Medial forebrain bundle structure is linked to human impulsivity

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Comparative research indicates that projections from midbrain dopamine nuclei [including the ventral tegmental area (VTA)] to the ventral striatum [including the nucleus accumbens (NAcc)] critically support motivated behavior. Using diffusion-weighted imaging and probabilistic tractography in humans, we characterized the trajectory and structure of two tracts connecting the VTA and NAcc, as well as others connecting the substantia nigra and dorsal striatum. Decreased structural coherence of an inferior VTA–NAcc tract was primarily and replicably associated with increased trait impulsivity and also distinguished individuals with a stimulant use disorder from healthy controls. These findings suggest that decreased coherence of the inferior VTA–NAcc tract is associated with increased impulsivity in humans and identify a previously uncharacterized structural target for diagnosing disorders marked by impulsivity.

INTRODUCTION

Although small in size and buried deep in the brain, the medial forebrain bundle (MFB) carries critical signals for fueling motivated behavior (1). In comparative studies, MFB lesions can blunt motivation, but electrical stimulation of this tract can energize motivated behavior (2–5). The MFB carries monoaminergic projections that ascend from focal midbrain nuclei to broadly modulate multiple subcortical and cortical circuits (1). Of these diverse projections, comparative research has specifically implicated dopaminergic neurons projecting from the ventral tegmental area (VTA) of the midbrain to the nucleus accumbens (NAcc) of the ventral striatum (VS) in motivating anticipation and pursuit of rewards (6, 7). Thus, the structure as well as the function of these tracts may hold relevance for motivated and impulsive behaviors—ranging from healthy to pathological (8).

In humans, assessing MFB structure has proven difficult. Challenges may arise from variation in cells within and next to the MFB, crossing fibers passing through the MFB, and limits on the spatial resolution of neuroimaging methods (9, 10). Recent advances in diffusion-weighted imaging (DWI) and probabilistic tractography, however, may support more precise assessment of these subcortical tracts in humans. Specifically, these methods allow statistical evaluation of evidence for tract existence and trajectory, as well as estimation of the qualities of identified tracts in humans (11, 12). For instance, researchers have recently identified MFB tracts by localizing specific structural targets in individuals’ native brain space (13) rather than warping the data into a standard brain space. Researchers have not yet characterized the trajectory of MFB tracts relative to other midbrain-striatal tracts nor have they examined whether qualities of the MFB are associated with traits related to motivated and impulsive behavior.

We combined DWI with probabilistic tractography to attempt to identify white matter tracts connecting the midbrain to the striatum and then characterized their coherence using standard diffusion metrics [e.g., fractional anisotropy (FA) and inverse mean diffusivity (1-MD)]. Next, we determined whether qualities of the identified tracts were associated with individual differences in trait impulsivity [assessed by self-report on the Barratt Impulsiveness Scale (BIS) (14) and delay discounting choices (15)] in a healthy sample, as well as a replication sample. Last, we examined whether tract coherence differed in individuals diagnosed with a disorder marked by impulsivity—stimulant use disorder (SUD) (16).

On the basis of comparative anatomical tract-tracing studies of monkeys [e.g., (7)], we predicted that DWI and probabilistic tractography would resolve MFB projections connecting the VTA and the NAcc as well as other midbrain–striatal tracts in healthy humans and that their connectivity would show similar ventromedial–dorsolateral topographical organization. We additionally predicted that measures of MFB tract coherence (i.e., FA and 1-MD) would replicably correlate with individual differences in impulsivity. Last, we predicted that measures of MFB tract coherence might distinguish individuals with a diagnosis of SUD (associated with high impulsivity) from healthy control subjects.

RESULTS

Identification of midbrain–striatal tracts

Probabilistic tractography successfully resolved all predicted midbrain–striatal tracts in every individual in the initial sample (n = 40) [seed and target volumes of interest (VOIs) are depicted in Fig. 1]. Visualization of results for midbrain to NAcc tracts further revealed that fibers connecting these VOIs took two distinct trajectories: one below the anterior commissure (labeled the “inferior NAcc tract”) and another above the anterior commissure that entered the NAcc from a more dorsal aspect (labeled the “superior NAcc tract”). To separately characterize the white matter properties of these distinct tracts, tractography was performed again with an exclusionary mask at the anterior commissure that isolated fibers in the inferior versus superior NAcc tracts. In each subject, this analysis identified an inferior NAcc tract running through the lateral hypothalamic area (adjacent to the mamillary bodies) and entering the NAcc from below the anterior commissure [consistent with the MFB trajectory described in human brain atlases (17)] and a superior NAcc tract running above the anterior commissure through the anterior limb of the internal capsule (ALIC) to enter the NAcc more dorsally [see also (18) and Fig. 1B]. Tracts connecting midbrain with caudate and putamen striatal VOIs were also identified in each individual, and
these traveled anterior to the corticospinal tract through the ALIC before diverging medially to terminate in the caudate or laterally to terminate in the putamen (Fig. 1).

**Midbrain-striatal tracts show a medial-lateral topographic organization**

To test for the medial-lateral gradient of midbrain origins of NAcc, caudate, and putamen tracts described in comparative research, the center of mass was calculated for each tract’s termination point in the midbrain VOI. Absolute values of the center of mass of coordinates in MNI (Montreal Neurological Institute) space in left and right hemispheres were then averaged. A repeated-measures one-way analysis of variance (ANOVA) of the center of mass was calculated for each tract and across left and right hemispheres, yielding single measures of FA and 1-MD for each fiber tract. We then calculated the correlation between these structural coherence metrics and trait scores on a self-reported measure of impulsivity (i.e., the BIS-11). Subject age and head motion during the magnetic resonance imaging scan were included as covariates of no interest, based on previous evidence that these variables might confound diffusivity measures (21, 22).

Analyses revealed that inferior NAcc tract coherence metrics (FA and 1-MD) were inversely associated with trait impulsivity such that inferior NAcc tract FA (r = –0.43, P = 0.008) and 1-MD (r = –0.39, P = 0.02) negatively correlated with impulsivity measures. Coherence metrics of other tracts, however, were not associated with impulsivity. Specifically, correlations of superior NAcc tract (FA: r = –0.07, P = 0.68; 1-MD: r = –0.04, P = 0.82), caudate tract (FA: r = –0.15, P = 0.36; 1-MD: r = –0.23, P = 0.16), and putamen tract (FA: r = –0.14, P = 0.41; 1-MD: r = –0.16, P = 0.34) coherence with impulsivity were not significant (Fig. 3; fig. S1 depicts a similar pattern in analyses that do not control for age and motion). To rule out potential volumetric confounds associated with impulsivity (23, 24), further analyses that controlled for the volumes of the brain regions of interest did not diminish the specific association between inferior NAcc tract coherence metrics and trait impulsivity [inferior NAcc tract FA β = –0.49, P = 0.01, age β = –0.15, motion β = 0.24, VTA/substantia nigra (SN) volume β = –0.01, NAcc volume β = –0.28, caudate volume β = 0.07, putamen volume β = 0.20; inferior NAcc tract 1-MD β = –0.44, P = 0.03, age β = 0.18, motion β = 0.00, VTA/SN volume
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**Inferior NAcc tract coherence is associated with SUD diagnosis**

Because trait impulsivity represents a risk factor for the development of addictive disorders (30, 31), we next tested whether structural...
coherence of the MFB differed between patients with an SUD (n = 63) and healthy controls (n = 40 from the first experimental sample; see tables S1 and S2 for group demographics). Comparison of coherence metrics revealed reduced FA in SUD versus healthy individuals in all midbrain-striatal tracts. After controlling for head motion, age, sex, education, depression scores, and smoking status (see table S1), reduced FA of the inferior NAcc tract remained significantly associated with SUD diagnosis (t_{50} = −2.16, P = 0.03; see table S3 for full regression results), whereas the other tracts did not (group effect for superior NAcc tract FA: t_{63} = −0.86, P = 0.39; caudate tract FA: t_{93} = −1.47, P = 0.14; putamen tract FA: t_{93} = −0.41, P = 0.68). In contrast, FA was not significantly associated with susceptibility to relapse in individuals diagnosed with SUD in any of the midbrain-striatal tracts (inferior NAcc tract FA: t_{54} = 0.14, P = 0.89; superior NAcc tract FA: t_{54} = 1.05, P = 0.30; caudate tract FA: t_{54} = 0.01, P = 0.99; putamen tract FA: t_{54} = 0.78, P = 0.44; Fig. 5). Inverse MD did not significantly differ by group (SUD patients versus healthy controls) or treatment outcome (SUD abstainers versus relapers at 6 months; fig. S5).

Bootstrapped accelerated mediation analyses further tested whether individual differences in trait impulsivity could account for the association of inferior NAcc tract coherence (indexed by FA and controlling for age and motion) with SUD diagnosis. The total effect of inferior NAcc tract coherence to SUD diagnosis was significant (Z = −3.29, P = 0.001), as were indirect paths from inferior NAcc tract coherence to trait impulsivity (Z = −1.99, P = 0.047) and from trait impulsivity to SUD diagnosis (Z = 5.28, P < 0.001). Including the indirect paths only partially mediated the influence of the direct path (indirect mediation effect: Z = −1.78, P = 0.08; direct effect: Z = −2.48, P = 0.01), suggesting that although they shared some variance, both inferior NAcc tract coherence and trait impulsivity could account for unique variance in explaining SUD diagnosis. Last, a signal detection analysis examined which factors contributed to classification of SUD diagnosis. Compared to 50% chance classification, area under the curve (AUC) for BIS impulsivity was 78% (d′ = 0.76), AUC for inferior NAcc tract structure was 64% (d′ = 0.69), and AUC for the combination of BIS impulsivity and MFB structure was 81% (d′ = 1.07), consistent with both features contributing to the classification of SUD diagnosis (Fig. 6). A final analysis conducted to test whether the duration of stimulant use (dated from SUD patients’ first use) was associated with inferior NAcc tract FA found no relationship (t_{61} = −0.15, P = 0.88).

**DISCUSSION**

By combining DWI with probabilistic tractography, we were able to visualize distinct white matter tracts connecting midbrain (including the VTA and SN) and striatum (including the NAcc, caudate, and putamen), as well as to characterize their qualities in humans. Results revealed two distinct midbrain projections to the NAcc—one inferior and another superior to the anterior commissure. Further, in both initial (n = 40) and replication samples (n = 31), reduced inferior NAcc tract coherence was associated with increased trait impulsivity. Last, patients with SUD, which was marked by increased impulsivity, showed reduced coherence of the inferior NAcc tract.

This work makes several novel contributions. First, these results extend comparative research by reliably identifying and distinguishing distinct projections connecting the midbrain and striatum in humans. Specifically, the findings reveal that projections from the midbrain to the NAcc include two tracts—one following an inferior trajectory, and the other following a more superior trajectory [see also (13)]. While fiber tracts projecting from the midbrain to striatum showed a clear medial-to-lateral gradient, tract termination points also showed some overlap. This spatial organization corresponds with the “ascending spiral” circuit organization described in anterograde and retrograde tracing studies of monkey midbrain connectivity (32)—a circuit architecture implicated in converting motivation into action (7, 33). Second, the findings resolved and replicated an association of decreased inferior NAcc tract coherence (i.e., FA and 1-MD) with increased trait impulsivity. This association was not apparent in the superior NAcc tract or in other adjacent tracts connecting the midbrain to the dorsal striatum. Inferior NAcc tract coherence was most robustly associated with individual differences in impulsivity, but not with other personality traits (see fig. S2). Third, the findings demonstrate that decreased inferior NAcc tract coherence also marked individuals diagnosed with SUD, which is associated with elevated trait impulsivity. Thus, both decreased inferior NAcc tract coherence and trait impulsivity contributed to the classification of having an SUD diagnosis.

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**Fig. 3. Association of tract diffusion measures with trait impulsivity (controlling for age and head motion).** FA and 1-MD of the inferior NAcc tract were both significantly associated with decreased trait impulsivity (BIS; top row), but other tracts’ coherence measures were not (bottom three rows).
The association of inferior NAcc tract coherence with individual differences in impulsivity adds a new structural dimension to existing translational findings. For instance, researchers have associated individual differences in impulsivity with decreased dopamine (D2/D3) receptor binding in the VTA and NAcc of both rodents and humans (34–36). Given its association with impulsivity, an interesting further step might involve determining whether inferior NAcc tract structure links to neurochemical correlates at tract endpoints. Finer-grained visualization of tract trajectories revealed that the association of reduced inferior NAcc tract coherence with trait impulsivity was most pronounced in the middle, near the lateral hypothalamus (Fig. 4), highlighting a specific anatomical target for future study. A rich tradition of comparative research has critically implicated the lateral hypothalamus in diverse motivated behaviors (e.g., including seeking food, sex, and drugs) via its connections with the VTA and NAcc, among other regions (37, 38). Future targeted investigations might explore how the structure and function of this circuit is associated with different motivated behaviors in healthy humans, as well as those with disordered impulse control. This anatomical localization also reinforces a growing body of human neuroimaging evidence suggesting that structural associations with function can vary along tract trajectories (39), confirming that probabilistic tractography can potentially add value to whole-brain analyses.

Although these findings associate reduced inferior NAcc tract coherence with SUD diagnosis, they cannot establish which occurs first (or whether they are causally linked). On the one hand, chronic stimulant use might progressively degrade the coherence of tracts carrying motivational signals that drive behavioral impulses. On the other hand, decreased coherence of the inferior NAcc tract may pose a preexisting risk factor for impulse control disorders (including SUD), because individuals with blunted motivation may seek out more intense stimuli (40). The association of inferior NAcc but not other midbrain-striatal tracts’ coherence with SUD diagnosis and the absence of an association of inferior NAcc coherence with years of use argue against a cumulative neurotoxic effect of stimulants. While reduced inferior NAcc tract coherence classified SUD diagnosis, it was not associated with subsequent relapse to stimulant use. Escalation from recreational to chronic stimulant use versus relapse from abstinence to renewed use may involve different circuits (e.g., subcortical versus cortical), so future research might profitably explore whether coherence of other tracts [e.g., frontostriatal (41)] are more implicated in stimulant use relapse than onset.

Relative to previous work, the current design features several strengths. We recruited healthy community members (rather than more convenient students), as well as a replication sample. The neuroimaging analyses identified specific tracts of interest based on comparative research and separately estimated their structural qualities.

**Fig. 4. Association of inferior NAcc tract coherence with trait impulsivity is strongest near the lateral hypothalamus.** (A) Each tube represents the core trajectory of one subject’s left inferior NAcc tract, transformed into MNI space. Colors indicate the strength of correlation between FA and trait impulsivity (BIS scores). The white dotted line shows the coronal slice with the strongest correlation (Y = –9). (B) Coronal view of fiber density at the peak slice [indicated by dotted line in (A)]. Fiber density is calculated across subjects to illustrate spatial specificity across subjects of the tract trajectory in MNI space. The hypothalamus [based on the CIT168 atlas (28)] is outlined in white to demonstrate the overlap of the inferior NAcc tract with this region. (C) Correlation between FA and BIS at peak association tract node [indicated by dotted line in (A)]. (D to F) Same analysis depicted in the replication sample. Peak coronal slice depicted in (E) is Y = –8.
in original brain space. These tractography analyses might resolve greater anatomical detail than popular whole-brain voxel-based analyses (e.g., TBSS), which require warping individual brains to a group template as well as warping white matter to a “skeleton”—procedures that could compromise coverage of small subcortical regions with crossing fibers (see fig. S5). Associations remained robust after controlling for potential confounds (e.g., age, sex, head motion, depression, education, and smoking) and were anatomically specific to a ventral but not more dorsal tracts connecting the midbrain and striatum. The association of inferior NAcc tract coherence with both healthy individual differences in impulsivity and clinical SUD diagnosis provides some convergent validation that this structure might scaffold a common underlying process.

The current design also has some limitations. DWI cannot resolve the directionality of projections between the midbrain and striatum, but triangulation with more invasive comparative probes could help resolve directional influences (7). The physiological substrates underlying diffusion coherence metrics are also ambiguous, because crossing fibers and iron deposition may decrease measurement accuracy (42). Comparative physiological studies might better clarify specific physiological contributions to these metrics. While the current findings focused on tracts connecting the midbrain and striatum, tracts connecting the frontal cortex and striatum have also been associated with individual differences in impulsivity (43–45), and so future work might combine the two. Although the malleability or plasticity of tract coherence metrics has not been resolved, tract metrics appear to show robust temporal stability within testing sessions (46), suggesting that they might offer a stable baseline for tracking subsequent change. To assess individual differences in impulsivity, we used a reliable and valid self-report measure [i.e., the BIS (14)], which showed some but not complete concordance with a related measure [i.e., delay discounting (15); fig. S2]. Future studies might augment these self-report measures of impulsivity with behavioral indices of impulsivity that feature comparable reliability and validity (47).

The novel association of inferior NAcc tract structural coherence with impulsive traits and related disorders suggests new research opportunities. Advances in comparative methods now allow researchers to characterize homologous tracts across species. Combining physiological methods (e.g., CLARITY) with DWI in animal models might better specify the location and direction of identified tracts and illuminate which physiological properties of white matter

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**Fig. 5.** Midbrain-striatal tract FA as a function of SUD diagnosis (SUD group, $n = 63$; controls, $n = 40$) and treatment outcome (relapsed <6 months = 24; abstained >6 months = 30; 9 lost to follow-up). Reduced FA of the inferior NAcc tract was associated with SUD diagnosis but not with relapse (top row). *$P < 0.05$.

**Fig. 6.** Mediation analysis and classification curves clarifying the contributions of inferior NAcc tract coherence and trait impulsivity as diagnostic markers of SUD. (A) Impulsivity only partially mediated the association between inferior NAcc tract FA and SUD diagnosis. *$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$. (B) Receiver operating characteristic curves illustrating different models’ classification of SUD diagnosis. Area under the curve (AUC) scores are in parentheses.
Materials and Methods

Subjects were scanned with DWI and then completed the BIS-11 (14) along with other questionnaires after scanning (see Supplementary Methods). Probabilistic tractography was performed to resolve tracts connecting the midbrain and each striatal VOI separately in each hemisphere. DWI coherence measures were then extracted along the anatomical trajectory of each tract and submitted to regression analyses with impulsivity (BIS) scores. Tract coherence metrics included PA and 1-MD, which respectively represent directional and (inverse) general movement of fibers. Consistent with these structural findings, researchers have reported reduced correlations in the resting activity of target regions of the inferior NAcc tract in more impulsive individuals and stimulant users (51, 52). Clinically, white matter tract coherence measures might extend to diagnosing, predicting, and tracking changes in impulsivity in relevant disorders [e.g., (45, 53, 54)]. Eventually, measures of deep brain tracts may help to not only improve the visualization and measurement of brain structures but also track changes in those structures that can promote impulse control.

Supplementary Materials

Supplementary material for this article is available at http://advances.sciencemag.org/cgi/content/full/6/38/eaba4788/DC1

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