Report

Neuron

White-Matter Tract Connecting Anterior Insula to Nucleus Accumbens Correlates with Reduced Preference for Positively Skewed Gambles

Highlights

- A novel tract connecting the anterior insula to the NAcc was traced and validated
- Tract coherence correlated with reduced preference for positively skewed gambles
- NAcc activity before risky choice mediated the association of structure with behavior

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In Brief

Leong et al. identify a white-matter tract connecting the anterior insula and nucleus accumbens. The tract's coherence is associated with reduced preference for positively skewed gambles. NAcc neural activity before choice statistically accounted for the association of structure with behavior.

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White-Matter Tract Connecting Anterior Insula to Nucleus Accumbens Correlates with Reduced Preference for Positively Skewed Gambles

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SUMMARY

Individuals sometimes show inconsistent risk preferences, including excessive attraction to gambles featuring small chances of winning large amounts (called "positively skewed" gambles). While functional neuroimaging research indicates that nucleus accumbens (NAcc) and anterior insula (AIns) activity inversely predict risky choice, structural connections between these regions have not been described in humans. By combining diffusion-weighted MRI with tractography, we identified the anatomical trajectory of white-matter tracts projecting from the AIns to the NAcc and statistically validated these tracts using Linear Fascicle Evaluation (LiFE) and virtual lesions. Coherence of the right AIns-NAcc tract correlated with reduced preferences for positively skewed gambles. Further, diminished NAcc activity during gamble presentation mediated the association between tract structure and choice. These results identify an unreported tract connecting the AIns to the NAcc in humans and support the notion that structural connections can alter behavior by influencing brain activity as individuals weigh uncertain gains against uncertain losses.

INTRODUCTION

Choice consistency is a hallmark of rationality (von Neumann and Morgenstern, 1944). Nonetheless, people sometimes choose inconsistently in predictable ways (Kahneman and Tversky, 1979). For instance, the profitability of casinos and lotteries suggests that people are seduced by "positively skewed" gambles that feature a small chance of winning a large amount combined with a large chance of losing a little (Kraus and Litzenberger, 1976). Neuroimaging experiments suggest that, when presented with positively skewed gambles, people report experiencing greater positive arousal (e.g., feelings akin to "excitement") and show increased brain activity in circuits associated with gain anticipation, including the nucleus accumbens (or NAcc), which might encourage risk taking (Wu et al., 2011).

Recent advances in neuroimaging have allowed researchers to visualize brain activity that not only correlates with presentation of risky options, but that also precedes and predicts choice among them (Knutson and Bossaerts, 2007). For instance, using fMRI, researchers have shown that increased NAcc activity predicts risk-seeking choices, but increased anterior insula (AIns) activity predicts risk-averse choices on a trial-to-trial basis (e.g., Kuhnen and Knutson, 2005). Comparative research suggests that these regions receive input from evolutionarily conserved dopaminergic and noradrenergic projections emanating from the midbrain, respectively, and theorists have speculated that release of these neurotransmitters in relevant terminal regions may promote approach or avoidance behavior (e.g., Knutson et al., 2014; Panksepp, 1998).

Although fMRI can provide information about which brain circuits promote choice, it cannot illuminate the structural connections between those circuits. Recently, investigators have used diffusion-weighted imaging (DWI) to trace ascending mesolimbic axonal projections from the ventral tegmental area to the NAcc, as well as descending projections from the medial prefrontal cortex (MPFC) to the NAcc (Coenen et al., 2012; Cohen et al., 2008; Draganski et al., 2008; Lehéricy et al., 2004), recapitulating anatomical tracing studies of nonhuman primates (reviewed in Haber and Knutson, 2010). Diffusion measures such as fractional anisotropy (FA) have been associated with white-matter density, alignment, and diameter (collectively referred to as "coherence" henceforth; Jones et al., 2013). Assuming that greater white-matter coherence promotes the transmission of functional signals, higher coherence might modulate brain activity in specific projection target regions, which might then influence behavior. For instance, the coherence of white-matter projections from the MPFC to the NAcc can account for individual differences in reward learning (Samanez-Larkin et al., 2012).

Whereas investigators have used DWI to estimate the coherence of prefrontal projections to the NAcc, other projections might also modulate NAcc activity. For instance, activity in both the NAcc and AIns precedes, but has opposing effects on, risky choice (Kuhnen and Knutson, 2005). To date, direct structural connections between the AIns and NAcc have not been documented in humans. Only two studies in other species

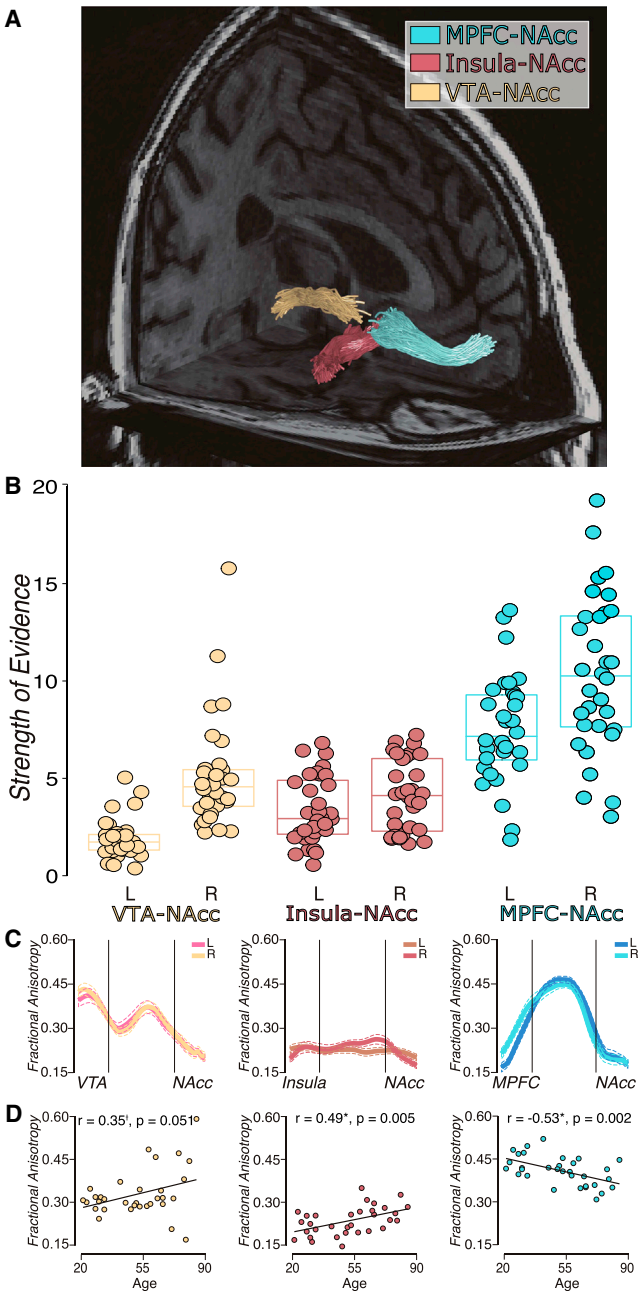

Figure 1. Trajectory and Validation of White-Matter Tracts

(A) Anatomy. White-matter tracts identified in a representative right hemisphere dataset.

(B) Statistical validation. Strength of evidence for the tracts in each individual brain (circles), with group median and interquartile-range boxplot (Supplemental Information).

(C) White-matter coherence along tract length. FA profiles for each tract, depicting mean FA and SE across individual brains (vertical bars delineate the middle 50% of nodes included in analyses in D).

(D) Associations of age with tract coherence replicated and extended previous findings (Supplemental Information).

have suggested the possibility of such a connection (Chikama et al., 1997; Reynolds and Zahm, 2005). While tracers implicated unidirectional glutamatergic projections from the AIns to the NAcc, the researchers could only visualize the destination but not the spatial trajectories of projections.

We investigated whether similar tracts project from the AIns to the NAcc in humans. Further, we explored whether the white-matter coherence of identified tracts might account for brain activity as well as behavior related to gambles. Since functional neuroimaging studies suggest that positively skewed gambles preferentially increase NAcc activity (Wu et al., 2012), we predicted that the coherence of an AIns-NAcc tract might decrease NAcc activity and choices of positively skewed gambles. We also tested for a more prominent association in the right hemisphere, since right AIns activity most consistently correlates with negative arousal and risk perception (Craig, 2009; Critchley et al., 2001; Paulus et al., 2003).

RESULTS

Analyses first identified and validated a white-matter tract connecting the AIns and NAcc, next verified previously documented mesolimbic white-matter tracts, then characterized functional predictors of positive-skew preference during a gambling task, and finally tested whether functional activity could account for the association of tract coherence with positive-skew preference.

Identification and Validation of White-Matter Tracts Connecting the AIns and NAcc

Probabilistic tractography identified three bilateral white-matter tracts in all subjects' brains (n = 32; Figure 1A). One pair of tracts projected through the subcaudate white matter from the AIns to the NAcc (Figure S1). Two other pairs of tracts projected from the MPFC to the NAcc and between the VTA and the NAcc, replicating previously described pathways (Samanez-Larkin et al., 2012).

Statistical evidence for these tracts was evaluated using the Linear Fascicle Evaluation method and virtual lesions approach (LiFE; Pestilli et al., 2014). Results revealed strong statistical evidence for the existence of all three bilateral tracts (i.e., connecting the AIns and NAcc, MPFC and NAcc, and VTA and NAcc; Figure 1B). FA was computed based on a standard tensor model (Basser and Pierpaoli, 1996) to index white-matter coherence for each tract. Each tract's FA profile was computed across each tract in each hemisphere and subject and then averaged across the middle 50% portion of each tract's profile to index coherence (Figure 1C; Supplemental Information). Effects of age on FA replicated and extended previous findings (Samanez-Larkin et al., 2012; Figure 1D; Supplemental Information).

Association of AIns to NAcc Tract Coherence with Reduced Positive-Skew Preference

Risk preference for all three gamble conditions and tract coherence for all three bilateral tracts were submitted to a repeated-measures multivariate analysis of variance, which revealed a significant tract by condition interaction for the AIns-NAcc bilateral tract (right: $F(2,50) = 4.10$, $p = 0.023$,

Table 1. Logistic Regression Results, Including Subjects as Random Effects

Variable	Contrast	Behavioral Model	Neural Model	Combined Model
Previous gamble outcome	gain > loss	−2.19* (−0.14, 0.06)		−2.55* (−0.17, 0.07)
	accept > reject	1.53 (0.13, 0.09)		2.01* (0.18, 0.09)
Domain of current earnings	loss	1.51 (0.40, 0.26)		1.71 (0.45, 0.26)
	gain	1.35 (0.35, 0.26)		1.52 (0.39, 0.26)
Skewness	positive > negative	6.16*** (0.36, 0.06)		5.50*** (0.32, 0.06)
	skewed > symmetric	−5.61*** (−0.49, 0.09)		−5.86*** (−0.52, 0.09)
Right NAcc			4.96*** (0.63, 0.13)	5.09*** (0.67, 0.13)
Right AIns			−3.30*** (−0.39, 0.12)	−3.00** (−0.36, 0.12)
Right MPFC			3.70*** (0.35, 0.10)	3.50*** (0.34, 0.10)
Pseudo R^2		0.27	0.27	0.30
AIC		2,644	2,666	2,594
BIC		2,689	2,695	2,657

Based on AIC, BIC, and a likelihood-ratio test for nested models, the best model for predicting trial-by-trial risky choice includes terms for right hemisphere neural activity, gamble type, previous gamble outcome, and domain of current earnings ($\chi^2(3) = 55.32$, $p < 0.0001$). Winning a previous gamble significantly predicted risk aversion on the following trial. A model including left-hemisphere neural activity did not improve model fit (Table S3). Z scores are shown with coefficient estimates and SE in parentheses. ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$.

$\eta^2 = 0.634$; left: $F(2,50) = 4.69$, $p = 0.014$, $\eta^2 = 0.726$; Table S1). We additionally found a significant effect of gamble condition on risk seeking ($F(2,50) = 4.01$, $p = 0.024$, $\eta^2 = 0.622$). Pairwise comparisons revealed that subjects who did not always choose to seek or avoid risk for any gamble condition (n = 20) preferred positively skewed to negatively skewed gambles (paired $t(19) = 2.13$, $p = 0.047$). This preference, however, varied across individuals (Figure S2).

Pairwise correlations showed that individual differences in right hemisphere AIns-NAcc tract coherence were associated with reduced preference for positively skewed gambles ($\beta = -0.40$, $t(30) = -2.38$, $p = 0.02$). This association remained significant after controlling for age and multiple comparisons for testing bilateral tracts ($\beta = -0.44$, $t(30) = -2.37$, $p = 0.02$). Further, this association remained robust after removing seven subjects who either never (n = 3) or always (n = 4) took positively skewed gambles ($\beta = -0.47$, $t(23) = -2.57$, $p = 0.02$). Right AIns-NAcc tract coherence was also marginally negatively associated with general risk taking across all gamble conditions ($\beta = -0.31$, $t(30) = -1.80$, $p = 0.08$), but not specifically for symmetric ($\beta = -0.08$, $t(30) = -0.46$, $p = 0.65$) or negative-skew ($\beta = -0.14$, $t(30) = -0.77$, $p = 0.45$) gambles. Left-hemisphere AIns-NAcc tract coherence was marginally associated with decreased risk taking for negatively skewed gambles ($\beta = -0.34$, $t(30) = -2.03$, $p = 0.06$), but not with risk taking in general or any other gamble condition (positive skew: $\beta = -0.10$, $t(30) = -0.54$, $p = 0.59$; symmetric: $\beta = -0.02$, $t(30) = -0.09$, $p = 0.93$; overall: $\beta = -0.23$, $t(30) = -1.27$, $p = 0.21$). Coherence of other tracts (i.e., the bilateral MPFC-NAcc tract and bilateral VTA-NAcc tract) was not associated with risk taking in general or in any gamble condition.

Association of Functional Brain Activity with Risky Choice

fMRI data were preprocessed and activity time courses extracted from predefined volumes of interest (Experimental Procedures). Logistic regressions indicated that activity immediately preceding choice predicted risk taking on a trial-to-trial basis within subjects. Specifically, right NAcc and MPFC activity predicted risk-seeking choices, whereas right AIns activity predicted risk-averse choices across all gambles (Table 1). Gamble type also predicted risk-seeking choices. These variables predicted choices to gamble even after controlling for other potentially relevant variables (e.g., the previous gamble's outcome, domain of current earnings relative to one's endowment). The best-fitting model included right hemisphere neural activity, gamble type, previous gamble outcome, and domain of current earnings (indicated by Akaike Information Criterion [AIC], Bayesian Information Criterion [BIC], and a likelihood-ratio test: $\chi^2(3) = 55.32$, $p < 0.0001$; Table 1).

Activity time courses were plotted and analyzed to verify that gamble type differentially altered neural activity in volumes of interest in a way that could influence choice. Findings indicated that presentation of positively skewed gambles elicited greater activity in the right and left NAcc prior to choice than did symmetric or negatively skewed gambles (right: positive skew > symmetric: $t(31) = 2.17$, $p = 0.04$; positive skew > negative skew: $t(31) = 2.80$, $p = 0.01$; left: positive skew > symmetric: $t(31) = 2.87$, $p = 0.01$; positive skew > negative skew: $t(31) = 3.02$, $p = 0.005$), but not in the AIns or MPFC (Figure 2).

Functional Mediation of the Association of Tract Coherence with Reduced Positive-Skew Preference

Individual differences in average right NAcc activity immediately prior to choice were entered as a statistical mediator of the association of right AIns-NAcc tract coherence with reduced preference for positively skewed gambles. Results from hierarchical regression analyses indicated that right AIns-NAcc tract coherence was associated with decreased right NAcc activity before gamble choice ($\beta = -0.35$, $p = 0.03$) and that right NAcc activity before gamble choice was associated with individual differences in positive-skew preference ($\beta = 0.46$, $p = 0.003$; Figure 3).

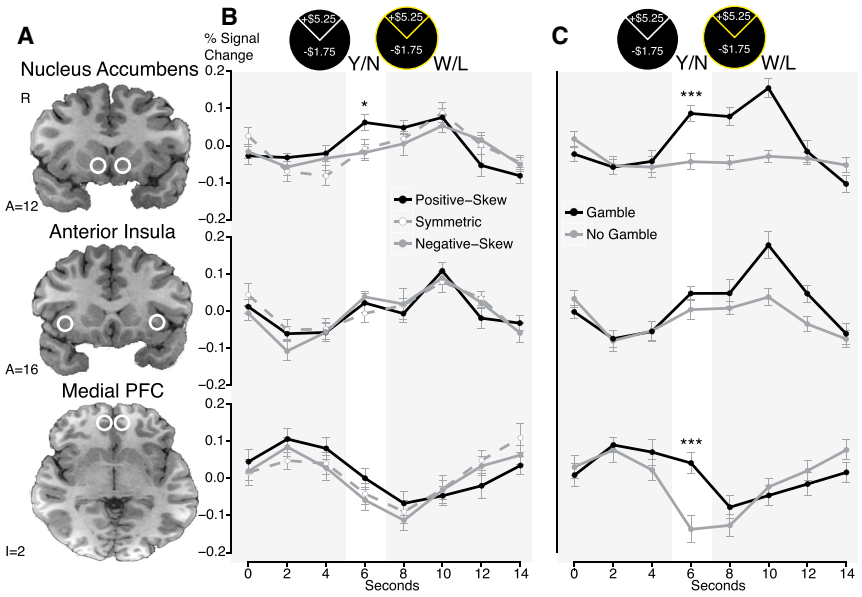

Figure 2. fMRI Activity Time Courses during Gambling Task

(A) Spherical volumes of interest (VOIs) used to obtain activity time course data.

(B) Mean activity and SEs plotted for each right hemisphere VOI by gamble condition. Positively skewed gambles elicited greater NAcc activity than symmetric and negatively skewed gambles during gamble choice (positive skew > symmetric: paired $t(31) = 2.17$, $p = 0.04$; positive skew > negative skew: paired $t(31) = 2.80$, $p = 0.01$).

(C) Right NAcc and MPFC activity were greater for accepted than rejected gambles across conditions (NAcc: paired $t(31) = 4.27$, $p = 0.0002$; MPFC: paired $t(31) = 4.06$, $p = 0.0003$). Left-hemisphere VOIs showed similar results (Figure S3).

Importantly, including the indirect effect of right NAcc activity before choice significantly decreased the direct association of right AIns-NAcc tract coherence with reduced positive-skew preference to nonsignificance ($\beta' = -0.24$, $p = 0.14$; $\beta = -0.40$, $p = 0.02$), consistent with statistical mediation. Additional mediation models specified with different terms (i.e., coherence of control tracts and activity of control volumes of interest) established that only right AIns-NAcc tract coherence and right NAcc activity before gamble choice were associated with positive-skew preference (Table S4). Further, confirmatory analyses of an independent fMRI dataset showed that functional coupling of the AIns and NAcc was associated with decreased positive-skew preference (Figure S4).

DISCUSSION

This research identifies an unreported white-matter tract connecting the AIns to the NAcc in humans. Consistent with a potential role in risk preferences, individual differences in AIns to NAcc tract coherence were associated with reduced preference for positively skewed gambles. Functionally, presentation of positively skewed gambles preferentially increased NAcc activity, which predicted subsequent risky choice. Decreased NAcc activity could statistically account for the association of AIns-NAcc tract coherence with reduced preference for positively skewed gambles, forging links from brain structure to brain function to behavior.

These findings illustrate the importance of leveraging comparative neuroanatomy to guide the discovery and characterization of structural connections in humans (e.g., Haber and Knutson, 2010). Only two comparative studies in monkeys and rats had previously suggested that a unidirectional glutamatergic projection existed from the AIns to the NAcc (Chikama et al., 1997; Reynolds and Zahm, 2005). Inspired by those findings, we were able to identify and trace the trajectory of AIns-NAcc tracts in humans. In addition, previously documented tracts (i.e., from the MPFC to the NAcc and connecting the midbrain and NAcc) were validated with novel methods, and their associations with age extended previous findings (Supplemental Information). Thus, structural tracings in animals can provide unique clues not only about where tracts begin and end, but also about their direction and chemical transmission, which can guide interpretations of findings in humans (e.g., Heimer et al., 1991; Lehman et al., 2011).

This investigation also illustrates how multimodal imaging can illuminate new discoveries about brain activity and behavior. The combination of DWI, fMRI, and behavior allowed us to trace a path from brain structure to brain function to behavior. While previous fMRI research suggests that increased NAcc activity promotes financial risk seeking while increased AIns activity instead promotes financial risk aversion (e.g., Kuhnen and Knutson, 2005), the present research begins to situate those findings within an anatomical framework. Specifically, increased AIns to NAcc coherence appeared to reduce preference for positively skewed gambles by decreasing NAcc activity during gamble presentation. Positively skewed gambles preferentially elevated NAcc activity, despite having the same expected value and variance as symmetric and negatively skewed gambles, which might account for the excessive but irrational attractiveness of these "lottery"-like gambles (Wu et al., 2012). Interestingly, by reducing NAcc activity to positively skewed gambles, the coherence of direct projections from the AIns to the NAcc might "rationalize" risky choice, even in the absence of modulation from more "reflective" prefrontal input.

Importantly, current tractography methods cannot quantify differential contributions of crossing fibers within a voxel (Jones et al., 2013). The AIns to NAcc tract traverses the lateral-medial axis of the brain, thereby intersecting with other tracts like the uncinate fasciculus in some subjects (Petrides and Pandya, 2007). Future research with improved methods will therefore need to determine the extent to which the AIns to NAcc tract represents a distinct component of the subcaudate white matter.

Together, these findings provide multimodal empirical support for an "Affect-Integration-Motivation" or AIM framework, which describes choice as arising from hierarchical processes of affective evaluation, integration, and motivation (Samanez-Larkin and

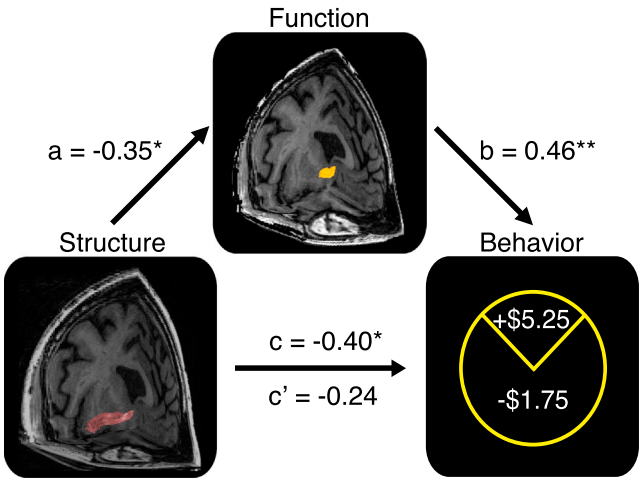

Figure 3. NAcc Functional Activity Mediated the Association between AIns-NAcc Tract Coherence and Positive-Skew Preference

AIns-NAcc tract coherence is associated with reduced NAcc activity during presentation of positively skewed gambles ($\beta = -0.35$, $p = 0.03$), and NAcc activity was associated with positive-skew preference ($\beta = 0.46$, $p = 0.003$). This indirect pathway mediated the association of tract coherence with positive-skew preference ($\beta' = -0.24$, $p = 0.14$; $\beta = -0.40$, $p = 0.02$). Path coefficients are standardized βs. No alternative combination of tract coherence and functional activity could reproduce this pattern of associations (Table S4).

Knutson, 2015). While the connections explored here pertain primarily to affective evaluation, future studies may focus on the connectivity of higher order components of the framework that can support value integration and motivation. The findings also add structural connectivity information to a growing functional neuroimaging literature implicating the NAcc in assessment of expected value, but the AIns in the assessment of risk (Knutson and Bossaerts, 2007; Mohr et al., 2010; Wu et al., 2012), in both financial and other uncertain choices (e.g., Sanfey, 2007). While cross-sectional mediation analysis can only model correlations between brain structure, function, and behavior, these findings also cohere with causal evidence indicating that AIns lesions (which should disconnect projections to the NAcc) can increase financial risk taking (Clark et al., 2008), as well as selectively impair loss but not gain learning (Palminteri et al., 2012).

These multimodal findings highlight new directions for physiological research. Although the findings are logically consistent with repeated demonstrations that NAcc fMRI activity promotes risky choice, it is not clear how glutamatergic projections from the AIns to NAcc might decrease fMRI activity in the NAcc. While comparative research suggests that phasic dopamine release may increase fMRI blood oxygen level-dependent (or BOLD) activity in the NAcc (Choi et al., 2006; Knutson and Gibbs, 2007), the influence of glutamate release on NAcc BOLD activity has not been characterized. One counterintuitive possibility raised by these findings is that glutamate release in the NAcc may interfere with or even decrease dopamine-elicited increases in BOLD activity, consistent with recent findings that combine optogenetics with fMRI (E.A. Ferenczi et al., personal communication).

Identification of a new tract naturally raises many questions for exploration. The anatomical connectivity of the rest of the insular cortex is ripe for additional characterization. Comparative studies suggest that projections from the posterior insula target regions in the AIns, possibly providing peripheral physiological input to affective responses (Chang et al., 2013; Craig, 2009). The AIns also directly connects to lateral cortical regions implicated in controlling and changing the course of action (Aron et al., 2007). Little is known about the trajectory or malleability of these white-matter tracts in humans, and rich opportunities exist for exploring changes in their coherence as a result of gradual (e.g., related to maturation and aging) or more rapid (e.g., experience and training) influences. Perhaps most tantalizing, identification and assessment of the stable properties of tracts may open the door to exploring how targeted interventions can alter their structure and related functions.

EXPERIMENTAL PROCEDURES

Thirty-seven right-handed healthy adults completed the study. Five were excluded from analyses because of head motion >2 mm during the fMRI scan, leaving a total of 32 subjects (14 females, age mean = 52, SD = 19.3, range = 21–85 years). The study was conducted at the Stanford Center for Cognitive and Neurobiological Imaging. Written informed consent was obtained from all subjects prior to participation. Subjects completed behavioral and self-report measures, including neuropsychological tests. Subjects then underwent functional and structural MRI scans and received $20 per hour plus the total earned on the gambling task. The study was approved by the Stanford Institutional Review Board.

Behavioral Task and Analysis

Subjects were scanned with fMRI as they performed a modified version of a gambling task (Wu et al., 2011) during which they made a series of choices to gamble (Figure S2). During each trial (n = 72; 24 per condition), gambles were depicted as circles with slices representing the probability of associated outcomes. If subjects chose to accept, the gamble's outcome was displayed as feedback that cumulated to a final payout, but if they chose to reject, no outcome accrued, which was also displayed as feedback. When prompted with the word "choose," subjects indicated their choices with a left or right button press (spatially counterbalanced across trials). Three gamble conditions were presented in a pseudorandom order: "Positive Skew" (25% probability of gaining $5.25 but 75% of losing $1.75), "Symmetric" (50% probability of gaining or losing $3.05), and "Negative Skew" (25% probability of losing −$5.25 but 75% probability of gaining +$1.75). Expected value ($\mu = \$0.00$) and variance ($\sigma^2 = 9.19$) were held constant across all gambles. Subjects received an endowment ($10.00) before entering the scanner plus their cumulative outcome in cash at the end of the experiment. To test the effect of domain (gain or loss) on trial-by-trial choice, the endowment was subtracted from current earnings. Preference for each gamble type was then calculated as the proportion of trials that subjects accepted each, and overall risk preference was similarly indexed by averaging these proportions across gamble types.

fMRI Acquisition and Analysis

Images were acquired with a 3T General Electric Discovery 750 scanner (GE), using a 32-channel head coil. Forty-six 2.9-mm thick slices (2.9-mm isotropic voxels, interleaved acquisition) extended axially from the mid-pons to the top of the skull. Whole-brain functional scans were acquired with a T2*-weighted gradient pulse sequence (TR = 2 s, TE = 24 ms, flip angle = 77). A high-resolution T1-weighted anatomical image was also collected using an axial fast spoiled grass sequence (TR = 7.2 ms, TE = 2.3 ms, flip = 12, 0.9 mm isotropic voxels) for co-registration of functional image and DWI data and for volume of interest specification. Functional imaging analyses were conducted using AFNI and followed previously described methods (Supplemental Information; Knutson and Greer, 2008).

Mean activity time courses of predicted volumes of interest were plotted and statistically compared with targeted t tests (Figure 2). Percent signal change

prior to gamble choice in each trial (i.e., the second volume acquisition in the trial) were included in a logistic regression model that used peak neural activity (in the NAcc, AIns, and MPFC) to predict trial-by-trial gamble choices, and subjects were modeled as random effects. Finally, bootstrapped mediation analyses were conducted to determine whether NAcc activity could statistically mediate the association of AIns-NAcc tract coherence with positive-skew preference (Figure 3).

DWI Acquisition and Analysis

DWI data were also acquired on the same 3T scanner and head coil. A dual-spin echo diffusion-weighted sequence was used to acquire 2-mm isotropic images in 96 diffusion directions (b = 2,500 s/mm^2; TE = 97.5 ms). Ten non-diffusion-weighted (b = 0) volumes were acquired. Preprocessing and probabilistic tractography followed previously described procedures (Supplemental Information; Tournier et al., 2007). After identification, tracts were statistically validated using LiFE with virtual lesions (Supplemental Information; Pestilli et al., 2014).

SUPPLEMENTAL INFORMATION

Supplemental Information includes Supplemental Experimental Procedures, four figures, and four tables and can be found with this article online at http://dx.doi.org/10.1016/j.neuron.2015.12.015.

AUTHOR CONTRIBUTIONS

B.K., G.R.S.-L., J.K.L., and F.P. designed the research. C.C.W. and G.R.S.-L. acquired the data. J.K.L., F.P., and B.K. analyzed the data. J.K.L., F.P., and B.K. wrote the paper.

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REFERENCES

Aron, A.R., Behrens, T.E., Smith, S., Frank, M.J., and Poldrack, R.A. (2007). Triangulating a cognitive control network using diffusion-weighted magnetic resonance imaging (MRI) and functional MRI. J. Neurosci. *27*, 3743–3752.

Basser, P.J., and Pierpaoli, C. (1996). Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. J. Magn. Reson. B. *111*, 209–219.

Chang, L.J., Yarkoni, T., Khaw, M.W., and Sanfey, A.G. (2013). Decoding the role of the insula in human cognition: functional parcellation and large-scale reverse inference. Cereb. Cortex *23*, 739–749.

Chikama, M., McFarland, N.R., Amaral, D.G., and Haber, S.N. (1997). Insular cortical projections to functional regions of the striatum correlate with cortical cytoarchitectonic organization in the primate. J. Neurosci. *17*, 9686–9705.

Choi, J.K., Chen, Y.I., Hamel, E., and Jenkins, B.G. (2006). Brain hemodynamic changes mediated by dopamine receptors: Role of the cerebral microvasculature in dopamine-mediated neurovascular coupling. Neuroimage *30*, 700–712.

Clark, L., Bechara, A., Damasio, H., Aitken, M.R.F., Sahakian, B.J., and Robbins, T.W. (2008). Differential effects of insular and ventromedial prefrontal cortex lesions on risky decision-making. Brain *131*, 1311–1322.

Coenen, V.A., Panksepp, J., Hurwitz, T.A., Urbach, H., and Mädler, B. (2012). Human medial forebrain bundle (MFB) and anterior thalamic radiation (ATR): imaging of two major subcortical pathways and the dynamic balance of opposite affects in understanding depression. J. Neuropsychiatry Clin. Neurosci. *24*, 223–236.

Cohen, M.X., Schoene-Bake, J.C., Elger, C.E., and Weber, B. (2008). Connectivity-based segregation of the human striatum predicts personality characteristics. Nat. Neurosci. *15*, 29–30.

Craig, A.D. (2009). How do you feel—now? The anterior insula and human awareness. Nat. Rev. Neurosci. *10*, 59–70.

Critchley, H.D., Mathias, C.J., and Dolan, R.J. (2001). Neural activity in the human brain relating to uncertainty and arousal during anticipation. Neuron *29*, 537–545.

Draganski, B., Kherif, F., Klöppel, S., Cook, P.A., Alexander, D.C., Parker, G.J.M., Deichmann, R., Ashburner, J., and Frackowiak, R.S.J. (2008). Evidence for segregated and integrative connectivity patterns in the human Basal Ganglia. J. Neurosci. *28*, 7143–7152.

Haber, S.N., and Knutson, B. (2010). The reward circuit: linking primate anatomy and human imaging. Neuropsychopharmacology *35*, 4–26.

Heimer, L., Zahm, D.S., Churchill, L., Kalivas, P.W., and Wohltmann, C. (1991). Specificity in the projection patterns of accumbal core and shell in the rat. Neuroscience *41*, 89–125.

Jones, D.K., Knösche, T.R., and Turner, R. (2013). White matter integrity, fiber count, and other fallacies: the do's and don'ts of diffusion MRI. Neuroimage *73*, 239–254.

Kahneman, D., and Tversky, A. (1979). Prospect theory: An analysis of decision under risk. Econometrica *47*, 263–292.

Knutson, B., and Bossaerts, P. (2007). Neural antecedents of financial decisions. J. Neurosci. *27*, 8174–8177.

Knutson, B., and Gibbs, S.E.B. (2007). Linking nucleus accumbens dopamine and blood oxygenation. Psychopharmacology (Berl.) *191*, 813–822.

Knutson, B., and Greer, S.M. (2008). Anticipatory affect: neural correlates and consequences for choice. Philos. Trans. R. Soc. Lond. B Biol. Sci. *363*, 3771–3786.

Knutson, B., Katovich, K., and Suri, G. (2014). Inferring affect from fMRI data. Trends Cogn. Sci. *18*, 422–428.

Kraus, A., and Litzenberger, R.H. (1976). Skewness preference and the valuation of risk assets. J. Finance *31*, 1085–1100.

Kuhnen, C.M., and Knutson, B. (2005). The neural basis of financial risk taking. Neuron *47*, 763–770.

Lehéricy, S., Ducros, M., Van de Moortele, P.F., Francois, C., Thivard, L., Poupon, C., Swindale, N., Ugurbil, K., and Kim, D.S. (2004). Diffusion tensor fiber tracking shows distinct corticostriatal circuits in humans. Ann. Neurol. *55*, 522–529.

Lehman, J.F., Greenberg, B.D., McIntyre, C.C., Rasmussen, S.A., and Haber, S.N. (2011). Rules ventral prefrontal cortical axons use to reach their targets: implications for diffusion tensor imaging tractography and deep brain stimulation for psychiatric illness. J. Neurosci. *31*, 10392–10402.

Mohr, P.N.C., Biele, G., and Heekeren, H.R. (2010). Neural processing of risk. J. Neurosci. *30*, 6613–6619.

Palminteri, S., Justo, D., Jauffret, C., Pavlicek, B., Dauta, A., Delmaire, C., Czernecki, V., Karachi, C., Capelle, L., Durr, A., and Pessiglione, M. (2012). Critical roles for anterior insula and dorsal striatum in punishment-based avoidance learning. Neuron *76*, 998–1009.

Panksepp, J. (1998). Affective Neuroscience: The Foundations of Human and Animal Emotions (New York: Oxford University Press).

Paulus, M.P., Rogalsky, C., Simmons, A., Feinstein, J.S., and Stein, M.B. (2003). Increased activation in the right insula during risk-taking decision making is related to harm avoidance and neuroticism. Neuroimage *19*, 1439–1448.

Pestilli, F., Yeatman, J.D., Rokem, A., Kay, K.N., and Wandell, B.A. (2014). Evaluation and statistical inference for human connectomes. Nat. Methods *11*, 1058–1063.

Petrides, M., and Pandya, D.N. (2007). Efferent association pathways from the rostral prefrontal cortex in the macaque monkey. J. Neurosci. *27*, 11573–11586.

Reynolds, S.M., and Zahm, D.S. (2005). Specificity in the projections of prefrontal and insular cortex to ventral striatopallidum and the extended amygdala. J. Neurosci. *25*, 11757–11767.

Samanez-Larkin, G.R., and Knutson, B. (2015). Decision making in the ageing brain: changes in affective and motivational circuits. Nat. Rev. Neurosci. *16*, 278–289.

Samanez-Larkin, G.R., Levens, S.M., Perry, L.M., Dougherty, R.F., and Knutson, B. (2012). Frontostriatal white matter integrity mediates adult age differences in probabilistic reward learning. J. Neurosci. *32*, 5333–5337.

Sanfey, A.G. (2007). Social decision-making: insights from game theory and neuroscience. Science *318*, 598–602.

Tournier, J.D., Calamante, F., and Connelly, A. (2007). Robust determination of the fibre orientation distribution in diffusion MRI: non-negativity constrained super-resolved spherical deconvolution. Neuroimage *35*, 1459–1472.

von Neumann, J., and Morgenstern, O. (1944). Theory of Games and Economic Behavior (Princeton, NJ: Princeton University Press).

Wu, C.C., Bossaerts, P., and Knutson, B. (2011). The affective impact of financial skewness on neural activity and choice. PLoS ONE *6*, e16838.

Wu, C.C., Sacchet, M.D., and Knutson, B. (2012). Toward an affective neuroscience account of financial risk taking. Front. Neurosci. *6*, 159.