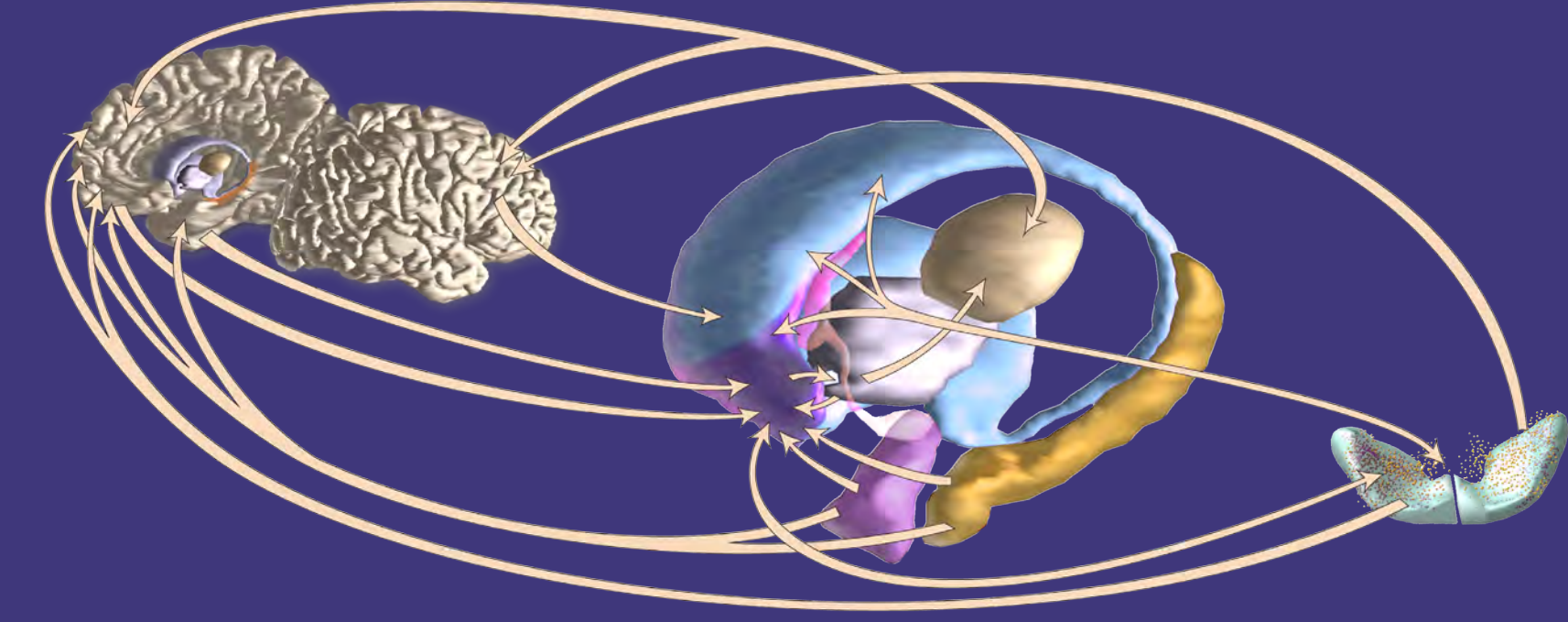


Cortical and subcortical pathways through the cingulum bundle: Implications for neuroimaging and psychiatric disorders.

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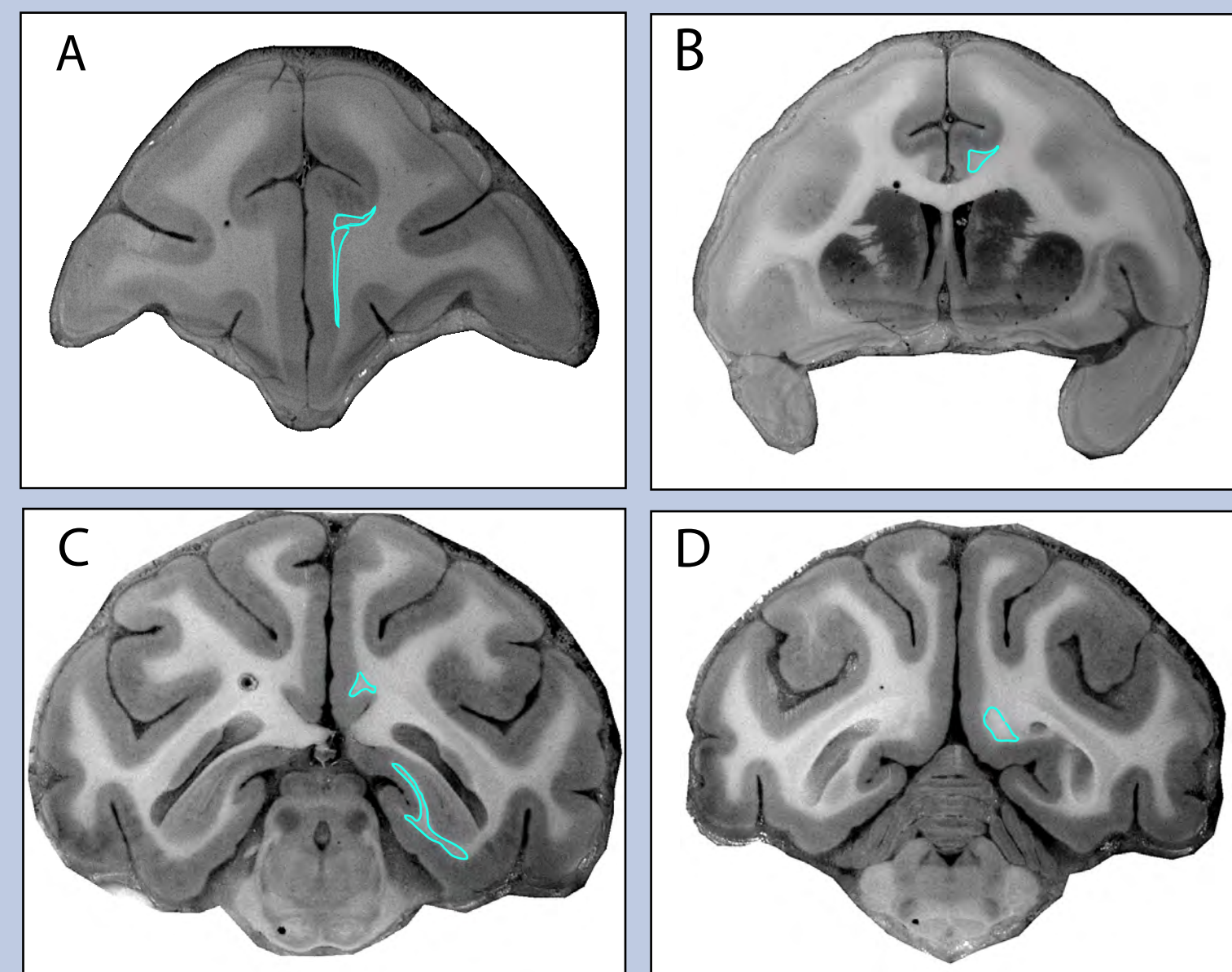
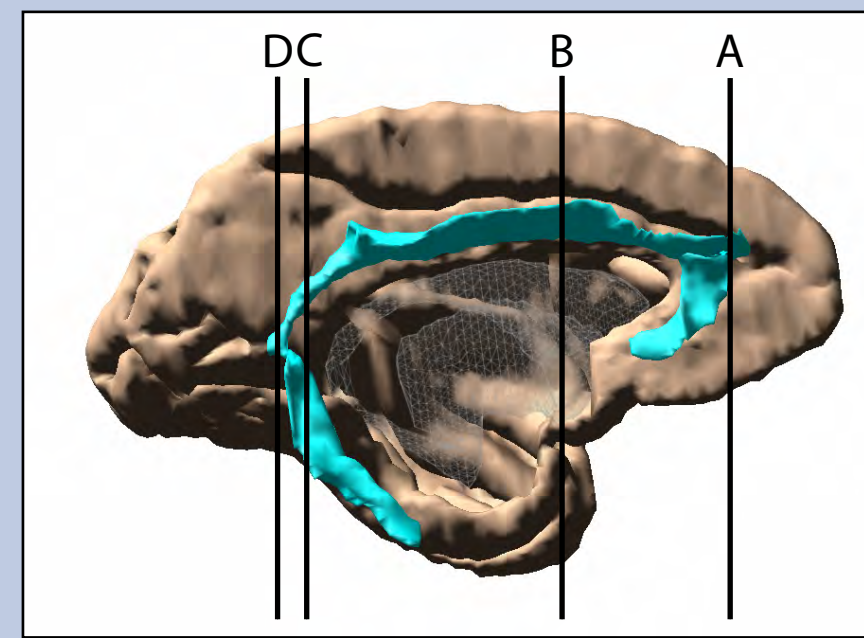
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INTRODUCTION

Diffusion tensor imaging (DTI) shows that the white matter in the cingulum bundle (CB) is abnormal in a variety of psychiatric disorders, including depression, obsessive-compulsive disorder (OCD), and schizophrenia. Intriguingly, the CB is also an effective target of ablative neurosurgical treatment for depression and OCD, along with other psychiatric disorders. The CB is a collection of fibers positioned laterally and ventrally to the cingulate gray matter stretching from the frontal lobe to the parietal and temporal lobes. Traditionally, the CB has been closely associated with the cingulate cortex, known primarily for the many cingulate-cingulate projections it carries. Investigations have shown that subcortical fibers also utilize the CB, although these studies were exclusively focused on the thalamus (Mufson & Pandya, 1984). Other, non-cingulate cortical regions may also travel within the CB to access cingulate cortex. Although the CB is crucial for understanding psychiatric disorders, we do not know the origins, destinations, and routes cortical and subcortical fibers take through it, and thus cannot know exactly which fibers are being targeted with DTI and surgical techniques.

THE CINGULUM BUNDLE



- Pregenually, fibers from the CB extend ventrally and caudally into subgenual cingulate cortex. At this stage, the divisions between the subgenual CB and the adjacent uncinate fasciculus remain unclear, so our models have focused on the dorsal CB.
- The CB carries fibers rostrally and caudally. Many fibers terminate in nearby cingulate gray matter.
- The CB is briefly present both dorsal and ventral to the corpus callosum. Caudally, it extends into the temporal lobe.
- At the splenium, the CB courses ventrally and curves back under the corpus callosum.

The goals of this study were to:

- Understand how the CB is organized with respect to specific cingulate pathways.
- Establish whether other prefrontal (non-cingulate) cortical areas utilize the CB.
 - Characterize their trajectories through the bundle.
- Delineate serotonergic, dopaminergic, and cholinergic trajectories through the CB to characterize how transmitter systems utilize this bundle.

RESULTS

Figures 1-3 show cingulate (1), non-cingulate cortical (2), and subcortical (3) fiber pathways through the CB. Sagittal CB sections illustrate the rostral-caudal position of each tracing. Red outlines indicate terminal fields; purple outlines indicate fiber bundles; unique colors indicate the CB for each case.

Figure 1: Cingulate pathways through the CB, from anterior cingulate (1A and B) and posterior cingulate (1C). Cingulate fibers enter the CB immediately. Many will leave quickly for other destinations: the internal capsule, external capsule, the LPFC, etc. Others join the CB and travel rostrally and caudally to terminate in anterior cingulate, posterior cingulate, and dorsomedial cortex.

Figure 2: Other cortical pathways through the CB, from vmPFC (2A), dlPFC (2B), and dmPFC (2C). VmPFC fibers enter the CB subgenually, then traverse its length to terminate in anterior cingulate, posterior cingulate, and dorsomedial cortex. Fibers initially occupy a ventral and medial part of the bundle, then extend dorsally. dlPFC fibers occupy a substantial portion of the CB. They course caudally to terminate in anterior and posterior cingulate. DmPFC fibers do not travel extensively within the CB.

Figure 3: Subcortical pathways through the CB (3A: nucleus basalis; 3B: SERT; 3C: TH). Nucleus basalis fibers enter the CB pregenually, having traveled there medially within the uncinate fasciculus. They first occupy a dorsal aspect of the CB, then a ventral and medial portion. They terminate extensively within cingulate and dorsomedial cortex, largely in superficial layers. They also terminate in the indusium griseum. Serotonergic and dopaminergic fibers travel within the CB, occupying mainly a dorsal and medial position. Serotonergic fibers also heavily innervate the indusium griseum.

Figure 1: Cingulate pathways through the CB, from anterior cingulate (1A and B) and posterior cingulate (1C).

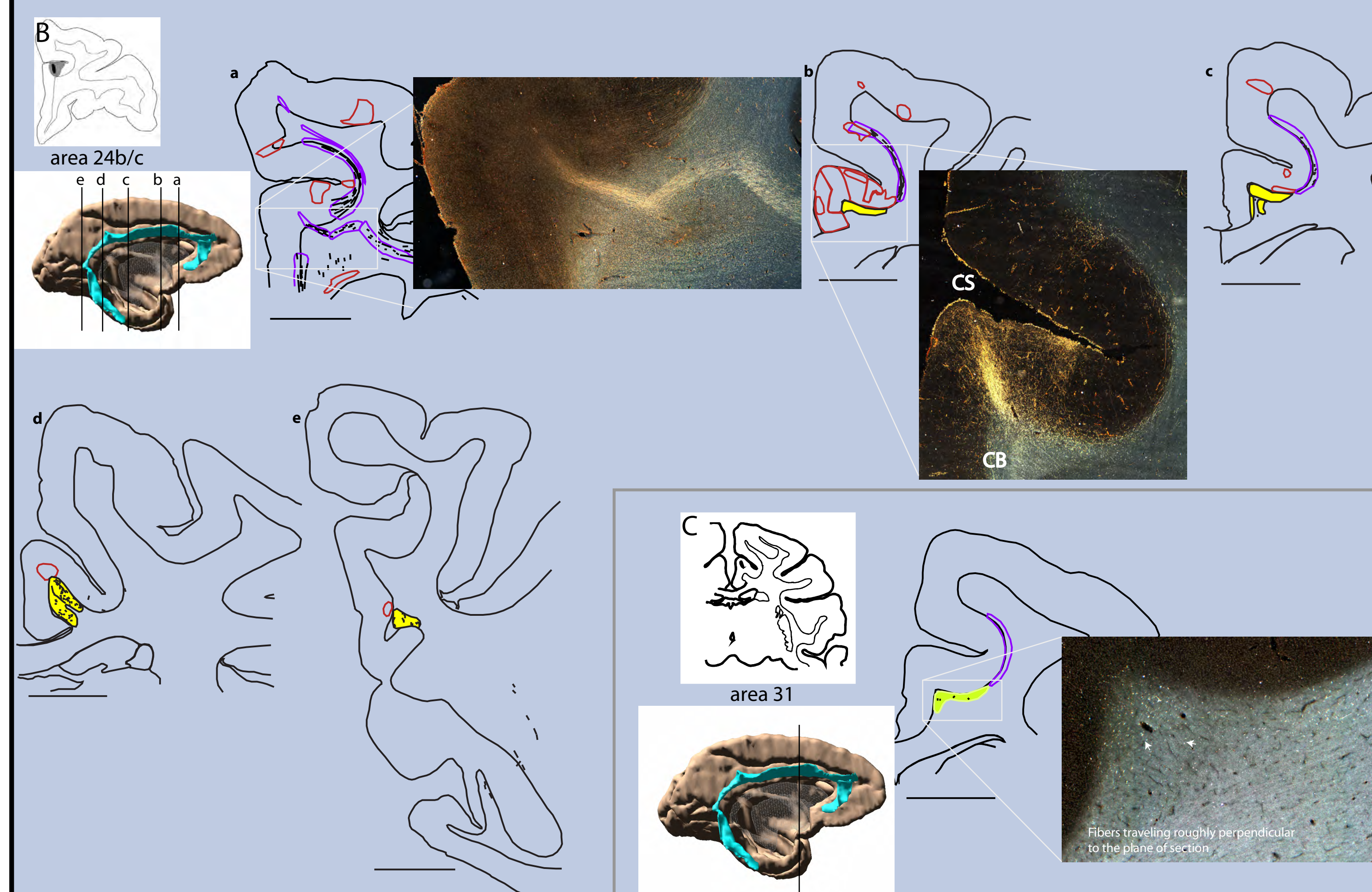
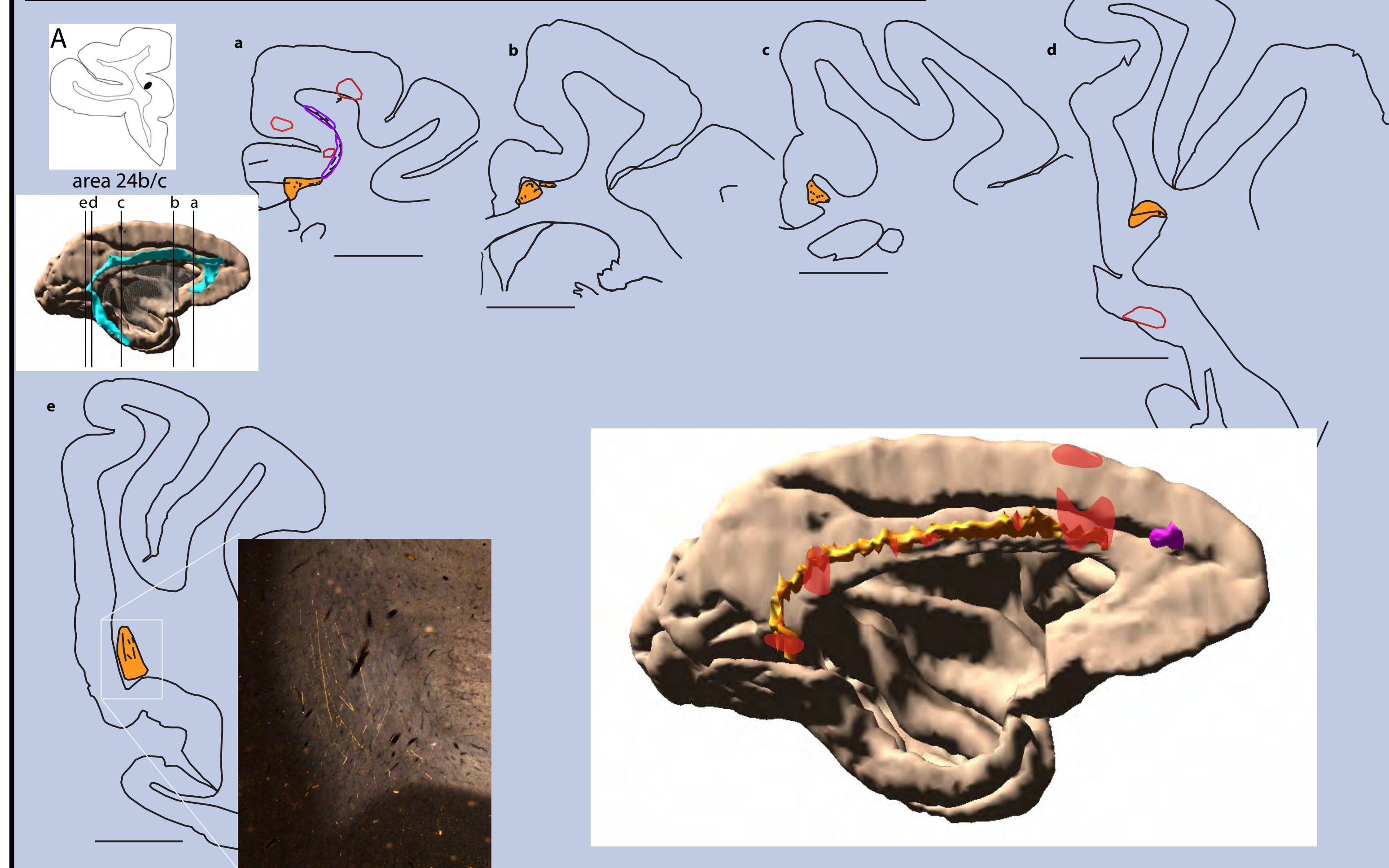


Figure 3: Subcortical pathways through the CB (3A: nucleus basalis; 3B: SERT; 3C: TH).

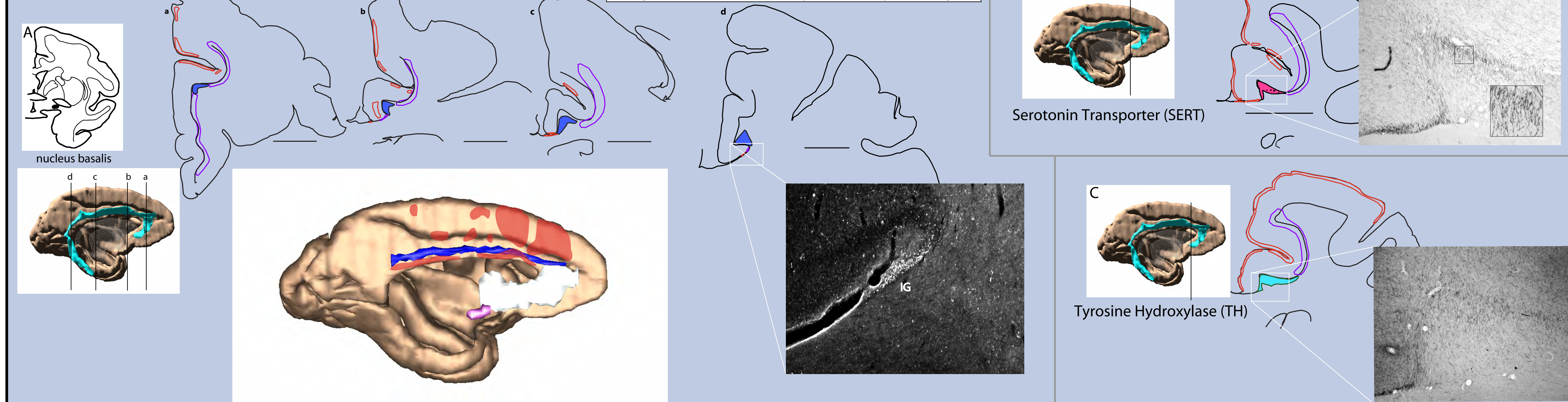


Figure 2: Other cortical pathways through the CB, from vmPFC (2A), dlPFC (2B), and dmPFC (2C).

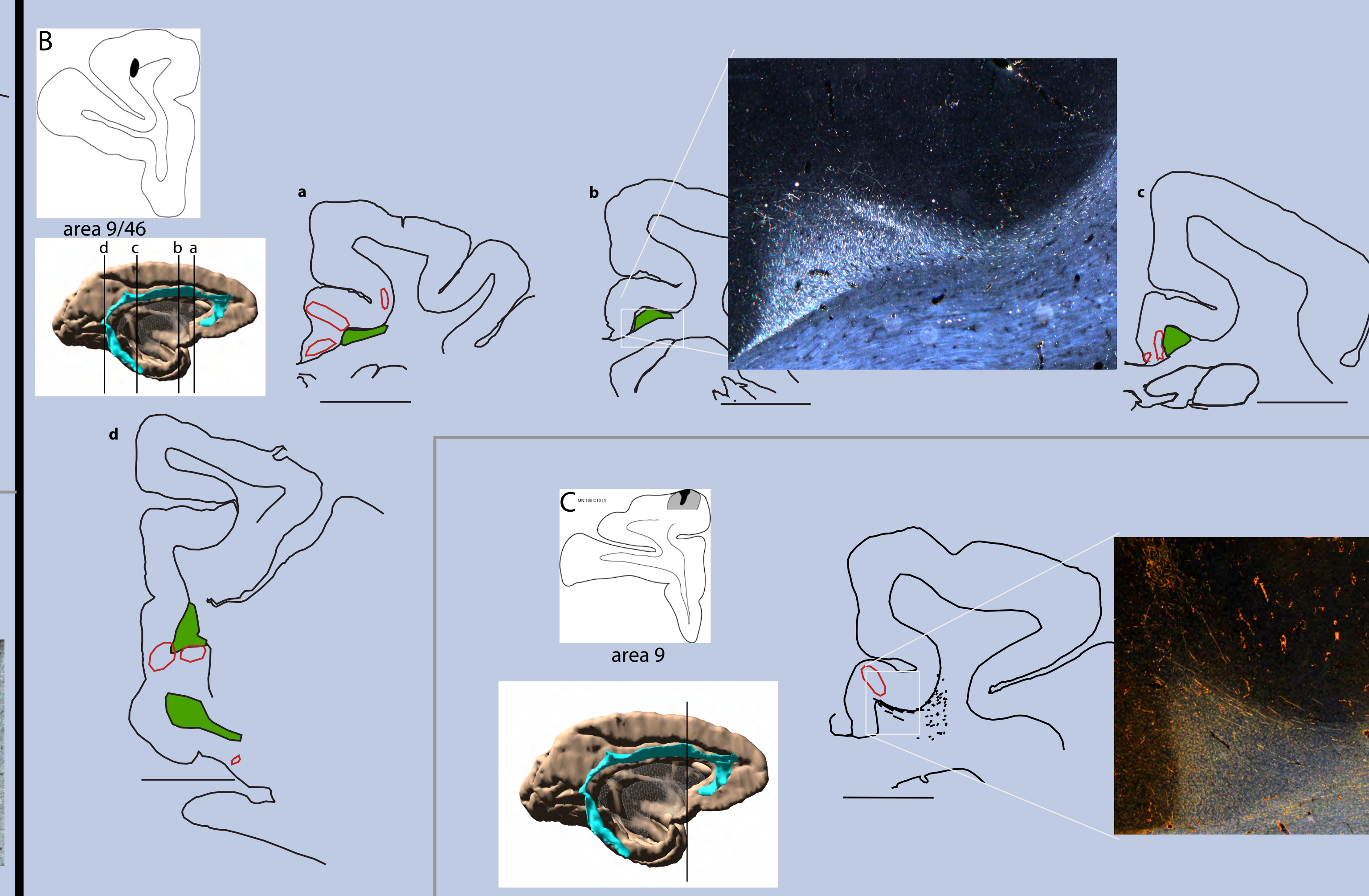
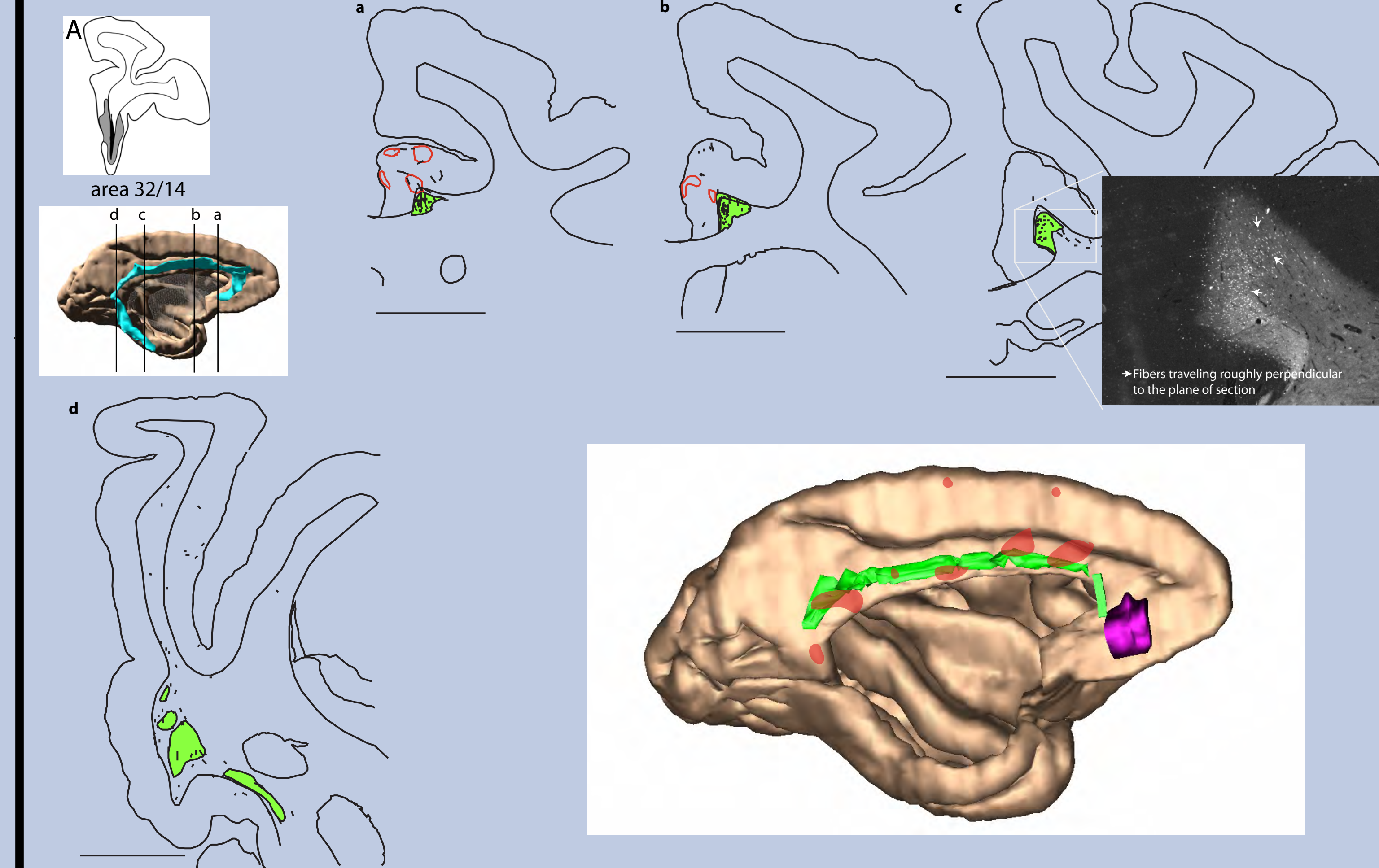
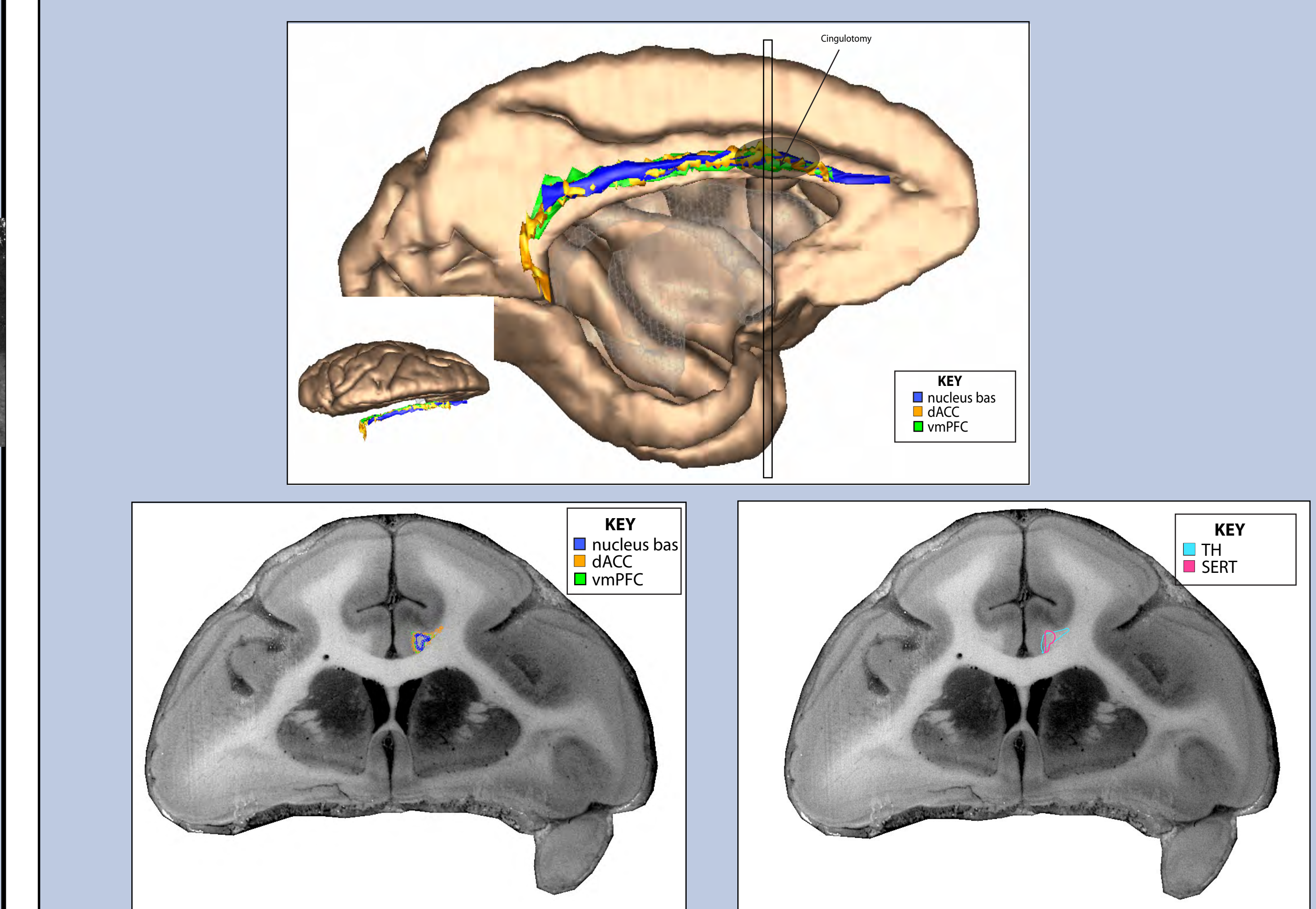


Figure 4: CB pathways likely interrupted by a cingulotomy lesion



CONCLUSIONS

Fibers originating or terminating in cingulate cortex pass through the CB, but many of these do not actually join the CB. Fibers that pass briefly through the CB include ascending, descending, and some cortical fibers.

Fibers that travel long distances within the CB include: a. cortical and subcortical fibers that terminate at specific points in cingulate. b. cortical and subcortical fibers that terminate at specific points in dorsomedial cortex. This subset of fibers exits the CB dorsally via short association pathways to terminate above the cingulate sulcus.

Neurotransmitter systems utilize the CB far more than previously believed. Cholinergic, serotonergic, and dopaminergic fibers travel within the CB to terminate in cingulate, dorsomedial cortex, and the indusium griseum.

The CB is closely linked with the indusium griseum, a small piece of gray matter resting between the corpus callosum and the cingulate. Subcortical fibers travel extensively within the CB before terminating in the indusium griseum.

In interpreting DTI and cingulotomy results, the CB should not be considered interchangeable with adjacent cingulate cortex. Any given CB region contains a wide range of passing fibers that neither originate nor terminate in nearby cingulate.

METHODS

Injections of bidirectional neural tracers (FR, FS, and LY) and anterograde tridiated amino acid (AA) were placed in cingulate cortex (areas 24b/c and 31), vmPFC (areas 14 and 32), dlPFC (areas 9 and 46), and the nucleus basalis of macaques. Other tissue was processed for tyrosine hydroxylase (TH) or serotonin transporter (SERT) immunocytochemistry to show dopaminergic and serotonergic fibers, respectively. Fiber pathways and resulting terminals through the cingulum bundle were charted on the ipsilateral side to the injection. For display purposes, tracings have been placed on the right hemisphere. For a subset of cases, mapped fibers and terminals were rendered in 3-D on a standard macaque brain. Experiments were conducted according to the Guide for the Care and Use of Laboratory Animals as adopted by the NIH.

Abbreviations

vmPFC=ventromedial prefrontal cortex
dlACC=dorsal anterior cingulate cortex
CS=cingulate sulcus
CB=cingulum bundle
IG=indusium griseum

DTI=Diffusion tensor imaging
TH=tyrosine hydroxylase
SERT=serotonin transporter
dlPFC=dorsolateral prefrontal cortex
dmPFC=dorsomedial prefrontal cortex

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