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Frontostriatal anatomical connections predict age- and difficulty-related differences in reinforcement learning

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ABSTRACT

Reinforcement learning (RL) is supported by a network of striatal and frontal cortical structures that are connected through white-matter fiber bundles. With age, the integrity of these white-matter connections declines. The role of structural frontostriatal connectivity in individual and age-related differences in RL is unclear, although local white-matter density and diffusivity have been linked to individual differences in RL. Here we show that frontostriatal tract counts in young human adults (aged 18–28), as assessed noninvasively with diffusion-weighted magnetic resonance imaging and probabilistic tractography, positively predicted individual differences in RL when learning was difficult (70% valid feedback). In older adults (aged 63–87), in contrast, learning under both easy (90% valid feedback) and difficult conditions was predicted by tract counts in the same frontostriatal network. Furthermore, network-level analyses showed a double dissociation between the task-relevant networks in young and older adults, suggesting that older adults relied on different frontostriatal networks than young adults to obtain the same task performance. These results highlight the importance of successful information integration across striatal and frontal regions during RL, especially with variable outcomes.

1. Introduction

Reinforcement learning (RL) is the use of the outcomes of one's own actions to improve behavior and increase rewards. Successful RL relies on a large brain network centered on the striatum (comprising nucleus accumbens, caudate nucleus, and putamen) and frontal cortical areas, including prefrontal areas such as orbitofrontal cortex (OFC) and lateral prefrontal cortex (lPFC), and medial frontal areas such as anterior cingulate cortex (ACC) and (pre)motor areas (Haber and Knutson, 2010; Maia, 2009; Rushworth et al., 2011). Dopaminergic midbrain structures (specifically, the ventral tegmental area and substantia nigra) send phasic input to the striatum and frontal cortex signaling the prediction error, the subjective difference between expected and actual outcomes (Glimcher, 2011; Schultz, 2013). Learning signals in the striatum and frontal cortex likely support different aspects of RL, where in the striatum prediction, error signals mainly support bottom-up, model-free learning and in the frontal state prediction, errors are thought to guide goal-directed, model-based learning (Daw et al., 2005, 2011; Frank et al., 2007; Gläscher et al., 2010). Thus, behavioral optimization requires information transfer between striatum and frontal cortex to integrate different types of learning signals.

The striatum and frontal cortex are heavily connected through white-matter fiber bundles (Di Martino et al., 2008; Haber and Knutson, 2010). The integrity of structural brain connections decreases with age, even in healthy aging. This decline is especially prominent in striatal and frontal white-matter connections (Bennett et al., 2010; Burzynska et al., 2010; Salat et al., 2009). Meanwhile, RL behavior becomes less efficient with age, with larger decreases for probabilistic learning (feedback is not always in line with the given response) compared with deterministic learning situations (see, e.g., Eppinger et al., 2008; Hämmerer et al., 2011; Mell et al., 2005; Pietschmann et al., 2008; Schmitt-Eliassen et al., 2007; Weiler et al., 2008). Studies of functional brain activation

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suggest that older adults use the RL network less effectively than young adults (Chowdhury et al., 2013; Eppinger et al., 2013; Fera et al., 2005; Samanez-Larkin et al., 2014) and in addition employ other areas in, for example, anterior prefrontal cortex (aPFC), lPFC, and parietal cortex (Fera et al., 2005; Mell et al., 2009; van de Vijver et al., 2014).

The strength and efficiency of structural connectivity can predict individual differences in cognitive capacities and behavioral characteristics, in both young and older adults (Grieve et al., 2007; Kanai and Rees, 2011; Ziegler et al., 2010). The age-related changes in functional brain activation supporting RL therefore evoke the question whether the pattern of structural frontostriatal connections underlying successful RL also changes with age. So far, only 2 studies have directly related white-matter characteristics to learning behavior. In a sample of young adults only, more successful learners demonstrated lower white-matter diffusivity compared with less successful learners in multiple major white-matter connections, including the corpus callosum and several more posterior pathways (Koch et al., 2010). In addition, in less successful learners, higher diffusivity in a large network comprising frontal, striatal, and parietal areas correlated negatively with the ability to decrease functional activation with increasing feedback predictability. With age, more successful learning was related to higher fractional anisotropy (FA; a measure of local white-matter density) in the tracts connecting dorsomedial thalamus and medial prefrontal cortex (mPFC), and mPFC and nucleus accumbens (Samanez-Larkin et al., 2012). However, this last study focused on age-related changes in a few preselected white-matter pathways. Whether the general network of frontostriatal connections that supports successful learning shifts with age remains unknown.

In the present study, we therefore investigated whether and how age-related changes in frontostriatal white-matter connections explained RL differences in young and older adults. More specifically, our approach complements the study by Samanez-Larkin et al. (2012) in 2 ways: (1) we looked at differences in all possible connections between striatum and frontal cortex instead of investigating only predefined pathways of interest and (2) rather than focusing on the local white-matter density per voxel, which does not provide information on the connection that a voxel is part of, we examined the distribution of connections specifically linking frontal cortex and the striatum and their relation with learning behavior. Based on the changes in functional brain activity underlying RL (Chowdhury et al., 2013; Eppinger et al., 2013; Fera et al., 2005; Mell et al., 2009; Samanez-Larkin et al., 2014; van de Vijver et al., 2014), we hypothesized that the connections that support successful RL in young adults would become less directly related to learning success with age, whereas learning in older adults would additionally depend on connections between striatum and aPFC and lPFC.

To investigate these hypotheses, 24 young (18–28 years) and 35 older adults (63–87 years) underwent diffusion-weighted magnetic resonance imaging (MRI) scanning (22 young and 22 older adults were included in group-level analyses; see Section 2). In a separate session, they completed a probabilistic RL task in which they learned arbitrary stimulus-response mappings by trial-and-error. Because we were interested specifically in the relation between frontostriatal white-matter connections and RL, we applied probabilistic tractography to estimate white-matter tracts between the striatum and other brain areas, rather than focusing on measures of local white-matter quality (such as FA and diffusivity). Probabilistic tractography provides a probability distribution of the likelihood of white-matter connections between the seed mask and each target voxel. We refer to the probability values that result from this procedure as the "tract count", the proportion of tracts that end up in a specific voxel. It is important to note that this term refers to the virtually estimated tracts not to the number of actual white-matter connections between the seed and the target voxel. Relating probabilistic tractography of structural connectivity to behavioral differences has already proven highly informative in studies investigating age-related changes in, for example, action control (Coxon et al., 2012; Harsay et al., 2011).

Because this is the first study investigating the relation between tract count and RL behavior and because we were interested in the general shift in the underlying brain network rather than in changes within specific connections, we applied an exploratory analysis approach: per age group, we first computed probabilistic tractography from striatal seed regions to all other brain voxels and correlated individual learning accuracy in the easy (90% valid feedback, see Section 2.2) and difficult (70% valid feedback) learning conditions separately with white-matter tract count at each voxel (multiple comparison testing was controlled by cluster-correction). Second, to quantify possible shifts in networks underlying learning, we combined separate clusters into more large-scale networks and statistically tested network-level differences between conditions and age-groups. More specifically, we investigated per age group whether the voxels that correlated significantly with learning behavior differed between the easy and difficult learning conditions. In addition, we examined whether the voxels that showed positive correlations with learning behavior in the difficult condition differed between young and older adults. Based on our hypothesis, we expected different networks of voxels to correlate with learning behavior in the 2 age groups, where the network related to learning in older adults would include additional connections with lPFC and aPFC. Thus, this procedure provided us with summary-level insights into the frontostriatal networks engaged in both groups as a function of RL difficulty.

2. Materials and methods

2.1. Participants

Twenty-four young (18–28 years) and 35 older adults (63–87 years) participated in this study. Although the age range was larger for older adults, age did not correlate with task performance in any task condition or age group (all p values greater than 0.3). Young adults were recruited from the University of Amsterdam campus, older adults were selected from Seniorlab (a database of older adults interested in participating in psychological research). Participants underwent telephone and face-to-face screening according to standard neurological and MRI exclusion criteria. Participants started the second day of 2-day behavioral testing with the current task (the results of the other, unrelated tasks they performed are reported elsewhere; Cavanagh et al., 2012b; de Wit et al., 2012). On a separate day between 8 and 143 days before the second behavioral session (young mean 55.95 days, SD 30.66, older mean 58.40, SD 15.87, no significant difference between age groups: $t[39] = -0.318$, $p = 0.752$), participants completed diffusion-weighted and T_1 MRI scans. Participants received course credits (2 young participants) or financial compensation (all other participants) for participation, and an additional, performance-dependent financial bonus. All procedures were executed in compliance with relevant laws and institutional guidelines, and the study was approved by the local ethics committee.

The data of 2 young and 1 older participant could not be processed because of MRI scan artifacts. Based on an independent neuroradiologist's rating of anatomical MRI scans, 3 older adults were excluded because of potential hippocampal atrophy (assessed using Scheltens' medial temporal lobe atrophy scores; Scheltens et al., 1992), and 3 additional older adults were excluded because

of severely enlarged ventricles. Finally, 6 older adults did not meet the criteria for successful learning (see Section 2.2).

The included 22 young adults ranged in age from 18 to 28 (mean 21.0, SD 2.33 years, 13 female) and the 22 older adults from 63 to 87 (mean 72.0, SD 6.08 years, 15 female; no signs of mild cognitive impairment or dementia on the Cognitive Screening Test; Deelman et al., 1989). All participants were right-handed and had normal or corrected-to-normal vision. Participants reported no diagnosed neurological or psychiatric disorders. Young and older adults did not differ in verbal intelligence on the Nederlandse Leesvaardigheidstest voor Volwassenen (Dutch Reading test for Adults; Schmand et al., 1991; young mean 85.43, SD 4.905, older mean 88.81, SD 9.611, $t[29.757] = -1.436$, $p = 0.161$) or in working memory on the Operation span task (Turner and Engle, 1989; young mean 61.7%, SD 17.28, older mean 58.1, SD 17.88, $t[42] = 0.665$, $p = 0.510$).

2.2. Task

Participants performed a probabilistic RL task in which they had to learn arbitrary stimulus-response relations using trial-and-error (Fig. 1A; adjusted from Haruno and Kawato, 2006). On each trial, a stimulus was presented until the participant pressed 1 of 2 response buttons (max 2000 ms). After a delay of 500 ms, feedback was presented for 1500 ms. An intertrial interval of 700–1200 ms separated feedback from the next stimulus. Three blocks of 60 trials were presented (separated by self-paced breaks), with feedback probabilities of 90%, 80%, and 70%, respectively (i.e., in 10%, 20%, and 30% of trials, feedback valence was opposite to the participant's response accuracy). Block order was counterbalanced over participants. Per block, 4 new stimuli were each presented 15 times, two to the left response button and two to the right response button. Stimuli were fractals with clearly distinct colors and shapes, which were randomly assigned to the 3 blocks. Feedback consisted of a red (incorrect) or green (correct) square, and a loss or gain of 0.25 points. Participants received 15% of their earned points in euros as financial bonus. If participants responded outside the response window, feedback consisted of the words "too late".

Participants received extensive instructions and performed 2 practice blocks with 4 nontask stimuli, one with 100% valid feedback and a 6000 ms response window and another with 90% valid feedback and a 2000 ms response window (the same window as in the real task). The first practice block ended when participants had made 3 consecutive correct choices for all stimuli (max 20 presentations per stimulus), and in the second practice block, stimuli were presented 7 times. Only participants that reached an average accuracy level of 60% in the 90% condition of the real task were included in the analyses.

2.3. Behavioral analyses

Because feedback was probabilistic (on each trial a random number determined feedback validity) and because participants sometimes responded late (young: mean 0.08%, SD 0.20%, range 0%–0.56%; old: mean 0.76%, SD 0.76%, range 0%–2.22%), experienced feedback probabilities did not exactly match the intended percentages. Per participant, we therefore computed the experienced probabilities (percentage of valid feedbacks in the trials the participant responded to) and selected the blocks with the highest and lowest probabilities for further analyses (accuracy scores in the 3 feedback validity conditions before and after condition rearrangement are presented in Supplementary Table 1). The experienced probabilities in the central condition (80% valid feedback) overlapped somewhat with the experienced probabilities in the other conditions. To optimize condition comparisons, this condition was excluded from the analyses. Because relative task difficulty increases with decreasing feedback probability, we refer to the remaining conditions as "easy" (90% valid feedback) and "difficult" (70% valid feedback), respectively.

Feedback probabilities in these new conditions were on average 90.9% (SD 3.82, range 78.3–98.3) and 70.2% (SD 5.24, range 55.0–80.0), and the difference between the conditions ranged from 5% to 38.3% over individuals (no significant difference between age groups, $t(42) = 0.085$, $p = 0.932$). Although the experienced feedback probabilities varied across participants, rank-correlations per age group and condition demonstrated that the experienced feedback probabilities were only related to learning accuracy in older adults in the difficult condition ($r_S = 0.571$, $p = 0.006$). To further ensure that our results were driven by individual differences in

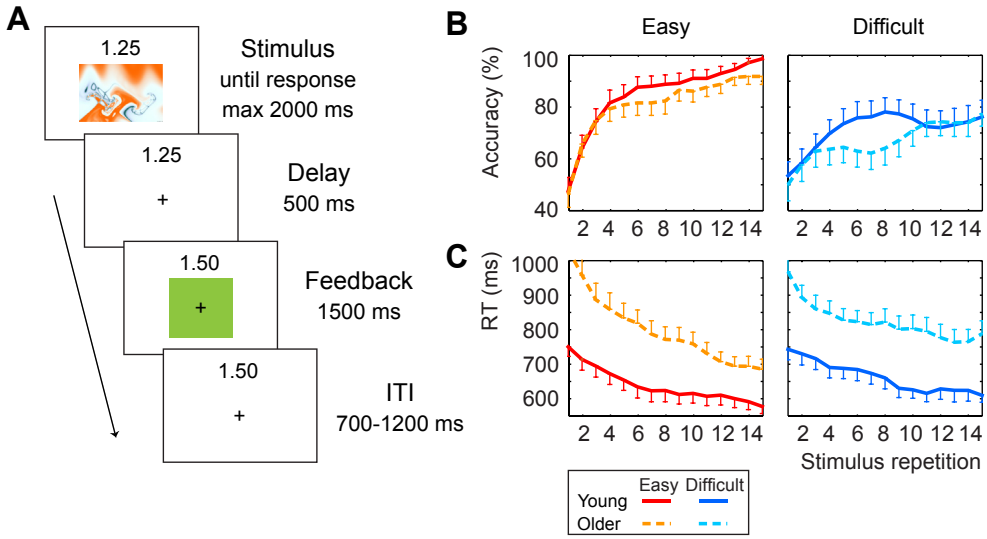

Fig. 1. Overview of the reinforcement learning (RL) task and behavioral performance. (A) Sequence of events in an example trial. Participants selected 1 of 2 response buttons while the stimulus was presented. (B) Average response accuracy per stimulus repetition as the percentage correct responses in the easy and difficult learning conditions. (C) Reaction times (RTs) per stimulus repetition averaged over responses within the response window in the easy and difficult learning conditions. Error bars represent 1 standard error of the mean. Abbreviation: ITI, inter-trial-interval.

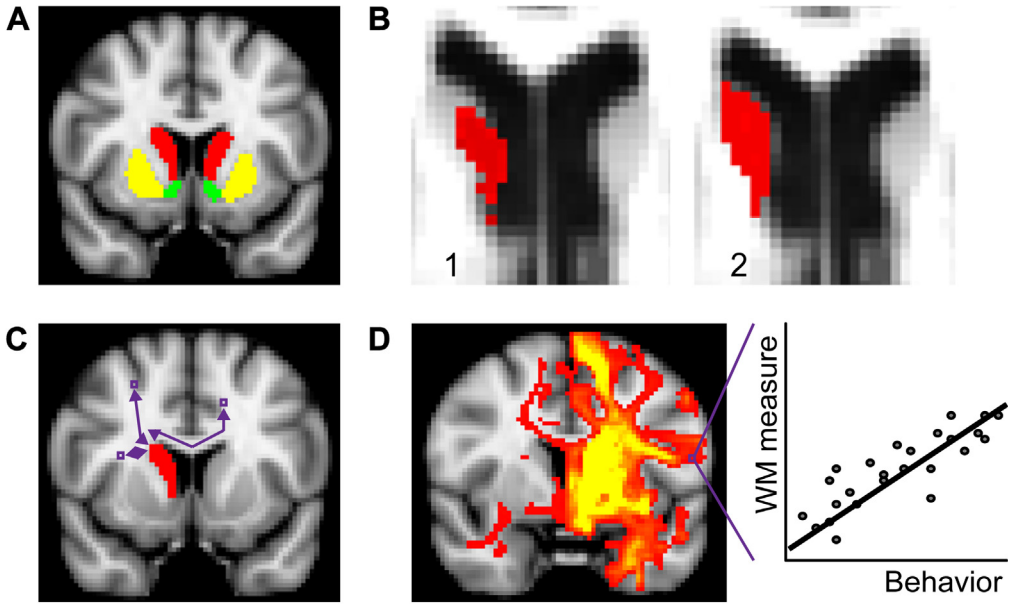

Fig. 2. Overview of DTI tractography procedure and analysis. (A) Masks of bilateral caudate nuclei, nuclei accumbens, and putamen were extracted from the Harvard-Oxford standard atlas. (B1) After automatically transforming all masks to participant-specific space, (B2) masks were manually adjusted using structural T_1 images to improve the fit with the intended regions. (C) For each mask, probabilistic tractography was run from all the voxels within the mask to all brain voxels, after which the results were merged over all voxels in the mask. (D) Per mask, we computed for each brain voxel the Spearman correlation over participants between white-matter tract count and learning accuracy (including FA values as covariate), to investigate which white-matter tracts were significantly related to RL accuracy (each simulated data point corresponds to a participant). Abbreviation: FA, fractional anisotropy.

behavior rather than in experienced feedback probabilities, we recomputed the correlations between behavior and tract count (see Section 2.6) while including the experienced probabilities as a covariate. This did not change the pattern of results in the subsequent network comparisons.

To test whether participants learned the correct stimulus-response mappings and how learning influenced their reaction times (RTs), we compared accuracy (percentage correct responses on all trials) and RTs in separate mixed analysis of variances with factors age (young, older), stimulus presentation (presentations 1–5, 6–10, 11–15), and learning condition (easy, difficult). We also investigated lose-switch and win-stay behavior, the amount of alternated or continued responses on the next appearance of the same stimulus after losses or wins, as percentages of the total numbers of losses and wins. Both measures were entered into mixed analysis of variances with factors age and learning condition. Greenhouse-Geisser corrections were applied where appropriate (uncorrected degrees of freedom are reported for ease of interpretability). Finally, we investigated for both age groups to what extent behavior in the easy and difficult conditions represented distinct aspects of learning: we rank-correlated accuracy between the conditions, and per condition we rank-correlated accuracy with win-stay and lose-switch behavior.

2.4. MRI data recording

MRI data were acquired on a Philips 3T scanner with an 8-channel array head coil. Diffusion-weighted data were obtained using spin-echo echo planar imaging (60 slices of 112 × 112 voxels, voxel size 2 × 2 × 2 mm, 50 noncollinear gradient directions, repetition time (TR) = 9.11 seconds, echo time (TE) = 65 ms). To increase sensitivity, 3 consecutive scans were obtained for each participant. A fourth scan was added if enough time was available. An anatomical T_1-weighted image (182 slices of 256 × 256 voxels, voxel size 1.2 × 0.883 × 0.883 mm, TR = 9.58 seconds, TE = 4.6 seconds) was also obtained.

2.5. MRI data processing

2.5.1. Preprocessing

All MRI data analyses were performed using the FSL MRI analysis program (Jenkinson et al., 2012; Smith et al., 2004) and custom-written Matlab scripts (The MathWorks, Natick, MA, USA). Per participant, diffusion tensor imaging (DTI) data of all runs were merged and eddy corrected. Brain shapes were automatically extracted from DTI and T_1 images with the FSL program "Bet-crawler". Extracted brains were visually inspected by 2 experimenters and adjusted and re-extracted when necessary. Finally, diffusion tensors were fit at each voxel using the FSL program "dtifit" to obtain FA values, and transformation matrices between DTI space, T_1 space, and standard 2 mm MNI (Montreal Neurological Institute) space were obtained.

2.5.2. Probabilistic tractography

The diffusion parameters per voxel were sampled in DTI space with the FSL program "bedpostX". Masks of bilateral nuclei accumbens, caudate nuclei, and putamen were acquired from the Harvard-Oxford subcortical atlas in FSL (Fig. 2A). All masks were automatically registered to participant-specific DTI space, thresholded at 0.8 to minimalize normalization-related spatial smoothing and corrected for overlap between masks (Fig. 2B1). The masks were visually compared with participant-specific high-resolution T_1 scans (registered to DTI space) by 2 experimenters and manually adjusted when necessary (Fig. 2B2).

Probabilities of white-matter connections were separately estimated from each mask to all brain voxels with the FSL program "probtrackX". Per seed mask, 5000 paths were drawn from each mask voxel, following the most likely white matter tract direction given the principal fiber directions. This analysis yields a map in which the value at each voxel reflects the statistical likelihood of a connection between this voxel and the mask. The resulting probability maps per seed-mask voxel were automatically combined in FSL (Fig. 2C and D), divided by the number of paths drawn and by

the number of voxels in the mask to correct for differences in mask sizes, and transformed to MNI space. Thus, the final spatial resolution was 2 × 2 × 2 mm. Normalized probability maps were smoothed per participant with a 3D 6 mm Gaussian kernel. Results in the cerebellum and brainstem are not reported because these regions were not completely in the MRI field of view for all participants. It is important to note that although we performed tractography from striatal masks to other voxels, the results do not provide information about the direction of tracts.

2.6. Relations between white-matter tract count and behavior

2.6.1. Age-related changes in frontostriatal white-matter connections

We first investigated general age-related changes in the distribution of white-matter tracts: for each seed mask, we used *t*-tests to compare tract count values per voxel between age groups. To correct for multiple comparisons, only voxels with p-value < 0.005 were considered significant, and only clusters of at least 50 contiguously significant voxels (400 mm^3) are reported.

2.6.2. Correlations between white-matter tract count and behavior

To investigate the relation between learning and white-matter tract count, we computed Spearman correlations between the individual tract count in each voxel and RL accuracy for each seed mask, age group, and condition (Fig. 2D). Again, only correlations with p-value < 0.005 were considered significant (in line with de Wit et al., 2012; van den Brink et al., 2014), and only clusters of at least 50 voxels are reported. Note, however, that although tract count correlated with behavior in these clusters these findings do not necessarily indicate the terminal points of any tract. Rather, it remains possible that these findings indicate differences within tracts that traverse these areas. FA values were included as covariate in all correlations to ensure that correlations were not biased by local white-matter density. Because of a lack of systematic differences, the final results are pooled over all 6 striatal seed regions.

2.6.3. Post hoc analyses of age and condition differences in brain-behavior correlations

To examine whether patterns of correlations differed significantly between learning conditions and between age groups, we combined the correlations into composite measures and statistically tested network-level differences. These analyses were conjectured post hoc, after having observed the outcomes of the preceding analyses, to test more detailed hypotheses emanating from the data patterns. Specifically, we investigated (1) whether in the young adults, the network of clusters correlating negatively with learning behavior in the easy condition was significantly different from the network correlating positively with learning behavior in the difficult condition, (2) whether the networks in older adults that correlated positively with learning in the 2 learning conditions were significantly different, and (3) whether the networks in young and older adults that correlated positively with learning in the difficult condition were significantly different.

To answer these questions, we combined clusters of correlating voxels into networks based on the correlation results: we created an easy-negative network in young adults (consisting of clusters correlating negatively with behavior in the easy condition in young adults), a difficult-positive network in young adults, and an easy-positive network and a difficult-positive network in older adults. Because difficult learning correlated with clusters in prefrontal cortex (PFC) in both age groups whereas only in older adults additional clusters were found in medial frontal cortex (MFC), only clusters in PFC were selected for the difficult-positive network in older adults.

For each of the 3 questions, we first calculated the amount of overlapping voxels between the 2 relevant networks, as a quantitative description of the similarity between networks. However, the presence of a significant correlation in only 1 condition or group does not necessarily imply that the correlations differ significantly between conditions or groups. Therefore, per network, age group, and condition, we calculated the Fisher's Z-transform of the correlation coefficients per voxel:

$$Z_{sep} = 0.5\ln\left(\frac{1+r}{1-r}\right)$$

These values were averaged per cluster, and, subsequently, over all clusters in a network. This provided us with 4 Z_{sep} values for each network: for young and older adults, in the easy and difficult learning conditions. Note that for each network, the Z_{sep} value is always significantly different from 0 in the condition and age group that were used to define a network because all voxels that were included to create the network showed a significant effect (e.g., in the easy-negative network in young adults, the Z_{sep} value of young adults in the easy condition is necessarily significant below 0).

Next, to examine the effects of learning condition and age, we calculated the normalized distance between the Z-transformed correlation values:

$$Z_{diff} = \frac{Z_{sep(a)} - Z_{sep(b)}}{\sqrt{\frac{1}{n_a-3} + \frac{1}{n_b-3}}}$$

where $Z_{sep(a)}$ and $Z_{sep(b)}$ are the Z_{sep} values and n_a and n_b are the n values of the 2 learning conditions or the 2 age groups, respectively. More specifically, to compare learning conditions, the difference (Z_{diff}) between easy and difficult conditions was computed separately for young and older adults, and to compare age groups, the difference (Z_{diff}) between young and older adults in the difficult condition was computed. Because Z_{diff} is normally distributed with mean 0 and variance of 1, it can be interpreted as a regular z-value.

However, because we defined our networks as consisting of voxels that demonstrated a significant correlation with behavior in 1 condition and age group, a statistical comparison of the correlations in these voxels between conditions or age groups is necessarily biased toward finding a significant difference (Kriegeskorte et al., 2009; Vul et al., 2009; but see also Lieberman et al., 2009). Therefore, for all 3 questions, we investigated the differences in 2 networks, defined separately in both conditions or age groups. When there is a double dissociation between networks and conditions or groups (e.g., correlations in the easy-positive network are significantly stronger in the easy than the difficult condition, and correlations in the difficult-positive network are significantly stronger in the difficult than the easy condition in the same age group), the networks supporting learning in the 2 conditions cannot show a significant amount of overlap, and the effects cannot be explained (solely) by a statistical bias.

3. Results

3.1. Influence of learning difficulty on behavioral performance

Increasing accuracy scores over stimulus presentations confirmed that participants learned the correct stimulus-response mappings (Fig. 1B; $F[2,41] = 50.599$, $p < 0.001$). Accuracy was higher in the easy than that in the difficult condition ($F[1,42] = 27.900$, $p < 0.001$), especially on later stimulus repetitions ($F[2,41] = 4.454$, $p = 0.015$). Young and older adults did not differ in accuracy ($F[1,42] = 1.201$, $p = 0.279$) nor did age interact with condition difficulty ($F[1,42] = 0.048$, $p = 0.827$), although a

marginally significant interaction of age and stimulus presentation indicated that learning reached asymptote earlier in young than in older adults ($F[2,41] = 3.064$, $p = 0.052$). The interaction of age, condition difficulty, and stimulus presentation was also not significant ($F[2,41] = 2.181$, $p = 0.119$). Although lose-switch and win-stay behaviors were lower in the difficult compared with the easy condition ($F[1,42] = 11.463$, $p = 0.002$ and $F[1,42] = 12.340$, $p = 0.001$) there were no effects of age or interaction effects of age and learning difficulty on lose-switch or win-stay behavior (all p values greater than 0.2).

In young adults, accuracy did not correlate between the easy and difficult conditions ($r_S = 0.135$, $p = 0.551$), whereas in older adults, this correlation was marginally significant ($r_S = 0.418$, $p = 0.053$). However, these correlations did not differ significantly between age groups (normalized distance between the Fisher's Z-transforms of both correlations: $Z = -1.05$, $p = 0.294$). In both young and older adults and in both difficulty conditions, accuracy correlated positively with win-stay behavior (all r's > 0.7, and p's < 0.001) and negatively with lose-switch behavior (all r's < -0.4 and p's < 0.05).

Older adults responded more slowly than young adults ($F[1,42] = 23.866$, $p < 0.001$; see Fig. 1C). RTs decreased over trials ($F[2,41] = 68.024$, $p < 0.001$), especially in older adults ($F[2,41] = 3.826$, $p = 0.035$). The decrease in RTs over trials was larger in the easy than that in the difficult condition ($F[2,41] = 5.639$, $p = 0.007$), and this effect was again larger in older than that in young adults ($F[2,41] = 4.566$, $p = 0.017$).

3.2. Age-related changes in frontostriatal connections

Tracts originating from the different striatal seed regions were in line with known connections and previous tractography findings in both age groups (Haber and Knutson, 2010; Harsay et al., 2011; Leh et al., 2007; Supplementary Figs. 1 and 2). Patterns of age-related differences in the distribution of tracts originating from the striatum showed high similarity for the different seed masks (Supplementary Fig. 3). Focusing on frontostriatal tracts, young adults demonstrated higher tract counts than older adults between the striatum and medial and lateral OFC, inferior frontal gyrus, and pre-, supplementary and central motor cortex. Older adults demonstrated higher tract counts than young adults between the striatum and anterior frontal cortex, the white matter in medial and anterior frontal cortex, and frontal corpus callosum. Note that as tract count is a relative measure (if 1 connection severely declines with age, more drawn tracts necessarily end up following other, relatively intact connections), this comparison does not directly reflect changes in white-matter integrity with age. Indeed, whole-brain comparisons between age groups of FA values and axial and radial diffusivity (AD and RD) were in line with previous studies (Bennett et al., 2010; Burzynska et al., 2010; Salat et al., 2009): FA showed a general decrease, and mean diffusivity (MD) and RD showed a general increase with age (Supplementary Fig. 4). The lower FA values in older adults were also present in the connections where they showed relatively higher tract counts.

3.3. Structural pathways predicting learning performance

Tract count in multiple connections between striatum and prefrontal cortex predicted learning (see Supplementary Table 2 for all easy-condition results and Supplementary Table 3 for all difficult-condition results). Here, we first describe the location of relevant clusters of tracts in a qualitative manner.

In both age groups, easy-condition learning correlated negatively with tracts between striatum and anterior lateral OFC (lOFC; Fig. 3A and E), whereas in young adults, difficult-condition learning was positively predicted by tracts between striatum and ventral lOFC (Fig. 3C). Easy-condition learning was also negatively predicted in young adults by tracts between striatum and clusters on the border of aPFC and lPFC (Fig. 3B). However, in both young and older adults difficult-condition learning correlated positively with tracts between striatum and dorsal lPFC (Fig. 3D and G). Tracts between striatum and anterior and lateral aPFC were positively predictive of learning in older adults in both learning conditions (Fig. 3F and G), and mPFC tracts also positively predicted difficult-condition learning in this age group (Fig. 3G).

A similar pattern is seen in the connections between striatum and MFC. In young adults, learning in the easy condition was also positively predicted by tracts between striatum and MFC (Fig. 4A), whereas easy-condition learning was negatively predicted by tracts between striatum and MFC in older adults (Fig. 4B). In older adults, difficult-condition learning was positively predicted by tracts between striatum and right MFC but negatively by tracts between striatum and left MFC (Fig. 4C).

3.4. Network shifts with increasing learning difficulty

Next, we combined the prefrontal clusters from the correlation analyses per age group and condition and examined the amount of overlapping significant voxels between conditions per age group. None of the 752 (unique) voxels in the easy-negative network in young adults overlapped with any of the 357 voxels in the difficult-positive network in this age group. Of the 408 voxels in the easy-positive network in older adults, 19 voxels were also part of the 1435 voxels in the difficult-positive network in this age group. This suggests that distinct networks were involved in the 2 learning conditions in both age groups.

Therefore, we tested within each network whether the correlations between tract count and behavior indeed differed significantly between learning conditions. More specifically, in this step, we directly compared correlations in the same clusters of voxels between conditions. In the easy-negative network defined in young adults, correlations between learning and tract count were indeed significantly stronger in the easy than those in the difficult learning conditions ($p = 0.012$; Fig. 5A). In the difficult-positive network defined in the same age group, correlations were stronger in the difficult than those in the easy condition ($p = 0.008$; Fig. 5A). Thus, although both easy-negative and difficult-positive networks contained connections between striatum and lOFC, lPFC, and aPFC, the specific structural networks related to behavior were significantly different between the easy and difficult learning conditions. In older adults, correlations with easy compared to difficult learning did not differ in the easy-positive ($p = 0.222$) or the difficult-positive network ($p = 0.173$; Fig. 5B). Thus, in contrast to young adults, in older adults, the structural frontostriatal networks related to learning performance were the same regardless of learning difficulty.

3.5. Age differences in learning-related network connectivity

Finally, we used the same aggregate networks to compare network correlations between age groups. Of the 357 voxels in the difficult-positive network in young adults, no voxels were also part of the 1435 voxels in the difficult-positive network in older adults. Relatedly, we observed a double dissociation between the frontostriatal networks that predicted RL performance in young compared with older adults (Fig. 5C), such that network connectivity that predicted performance in young adults did not predict performance in older adults, and vice-versa: correlations with difficult-condition learning differed significantly between age groups in both the difficult-positive network defined in young adults ($p = 0.037$) and the difficult-positive network defined in

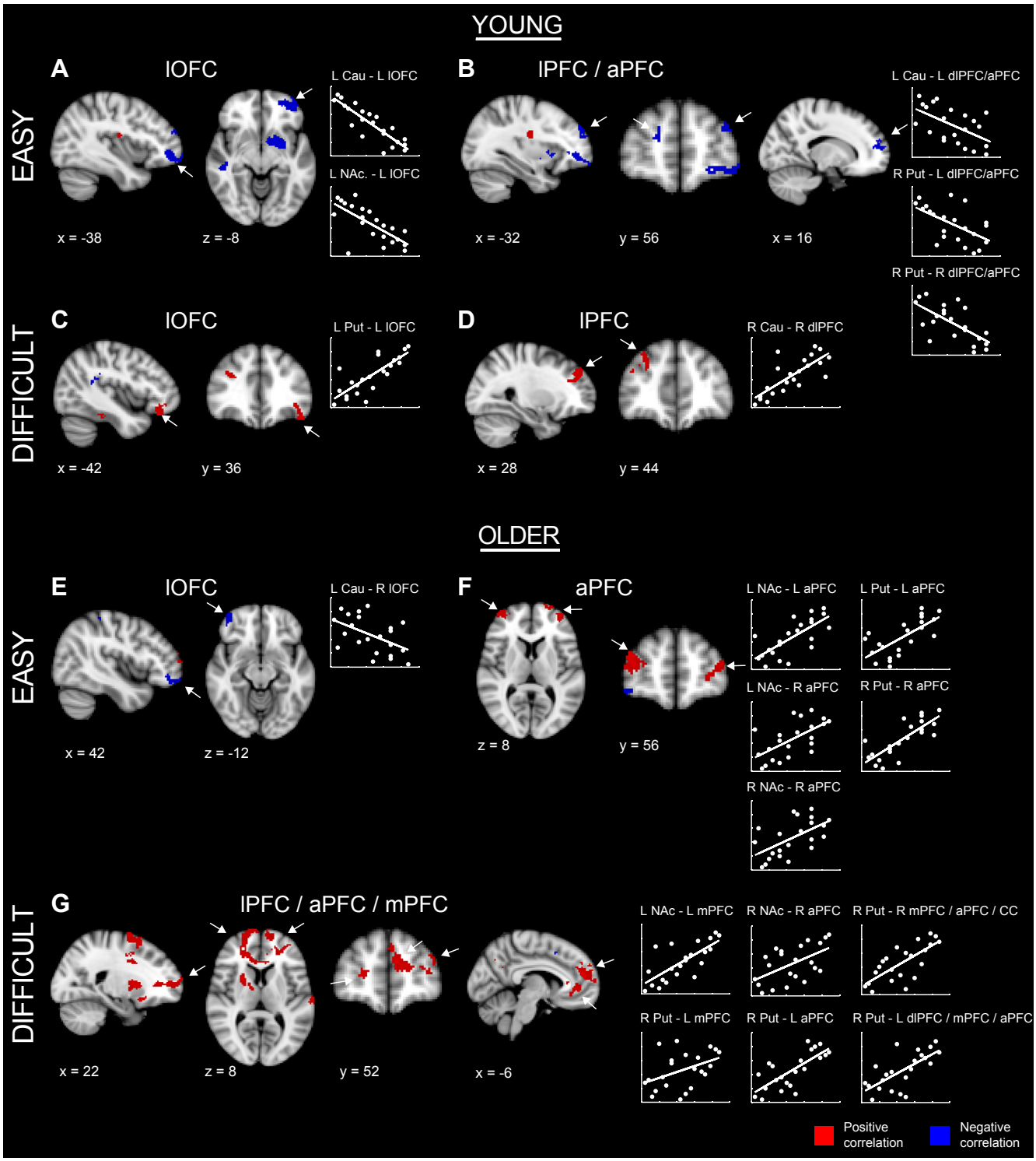

Fig. 3. Significant correlations in young and older adults between accuracy in the easy and difficult learning conditions and white-matter tract count between striatum and PFC. In young adults, learning in the easy condition correlated negatively with tract count between (A) striatum and lOFC and (B) striatum and clusters comprising lPFC and aPFC, whereas learning in the difficult condition correlated positively with tract count between (C) striatum and lOFC and (D) striatum and lPFC. In older adults, learning in the easy condition correlated (E) negatively with tract count between striatum and lOFC but (F) positively with tract count between striatum and aPFC. (G) Learning in the difficult condition correlated positively with tracts between striatum and a wide range of prefrontal brain areas, including mPFC, aPFC, and lPFC, in older adults. Results from all striatal masks are combined in the plots. Blue patches represent negative correlations, red patches represent positive correlations. Scatter plots represent voxels with peak correlations, with behavioral accuracy on the x-axis, and tract count on the y-axis (both rank transformed, FA values not included as covariate). Images are shown in radiological convention, X, Y, and Z coordinates indicate the location of the displayed slice in the brain in mm. Abbreviations: aPFC, anterior prefrontal cortex; Cau, caudate nucleus; CC, corpus callosum; dlPFC, dorsolateral prefrontal cortex; FA, fractional anisotropy; lOFC, lateral orbitofrontal cortex; lPFC, lateral prefrontal cortex; mPFC, medial prefrontal cortex; NAc, nucleus accumbens; Put, putamen. See also Supplementary Tables 2 and 3). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

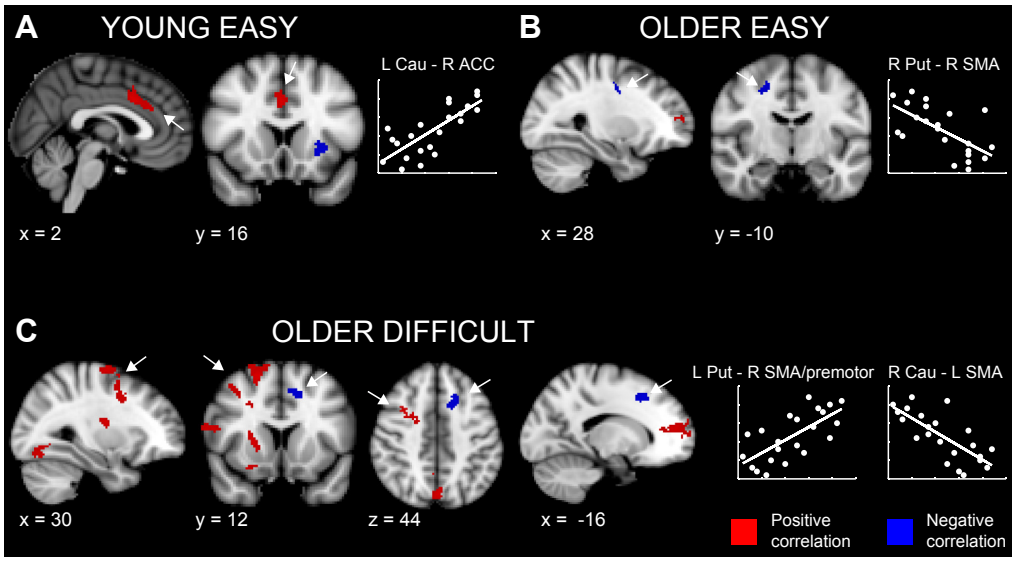

Fig. 4. Significant correlations in young and older adults between accuracy in the easy and difficult learning conditions and white-matter tract count between striatum and MFC. (A) In young adults, learning in the easy condition correlated positively with tract count between striatum and MFC. In older adults, (B) learning in the easy condition correlated negatively with tract count between striatum and MFC, whereas (C) learning in the difficult condition showed both positive and negative correlations with tracts between striatum and MFC areas. Results from all striatal masks are combined in the plots. Blue patches represent negative correlations, red patches represent positive correlations. Scatter plots represent voxels with peak correlations, with behavioral accuracy on the x-axis and tract count on the y-axis (both rank transformed, FA values not included as covariate). Images are shown in radiological convention, X, Y, and Z coordinates indicate the location of the displayed slice in the brain in mm. Abbreviations: ACC, anterior cingulate cortex; Cau, caudate nucleus; FA, fractional anisotropy; MFC, medial frontal cortex; NAc, nucleus accumbens; premotor, premotor cortex; Put, putamen; SMA, supplementary motor area. See also Supplementary Tables 2 and 3). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

older adults ($p = 0.006$). These results suggest that the structural networks positively related to learning performance differed between young and older adults: different parts of lPFC and aPFC correlated with difficult learning in the 2 age groups, and the learning network that correlated with difficult learning in older adults comprised additional parts of aPFC and mPFC that did not correlate with difficult learning in young adults.

4. Discussion

Our findings demonstrate that successful RL behavior is related to the availability of frontostriatal white-matter connections. Previous studies have demonstrated (1) the relevance of both brain areas for learning success (for reviews see, e.g., Maia, 2009; Rushworth et al., 2011), (2) widespread structural and functional connections between those areas (Di Martino et al., 2008; Haber and Knutson, 2010), and (3) the relation between learning success and local white-matter density and diffusivity (Koch et al., 2010; Samanez-Larkin et al., 2012). Here, we combined these lines of evidence by directly linking learning success to the likelihood of white-matter tracts specifically connecting striatum and frontal cortex. Our results suggest that the extent to which separate parts of the learning network together produce successful behavior depends on their specific pattern of connectivity.

In this study, a higher likelihood of frontostriatal connectivity coincided with better learning when feedback validity was low. This suggests that with reduced connectivity, frontal structures are less efficient at directing learning under these circumstances. Frontal areas are involved in high-level aspects of RL, such as favoring long-term over short-term decision consequences (McClure et al., 2004; Tanaka et al., 2004) and exploring alternative courses of action (Boorman et al., 2009; Cavanagh et al., 2012; Daw et al., 2006). The current correlations between accuracy and lose-switch and win-stay behaviors suggest that worse-performing participants were indeed less able to integrate outcomes over time.

In young adults, separate brain networks predicted learning with different feedback probabilities, consistent with the nonsignificant correlation between accuracy in the 2 conditions. Tracts between striatum and lateral frontal areas correlated negatively with easy-condition learning but positively with difficult-condition learning. Successful learners are better able to increase frontal activation with decreasing feedback predictability (Koch et al., 2010). Thus, we speculate that the negative correlation between easy learning and frontostriatal tracts reflects the necessity of a dissociated frontal system in this condition. Conversely, in the difficult condition, a well-connected frontostriatal network supports successful long-term integration. These differences suggest that the capacity of young adults to adapt their behavior to different feedback circumstances depends on the availability of specific frontostriatal connections.

Age-related connectivity differences were more widespread, although behavioral accuracy did not differ between groups. In line with our hypotheses, different tracts correlated with learning success in the 2 age groups. In older adults, these tracts indeed included additional connections between the striatum and aPFC and lPFC. Relatedly, direct comparisons of frontostriatal tract count between age groups indicated that the relative probability of tracts between striatum and aPFC and mPFC (compared to other frontostriatal tracts) was higher in older compared with young adults. Together these results suggest that when the central RL network declines, older adults recruit relatively preserved white-matter connections, perhaps as a compensatory strategy.

Interestingly, in a recent electroencephalographic study, we found age-related decreases in learning-related theta-band oscillations (4–8 Hz) over MFC, whereas the same oscillations over aPFC remained intact (van de Vijver et al., 2014). Posterror MFC theta-band oscillations have also been related to white-matter tract count between MFC and the striatum (Cohen, 2011a, b). This suggests that the respective changes in learning-related MFC and aPFC theta oscillations with age may depend on changes in white-matter

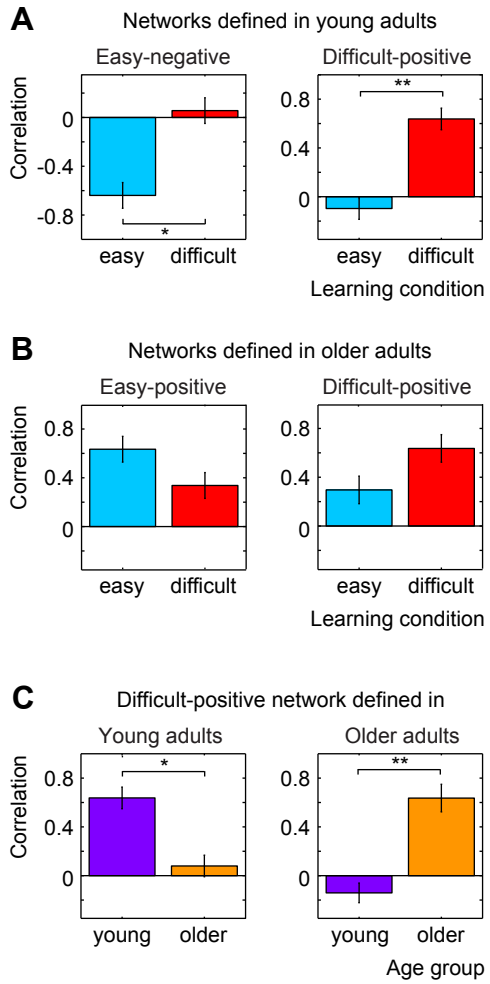

Fig. 5. Comparison of learning-related frontostriatal white-matter networks between learning conditions and age groups. For young and older adults, separate networks were defined based on the positive and negative correlations found with learning in the easy and difficult condition. In the current plots, the correlations in the voxels of each network are compared between (A and B) easy and difficult conditions, or (C) age groups (x-axis). (A) Results indicate that in young adults the easy-negative network correlates more negatively with accuracy in the easy compared with the difficult condition, whereas the difficult-positive network correlates more strongly with accuracy in the difficult compared with the easy condition. (B) Correlations did not differ between the easy-positive and difficult-positive learning conditions in older adults. (C) White-matter tract count in the difficult-positive network that correlated with learning success in young adults correlated significantly less with learning success in older adults, and vice versa ($^{*}p < 0.05$, $^{**}p < 0.05/6 = 0.0083$, correction for 6 performed tests). Error bars represent 1 SD in a distribution consisting of correlations between the tract count values and 500 permutations of the behavioral data (with FA values included as covariates). Per permutation, correlations were averaged over voxels and clusters in a network in the same way as the real correlations. Error bars do not differ between behavioral conditions because rank correlations were used and the permuted behavioral data values were the same across conditions. Abbreviation: FA, fractional anisotropy.

connections between the striatum and these 2 areas. Thus, a study including both DTI and electroencephalographic could greatly advance our understanding of how age-related changes in structural connectivity relate to changes in learning-related functional connectivity.

The additional learning-related frontostriatal connections in older adults are also in line with functional activation studies demonstrating the recruitment of additional cortical areas (Fera et al., 2005; Mell et al., 2009; van de Vijver et al., 2014). They seem to provide support for the compensation-related utilization of neural circuits hypothesis, which states that "processing inefficiencies cause the aging brain to recruit more neural resources to achieve computational output equivalent to that of a younger brain" (Reuter-Lorenz and Cappell, 2008). Interestingly, prefrontal white matter declines relatively early with age (Grieve et al., 2007; Salat et al., 2005, 2009). The current results therefore suggest that the ability to compensate depends on the relative intactness of frontostriatal connectivity.

Relatedly, we only included healthy older adults. Inclusion criteria comprised the participant's medical history and qualification for MRI but also their task performance and a lack of identifiably brain atrophy. These strict criteria may have resulted in the inclusion of only high-functioning older adults. Indeed, our groups of young and older participants did not differ in working memory performance, whereas most studies show age-related working memory decreases (see, e.g., Hedden and Gabrieli, 2004; Mattay et al., 2006). However, comparisons of the current working memory scores with comparable studies (de Wit et al., 2014; van de Vijver et al., 2015) suggest that the absence of age differences is due not only to high-scoring older adults but also to low-scoring young adults.

Young and older adults also showed comparable learning success. Although most previous studies suggest that learning decreases with age, especially when feedback is probabilistic (see, e.g., Eppinger et al., 2008; Hämmerer et al., 2011; Mell et al., 2005; Pietschmann et al., 2008), some studies have also found equivalent performance in young and older adults (Kolev et al., 2005; López-Crespo et al., 2009; Samanez-Larkin et al., 2014; Worthy et al., 2011). Indeed, our finding that learning reached asymptote earlier in young than that in older adults is consistent with a recent study showing that older adults can achieve the same learning performance as young adults after enough trial repetitions (Samanez-Larkin et al., 2014).

The comparable choice performance of young and older adults likely resulted from the exclusion of poorly performing participants and from task characteristics such as the relatively small number of stimuli per block and the long presentation times of stimuli and feedback, which made learning easier. Importantly, the comparable performance of young and older adults in the present study ensured that differences in the relation between behavior and structural connectivity could not have been attributable to performance differences and can be more safely attributed to the difference in age.

Still, our strict inclusion criteria limit the generalizability of our results: although the current set of older adults reached the same performance level as young adults, this achievement is less likely in older adults with increased brain deficits or cognitive decline. Indeed, compensation may fail when the burden gets too high (Cappell et al., 2010; Mattay et al., 2006). Thus, the extent to which older adults with increasing brain changes or cognitive decline rely on the same frontostriatal connections remains to be determined.

Although networks significantly differed between age groups, in older adults, networks did not differ depending on feedback validity. This is in line with behavioral evidence indicating that older adults are less able than young adults to adapt their decision strategy to the environment (Lemaire, 2010; Mata et al., 2010). This deficit becomes most prominent during difficult tasks, when the limited processing resources of older adults force them to rely on simpler strategies. Importantly, however, the current absence of age-related behavioral differences indicates that despite possible changes in strategy adjustment older adults still managed to reach the same performance as young adults.

One limitation of the present study is the nonindependence of the definition of task-relevant networks and their subsequent comparison between conditions and age groups: voxels were selected based on their correlation values, which were also used as

input in the network comparisons. This nonindependence may have somewhat increased condition- and age-related differences between different networks (Kriegeskorte et al., 2009; Vul et al., 2009; but see also Lieberman et al., 2009). Unfortunately, structural imaging data does not allow assessing brain-behavior correlations within participants, or using separate parts of the data of each participant for selecting task-relevant areas and for testing differences within these areas. As such, this aspect of our study must be considered exploratory, and the results should be validated in independent samples of participants.

Yet, we believe the nonindependence in our methods does not invalidate our main conclusions: (1) the nonindependence is unrelated to the correlations between individual pathways and learning, it only applies to the subsequent network selection procedure. (2) Because the nonindependence of network selections and comparisons may increase rather than decrease condition differences, it cannot explain the absence of condition differences in older adults. (3) In young adults, the networks defined in the 2 learning conditions showed a double dissociation, as did the networks that were defined in the separate age groups in the difficult condition. Even if correlations were inflated, such double dissociations would have been impossible with substantial overlap between the involved networks.

We only related white-matter tract count to behavioral performance. Although this allowed us to assess stable differences in structural connectivity, future studies should assess the relation between the same frontostriatal functional connections and learning performance (Bennett and Rypma, 2013; Messé et al., 2014). To estimate structural connectivity, we applied probabilistic tractography to diffusion-weighted MRI scans. The exact neural underpinnings of this type of statistical fiber tracking are unknown, and the results can be influenced by multiple biological factors (Beaulieu, 2002; Johansen-Berg et al., 2005; Roebroeck et al., 2008). However, they are consistent with invasive histological white-matter tracing (Dauguet et al., 2007; Dyrby et al., 2007; Leergaard et al., 2010; Seehaus et al., 2013), and tract counts in specific white-matter pathways are related to individual differences in various stable behavioral traits (Cohen, 2011a, b; de Wit et al., 2012; Harsay et al., 2011; van den Brink et al., 2014).

No systematic differences were found between the separate striatal seed regions in behavior-related connectivity patterns. Previous studies have indicated that ventral striatal subregions are important for acquiring new stimulus-response associations based on prediction errors, whereas dorsal subregions support the application of already-learned associations (Atallah et al., 2007; Haruno and Kawato, 2006; O'Doherty et al., 2004). Because we averaged behavioral accuracy over all trials, a mixture of both processes may have been reflected in this measure and, thus, in the related white-matter tracts.

Motivated by these findings, future studies could use specifically designed tasks amenable to computational modeling to identify the relationship between subprocesses of learning and specific frontostriatal white-matter connections. At least 2 lines of models can provide important additional insights. First, RL models (Rescorla and Wagner, 1972; Sutton and Barto, 1998) quantify the expected value of each decision option on each trial, and the subsequent prediction error. They can estimate, for example, the learning rate (the number of previous outcomes taken into account in the current decision) and the forgetting rate (the decay of information). Indeed, RL models can add to the investigation of age-related changes in learning: 2 recent studies showed that decreased reward-based learning in older adults coincides with decreased functional activation in the ventral striatum for reward prediction errors (Eppinger et al., 2013) and that individual differences in prediction errors were tightly coupled with the integrity of white-matter tracts between the striatum and the midbrain dopaminergic nuclei (Chowdhury et al., 2013).

In addition, models examining how behavior reflects the uncertainty in the environment may provide information on the influence of the learning circumstances (Nassar et al., 2010, 2012; O'Reilly, 2013). A lower feedback validity provides a more variable environment. Condition differences may depend on how well an individual adapts to such an environment, or the willingness to adjust the learning rate. The anterior cingulate cortex has been related to learning-rate adjustments with changing circumstances (Behrens et al., 2007), and aPFC is involved in the arbitration between exploration and exploitation (Boorman et al., 2009, 2011; Raja Beharelle et al., 2015). Thus, age-related changes in learning rates, their flexible adjustment, and their relation to brain connectivity provide interesting avenues for future research.

To conclude, the present study shows that in young adults, frontostriatal white-matter connectivity shapes the flexibility to adjust decision-making to changing circumstances. We speculate that in older adults, the condition of structural connectivity in a widespread frontostriatal network determines the capacity to compensate and maintain the same performance level as young adults. Together these findings illustrate how the age-related quantitative decline in white-matter connectivity induces qualitative differences, and how frontostriatal networks support successful RL behavior.

Disclosure statement

The authors have no conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neurobiolaging.2016.06.002.

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