation of the FCT |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Segment</th>
<th>Trajectory</th>
<th>Ventrall Termination</th>
<th>Dorsal Termination</th>
<th>Functional Area</th>
<th>% (no.) (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FCTd</td>
<td>FCTd fibers arise from pre-SMA &amp; DLPFC, follow straight trajectory &amp; finally exhibit hook-like trajectory before terminating on body of caudate nucleus</td>
<td>Body of caudate nucleus</td>
<td>BA 6 (anterior)</td>
<td>Premotor cortex/pre-SMA</td>
<td>100% (10)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>BA 8</td>
<td>DLPFC</td>
<td>100% (10)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>BA 9</td>
<td>DLPFC &amp; DMPFC</td>
<td>100% (10)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>BA 32 (dorsal)</td>
<td>ACC</td>
<td>100% (10)</td>
</tr>
<tr>
<td>FCTv</td>
<td>FCTv fibers arise from frontal pole, FOC, &amp; VLPFC &amp; follow straight trajectory toward head of caudate nucleus</td>
<td>Head of caudate nucleus</td>
<td>BA 10, BA 11, BA 47</td>
<td>FPPFC</td>
<td>100% (10)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>BA 11</td>
<td>FOC</td>
<td>100% (10)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>BA 47</td>
<td>VLPFC</td>
<td>100% (10)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>BA 32 (ventral)</td>
<td>ACC</td>
<td>100% (10)</td>
</tr>
</tbody>
</table>

FPPFC = frontopolar prefrontal cortex.
FIG. 4. Spatial relationship of the FCT with adjacent structures. Progressive lateromedial dissection of a right hemisphere. In the superior view (upper left), the different fiber layers of the frontal white matter can be appreciated. The respective planes of the CS (above the level of the lateral ventricle), CR (at the level of the lateral ventricle), and internal capsule (below the level of the lateral ventricle) are marked with dashed lines. At the level of the CS and CR the different fiber pathways cannot be differentiated. Below the level of the lateral ventricle, the different tracts can be distinguished based on their termination areas. Different colors are used for the various bundles: yellow for the FAT, green for the external capsule, red for the internal capsule, and blue for the FCT. The frontal horn is entered to give a perspective of depth to the reader. The FCT forms the inner layer of the CS/CR white matter before entering the ventricle. Upper inset: Lateral view of the same hemisphere without colored highlights. FIG. 4. (continued)→
the frontostriatal tract proposed in the paper by Kinoshita et al. was further supported by Bozkurt and colleagues in a DTI and fiber dissection study.24 Again, the frontostriatal tract was identified as a fiber bundle connecting the pre-SMA with the caudate nucleus. However, in contrast to this anatomofunctional framework, recent DTI studies support the notion that the fronto-caudate pathway extends to a wider termination area than previously thought, including the dorsolateral, fronto-orbital, and ventrolateral prefrontal cortices.25–27 Similarly, accumulating evidence supports the theory that the FCT is also heavily implicated in behavioral symptoms, including apathy in patients with attention deficit hyperactivity disorder (ADHD).

It is therefore evident that the nomenclature used across

\[ \text{TABLE 2. DTI and dissection studies offering structural evidence on the morphology and connectivity of the FCT} \]

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Method of Investigation</th>
<th>Segmentation Terminology</th>
<th>Connectivity/Segmentation</th>
<th>Functional Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lehéncy et al., 200423</td>
<td>DTI</td>
<td>Frontostriatal tract</td>
<td>Caudate nucleus found to be more densely connected w/ ipsilateral pre-SMA than SMA &amp; MC</td>
<td>Motor preparation</td>
</tr>
<tr>
<td>Kamali et al., 201027</td>
<td>DTI</td>
<td>Prefronto-caudate pathway</td>
<td>Fibers originate from prefrontal cortex, pass through head of caudate nucleus (medially to ATR fibers), &amp; terminate at thalamus</td>
<td>Potential clinical applications in assessment of schizophrenia &amp; other cognitive disorders as well as PD, HD, &amp; MS</td>
</tr>
<tr>
<td>Rigoard et al., 201125</td>
<td>Dissection</td>
<td>Frontostriatal pathway</td>
<td>3 types of projections arising from OPFC: accumobfrontal fasciculus; connects most medial part of OMPFC w/ nucleus accumbens; intermediate fasciculus: remaining part of OMPC to inferiormedial part of head of caudate nucleus; &amp; lateral fasciculus: orbitolateral prefrontal cortex projection fibers to caudate nucleus</td>
<td>NM</td>
</tr>
<tr>
<td>Catani et al., 201228</td>
<td>DTI &amp; dissection</td>
<td>Frontostriatal tract</td>
<td>Connects premotor cortex &amp; frontal pole w/ head of caudate nucleus</td>
<td>Connections b/w caudate nucleus &amp; IFG participate in syntactic processing</td>
</tr>
<tr>
<td>Shang et al., 201326</td>
<td>DTI</td>
<td>Frontostriatal tract</td>
<td>4 connections: dorsolateral caudate, medial prefronto-caudate, orbitofronto-caudate, &amp; ventrolateral caudate</td>
<td>Children w/ ADHD had significantly lower GFA values in frontostriatal tracts</td>
</tr>
<tr>
<td>Lin et al., 201425</td>
<td>DTI</td>
<td>Frontostriatal tract</td>
<td>4 connections: caudate-DLPFC, caudate-VLPFC, caudate-MPFC, &amp; caudate-FOC</td>
<td>Youths w/ ADHD had significantly lower GFA values than controls in 4 pairs of frontostriatal tracts</td>
</tr>
<tr>
<td>Kinoshita et al., 201521</td>
<td>DTI &amp; mapping</td>
<td>Frontostriatal tract</td>
<td>Connects anterior part of caudate w/ pre-SMA (in pre-SMA intermingled w/ FAT fibers, w/ lateral found more anterior &amp; lateral)</td>
<td>Stimulation of FST in both sides resulted in motor initiation inhibition; FST stimulation linked to verbal fluency deficits</td>
</tr>
<tr>
<td>Chiang et al., 201527</td>
<td>DTI</td>
<td>Frontostriatal tract</td>
<td>Three connections: caudate-VLPFC, caudate-DLPFC, &amp; caudate-FOC tracts</td>
<td>ADHD pts had statistically significantly lower GFA in 3 lt FSTs than controls; GFA values of rt caudate–VLPFC &amp; bilateral caudate–DLPFs negatively correlated w/ inattention symptoms in youths w/ ADHD</td>
</tr>
<tr>
<td>Bozkurt et al., 201624</td>
<td>DTI &amp; dissection</td>
<td>Frontostriatal tract</td>
<td>Connects pre-SMA w/ head of caudate nucleus</td>
<td>NM</td>
</tr>
<tr>
<td>De Paepcke et al., 201912</td>
<td>DTI</td>
<td>Fronto-caudate connections</td>
<td>2 types of fronto-caudate connections: pre-SMA-caudate, DLPFC-caudate</td>
<td>HD pts w/ elevated MD in lt DLPFC-caudate nucleus white matter presented w/ higher levels of cognitive apathy; rt FST also exhibited increased MD associated w/ higher cognitive apathy levels</td>
</tr>
</tbody>
</table>

FST = frontostriatal tract; GFA = generalized fractional anisotropy; HD = Huntington disease; IFG = inferior frontal gyrus; MC = motor cortex; MD = mean diffusivity; MPFC = medial prefrontal cortex; MS = multiple sclerosis; NM = not mentioned; OMPFC = orbitomedial prefrontal cortex; OPFC = orbital prefrontal cortex; PD = Parkinson disease.

FIG. 4. Middle inset: Close-up of the frontal area. Arrows indicate the relative trajectory of the different tracts within the frontal white matter. The inferior view (lower left) illustrates the relationship of the FCT with respect to the CC and CRads. The dorsal segment of the FCT has been removed and the frontal horn is entered. The FCT lies lateral to the fibers of the CRads and medial to the fibers of the ATR and ALIC. Lower inset: The CC and CRads are highlighted in green, the FCT in blue, and the ATR in red. AF = arcuate fasciculus; ALIC = anterior limb of the internal capsule; ATR = anterior thalamic radiations; Caud = caudate nucleus; CC = corpus callosum; Cdb = body of the caudate nucleus; CdH = head of the caudate nucleus; CR = corona radiata; Crad = callosal radiations; CS = centrum semiovale; ExC = external capsule; FAT = frontal aslant tract; FCT = fronto-caudate tract; FCTd = dorsal component of the fronto-caudate tract; FCTv = ventral component of the fronto-caudate tract; Fh = frontal horn; GFA = generalized fractional anisotropy; GP = globus pallidus; IC = internal capsule; Ins = insula; Pop = pars opercularis; SLF = superior longitudinal fasciculus. Copyright Spyridon Komaitis. Used with permission. Figure is available in color online only.

Lower inset: FIG. 4. Close-up of the frontal area. Arrows indicate the relative trajectory of the different tracts within the frontal white matter. The inferior view (lower left) illustrates the relationship of the FCT with respect to the CC and CRads. The dorsal segment of the FCT has been removed and the frontal horn is entered. The FCT lies lateral to the fibers of the CRads and medial to the fibers of the ATR and ALIC. Lower inset: The CC and CRads are highlighted in green, the FCT in blue, and the ATR in red. AF = arcuate fasciculus; ALIC = anterior limb of the internal capsule; ATR = anterior thalamic radiations; Caud = caudate nucleus; CC = corpus callosum; Cdb = body of the caudate nucleus; CdH = head of the caudate nucleus; CR = corona radiata; Crad = callosal radiations; CS = centrum semiovale; ExC = external capsule; FAT = frontal aslant tract; FCT = fronto-caudate tract; FCTd = dorsal component of the fronto-caudate tract; FCTv = ventral component of the fronto-caudate tract; Fh = frontal horn; GP = globus pallidus; IC = internal capsule; Ins = insula; Pop = pars opercularis; SLF = superior longitudinal fasciculus. Copyright Spyridon Komaitis. Used with permission. Figure is available in color online only.

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studies is variable since some authors use the term “fronto-caudate tract” or “frontostrial tract” to describe the connectivity between the pre-SMA and caudate, while others use the same term to include additional fibers originating from the frontal pole and the dorsolateral, ventrolateral, and fronto-orbital cortices. This lack of consistent terminology paired with the diverse structural data met among different research groups adds confusion on the anatomy and functional significance of the FCT.

In an effort to elucidate this controversial issue, we used focused fiber dissections with the aim to offer sound evidence on the anatomy and essential characteristics of the FCT. We intentionally employed the white matter dissection technique as our basic method of investigation since it is documented to yield direct structural data of high accuracy and, as such, is currently used as one of the gold standards for validating DWI results. It needs to be stressed that although the DWI tractographic technique is a fast and noninvasive method that allows for real-time fiber dissections, it is unfortunately prone to erroneous results, mainly due to the effect of noisy peaks and ambiguous “crossing and kissing” configurations of fiber populations. Therefore, it has been repeatedly emphasized that even under ideal conditions the accuracy of such an indirect method like the DWI is inherently limited and further validation is necessary.13-20

Hence, by using fiber dissections we were able to consistently identify a deep-seated fiber tract seen to connect a wide area of the prefrontal cortex with the head and anterior part of the body of the caudate nucleus. This tract, for which we use the name “fronto-caudate tract” after its connectivity pattern, exhibits a fan-shaped configuration with wide axonal terminations recorded toward the DLPFC, VLPFC, pre-SMA, orbitopolar prefrontal cortex (OPPFC), and FOC. We were also able to parcellate and differentiate the fibers radiating from the pre-SMA and DLPFC from those coming from the frontopolar, fronto-orbital, and ventrolateral prefrontal cortices. The former group of fibers was invariably observed to end posterior to the point marked by the transition of the head to the body of the caudate nucleus, i.e., a point that corresponds to the foramen of Monro, while the latter group terminated anterior to this point. In this way, we could divide the tract into two distinct segments, i.e., a dorsal one (FCTd) connecting the pre-SMA and DLPFC with the anterior part of the body of the caudate, and a ventral one (FCTv) connecting the OFPFC, OPPFC, and VLPFC with the head of the caudate nucleus. This structural segmentation pattern is in agreement with previous studies advocating a functional distinction between a limbic and a cognitive frontostrial stream.

Further, our findings on the topography and spatial relationships of the FCT are in line with the relevant literature. The FCT was always encountered to reside lateral to the CRAd and medial to the fibers of the CR/internal capsule. Interestingly, the FCTv was seen to lie medial to the anterior limb of the internal capsule, while the FCTd was encountered medial to the fibers of the ATR that bypass the caudate nucleus to reach the thalamus. Left to right asymmetries were not observed, but instead we recorded an asymmetry within the FCT itself, with the ventral segment always being thicker and bulkier than the dorsal one. One can therefore hypothesize that the caudate nucleus exhibits stronger connectivity with the frontopolar and fronto-orbital cortices than with the pre-SMA and DLPFC.

Putative Functional Role of the FCT

The results of the current study lend support to traditional theories on the functional significance of prefronto-caudate connectivity. Alexander describes three discrete frontostrial circuits: a sensorimotor circuit processing information related to somatomotor and oculomotor function, an association (or cognitive) circuit connecting the pre-SMA and DLPFC to the striatum, and a limbic circuit connecting the FOC to the striatum.4 The association circuit is believed to orchestrate cognitive motor functions, such as visuomotor association, sequencing, and motor learning. Awake stimulation evidence also supports the notion that the association circuit is heavily involved in motor initiation and verbal fluency.23 The limbic circuit in turn is implicated in behavioral inhibition, decision-making, and motivation. In this framework, the frontostrial loop has been linked with a wide spectrum of motor and behavioral clinical entities, like autism, Parkinson disease, Huntington disease, schizophrenia, and ADHD.7,8,12,30 Indeed, our proposed connectivity and segmentation pattern offers a sound structural basis for Alexander’s functional paradigm. In that respect, the dorsal FCT seems to equal the association stream, while the ventral FCT is homologous to the limbic stream.

Overall, the FCT is documented to participate in the functional connectivity of the caudate nucleus with pre-motor and prefrontal areas. Hence, it can be conceptualized as a pathway bridging cognitive and motor behaviors. The caudate nucleus has been advocated to participate in a plethora of motor and nonmotor processes, such as procedural and associative learning and motor initiation and/or inhibition.21 Likewise, the premotor cortex orchestrates motor planning, sequencing, and modification by integrating internal cognitive and external sensory cues.31 The SMA/pre-SMA complex, in turn, controls motor sequencing, internal generated movement, locomotion, and postural stability and also plays a key role in motor ignition during volitional movement.22 Finally, the dorsal prefrontal, fronto-orbital, and frontal pole cortices are linked to a wide spectrum of cognitive and behavioral functions, including execution, attention, decision-making, complex behavioral planning, and social control.33 Since one way to infer the function of subcortical pathways is to map their axonal connectivity, it can be postulated that the FCT is implicated in integrating high-order behaviors such as motor and speech initiation, inhibition and sequencing, postural and gait stability, locomotion, attention preservation and shift, reward/reinforcement processes, planning, and motivation. It is clear, however, that more clinical data are needed for a thorough understanding of the tract’s anatomo-functional significance.

Role of the FCT in Modern Neurosurgery: Implications, Applications, and Complications

The role of the ventral internal capsule/ventral striatum (VCVS) as an effective and feasible target for deep
brain stimulation (DBS) in patients with depression- and obsessive compulsive disorder–related conditions has been thoroughly addressed by recent well-designed clinical studies.\textsuperscript{34–36} This surgical application arises from the hypothesis that DBS may act indirectly on the cortex, by intervening with the underlying white matter.\textsuperscript{37} Because of the wide cortical distribution pattern of fiber pathways, stimulating a confined area of white matter can putatively affect multiple cortical territories. In this regard, by stimulating the VCVS one could modify the activity of the fronto-orbital and medial prefrontal cortices, which are believed to participate in cognitive processes such as that of behavioral shaping driven by environmental cues. Hence, a better understanding of the spatial distribution of frontal fibers and their respective termination areas could contribute to a more effective and sophisticated DBS planning. In this framework, the confined area in which the FCT converges either to the head of the caudate as the FCTv or to the transition of the caudate head and body as the FCTd may potentially offer novel DBS targets for motor or psychiatric disorders. This also holds true for the newly introduced stereotactic ablative procedures used in modern functional neurosurgery.

In modern glioma surgery, awareness should be raised with regard to the implication of the FCT in what is known as the “negative motor modulatory network.”\textsuperscript{38} Evidence from awake brain mapping studies has linked the stimulation of the frontostriatal circuitry with intraoperative unilateral or bilateral movement disorders for both hemispheres and verbal fluency deficits for the dominant one.\textsuperscript{23} Nevertheless, the risk of a permanent and complete SMA syndrome (contralateral akinesia and mutism) is not high when resecting or transgressing negative motor areas; indeed, deficits in the control of fine motor behaviors, bimanual coordination, and dexterity may be present and should be carefully balanced in preoperative planning and decision-making.\textsuperscript{39,40} A tailored approach to achieve the optimal onco-functional balance for a given patient taking into consideration oncological, functional, occupational, and quality-of-life characteristics along with the patient’s personal will and consent is the mainstay of modern neuro-oncological treatment.\textsuperscript{41} This becomes even more relevant with regard to the emerging concept of “supratotal resections” applied in both low- and high-grade lesions to extend progression-free and overall survival, for which very balanced decisions along the aforementioned lines should be carefully made by patients and their physicians.

**Study Strengths and Limitations**

Klingler’s preparation entails the fixation of cerebral hemispheres in a formalin solution followed by a freeze-thaw process.\textsuperscript{42} The ice crystals that form during the freeze-thaw process separate the white matter fibers apart, and therefore one can subsequently identify and dissect them in the setting of a microneurosurgical laboratory. As recently documented by Zemmoura and colleagues, this procedure preserves the structural integrity of the nerve axons, and therefore the direct anatomical evidence provided is of high sensitivity and accuracy.\textsuperscript{43} Furthermore, the 3D architecture of the subcortical pathways and their spatial relationships are maintained and can be explored. For these reasons, the fiber dissection technique is one of the gold-standard direct anatomical methods used to validate indirect structural data coming from DWI tractographic protocols.\textsuperscript{13} More specifically, in the case of the FCT, the ability of tractography to readily differentiate this bundle from the adjacent ATR and ALIC is inherently limited, and that is what particularly accounts for the difficulty seen in previous tractographic studies to offer consistent structural evidence on the morphology, topography, and connectivity of the FCT.

The fiber microdissection method is, however, an expensive, time-consuming, operator-dependent in vitro technique. The spatial resolution of the data provided is lower in comparison with histology, optical coherence tomography, and polarized light imaging, and there are also limitations when simultaneously exploring fiber tracts with intermingling perpendicular trajectories because the proper dissection of the one can result in the destruction of the other.\textsuperscript{44,45}

**Conclusions**

Literature on the structure of the human fronto-caudate tract (FCT) has been not only scarce but also vague and at times inconsistent. With the fiber microdissection technique in our armamentarium, we were able to provide direct evidence of high accuracy in our analysis of the topography, morphology, and axonal connectivity of the FCT. We therefore consistently recorded the FCT as a discrete group of fibers stemming from a wide cortical area, including the pre-SMA, prefrontal cortex, and frontal pole, and terminating at the head and anterior part of the body of the caudate nucleus. The tract could be divided into two segments—dorsal and ventral—according to the respective connectivity pattern observed. These findings seem to be in agreement with the putative functional significance attributed to the frontostriatal circuitry in the neuroscientific literature and can potentially inform current surgical practice in the area of neuro-oncology and functional neurosurgery.

**References**

Disclosures
The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions
Conception and design: Komaitis, Koutsarnakis. Acquisition of data: Komaitis, Koutsarnakis, Lani. Analysis and interpretation of data: all authors. Drafting the article: Koutsarnakis, Komaitis. Critically revising the article: Koutsarnakis, Komaitis, Kalamatianos, Kalyvas, Stranjalis. Reviewed submitted version of manuscript: Koutsarnakis, Komaitis. Approved the final version of the manuscript on behalf of all authors: Koutsarnakis. Administrative/technical/material support: Stranjalis. Study supervision: Koutsarnakis, Stranjalis.

Supplemental Information
Videos

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