Predicting Planning Performance from Structural Connectivity Between Left and Right Mid-Dorsolateral Prefrontal Cortex: Moderating Effects of Age During Postadolescence and Midadulthood

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Complex cognitive processes such as planning are known to critically rely on activity of bilateral mid-dorsolateral prefrontal cortex (mid-dlPFC). However, the functional relevance of the structural connectivity between left and right mid-dlPFC is yet unknown. Here, we applied global tractography to derive streamline counts as estimates of the structural connectivity between mid-dlPFC homologs and related it to planning performance in the Tower of London task across early to midadulthood, assuming a moderating effect of age. Multiple regression analyses with interaction effects revealed that streamline counts between left and right mid-dlPFC were negatively associated with planning performance specifically in early postadolescence. From the fourth life decade on, there was a trend for a reversed, positive association. These differential findings were corroborated by converging results from fractional anisotropy and white-matter density estimates in the genu of the corpus callosum where fibers connecting mid-dlPFC homologs traversed. Moreover, the results for streamline counts were regionally specific, marking the strength of mid-dlPFC connectivity as critical in predicting interindividual differences in planning performance across different stages of adulthood. Taken together, present findings provide first evidence for nonadditive effects of age on the relation between complex cognitive abilities and the structural connectivity of mid-dlPFC homologs.

Keywords: age effects, diffusion tensor imaging, global tracking, mid-dorsolateral prefrontal cortex, planning ability

Introduction

Goal-directed behavior in many situations beyond everyday routine necessitates prior planning, which is the mental anticipation and evaluation of alternative chains of interdependent actions and their consequences (Goel et al. 2012; Graffman et al. 2005). Planning processes transcend the inflexibility of concrete stimulus-response mappings toward a highly adaptive action selection based on situation-contingent modeling of future behavior (Mesulam 2002) and thus constitute one of the peak achievements of (human) cognition. But although it is widely agreed that the integrity of the mid-dorsolateral prefrontal cortex (mid-dlPFC) is crucial for planning behavior (Unterrainer and Owen 2006), the presumably differential functional contributions of its left and right homologs remain elusive (e.g., Newman et al. 2003; Byrd et al. 2011; Kaller, Rahm, Spreer et al. 2011; Crescentini et al. 2012; Ruh et al. 2012; Goel et al. 2013; Kaller et al. 2013; see also Vallesi 2012; Grafman et al. 2005).

Recent evidence from functional neuroimaging indicates that the often observed patterns of bilateral mid-dlPFC activations in planning may reflect concomitant operation of different cognitive processes with opposing lateralizations (Kaller, Rahm, Spreer et al. 2011). Activation in left mid-dlPFC seems to be stronger associated with early processes of internalizing, comprising the extraction of goal information and the generation of an internal problem representation, whereas activation in right mid-dlPFC seems to be more attributable to later processes of mental transformations of this representation (Nitschke et al. 2012; Ruh et al. 2012; see also Byrd et al. 2011). However, the nature of this hemispheric specialization is not absolute but relative. Although to different extents, neural assemblies in mid-dlPFC on either side are presumably involved in the same cognitive operations (Kaller, Rahm, Spreer et al. 2011), hence implicating a strong functional interaction between homolog cortical areas via transcallosal fiber connections. Current theories on interhemispheric transfer and callosal function emphasize either 1) inhibitory processes and the maintenance of independent processing or 2) excitatory processes and the integration of information, or 3) both (for review, see, e.g., van der Knaap and van der Ham 2011). Recent findings from transcranial magnetic stimulation (TMS) point to the significance of transcallosal inhibition between left and right mid-dlPFC during planning (Kaller et al. 2013). Moreover, Voineskos et al. (2010) revealed an inverse relationship between TMS-induced interhemispheric signal propagation between left and right (mid-)dlPFC and the fractional anisotropy of the underlying transcallosal fiber connections, indicating that the corpus callosum determines the preservation of functional asymmetries between (mid-)dlPFC homologs and that a considerable between-subject variation exists therein. Differences in structural connectivity may hence constitute a key determinant on the individual level concerning both 1) the strength of task demand-“dependent” functional dissociations between left and right mid-dlPFC activation and different cognitive operations during planning as revealed by functional neuroimaging (cf. Kaller, Rahm, Spreer et al. 2011; Ruh et al. 2012) and 2) the strength of task-demand-“independent” functional asymmetries between left and right mid-dlPFC contributions in planning as revealed by TMS (cf. Kaller et al. 2013).

In addition, the extant literature on maturation and degradation of white matter in prefrontal cortex provides a wealth of...
evidence for a substantial influence of age on the individual strength of prefrontal fiber connections (for an overview, see, e.g., Lenroot and Giedd 2006; Raz 2000; Raz and Kennedy 2009; Schmithorst and Yuan 2010; Kochunov et al. 2012). For instance, findings from diffusion tensor imaging (DTI) revealing age-related increases in fractional anisotropy indicate that the myelination of fiber connections in prefrontal cortex continues throughout childhood and adolescence (e.g., Klingberg et al. 1999; Barnea-Goraly et al. 2005) well into adulthood (e.g., Asato et al. 2010; Qiu et al. 2010; Kochunov et al. 2012). Developmental changes in fractional anisotropy are paralleled by regional increases of frontal white-matter volume (Reiss et al. 1996; but see also Giedd et al. 1999).

Following increases until early adulthood, white-matter volume in frontal lobe was reported to plateau around mid-30s to mid-40s and to decline thereafter (Bartzokis et al. 2001; Allen et al. 2005). Age-related declines in fractional anisotropy were also revealed to be most pronounced in prefrontal white matter (e.g., Pfefferbaum et al. 2005; Salat et al. 2005; Michielse et al. 2010) and anterior parts of the corpus callosum (Sullivan et al. 2006; Kochunov et al. 2012). Concomitant regional increases of dorsal prefrontal white-matter lesions were found to be associated with decreases of glucose metabolism in dlPFC (Reed et al. 2004) as well as in brain areas anatomically and functionally connected with dlPFC (Nordahl et al. 2006). Conversely, reduced dlPFC glucose metabolism is associated with age-related declines in fractional anisotropy of the genu, but not the splenium of the corpus callosum (Inoue et al. 2008).

In consequence, age is likely to be an important moderator for the brain–behavior relationship between the microstructural features of transcallosal white-matter tracts connecting homolog mid-dlPFCs and interindividual differences in planning ability. This is further suggested by recent behavioral evidence on continuing improvements of planning ability even beyond adolescence (Albert and Steinberg 2011) that is followed by performance declines thereafter (Gilhooly et al. 2002; Bugg et al. 2006; see also De Luca et al. 2003). Sex may constitute another moderator variable (see Kaller, Heinze et al. 2002, for findings on gray-matter density in mid-dlPFC), but previous anatomical findings on sex differences in prefrontal white matter seem less consistent (e.g., Raz et al. 2004; Schmithorst et al. 2008; for an overview, see Schmithorst and Yuan 2010).

Taken together, these findings suggest 1) that interindividu
differences in planning ability may be at least to some extent determined by microstructural properties of transcallosal fibers connecting left and right mid-dlPFC and 2) that this relation may be moderated by other variables such as age and sex. In consequence, the present research addressed the specific questions of whether individual planning accuracy is related to the structural connectivity between left and right mid-dlPFC, and whether this relation is moderated by age, sex, or both. To this end, structural connectivity was quantitatively assessed using streamline counts derived from a recently developed approach for global tracking (Reisert et al. 2011) shown to be superior to other available methods in reconstructing transcallosal connections (Fillard et al. 2011; Mangin et al. 2013; see also Li et al. 2012). Finally, to evaluate potential issues of specificity, transcallosal fiber connections between homolog cortical areas in the frontal eye fields (FEFs) and posterior parietal cortex (PPC), which are both also involved in planning (Kaller, Rahm, Spreer et al. 2011), were also reconstructed and resulting streamline counts related to individual planning accuracy.

**Materials and Methods**

**Subjects**

Present analyses were based on a sample of healthy volunteers recruited as control subjects for investigations of prefrontal functions in psychiatric patients (e.g., Katzev et al. 2013; Kaller et al. under review). A total of 48 datasets of normal volunteers including behavioral assessments and DTI were available. Due to extremely poor performance in the Tower of London task (overall accuracy, $z=-3.905$), 1 subject was excluded prior to the analyses. The final sample comprised 47 right-handed subjects (26 males; mean age ± standard deviation, 30.29 ± 9.68 years) with normal or corrected-to-normal visual acuity. None of the subjects was under medical treatment or reported a history of psychiatric or neurological illness. Written informed consent was obtained prior to participation. The study protocol was approved by local ethics authorities. Subjects received monetary compensation for their participation (~E10/h).

**Tower of London Task**

The Tower of London task (Shallice 1982) is a well-established neuropsychological test for the assessment of planning ability in various clinical and healthy populations (Sullivan et al. 2009; Kaller, Rahm, Köstering et al. 2011). In its original version, 3 balls of different colors are placed on 3 rods of different lengths (for a review, see Berg and Byrd 2002). Subjects are presented with a start state and instructed to transform it to match a predetermined goal state (e.g., see Fig. 1). For an optimal solution of problems in the minimally possible number of moves, subjects are thus required to plan ahead a solution before manually executing the moves. Three rules have to be followed: 1) Only 1 ball can be moved at a time, 2) balls cannot be placed outside the rods, and 3) if more than 1 ball is stacked on a rod, only the topmost ball can be moved.

The Tower of London problem selection used here consisted of an optimized problem set recently suggested by Kaller, Rahm, Köstering et al. (2011). In its extended version, this problem set comprises problems of 4–7 moves instantiating a linear increase of problem difficulty (for detailed psychometric evaluations, see Kaller, Unterrainer et al. 2012). However, for the purpose of investigating deteriorations of planning ability in psychiatric populations, a subset of 8 3-, 4-, and 5-move problems was applied here (see also Köstering et al. 2013). Subjects were tested individually in quiet laboratory rooms and performed a computerized version of the original Tower of London. The computer program did not allow rule-incongruent moves. Start state and goal state of each problem were presented in the lower and upper half of the screen, respectively. For each problem, the minimum number of moves was indicated on the left side of the start state. Problem presentations were carried out on a 12.1” touch-sensitive screen of an IBM ThinkPad X41 Tablet laptop computer (IBM Corp., Armonk, NY, USA). The presentation of a single trial was limited to 1 min (cf. Shallice 1982). Instructions placed strict emphasis on planning ahead before starting any move execution. Planning accuracy represented the main variable of interest here and was quantified as the percentage of problems solved correctly within the minimum number

![Figure 1](http://cercor.oxfordjournals.org/) Illustration of the Tower of London planning task that requires to transform a given start state into a given goal state within the minimum number of moves. In the present example problem, an optimal solution can be accomplished within 5 moves.
of moves without exceeding the time limit of 1 min (see above). If the time limit was exceeded on 3 consecutive trials, the task was automatically aborted.

Magnetic Resonance Imaging Acquisition

All subjects were administered T1-weighted high-resolution anatomical brain imaging on a 3-Tesla TIM TRIO whole-body magnetic resonance imaging (MRI) scanner (SIEMENS, Erlangen, Germany) applying magnetization-prepared rapid gradient echo (MPRAGE) imaging with the following scan acquisition parameters: Repetition time, 2200 ms; echo time, 4.11 ms; inversion time, 1100 ms; flip angle, 12°; 160 sagittal slices; matrix size, 256 × 256; field of view, 256 mm; voxel size, 1 × 1 × 1 mm³. In addition, DTI data were acquired using a diffusion-sensitive single-shot spin-echo echo-planar imaging (EPI) sequence, with cerebrospinal fluid (CSF) suppression and the following specifications: 61 diffusion encoding gradient directions (b-factor, 1000 s/mm²); repetition time, 11800 ms; echo time, 96 ms; inversion time, 2300 ms; 69 axial slices; matrix size, 104 × 104; field of view, 208 mm; voxel size, 2 × 2 × 2 mm³. Nine additional scans without diffusion weighting (b-factor, 0 s/mm²) were equally distributed across the acquisition series, resulting in a total of 70 volumes. Motion and distortion artifacts were corrected during image reconstruction based on a reference measurement (Zaitsev et al. 2004).

Preprocessing of Anatomical and Diffusion Tensor Images

Anatomical T1 images were processed using the SPM8 (release r4667; http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) and VBM8 (release r435; http://dbm.neuro.uni-jena.de) software packages both running on MATLAB 7.9.0 (R2009b; The Mathworks, Inc., Natick, MA, USA). Manual reorientation of T1 images was performed by placing the coordinate system’s origin into the anterior commissure and the posterior commissure into the intersecting xy-plane. VBM8 was used for segmentation of individual brains into gray and white matter and CSF compartments. Segmentation was based on the default estimation options i.e., very light bias regularization, 60 mm cutoff for estimating the Gaussian smoothness of bias in image intensity; International Consortium for Brain Mapping (ICBM) European template for initial affine transformation) and tissue probability maps (modified version of ICBM tissue probabilistic atlases). Spatial normalization into the Montreal Neurological Institute (MNI) standard space was carried out using the high-dimensional diffeomorphic anatomical registration through exponentiated lie algebra (DARTEL; see Ashburner 2007) approach within VBM8 with the default options such as multithreaded spatial adaptive nonlocal means denoising, light clean-up of partitions, and weighting of Hidden Markov-Random Fields by a factor of 0.15 were used.

DTI data were processed and analyzed using a MATALB-based in-house toolbox for fiber tracking (http://www.uniklinik-freiburg.de/mr/live/arbeitsgruppen/diffusion/fibertools_en.html; see also Kreher et al. 2008; Reisert et al. 2011). At first, the effective self-diffusion tensor was computed (Basser et al. 1994) on diffusion data corrected for motion and distortion artifacts. Present assessments of structural connectivity were based on global tractography which refers to a class of algorithms that reconstruct fibers (or streamlines) simultaneously instead of one by one (Kreher et al. 2008; Fillard et al. 2009, 2011). The global structure is revealed during iterations of a simulated annealing operation of the preselections for the individual ROIs (for an illustration, see Fig. 2). The resulting number of connecting streamlines resembled an estimation of the structural connectivity between homolog regions. Although streamline counts cannot be directly taken as a quantitative measure of connectivity in terms of the numbers of axons (see, e.g., Jones et al. 2013), one can expect it to be an indicator of interindividual differences in white-matter properties at the level of fiber bundles (see also Discussion).

The number of streamlines estimated by global fiber tracking is sensitive to differences in brain size. For instance, in the present sample, total intracranial volume (summation of segments for gray matter, white matter, and CSF derived from VBM8) was highly correlated (r = 0.878, P < 0.001) with the total number of streamlines in the entire brain. Consequently, an appropriate correction is mandatory, and streamline counts between ROIs were divided by individual subjects’ total intracranial volume. This approach corresponds to a multiplicative correction of brain size as, for instance, suggested in VBM8 for the modulation of gray- and white-matter density maps (see also Käller, Heinze et al. 2012).

For visualization purposes (cf. Fig. 3), individual streamline selections were converted into spatial maps of streamline counts, normalized into MNI space, and finally averaged across subjects.

Multiple Regression Analyses with Interaction Effects

Although only rarely applied to neuroimaging data so far, interactions between regressors in multiple regression (i.e., nonadditive effects) can be assessed by simply extending the “main effects” model (i.e., additive effects) with product terms for the interaction between

Parameters for global tracking were chosen as suggested by Reisert et al. (2011) with a cylinder width of 1 mm and a cylinder length of 3 mm. The weight of a cylinder segment was set to one-fourth of the brain-averaged anisotropic signal component, resulting in a “dense” reconstruction with an average of 30 cylinders per voxel. Note that the weight parameter is comparable to a fractional anisotropy threshold: For higher weights, the number of streamlines is reduced and a significant amount of streamlines is only revealed for regions with a highly anisotropic diffusion distributions. Conversely, a lower weight leads to high number of streamlines, even in regions with a low fractional anisotropy seen through the low weight selected here, the number of iterations was set to 3 × 10³. Finally, the temperature schedule for the cooling phase of the polymerization process was chosen exponentially with a starting temperature of 0.1 to a stop temperature of 0.001 (cf. Reisert et al. 2011).

Regions-of-Interest Specification and Streamline Selection

Streamline selection was performed specifying regions-of-interest (ROIs) in mid-dlpFC based on a previous fMRI study that revealed disso- ciable contributions of left and right mid-dlpFC in planning (Käller, Rahm, Speer et al. 2011; Ruh et al. 2012). Whereas activation contrasts reported in the fMRI study focused on differences in task-demand- dependent lateralization in mid-dlpFC, here we specified ROIs based on fMRI activation patterns associated with planning, that is, irrespective of experimental manipulations of planning demands (cf. Käller, Heinze et al. 2012, for an identical approach for voxel-based morphometric [VBM] analyses). The whole-brain analysis (corrected for familywise error) yielded a cluster in left and right mid-dlpFC (peak coordinates in MNI stereotactic space: [−36 38 28] and [36 40 34], respectively). Based on these coordinates, spherical ROIs with a radius of 12 mm were specified (cf. Fig. 3A). For additional analyses of regional specificity, further ROIs were defined at the maximum activation peaks of activation associated with planning in the FEVs (left [−30 −8 −6] and right [30 −2 62]; cf. Fig. 3B) and in the PPC (left [−24 −62 58] and right [22 −64 56]; cf. Fig. 3C).

As global tracking estimations of fiber connections were conducted in individual subjects’ native space, binary ROI masks for streamline selection were re-normalized from MNI using the inverse deformation fields derived from VBM8. Prior co-registration of T1 and b0-images ensured that DTI data remained stationary throughout all analyses. Re-normalized ROI masks were then used to preselect all intersecting streamlines. Commisural fibers (or streamlines) connecting homolog ROIs in left and right hemisphere were identified using a logical AND operation of the preselections for the individual ROIs (for an illustration, see Fig. 2). The resulting number of connecting streamlines resembled an estimation of the structural connectivity between homolog regions. Although streamline counts cannot be directly taken as a quantitative measure of connectivity in terms of the numbers of axons (see, e.g., Jones et al. 2013), one can expect it to be an indicator of interindividual differences in white-matter properties at the level of fiber bundles (see also Discussion).

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regressors, that is, the nonadditive components (for introductions, see Cohen et al. 2003; Jaccard and Turrisi 2003). As an example, Equation (1) describes the least squares regression model for predicting an outcome variable \( Y \) from 2 predictor variables \( X \) and \( Z \). In this commonly used model, the main effects of \( X \) and \( Z \) contribute in a purely additive fashion to the prediction of \( Y \):

\[
Y = a + b_1X + b_2Z + e
\]

In contrast, Equation (2), the regression model is complemented by a nonadditive part, that is, the product term \( XZ \) that reflects the interaction between \( X \) and \( Z \) where the effect of one predictor \( (X) \) on the outcome \( Y \) is a linear function of the other predictor variable \( (Z) \). In other words, the model is able to account not only for a linear relationship between \( X \) and \( Y \) but also for linear changes of this relation depending on the value of a third variable \( Z \). This influence of a third variable \( Z \) on the regression of a criterion variable \( Y \) onto a predictor variable \( X \) is interpreted as a moderator effect (Jaccard and Turrisi 2003). In this framework, \( X \) as the primary predictor of interest is then termed the focal variable, whereas \( Z \) is called moderator variable. Here, streamline counts were treated as the focal variable and age and sex were treated as first- and second-order moderator variables, respectively (cf. Jaccard and Turrisi 2003). Since recent evidence demonstrates the merit of multiple regression with interaction effects, for instance, for investigating moderating effects of age and sex on brain-behavior relationships (e.g., Kaller, Heinze et al. 2012), this statistical approach was also adopted in the present analyses.

In common analyses using statistical parametric mapping, indices of brain structure or function are usually regressed onto a set of behavioral or demographic variables. In contrast, here we invented this common research scheme by asking 1) whether individual planning ability can be predicted by quantitative estimations of the structural connectivity of homolog areas in left and right mid-dLPPFC and 2) how this putative relation varies depending on subjects’ age and sex. That is, planning accuracy was entered as dependent variable and streamline counts between left and right mid-dLPPFC ROIs (corrected for total intracranial volume) constituted the focal independent regressor. To investigate their possible moderating effects, age and sex as well as the resulting product terms for all possible 2- and 3-way interactions were also added to the model as regressors (for more detailed descriptions, see also Kaller, Heinze et al. 2012).

In multiple regression analysis with interaction effects, resulting test statistics (e.g., regression coefficients) are conditional, that is, their specific values are only valid for a given centering of the other predictor variables (Cohen et al. 2003; Jaccard and Turrisi 2003). To yield meaningful results, all statistics reported here were computed for mean centerings of the focal and moderator variables, thus reflecting the parameter estimates for the average characteristics of the sample. To ease the interpretation of possible interaction effects, the test statistics (i.e., regression weight, predicted value of planning accuracy) for the effect of regressing planning accuracy on the focal variable streamline counts were hence computed for 3 different centerings of the continuous first-order moderator variable age based on mean and standard deviation of subjects’ age (i.e., M – SD, M, M + SD with M = 30.29 and SD = 9.68 years). The second-order moderator sex as a dichotomous variable was dummy-coded and observed in 2 different instances (male/female = 0/1 and vice versa). The dependent variable planning accuracy was not mean-centered.

Analyses were conducted with SPSS Statistics 20 (IBM Corp.) using the PROCESS macro for computation of moderator and mediator effects in multiple regression (Hayes 2013; see also www.afhayes.com). In particular, model type 3 of the PROCESS macro was used specifying planning performance as outcome variable \( Y \), streamline counts as focal predictor \( X \), age as first-order moderating variable \( M \), and sex as second-order moderator \( W \), whereas model type 1 was used for the analyses omitting all regressors involving the variable sex (see below). The \( \alpha \) level was set to 0.05 for the primary analyses of interest on mid-dLPPFC connectivity. Given that the additional analyses for FEFs and PPC aimed at exploring a potential specificity of the moderation effect found for mid-dLPPFC (i.e., hypothesizing a failure to detect significant effects for these other regions), the \( \alpha \) level of 0.05 in these subsequent tests was not adjusted for multiple comparisons in order to prevent false-negative results. However, specificity was also formally assessed by comparing the standardized \( \beta \) coefficients of the interaction effects of age on the relation between planning accuracy and streamline counts for mid-dLPPFC, FEFs, and PPC.

**ROI-Based Extraction of Fractional Anisotropy and White-Matter Density**

Supplementary analyses concerned additional indices of structural connectivity, namely, the fractional anisotropy and white-matter density in those regions of the corpus callosum where transcallosal
fibers connecting mid-dlPFC, FEFs, and PPC traverse. To this end, averaged normalized spatial maps of streamline counts (cf. Fig. 3) were binarized at a threshold of 0.05 (i.e., including only those voxels in which at least 1 traversing streamline was estimated in 5% of subjects). Based on the binary tracts, ROIs were then specified covering ±4.5 mm from the mid-sagittal slice. Fractional anisotropy and white-matter density were extracted from the respective ROIs in individual normalized images. Images were normalized into MNI space using the high-dimensional DARTEL approach implemented in VBM8 (see above). Normalization of white-matter density images additionally comprised a nonlinear but not affine modulation, thereby multiplicatively correcting for total intracranial volume (see also Kaller, Heinze et al. 2012). Furthermore, images remained unsmoothed given that extracted data were aggregated by using the first eigenvariate.

**Results**

**Assessment of Planning Accuracy**

A repeated-measurements ANOVA on planning accuracy was performed with minimum number of moves as within-subjects factor. As expected, the main effect of minimum moves was significant ($F_{2,92} = 69.621$, $P < 0.001$): Planning accuracy decreased systematically from 3- (M ± SD, 94.68 ± 9.66%) to 4- (86.2 ± 15.47%) and 5-move problems (63.03 ± 18.05%). Individual performance of subjects ranged from 62.5% to 100% (M = 81.29%, SD = 9.94%). Planning accuracy was found to be negatively correlated with age ($r = -0.307$, $P = 0.036$) which was to be expected given the broad age range in the present sample (18.31–54.34 years). No significant difference in planning accuracy was found for sex ($t_{45} = 0.700$, $P = 0.488$).

**Regressing Planning Accuracy on Streamline Counts Between Left and Right Mid-DLPFC**

Transcallosal fiber connections between homolog ROIs in mid-dlPFC were reconstructed for all of the 47 included subjects using the global tracking algorithm described in Reisert et al. (2011). An overview on the resulting trajectory is presented in Figure 3A. Multiple regression analysis on planning accuracy comprised 3 regressors for the simple effects of the focal variable of interest (i.e., streamline counts between left and right mid-dlPFC) and the 2 moderator variables (age, sex).

![Figure 3. Commissural fibers (or streamlines) connecting a priori-defined ROIs in left and right (A) mid-dorsolateral prefrontal cortex, (B) frontal eye fields, and (C) posterior parietal cortex. ROI masks are illustrated on renderings of the average brain of the present sample, streamline trajectories are depicted on the respective coronar slices. Numbers below slices indicate MNI coordinates in anterior–posterior (y) direction.](http://cercor.oxfordjournals.org/)

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results revealed a significant simple effect of age ($t_{(38)} = -2.423$, $P = 0.020$) and a significant moderator effect of age on streamline counts ($t_{(38)} = 2.135$, $P = 0.039$) for predicting planning accuracy. None of the other regressors was significant, so that also the overall model fit was not significant ($F_{7,39} = 1.557$, $P = 0.177$, $R = 0.467$, $R^2 = 0.2185$). An overview on inferential statistics for all regressors is listed in Table 1. As sex did not provide any significant additive or nonadditive contributions, we repeated the above multiple regression omitting all regressors involving the variable sex (i.e., for the simple effect and interactions). The overall fit of this reduced model reached significance ($F_{3,43} = 3.254$, $P = 0.031$, $R = 0.430$, $R^2 = 0.185$), indicating a satisfactory and reasonable contribution to the prediction of planning accuracy. As before, the simple effect of age ($t_{(42)} = -2.479$, $P = 0.017$) and its interaction with streamline counts ($t_{(42)} = 2.107$, $P = 0.041$) were found to be significant, whereas the simple effect of streamline counts failed to approach significance ($t_{(42)} = -1.179$, $P = 0.245$). Notably, the increase in explained variance $R^2$ due to the significant interaction effect was at $R^2_{\text{change}} = 0.084$. As is evident from Figure 4 (left panel), the moderator effect of age on the relation between streamline counts and planning accuracy followed a disordinal developmental pattern: At younger ages (~20 years), streamline counts were negatively linked to planning accuracy indicating a beneficiary effect of decreased streamline counts between left and right mid-dLPFC. Around the age of 30 years, this negative relationship almost leveled out, whereas it turned into a positive relation at older ages of around 40 years and later.

Regional Specificity
In order to assess the regional specificity of the results for mid-dLPFC, additional regression analyses concerned streamline counts between homolog ROIs in left and right FEFs and PPC. Fiber tracts between homolog ROIs in FEFs and PPC were found for all of the 47 included subjects. An overview on the respective trajectories via the corpus callosum is presented in Figure 3B,C. The overall fit of multiple regression models on planning accuracy with the focal independent variable streamline counts and the moderator variables age and sex did not reach significance, neither for streamline counts between FEFs ($F_{7,39} = 1.598$, $P = 0.165$, $R = 0.472$, $R^2 = 0.223$) nor between PPC homologs ($F_{7,39} = 1.404$, $P = 0.231$, $R = 0.449$, $R^2 = 0.201$). Inferential statistics for individual regressors, none of which was significant, are listed in Table 1. Overall model fits could not be improved significantly by removing all regressors involving sex (FEFs: $F_{3,43} = 2.208$, $P = 0.101$, $R = 0.365$, $R^2 = 0.134$; PPC: $F_{3,43} = 2.443$, $P = 0.077$, $R = 0.382$, $R^2 = 0.146$) as was also true for the simple effect of streamline counts (FEFs: $t_{(42)} = -0.164$, $P = 0.870$; PPC:

![Figure 4](http://cercor.oxfordjournals.org/)

**Figure 4.** Moderation effect of age on the relation between planning accuracy and different indices of the structural connectivity between left and right mid-dLPFC. Streamline counts refer to the number of streamlines connecting left and right mid-dLPFC ROIs, whereas fractional anisotropy and white-matter density were extracted from a ROI in the corpus callosum specified by the transcallosal fibers connecting mid-dLPFC homologs. The location of the callosal ROI is illustrated on the sagittal brain slice (in red color). Given its conditional nature (see Materials and Methods), the moderating effect of age is evaluated at 3 different centerings of the age regressor, namely, the mean age ($M \pm 1$ SD; 30.26 years; gray dots) of the sample, the value corresponding to the mean minus one standard deviation ($M - SD$, 20.61 years; white dots), and the value corresponding to the mean plus one standard deviation ($M + SD$, 39.97 years; black dots). Medium, high, and low values of the focal variables on the abscissa (streamline counts, fractional anisotropy, and white-matter density) likewise correspond to the respective mean plus/minus one standard deviation ($M \pm 1$ SD).
streamline counts estimates between FEF homologs (these nonsignificant counts in mid-dlPFC and planning accuracy was driven by counts between homolog ROIs in mid-dlPFC (ov)

Robustness of Results

Although prior tests did not yield any significant deviations from normal distribution, neither for planning accuracy (Kolmogorov–Smirnov, P = 0.105) and age (P = 0.390), nor for streamline counts between homolog ROIs in mid-dlPFC (P = 0.275), in FEFs (P = 0.760), and in PPC (P = 0.831), visual inspections however indicated a bimodal distribution for planning accuracy as well as a positive skewness for age (see Fig. 5). In order to preclude that the present moderation of age on the relation between streamline counts in mid-dlPFC and planning accuracy was driven by these nonsignificant but potentially distorting deviations from normality, multiple regression analysis was repeated after gaussianization of planning accuracy and age. Despite a marginal decline in the overall model fit (F(3,43) = 2.312, P = 0.089, R = 0.373, R² = 0.139), results revealed a strong trend for an interaction between streamline counts in mid-dlPFC and age (t(42) = 1.930, P = 0.060). Gaussianization of age and planning accuracy did not significantly improve predictions based on streamline counts estimates between FEF homologs (F(3,43) = 1.376, P = 0.263, R = 0.296, R² = 0.088) and PPC (F(3,43) = 1.690, P = 0.183, R = 0.325, R² = 0.106). Also gaussianization of streamline counts estimates did not change the present results (overall model fit, mid-dlPFC, F(3,43) = 2.647, P = 0.061, R = 0.395, R² = 0.156; FEFs, F(3,43) = 2.139, P = 0.109, R = 0.360, R² = 0.130; PPC, F(3,43) = 2.212, P = 0.104, R = 0.366, R² = 0.134). Thus, albeit present data did not perfectly meet assumptions on normality, supplementary analyses following gaussianization substantiated the moderation effect of age for regressing planning accuracy on streamline counts estimates in mid-dlPFC.

Complementary Analyses on Fractional Anisotropy and White-Matter Density

Multiple regression analyses on predicting planning accuracy were repeated with fractional anisotropy and white-matter density as focal variables. As explicated in Materials and Methods, measures of fractional anisotropy and white-matter density were extracted from a ROI in the corpus callosum, specifically the transcallosal fibers connecting mid-dlPFC homologs. Initial analyses included moderator effects of age and sex, but as sex had neither a direct nor an indirect contribution, only the reduced models including the respective focal variable, age, and their interaction will be reported here (see above).

Using fractional anisotropy as focal variable, the overall model fit was significant (F(3,43) = 3.194, P = 0.033, R² = 0.427, R² = 0.182). Results revealed a moderator effect of age in terms of a significant interaction between fractional anisotropy and age (t(42) = 2.148, P = 0.037), whereas the simple effects of fractional anisotropy (t(42) = 0.871, P = 0.389) and age (t(42) = −1.667, P = 0.103) did not reach significance. Also for using white-matter density as focal variable, the overall model fit was significant (F(3,43) = 4.164, P = 0.011, R² = 0.225). Results again revealed a significant interaction effect (t(42) = 2.674, P = 0.011). In addition, the simple effect of age was found to be significant (t(42) = 2.135, P = 0.039), whereas the simple effect of white-matter density was not (t(42) = 0.575, P = 0.569).

Taken together, regressing planning accuracy onto fractional anisotropy and white-matter density in the callosal region connecting homolog mid-dlPFC closely replicated the moderator effect as found in the main analyses for streamline counts (Fig. 4). Further decomposition of the interactions by using Johnson–Neyman confidence bands (cf. Bauer and Curran 2005; Preacher et al. 2007; Hayes 2013) revealed that streamline counts had a negative predictive value for planning accuracy primarily at ages below 30, whereas fractional anisotropy had a positive predictive value for planning accuracy mainly at ages above 40. In contrast, white-matter density allowed to reliably uncover both the negative relationship with planning accuracy in postadolescence and the positive relationship starting from midadulthood (Fig. 6).

Analyses of fractional anisotropy and white-matter density were also repeated for callosal ROIs connecting homolog FEFs and PPC (Fig. 7B). Multiple regressions with fractional anisotropy as focal variable (overall model fits: FEFs, F(3,43) = 1.593, P = 0.205, R = 0.316, R² = 0.100; PPC, F(3,43) = 3.265, P = 0.030, R = 0.431, R² = 0.186) revealed trends for a negative relation with age (FEFs, t(42) = −1.974, P = 0.055; PPC, t(42) = −1.835, P = 0.074), but neither a simple effect of fractional anisotropy (FEFs, t(42) = 0.515, P = 0.612; PPC, t(42) = 1.614, P = 0.114) nor an interaction (FEFs, t(42) = 0.215, P = 0.831; PPC, t(42) = 1.513, P = 0.138). Multiple regressions with white-matter density as focal variable (overall model fits: FEFs, F(3,43) = 2.722, P = 0.056,

Figure 5. Histograms on the distributions of planning accuracy, age, and the streamline counts between homolog ROIs in mid-dlPFC, frontal eye fields (FEFs), and posterior parietal cortex (PPC). Variables were z-transformed for better comparability. The shape of the normal distribution is indicated by solid black lines.
Potential Dependencies on ROI Radius

Spherical ROIs for the streamline extraction in left and right mid-dLPFC were specified based on the group-level peak activation coordinates in an fMRI study on planning ability using a radius of 12 mm (see Regions-of-Interest Specification and Streamline Selection). This specific sphere radius had already been chosen for ROI analyses in a previous VBM study on planning ability as an approximation of the fMRI cluster extents (Kaller, Heinze et al. 2012) and was kept identical in the present analyses for sake of comparability. However, given that the individual size of the relevant mid-dLPFC area may vary with the individual performance level in planning ability, the present interaction effect between mid-dLPFC streamline counts and age could have been artificially introduced by the fixed radius selection. In order to rule out this possibility, the dependency of the interaction effect on ROI radius was explored across different additional ROI sphere sizes with radii of 9, 15, 18, and 24 mm. Compared with the results at 12 mm radius (regression model without sex as predictor), the interaction effect was slightly diminished and at borderline significance for 9 mm radius ($t_{(42)} = 1.984$, $P = 0.054$, $R^2_{\text{change}} = 0.075$; overall model fit: $F_{3,43} = 3.235$, $P = 0.031$, $R = 0.430$, $R^2 = 0.185$) but improved for 15 mm radius ($t_{(42)} = 2.389$, $P = 0.006$, $R^2_{\text{change}} = 0.105$; overall
model fit: $F_{3,43} = 3.755, P = 0.018, R = 0.456, R^2 = 0.208$), whereas it progressively declined again for radii of 18 mm ($t_{42} = 1.870, P = 0.068, \text{change} = 0.068$); overall model fit: $F_{3,43} = 2.793, P = 0.059, R = 0.404, R^2 = 0.163$) and 24 mm ($t_{42} = 1.692, P = 0.098, \text{change} = 0.056$); overall model fit: $F_{3,43} = 2.735, P = 0.055, R = 0.400, R^2 = 0.160$).

Taken together, these results indicate that the present brain–behavior relationship of interest was reasonably reflected and not biased by the chosen radius of 12 mm, as it was found to be stable for ROI radii in a range between 9 and 18 mm and to be only attenuated at a larger radius of 24 mm.

**Replication**

To the best of our knowledge, the present analyses constitute the first approach that streamline counts from global tracking were used as quantitative estimates of structural connectivity as far as the Reisert et al. (2011) algorithm is concerned. Although the primary findings and the additional analyses reported above result in a coherent picture, the plausibility of the here demonstrated moderating effect of age on the relation of planning accuracy and the structural connectivity between mid-dlPFC homologs would be considerably strengthened by converging evidence from an independent dataset. In particular, the negative association at postadolescent/young adult age warrants replication given that the opposite pattern could also have been expected (cf. Discussion).

In the following, we report streamline-count analyses based on DTI data that were available for 35 of 130 subjects from a behavioral study on the psychometric properties of the Tower of London task (Kaller, Unterrainer et al. 2012) due to their later participation in a neuroimaging experiment on working memory processes (C.P. Kaller, unpublished data/forthcoming). For 8 of these 35 subjects, even 2 DTI measurements were available, thus allowing for a first approximation of the re-test reliability of streamline counts.

Given the above results and the replication sample’s young age in the early 20s (see below), the following hypotheses were tested (1-tailed): A negative relation between streamline counts and planning accuracy was expected for mid-dlPFC homologs, whereas no such association should manifest for ROIs in FEFs and PPC. In addition, the strength of this negative association for mid-dlPFC connectivity should attenuate with increasing age.

**Sample Descriptives and Assessment of Planning Accuracy**

Of the 35 additional datasets available for replication analyses, one subject had to be excluded from the analyses given an extremely poor performance in the Tower of London task (overall accuracy, $z = -3.268$). The final sample comprised 34 right-handed subjects (18 males; mean age ± standard deviation, 22.75 ± 2.73 years) with normal or corrected-to-normal visual acuity. None of the subjects was under medical treatment or reported a history of psychiatric or neurological illness.

As in the main experiment reported above, planning was assessed using the optimized Tower of London problem set suggested by Kaller, Rahm, Köstering et al. (2011) that was, however, applied in its extended version comprising problems of 4–7 moves (8 problems each; for detailed descriptions of experimental procedures, see Kaller, Unterrainer et al. 2012). Planning accuracy as the main variable of interest was quantified as the percentage of problems solved correctly within the minimum number of moves without exceeding the time limit of 1 min (also see above).

**Diffusion Tensor Imaging and Global Tracking**

Magnetic resonance imaging was performed on another 3 Tesla TIM TRIO whole-body MRI scanner (SIEMENS, Erlangen, Germany) using the same protocol for DTI as in the main study with a diffusion-sensitive single-shot spin-echo EPI sequence with CSF suppression. All aspects of data preprocessing, corrections of motion and distortion artifacts (cf. Zaitsev et al. 2004), global tractography estimations (cf. Reisert et al. 2011), and extraction of streamline counts for ROIs in bilateral mid-dlPFC, FEFs, and PPC were kept identical to the main experiment (see Materials and Methods).

**Results**

Planning accuracy decreased almost linearly ($F_{3,39} = 62.54, P < .001$) across 4- (M ± SD, 88.60 ± 12.82%), 5- (63.24 ± 17.93%), 6- (53.31 ± 21.83%), and 7-move problems (33.82 ± 17.28%). Individual performance of subjects ranged from 40.63% to 78.13% (M = 59.74%, SD = 10.17%).

As expected, planning accuracy was negatively correlated with streamline counts between mid-dlPFC homologs ($r = -0.296, P = 0.045$), whereas no significant association was found for FEFs ($r = -0.212, P = 0.114$) and PPC ($r = -0.023, P = 0.448$).

Multiple regression analysis on planning accuracy including the simple effects of the focal variable of interest (i.e., streamline counts between left and right mid-dlPFC) and the moderator variable age and their interaction did not result in a significant fit of the overall model ($F_{3,30} = 1.295, P = 0.294, R = 0.339, R^2 = 0.115$)—most likely due to the narrow age distribution of 22.75 ± 2.73 years and the smaller sample size compared with the main analyses, both resulting in a lack of test power. Nonetheless, shifted centering of the moderator variable indicated that the negative association between planning accuracy and mid-dlPFC streamline counts seemingly decreased with growing age (Fig. 8A). Application of the Johnson-Neyman technique (Hayes 2013) revealed that the negative association was significant (or showing at least a trend thereof) in the range from 19.1 to 23.5 years (Fig. 8B) mainly covering the lower half of the sample’s age distribution. Thus, the replication analyses corroborated the above reported evidence of a negative association between mid-dlPFC streamline counts and planning accuracy at postadolescent/young adult age and also provided further support for claiming a non-additive effect of age on this association across the lifespan.

Finally, as 2 independent DTI measurements were available for 8 of the 34 subjects, we also explored the re-test reliability of streamline counts (1-tailed) that was satisfactory for overall streamline counts ($r = 0.786, P = 0.010$) as well as for homolog ROIs in mid-dlPFC ($r = 0.890, P = 0.002$) and PPC ($r = 0.695, P = 0.028$). The re-test reliability for streamline counts between homolog FEFs only reached a moderate correlation ($r = 0.509, P = 0.122$, after exclusion of an extreme case in the second measurement, $z = 2.07$).

**Discussion**

The present study addressed the functional relevance of structural connectivity as quantified by streamline counts between
homolog mid-dlPFC areas for planning ability. In support of our assumptions, age was found to be an important moderator for the relationship between interindividual differences in planning accuracy and the microstructural features of transcallosal fiber tracts connecting homolog mid-dlPFCs (Figs 4 and 6). It was revealed that “lower” estimates of transcallosal streamlines connecting left and right mid-dlPFC was predictive of “better” planning accuracy specifically in young adulthood around the age of 20—a finding that was replicated here in independent data (Fig. 8). In later adulthood, this “negative” relationship was found to progressively level out, with a trend for a change into a “positive” direction for adults from the end of the fourth life decade on. As no moderating effects of sex did emerge, these patterns are suggested to be equally valid for males and females. The model omitting any effects of sex was significant overall, hence indicating that streamline counts and age, accounting for nearly 19% of variance in Tower of London performance, are sufficient for significantly predicting planning accuracy.

In support of these main results, a moderating effect of age was likewise found for the relations between planning accuracy and other indices of structural connectivity between left and right mid-dlPFC homologs that were extracted from the respective region of the corpus callosum (cf. Fig. 4). But whereas findings on the directionality of fibers, as indexed by fractional anisotropy, may be seen to convey DTI information highly correlated with streamline counts from global tracking, converging evidence from white-matter density estimates is completely independent thereof as it is derived from a different imaging modality (T₁-weighted MPRAGE). This further implies that similar developmental trajectories can be observed both for micro- and macrostructural measures of connectivity presumably reflecting changes in myelination or the number of axons or both.

Interestingly, the positive effect of structural connectivity for better planning accuracy in midadulthood was most strongly evident in local measures, that is, in fractional anisotropy and white-matter density estimates confined to the corpus callosum (cf. Fig. 6). The negative effect of structural connectivity in early adulthood was, by contrast, only detectable with the global measure of streamline counts that are sensitive to variations in structural connectivity across the whole length of the interhemispheric connection (cf. Fig. 6; Reisert et al. 2011). Streamline estimates from global tractography hence provide unique and valuable information above and beyond what can be gained from more common approaches.

In this regard, it also has to be noted that a significant interaction of white-matter density estimates and age was found for callosal regions connecting FEFs and PPC homologs (Fig. 7), indicating that higher white-matter density is predictive of better planning accuracy in midadulthood analogously to effects for mid-dlPFC. Thus, the positive effect of connectivity measures for planning accuracy is not regionally specific, but uniformly present throughout the frontoparietal network, possibly reflecting more general effects of aging in midadulthood (and beyond) on measures of structural connectivity (cf. Stadlbauer et al. 2012), rather than a specific association of structural connectivity with cognitive processes as found for streamline counts of mid-dlPFC homologs at postadolescent ages.

**Negative Relation Between Streamline Counts and Planning Accuracy in Postadolescence**

In marking early postadolescence as a critical stage for the impact of the quantity of commissural fibers connecting the mid-dlPFCs on cognitive planning abilities, present results conform to accounts on continuing developmental changes in the white matter of the prefrontal cortex as well as the corpus callosum beyond adolescence (Reiss et al. 1996; Asato et al. 2010; Qiu et al. 2010; Kochunov et al. 2012). Present results also complement previous findings on a similar age-dependent negative association between mid-dlPFC gray-matter volume and planning accuracy—albeit only in males—specifically in early postadolescence (Kaller, Heinze et al. 2012). But whereas a decrease in gray-matter volume of dlPFC due to maturational processes such as synaptic pruning are well documented to occur after adolescence (Huttenlocher and Dabholkar 1997; Petanjek et al. 2011), white-matter development typically unfolds in a continuing increase of volume and fiber

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**Figure 8.** Replication analyses in an independent postadolescent sample. (A) As expected, analyses corroborated the significant negative association between planning accuracy and mid-dlPFC streamline counts in the early 20s. Although the moderation effect of age did not reach significance, shifted centerings of the age regressor (M 22.75 years, gray dots; M SD, 20.02 years, white dots; M + SD, 25.48 years, black dots) suggested that the negative association between planning accuracy and mid-dlPFC streamline counts was attenuated with increasing age and leveled out in the late 20s. (B) Calculation of Johnson-Neyman confidence bands confirmed that the negative association between planning accuracy and the focal variable mid-dlPFC streamline counts (z-transformed for comparability) was only significant or showed a trend thereof in the age range between 19.1 and 23.5 years.
myelination until the middle of the fourth decade (Asato et al. 2010; Qiu et al. 2010; Kochunov et al. 2012). Accordingly, post-adolescent developmental gains in cognitive functions are mostly positively associated especially with directionality of fibers as indexed by fractional anisotropy (e.g., Muetzel et al. 2008; for an overview, see Schmithorst and Yuan 2010), so that a similar positive relationship between variations in streamline counts and planning ability in young adults—instead of the negative relation found here—could have been expected. However, the negative association between streamline counts and planning accuracy at younger ages established in the primary analyses (Figs 4 and 6) was replicated in an independent dataset (Fig. 8), hence demonstrating the robustness of these results.

Maturational pruning processes do not only entail loss of excess synapses, but also corresponding elimination of inefficient or superfluous axonal fibers (Huttenlocher and Dabholkar 1997; cf. Schmithorst and Yuan 2010). As a consequence, regionally specific decreases in measures such as fractional anisotropy and negative correlations with cognitive function—putatively due to prolonged pruning—can also be observed (Schmithorst et al. 2008; Schmithorst 2009), which is particularly plausible for the late-maturing dIPFC (Petanjek et al. 2011; cf. Casey et al. 2000; Badre and D’Esposito 2009). It furthermore has to be noted that current results reflect cross-sectional interindividual differences in the association between structural connectivity and cognitive function, which does not necessarily preclude a longitudinal increase in intrindivdual density of connecting dIPFC fibers across early adulthood.

What is more, recent evidence suggests a role for genetic polymorphisms of Catechol-O-methyltransferase (COMT) in modulating structural properties of white matter (Liu, Li et al. 2010; Thomason et al. 2010; see also Zinkstok et al. 2006; Dutt et al. 2011). This bears functional relevance for the current findings in that genotypes inducing lower activity of the COMT enzyme and thus leading to elevated levels of dopamine in PFC were found to be associated both with reduced fractional anisotropy values in the callosal genu of children and adolescents (Thomason et al. 2010) as well as in bilateral PFC of young adults (Liu, Li et al. 2010) and with better planning performance on the Tower of London task in the latter age group (Roussos et al. 2008). However, albeit plausible, this putative mediation effect of COMT polymorphisms in establishing a negative relationship between streamline counts and planning ability has yet to be formally investigated.

Positive Relation Between Streamline Counts and Planning Accuracy after Maturity

In addition to the effects of structural connectivity during early adulthood, the positive association of planning accuracy with fractional anisotropy as well as with white-matter density in the callosal area containing the connecting fibers of mid-dIPFC homologs with progression to midadulthood found here (as well as the concording trend for streamline counts; cf. Fig. 6) concurs with reports on age-related decreases in prefrontal and anterior callosal fractional anisotropy (Pfefferbaum et al. 2005; Salat et al. 2005; Sullivan et al. 2006; Michie1se et al. 2010; Kochunov et al. 2012; Stadlbauer et al. 2012) and white-matter density (Raz et al. 1997; Salat et al. 1999; Brickman et al. 2006) from the beginning of the fourth decade on. Conversely to its late maturation, the genu of the corpus callosum is one of the earliest and most strongly affected regions to experience age-related declines in fractional anisotropy (Kochunov et al. 2012). Primate studies confirm that normal aging entails decreased amounts of myelinated fibers and degeneration of myelin sheaths in dIPFC (Peters and Sethares 2002) as well as in the corpus callosum (Bowley et al. 2010), leading to reduced conduction speed of nerve fibers and associated impairments in cognition (for a review, see Luebke et al. 2010). Hence, present results argue for a beneficial role of higher fractional anisotropy of dIPFC-connecting callosal fibers and higher white-matter density of these callosal regions in preserving normal neuronal function in face of the incipient age-related white-matter degradation from the fourth decade of life onward.

Implications for the Roles of Left and Right Mid-DLPCS Homologs in Planning

Hemispheric lateralization of planning processes in the (mid-dorsolateral) prefrontal cortex has been a matter of debate since the seminal study of Shallice (1982) on the performance of patients with frontal lobe lesions in the Tower of London task. For instance, by emphasizing the conceptual differences between planning in laboratory tasks and in real-world situations, Goel (2010) recently put forward the hypothesis that left and right PFC contribute to planning under well-defined and ill-defined constraints, respectively (see also Goel et al. 2013). Evidence from lesion studies supportive of a mainly left prefrontal involvement in planning in well-defined tower tasks is however inconsistent (for an overview, see Sullivan et al. 2009). In addition, qualitative surveys of the plethora of functional neuroimaging studies on the Tower of London task only suggest a relative preponderance of left (Morris et al. 1993; Owen et al. 1996, 1998; Rowe et al. 2001; Beauchamp et al. 2003) over right dIPFC (Dagher et al. 1999; Van den Heuvel et al. 2003) in well-defined planning, if just those few studies are considered that revealed exclusively unilateral dIPFC activations. However, the overwhelming majority of studies reported bilateral dIPFC activations in well-defined planning (for overviews, see Cazalis et al. 2003; Kaller, Rahm, Speer et al. 2011).

The extant literature hence indicates that left and right (mid-) dIPFC homologs are both involved in planning in the Tower of London task. Nevertheless, these bilateral contributions are not necessarily related to the concomitant operation of identical cognitive processes, but may also reflect different cognitive processes with opposing lateralization (Grafman et al. 2005; Kaller, Rahm, Speer et al. 2011; Crescentini et al. 2012; Vallesi 2012) and with different times of activation (Newman et al. 2003; Byrd et al. 2011; Ruh et al. 2012). In this regard, a pattern consistently observed across studies is that initial left dIPFC activation precedes subsequent right dIPFC activation (Newman et al. 2003; Byrd et al. 2011; Ruh et al. 2012). This temporal order is also reflected in task-demand-dependent dissociations of strongly lateralized, yet bihemispherically distributed responses of left and right mid-dIPFC during planning (Kaller, Rahm, Speer et al. 2011; Nitschke et al. 2012; Ruh et al. 2012), thus indicating that the differential engagement of left and right mid-dIPFC effectively hinges on the cognitive requirements imposed by a given planning problem, but that a certain degree of interhemispheric integration of information is nonetheless operative. In close relation to this, also well-defined and ill-defined planning tasks are likely to differ in the involvement of distinct cognitive processes (cf. Goel 2010) that, if formulated in a relative rather than an absolute sense, may rely more (but not exclusively) on either left or right PFC, respectively.
Functional brain development during adolescence is assumed to unfold in an increasing fine-tuning of activity from diffuse recruitment of larger prefrontal areas toward focal activation of specific subregions (Casey et al. 2008). Hence, the present data on a negative association between streamline counts and planning ability in early postadolescence are likely to reflect the structural correlate of the presumably protracted development of a functional lateralization of distinct cognitive processes involved in planning. Albeit speculative, this functional lateralization may represent an optimal balance of interhemispheric segregation versus integration of information processing between mid-dlPFC homologs. In this respect, fewer streamlines counts may express structural refinement either by an amplification of transcallosal inhibition or by a focusing of interhemispheric communication or both (van der Knaap and van der Ham 2011). Besides differences in task demands (see above), the strength of lateralization may thus also be driven by interindividual differences and age-related maturational processes.

The functional mechanisms behind the positive relationship between measures of structural connectivity and planning performance in midadulthood also remain to be clarified. Previous reports found an association between higher callosal values in fractional anisotropy and preserved functional asymmetry of dlPFC homologs in a subsample with a mean age of 35.7 years (Voineskos et al. 2010). As the callosal genu is mainly made up of thinly myelinated, densely packed axonal fibers of small diameter requiring longer transmission times for signal propagation than more posterior callosal fibers of larger diameter (Aboitiz et al. 1992), interhemispheric transfer of information might be relatively costly in terms of processing time and energy for associated cognitive functions (van der Knaap and van der Ham 2011). Hence, the positive relation between fractional anisotropy values and planning ability in middle-aged adults over 30 years found here putatively signifies a functional benefit of higher fractional anisotropy by way of mediating less interhemispheric communication between dlPFC homologs. However, Voineskos et al. (2010) only investigated signal propagation from left to right dlPFC, whereas TMS-induced inhibition of the left and right dlPFC is associated with a markedly different modulation of planning processes (Kaller et al. 2013). Thus, a thorough examination of the structural correlates of functional asymmetries and related bidirectional inhibitory processes between left and right dlPFC in mid- to late-adulthood is warranted to disentangle age-related changes and interindividual differences in lateralization of planning processes.

In sum, although the present data cannot decide between different theoretical conceptualizations on the functional lateralization of planning processes, the results highlight the significance of transcallosal connections between mid-dlPFC homologs for efficient planning and, given the successful replication, provide an auspicious model for future explorations of the associated neurophysiological mechanisms whereby mid-dlPFC structural connectivity exerts its differential effect on planning performance across different stages of adulthood (cf. Voineskos et al. 2010).

Methodological Implications

The negative relationship of streamline counts with planning accuracy at postadolescent/young adult age appeared to be regionally specific for the mid-dlPFC, as streamline estimates connecting the homolog FEFs and PPCs were not predictive of planning accuracy, neither on their own nor in interaction with age. This specificity was found both in the primary study and in the replication analyses. That is, although all 3 regions investigated here form part of the frontoparietal network subserving visuo-spatial planning performance, only structural connectivity of the mid-dlPFC has bearing on the actual planning processes, thus according with its pivotal role as evidenced by functional imaging studies (Unterrainer and Owen 2006). However, exploratory analyses on the re-test reliability of streamline counts between the different regions of interest indicated that global tractography resulted in highly reliable estimates of the structural connectivity between mid-dlPFC homologs, whereas streamline counts for PPC and particularly the FEFs appeared to manifest a lower reliability. These reliability analyses were based on only 8 cases and have to be interpreted with caution, especially regarding the limited reliability of estimates in FEFs. However, it cannot be excluded that the present specificity is rather relative than absolute and that a negative association between planning accuracy and streamline counts might also be found for FEFs and PPC when investigated in larger samples with increased statistical power. Yet, besides differences in statistical significance, the different signs of the respective regression coefficients for the interaction effect of age in the models for mid-dlPFC (significant positive) versus for FEFs and PPC (insignificant negative) also point to regionally different developmental trajectories and once more highlight the fundamental role of mid-dlPFC for planning.

It furthermore has to be borne in mind that the streamline counts mathematically estimated from global tractography can by no means be simply equalized to the actual number of white-matter axonal fibers, given that estimates are sensitive to various tissue properties such as axon diameter, thickness, and integrity of myelin sheaths, and axon density itself as well as to confounding factors such as tract length, curvature, and the amount of fibers deviating from the principal diffusion direction within a given voxel (for reviews, see Johansen-Berg and Rushworth 2009; Jbabdi and Johansen-Berg 2011; Jones et al. 2013). Although it has been recently shown that both streamline counts and fractional anisotropy correlate significantly with the myelin-to-water fraction, a more direct measure of myelination (Liu, Vidarsson et al. 2010), the exact biological foundations of tractography-based measures still remain unclear. Notwithstanding this, multiple studies have demonstrated the functional relevance of measures derived from diffusion imaging (e.g., Zahr et al. 2009; Forstmann et al. 2010; Davis et al. 2011; for reviews, see Johansen-Berg and Rushworth 2009; Jbabdi and Johansen-Berg 2011) and a high concordance between resting-state functional connectivity and tractography-based structural connectivity, especially for common neural networks such as the default mode network (Skuddalaski et al. 2008; Honey et al. 2009). Thus, it can be assumed that the age-related effects of structural connectivity between mid-dlPFC homologs on planning performance found here consistently across 3 measures from 2 different imaging modalities provide a valid indication of the functional relevance of mid-dlPFC structural connectivity for higher-order cognitive processes. This assumption is further corroborated by the successful replication as well as the high re-test reliability particularly for mid-dlPFC streamline counts.

Conclusion

Taken together, here it was demonstrated for the first time that age exerts nonadditive effects on the relationship between
planning performance and the structural connectivity of mid-dlPFC homologs. That is, the association between complex cognitive abilities and mid-dlPFC connectivity is not uniform across early to midadulthood, but displays a systematic variability in its strength and direction. Furthermore, whereas the impact of general aging-related processes on white-matter tracts in mid-adulthood are evident in local estimates of structural connectivity such as fractional anisotropy and white-matter density, the regionally specific and putatively more subtle interindividual differences during early adulthood are only detectable by globally estimated streamline counts. Global tractography is thus a promising candidate for future assessments of the white-matter architecture of brain networks in developmental and clinical samples, because it provides unique information on brain–behavior relationships. Here, by applying a global tractography approach and by modeling moderator effects of age, planning performance of healthy adults could be significantly predicted from structural connectivity between left and right mid-dlPFC. A comprehensive understanding of the neural bases of complex cognitive abilities hence necessitates not only knowledge on the functional interplay of critical brain regions, but also knowledge on the structural properties of the fibers whereby functional connectivity is realized.

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**Notes**

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