The Accumbofrontal Tract: Diffusion Tensor Imaging Characterization and Developmental Change from Childhood to Adulthood

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Abstract: The presence of an anatomical connection between the orbitofrontal cortex and ventral striatum, forming a so-called reward network, is well established across species. This connection has important implications for reward processing and is relevant to a number of neuropsychiatric disorders. Moreover, white matter (WM) is known to continue to mature across adolescence and into early adulthood, and developmental change in the reward network is an important component of models of decision making and risk taking. Despite the importance of this connection, the underlying WM has only recently been characterized in humans histologically, and not yet in-vivo using brain imaging. Here, we implemented diffusion tensor imaging (DTI) in a large cross-sectional sample of 295 healthy individuals ages 8–68 to further characterize the WM of this connection and its development from childhood into adulthood. We demonstrate that the accumbofrontal tract, connecting the orbitofrontal cortex and nucleus accumbens, can be identified using standard DTI sequences. Using Poisson modeling, we show that the accumbofrontal tract undergoes significant change across the lifespan, with males showing a higher and earlier peak compared to females. Moreover, the change occurs in a pattern consistent with developmental models of decision-making. These findings support the hypothesis that developmental differences in WM integrity may be a contributing factor to the observed risk taking that occurs in adolescence. The accumbofrontal tract is not yet included in standard WM atlases, but may be important for inclusion in studies investigating fronto-striatal networks, as well as in

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INTRODUCTION

Anatomical connections between the prefrontal cortex (PFC) and striatum have been well established across a number of species, with the pathways arranged in a series of parallel and functionally distinct circuits [Alexander, et al., 1990; Haber, et al., 1995]. One pathway of interest is the connection of the orbitofrontal cortex (OFC) to the nucleus accumbens (NAcc), due to its association with reward processing. However, although the *functional* relationship between the NAcc and OFC has been frequently described, the *structural* basis of this connection has not been fully investigated in humans. A recent histological report in 30 brain specimens demonstrated for the first time the physical presence of an "accumbofrontal" tract in humans [Rigoard, et al., 2011], consistent with results from studies in primates [Haber, et al., 1995]. Diffusion tensor imaging (DTI) has the potential to elucidate a number of important features of this tract in-vivo.

Functional anatomy of the ventral striatum (or NAcc) has long been associated with reward sensitivity [Koob, 2000; Saddoris, et al., 2013]. The NAcc is divided into two subregions, the shell and the core, which differ in their connectivity [Brog, et al., 1993]. NAcc-OFC connections project primarily from the core region [Haber, et al., 1995]). While their respective roles are to some degree task or situation dependent, generally the shell has been shown to be associated with dopaminergic changes in response to drugs of abuse [Pontieri, et al., 1995]. Alternately, the core may have a role in cognitive computations such as cost-benefit analyses in reward based decision making [Saddoris, et al., 2014], which is consistent with its PFC connections. Along with the NAcc, the OFC is also sensitive to reward valence and outcome [Knutson, et al., 2003; O'Doherty, 2004; Rolls and Grabenhorst, 2008]. The OFC is thought to regulate the formation of associations between rewards and other stimuli, in part by modulating the weighting of reward, and then using that information to guide the selection of actions [Li, et al., 2003]. Accordingly, functional magnetic resonance imaging (fMRI) studies have revealed OFC activation during salience attribution [Volkow, et al., 2012] and reward anticipation [Galvan, et al., 2005].

Developmentally, the OFC and NAcc have special relevance as they have been proposed to comprise part of a larger reward network that, along with a cognitive control network, is implicated in models of decision-making development. The cognitive control network consists of grey matter regions such as the dorsolateral PFC, frontal eye field, anterior cingulate, and parietal cortex, as well as the primary fronto-parietal white matter connection, the superior longitudinal fasciculus (SLF) which plays a well established role in executive function [Karlsgodt, et al., 2008; Karlsgodt, et al., 2010; Peters, et al., 2014]. The reward network in part consists of the OFC and striatal regions, which include the NAcc. Previous work indicates that reward and executive functions do not mature in tandem. Rather, there is behavioral evidence that the reward network matures earlier resulting in higher reward sensitivity, or a stronger motivation to seek out opportunities perceived as rewarding. The cognitive control or executive network matures slowly, leaving the reward sensitive adolescent with a decreased ability to regulate behavior [Figure 1; Casey, et al., 2008; Crone and Dahl, 2012; Ernst, et al., 2006; Luna, et al., 2010]. This model has been investigated using fMRI and behavioral measures. However, despite the fact that myelination is known to continue into adolescence and early adulthood, no work assessing the potential contribution of white matter structural maturation to this model is available.

The goal of this study was to characterize, in vivo, the white matter connection between the ventral striatum and the orbitofrontal cortex using DTI tractography. An additional goal was to examine age-associated changes in this
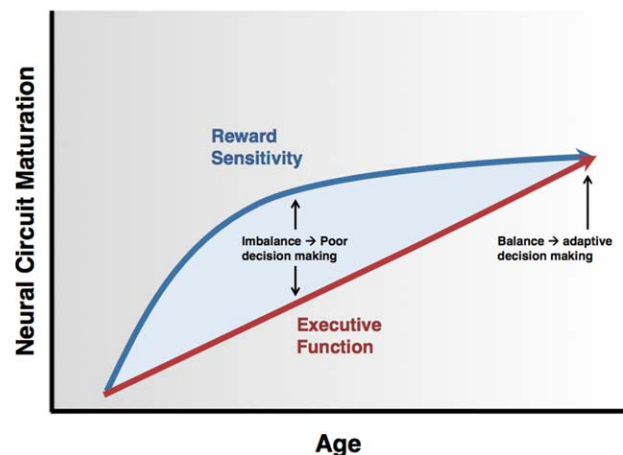

Figure 1.

Model of development of decision making, as a result of differences between patterns of maturation in the executive and reward networks (Ernst, 2006; Casey, 2008; Crone, 2012; Luna, 2010). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

bundle and assess sex differences in peak maturation. Our intention was also to describe the changes in this region with age and its relationship to other tracts in the executive network, in accordance with decision making models.

METHODS

Two-hundred and ninety-five healthy individuals (51.6% male) between the ages of 8.1 and 68.1 years (mean 29.72 ± 14.31; median 25.97) were recruited through local advertisements and by word of mouth and participated in MRI scans through research studies at Zucker Hillside Hospital. Of the scans included in this analysis, 196 overlap with data described in a previous study from our group [Peters, et al., 2012], although the previous work did not include the accumbofrontal tract. Written informed consent was obtained from participants or from a parent or guardian if the participant was a minor; all minors provided assent. Participants had no history of a DSM-IV Axis I major mood or psychotic disorder as assessed by structured clinical diagnostic interview [First, et al., 1997]. Other exclusion criteria included (1) intellectual or learning disability, (2) medications with known adverse cognitive effects, (3) magnetic resonance imaging contraindications, (4) pregnancy, and (5) significant medical illness that could affect brain structure or function. Mean IQ as estimated from the Wide Range Achievement Test 3 (WRAT-3)-reading subtest was available for 262 participants, mean 103.29 ± 0.74 [Wilkinson, 1993]. Handedness was determined using the Edinburgh Handedness Inventory [Oldfield, 1971], in 262 participants with available data. A laterality quotient was calculated by calculating the total number of right and left hand items and computing a score as follows: (Total R − Total L)/(Total R + Total L) yielding a range from +1.00 (totally dextral) to −1.00 (totally nondextral). Individuals with a laterality quotient greater than 0.70 are considered dextral and the rest as nondextral. In our sample the mean laterality quotient was 0.75 ± 0.03. This study was approved by the Institutional Review Board of the North Shore–Long Island Jewish Health System.

All subjects received a DTI exam at the North Shore University Medical Center, Manhasset, New York, on a GE Signa HDx 3.0 T system (General Electric, Milwaukee, Wisconsin). The sequence included volumes with diffusion gradients applied along 31 nonparallel directions (bvalue: 1,000 s/mm2) and five volumes without diffusion weighting (repetition time: 14 s, echo time = minimum, matrix: 128 × 128, field of view: 240 mm). Each volume consisted of 51 contiguous 2.5-mm axial slices acquired parallel to the anterior-posterior commissural line using a ramp sampled, double spin-echo, single shot echo-planar imaging method. All scans were reviewed by a radiologist, and all images were visually inspected to ensure that no gross abnormalities or artifacts were evident. Image processing was conducted using the Functional Magnetic Resonance Imaging of the Brain Software Library (FSL version 5.1; Oxford, United Kingdom; http://fsl.fmrib.ox.ac.uk/fsl). Eddy-current induced distortions and head-motion displacements were corrected through affine registration of the 31 diffusion volumes to the first b0 volume using FSL's Linear Registration Tool. The b-vector table (i.e., gradient directions) for each participant was then adjusted according to the rotation parameters of this linear correction. Non-brain tissue was removed using FSL's Brain Extraction Tool. Fractional anisotropy (FA), an index of white matter integrity, and diffusivity measures were then calculated at each voxel of the brain by fitting a diffusion tensor model to the raw diffusion data using weighted least squares in FSL's Diffusion Toolbox. FA was chosen as the primary measure for analysis because it has been the most widely used measure in relevant studies and thereby provides optimal between-study comparability. Ancillary analyses investigated axial, radial, and mean diffusivity.

Tractography

The probable trajectory of the accumbofrontal tract was traced as follows. Within-voxel probability density functions of the principal diffusion direction were estimated using Markov Chain Monte Carlo sampling in FSL's BED-POSTX tool [Behrens, et al., 2003]. A spatial probability density function was then estimated across voxels based on these local probability density functions using FSL's PROBTRACKX tool [Behrens, et al., 2003], in which 5,000 samples were taken for each input voxel with a 0.2 curvature threshold, 0.5-mm step length, and 2,000 steps per sample. For each tract, seed masks, waypoints, termination and exclusion masks were defined on the MNI152 T1 1-mm template. For the accumbofrontal tract, exclusion maps included the entire contralateral hemisphere, superior frontal regions, and regions posterior to the striatum, and the seed masks were Harvard-Oxford atlas defined ROIs of the NAcc and OFC. Masks were normalized to each subjects' diffusion space using FSL's Linear Registration Tool [Jenkinson and Smith, 2001] applying the affine parameters obtained by coregistering the first b0 volume to the MNI152 T1 1-mm template. The resulting tracts were thresholded at a normalized probability value of 0.01 and visually inspected to confirm successful tracing in each individual subject (http://karlsgodtlab.org/HBM_accumbofrontal). While the tract was robustly detectable, it is notably located in a region subject to susceptibility artifacts. These should be alleviated as much as possible through quality control measures on completed data, and through optimization of individual scan sequences for new data. Mean FA of the entire tract was then extracted for analysis. The fronto-parietal connection, the SLF, was also traced, as a comparison tract that is involved in executive functioning, and the methods for SLF extraction are described in Peters et al. (2014).

Statistical Analyses

To investigate differences in white matter across the lifespan, we first assessed FA, a putative measure of white matter integrity that may index tract myelination and organization. To calculate the cross-sectional measure of age-related change in FA, a poisson model was used, because it has previously been demonstrated to be the most sensitive model of age related DTI changes, and it permits different slope and curvatures on both sides of the age peak (Peters, 2014; Lebel, 2012). Age-FA curves were fitted with a Poisson model ($c + a * Age * exp (-b * Age^2)$) using the nls2 package in R. Model fits were assessed with Akaike's information criterion [AIC [Akaike, 1974]. Separate Poisson models/curves were fit for each displayed trajectory (left, right, left-right mean). Bootstrap resampling methods were used to estimate the standard errors of the peaks.

Because evidence suggests sex differences across neurodevelopment, we next assessed sex differences in age-related changes. The difference in trajectories between males and females (i.e., age × sex interaction) was determined by computing the difference in the "a" coefficients and "b" coefficients in the Poisson model separately. Note, both "a" and "b" contribute to the shape of the trajectories. The difference in the "a" coefficients between males and females was divided by the pooled standard error to obtain a t-statistic. The p-value was obtained by calculating the two-tails area of the corresponding null t-distribution. The p-value for difference in "b" coefficients was similarly obtained.

Finally we used DTI measures from the SLF and accumbofrontal tracts, in each subject, to determine whether there was a significantly different pattern of maturation between the two tracts. This analysis was performed by creating an indicator variable for SLF and accumbofrontal tracts, and assessing its interaction with the age variable. As this analysis had to take into account the within subject correlation for SLF and accumbofrontal tracts, we used mixed models with the "PROC MIXED" procedure in SAS. The mixed model included the indicator variable mentioned above, age, age^2 and the interaction terms of the indicator variable with age and age^2.

RESULTS

Tractography

First, we performed tractography between regions in the NAcc and the OFC, to establish the location of the tract. Our analysis shows that it is possible to visualize the accumbofrontal tract, with in vivo DTI tractography (see Fig. 2). Figure 2 includes images of the histological findings of Rigoard, for visual comparison purposes. Moreover, visual inspection of each individual's data demonstrated that the tract was present in all subjects scanned. The tract is adjacent to, but not the same as, the anterior thalamic radiation and the superior portion of the uncinate fasciculus. This is consistent with the histological data indicating that this is a specific and unique projection from the striatum to the frontal lobe [Rigoard, et al., 2011; Fig. 3].

Age related change in FA

Next, we cross-sectionally assessed age-related change in FA of the accumbofrontal tract across the lifespan. Overall, average FA in the accumbofrontal tract showed significant change with age across the lifespan (Fig. 4). This took the form of an early peak, at age 14.8(1.76) (all results reported as peak(bootstrap standard error)), which then decreased rapidly and then leveled out. This peak is substantially earlier than the previously reported peaks in other tracts in analyses from a substantially overlapping sample [Peters, et al., 2014]. There were no hemispheric effects in FA, the peaks of 14.02(1.98) on the left and 14.72(1.60) on the right were not significantly different ($P = 0.4406$ for the a term and $P = 0.2786$ for the b term; in the Poisson model both terms must be significant).

Sex Differences

Due to findings in the literature of developmental differences between males and females, we tested for effects of sex on the developmental trajectory. There was a significant sex difference in age related change, such that males showed a higher and earlier peak [age 13.9(6.85)] during adolescence compared to females [peak age 18.6(3.79)] $P < 0.0001$ for the a term, $P < 0.0001$ for the b term in the Poisson model), while the trajectories became more similar with age (Fig. 5). This was consistent for both the left hemisphere (peak age 14.7(8.05) for males and 17.3(3.78) for females; $P = 0.0011$ for the a term, $P < 0.0001$ the b term of the Poisson model), and the right hemisphere (peak age 12.8(8.93) for males and 19.1(3.29) for females; $P = 0.0004$ for the a term, $P < 0.0001$ for the the b term of the Poisson model).

Additional Diffusion Tensor Imaging Measures

To better characterize the changes occurring across development in the accumbofrontal tract, we also assessed other measures of white matter integrity including radial diffusivity, axial diffusivity, and mean diffusivity. In the accumbofrontal tract, radial diffusivity, which measures diffusion perpendicular to the axons, is a putative measure of myelin thickness and tract spacing [Song, et al., 2003; Song, et al., 2002], peaked at age 18.41(1.70) (slightly later on the left, 20.07(1.66), compared to the right 17.51(1.73) ($P = 0.0111$ for the a term and $P = 0.0187$ for the b term of the Poisson model). Axial diffusivity, putatively indexing tract organization [Song, et al., 2003; Wozniak and Lim, 2006], peaked later at 26.95(1.65) (30.43(3.07) on the left,
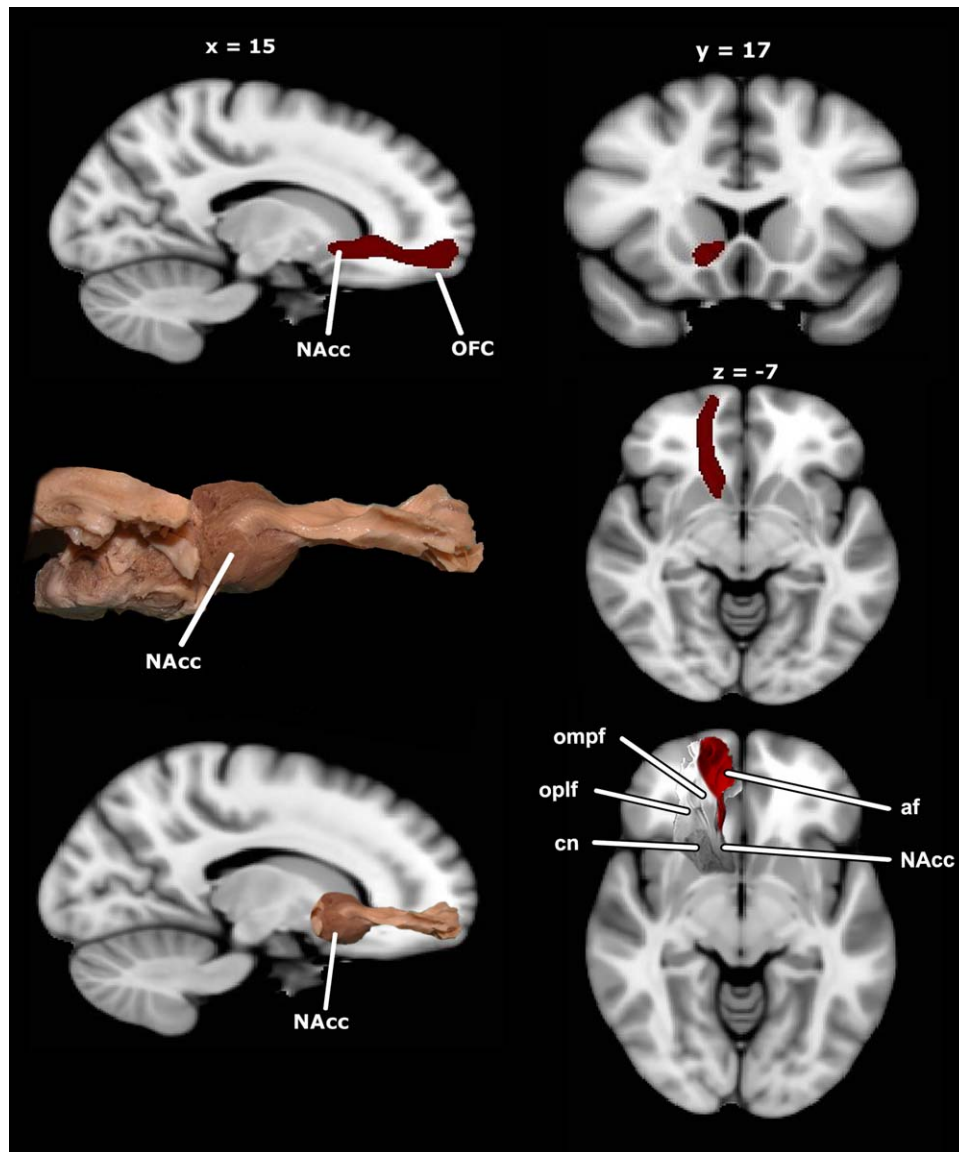
Figure 2.

Diffusion tensor imaging (DTI) characterization of the accumbofrontal tract, from the nucleus accumbens (NAcc) to orbitofrontal cortex (OFC). Upper left: sagittal view of accumbofrontal tractography in the right hemisphere; upper right: coronal view of accumbofrontal tractography, right hemisphere; middle left: histological dissection of accumbofrontal tract for visualization purposes (Rigoard, 2011); middle right: axial view of accumbofrontal tractography, right hemisphere; lower left: overlay of histological dissection and standard space MRI for visualization purposes; lower right: visualization of the histological relationship between accumbofrontal tract (af) and the adjacent orbitomedial prefrontal cortex (ompf) and orbitolateral prefrontal cortex (oplf), based on dissections by Rigoard (personal communication).

24.62(1.66) on the right with a significant difference between hemispheres ($P = 0.0189$ for the a term, and $P = 0.039$ for the b term of the Poisson model). Finally, mean diffusivity, an overall measure of tissue spacing, peaked at 20.42(1.67) (22.36(1.69) on the left, 19.07(1.74) on the right).

Comparison with SLF (Executive Network) White Matter

Finally, due to the hypothesized difference in the maturation of the executive and reward networks, and the relationship to decision making, we also compared the pattern
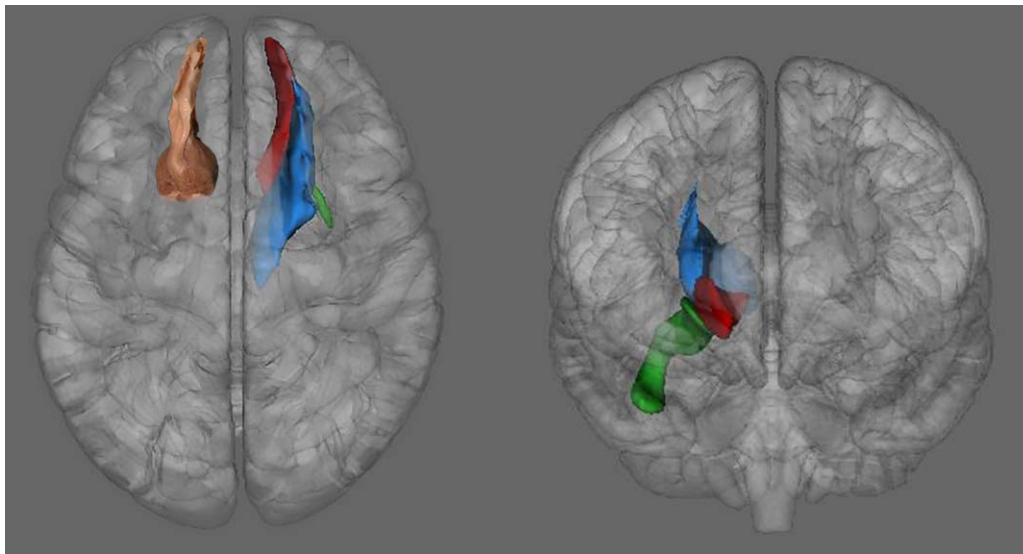
Figure 3.

Visualization of the accumbofrontal tract from the current sample (red) alongside the uncinate fasciculus (green) and the anterior thalamic radiation (blue) from Peters, 2014. Left panel: 3D axial view, with histological overlay for visual comparison (Rigoard, 2011). Right panel, coronal 3D view of the three tracts.

of age related differences between the SLF and accumbofrontal tract (Fig. 6). The SLF had a later peak (30.43(1.59)) than did the accumbofrontal tract; however the SLF showed no significant sex differences across development ($P = 0.102$ for the a term, $P < 0.0001$ on the b term in the Poisson model). Importantly, there was a significant interaction between the age related change in the accumbofrontal tract and the SLF ($P < 0.0001$ for both a and b terms), which remained true on both the left ($P < 0.0001$ for both the a and b terms), and the right ($P < 0.0001$ for both a and
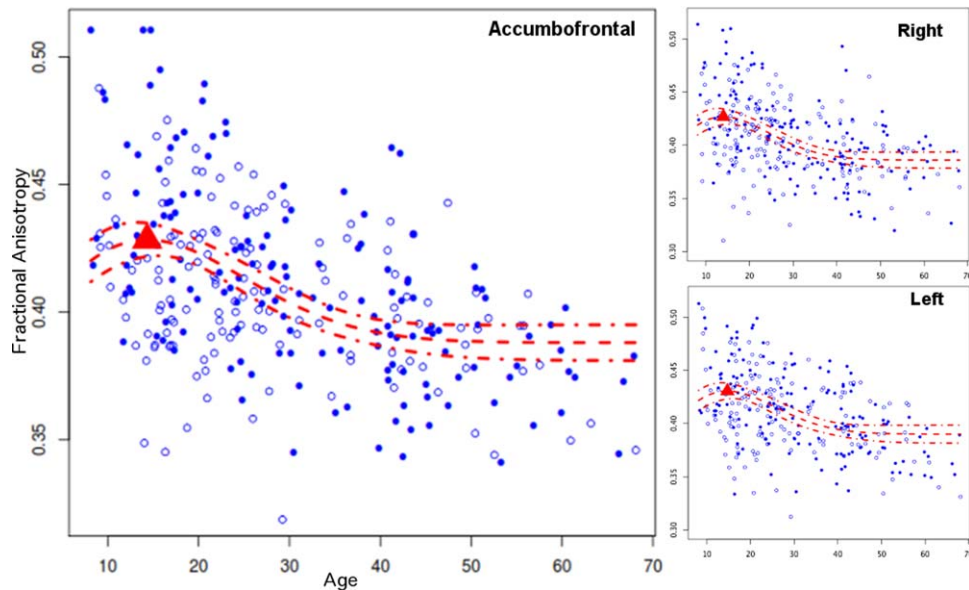

Figure 4.

Pattern of age related change in the accumbofrontal tract, demonstrating an early peak in fractional anisotropy (FA) on average, and in each of the left and right hemispheres. Solid dots, male subjects; open dots, female subjects.
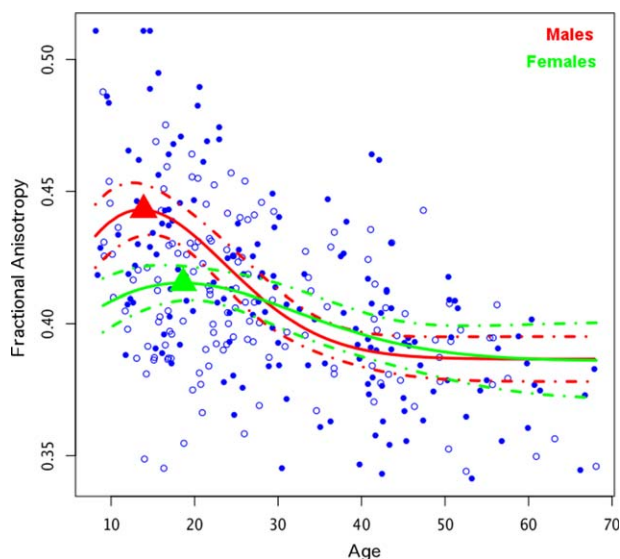
Figure 5.
Sex differences were observed in the pattern of maturation of the accumbofrontal tract such that males showed an earlier and more pronounced peak in fractional anisotropy.

b terms). The difference between tracts was such that the accumbofrontal tract showed a significantly earlier peak than the SLF.

DISCUSSION

We demonstrate for the first time that the "accumbofrontal tract," which has previously been described using histology, is detectable in vivo with standard DTI in humans. Moreover, this tract shows age related changes, and matures in a manner different than a tract associated with executive function. Importantly, the pattern observed, in which the accumbofrontal "reward tract" matures earlier than the fronto-parietal "executive tract," is consistent with models of reward network development during adolescence, and thus has important implications regarding the neural basis of maturational changes associated with decision making. While future work using longitudinal designs will be important to further probe development of this tract, the cross-sectional design used here allowed the use of a large age range spanning childhood to late adulthood.

The newly characterized tract assessed using DTI is highly consistent with findings from histological studies. Importantly, human histology has revealed three separate frontostriatal projections, with the accumbofrontal tract representing a unique bundle specifically connecting to the more medial aspects of the OFC [Rigoard, et al., 2011]. Accordingly, although the terminal tractography ROI in the frontal lobe included the entire orbitofrontal region, the resulting connection was limited to the medial region of the white matter. Likewise, the tractography analysis

showed the tract to be separate from other adjacent tracts and from those defined in the JHU white matter atlas [Oishi, et al., 2011], in particular from the anterior thalamic radiation (ATR) and uncinate fasciculus (UF). We also compared the tract to ROIs created in analyses from previous tractography studies [Peters, et al., 2014; Peters, et al., 2012], both of which used a sample that heavily overlapped with this one, with 196 of the same subjects. The accumbofrontal tract is more medial than either the ATR or UF as well as being superior to the UF. In the more rostral regions of the tract, the ATR and accumbofrontal tract appear to run alongside each other, with the accumbofrontal tract more medial (Fig. 3).

There have been a few studies that include white matter in an anatomical region likely to include some portion of this tract. Samanez-Larkin and colleagues used a small sample (25 healthy subjects) age 21–85, and performed tractography in three fronto-striatal tracts, including one originating in the NAcc. They demonstrated a linear decrease with age in this age range, and a positive relationship of FA to probabilistic reward learning [Samanez-Larkin, et al., 2012]. However, while the pattern is indeed consistent with what is observed at the higher end of our age range, this sample is relatively small, does not include the full age range of our study, and only examined linear relationships. Other studies focused specifically on substance users have reported white matter deficits in regions that likely include this tract but their methods do not allow for the specific localization of the findings within the broader prefrontal white matter [Alicata, et al., 2009; Yeh, et al., 2009]. Finally, in an investigation focused on functional anatomical correlations, Bjornebekk and colleagues reported a correlation of a Reward Sensitivity index, as measured by the Cloningers Temperament and Character Inventory (TCI) [Cloninger, 1994] in frontal white matter that likely included the accumbofrontal tract [Bjornebekk, et al., 2012].

A few studies have previously investigated development of long range white matter tracts across the lifespan [Kochunov, et al., 2011; Kochunov, et al., 2010; Lebel, et al., 2012; Ostby, et al., 2009; Peters, et al., 2014], but none of these studies have included this tract or region. Peters et al used tractography in a sample aged 8–68 to assess eight tracts, finding the anterior thalamic radiation to have the earliest peak, and the SLF, cingulum, and uncinate to have the latest peaks [Peters, et al., 2014]. Westlye et al used tract based spatial statistics (TBSS) in a sample aged 8–85 to investigate patterns of maturation across the whole brain, and found early maturation of corticospinal regions, forceps minor, and occipital regions, and the latest maturation of the cingulum bundle and parahippocampal regions [Westlye, et al., 2010]. Lebel et al. investigated individuals aged 5–83, using DTI tractography in 12 tracts, and found the earliest peaks in the fornix and callosal regions, with the latest peak in the cingulum bundle [Lebel, et al., 2012].
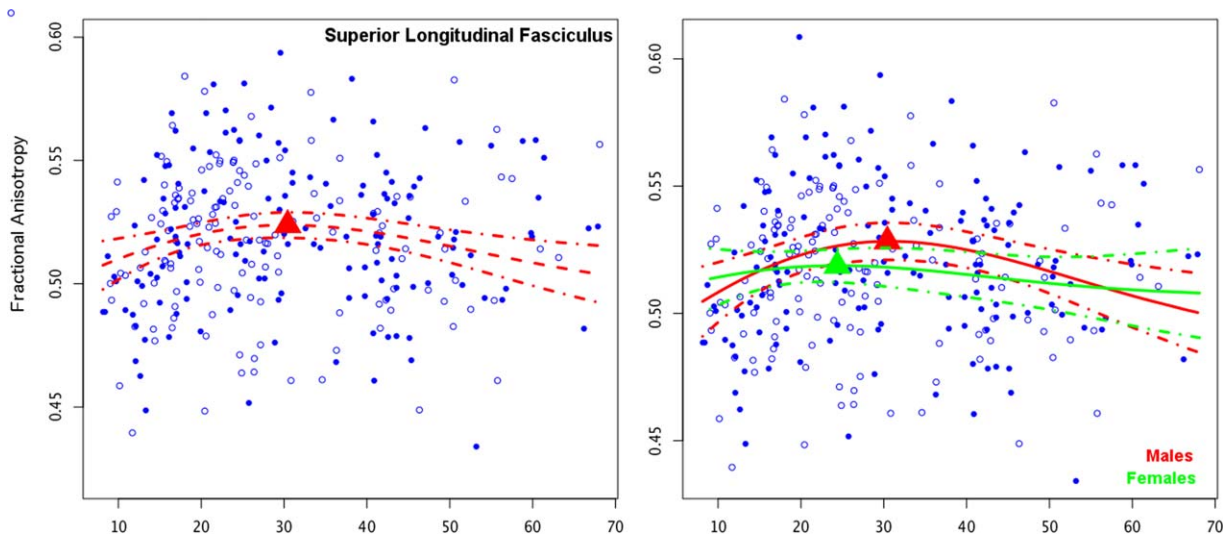
Figure 6.

As a comparison, maturation of the superior longitudinal fasciculus (SLF), the white matter underlying the executive network, showing a later peak (left) than the accumbofrontal tract; no sex differences were observed (right).

The finding that the accumbofrontal tract shows a significantly different age related change across the lifespan compared to the SLF has important implications for models of decision making development. Such models have hypothesized that a discrepancy in the relative maturation of these tracts during adolescence may play a role in the increased risk taking observed during this age range [Blakemore and Robbins, 2012; Casey and Jones, 2010; Ernst, et al., 2006]. Although this hypothesis has not yet been tested empirically for this tract, there are data available from other imaging modalities that support this possibility. For instance, Galvan et al. noted different functional MRI activation patterns with age in frontal and striatal regions, with the NAcc showing a peak in adolescents (age 13–17) relative to children and adults, while the orbital frontal cortex in adolescents was more similar to that in children than adults [Galvan, et al., 2006]. Although the precise relationship of cortical activation to structural integrity of the adjacent white matter is unknown, the corresponding peaks may indicate that these two modalities are related. In addition, there is evidence for structural differences in striatal regions between adolescence and adulthood. For instance, it was found that there is higher nucleus accumbens volumes in adolescents than in adults [Urosevic, et al., 2012]. In addition, NAcc volume also peaks during later adolescence (age 13-17) compared to childhood and adult volumes [Urosevic, et al., 2012] supporting the notion that adolescence may be associated with not just functional but structural differences in reward circuitry. Furthermore, the sex difference observed in our study is consistent with findings that there are higher levels of risk taking during this age in males than

in females [Steinberg, 2008] and provides a potential biological and structural explanation for this difference. Taken together, these findings indicate that individual differences in white matter microstructure should be explored in relationship to decision making and risk taking during this developmental period.

In conclusion, we demonstrate that the anatomical connection between the ventral striatum and orbitofrontal cortex can be identified in-vivo using DTI tractography, and is consistent with studies using tracing techniques in non-human primates, including histology in human specimens. This tract is not yet incorporated into standard white matter atlases, but may be important for inclusion in studies investigating fronto-striatal networks, as well as investigations of substance abuse and decision making. Moreover, this region shows a distinct pattern of maturation across the lifespan that differs from the trajectories of other tracts such as the SLF within the executive network. The developmental distinction between the SLF and accumbofrontal tract is remarkably consistent with models of development of adolescent decision making, and thus suggests that developmental differences in white matter connections may be a contributing factor to the observed risk taking that occurs in adolescence.

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