Cortico-striatal connectivity and cognition in normal aging: A combined DTI and resting state fMRI study

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ABSTRACT

Resting state fMRI studies have found that cognitive decline in aging is associated with alterations in functional connectivity of distributed neural systems in the brain. While functional connections have been shown to rely on the underlying structural connectivity, direct structural connections have been studied in only a few distributed cortical systems so far. It is well known that subcortical nuclei have structural connections to the entire cortex. We hypothesized that structural subcortico-cortical connections may provide integral routes for communication between cortical resting state networks, and that changes in the integrity of these connections have a role in cognitive aging. We combined anatomical MRI, diffusion tensor MRI, and resting state fMRI in 100 healthy elderly to identify fiber bundles connecting cortical resting state networks to subcortical nuclei. In identified tracts, white matter fiber bundle integrity measures were compared to composite cognitive measures on executive function, processing speed, and memory performance. The integrity (FA values) in selected fiber bundles correlated strongly with cognitive measures on executive function and processing speed. Correlation was most pronounced between executive function and fiber bundles connecting the putamen to the dorsal attention network (r=0.73, p<0.001). Our findings show that unique cortico-subcortical fiber bundles can be identified for a range of cortical resting state networks, and indicate that these connections play an important role in cortical resting state network communication and cognition.

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Introduction

Aging is associated with cognitive decline. Based on observations of white matter degeneration, several studies have suggested that structural disconnection between distributed neural systems plays a fundamental role in age-related cognitive decline (Madden et al., 2009; O’Sullivan et al., 2001). In particular, decline in executive function and processing speed have been associated to decreasing integrity of normal appearing white matter in studies applying diffusion tensor imaging (DTI) (Correia et al., 2008; Turken et al., 2008). Associations between age-related decline in episodic memory function and white matter integrity have also been found (Kennedy and Raz, 2009). A central theme of DTI research has thus been an analysis of the effects of white matter degeneration as a mechanism for disconnection within neural systems mediating cognitive functioning (Bartzokis et al., 2004; Charlton et al., 2006; Madden et al., 2009; Sullivan and Pfefferbaum, 2006). This approach calls for integration of findings from DTI, neuropsychological measures of cognition, and findings from functional magnetic resonance imaging (fMRI) studies (Ramnani et al., 2004).

While traditional applications of fMRI have focused on task-related activation, investigations of spontaneous fluctuations within brain systems using resting state functional MRI (rs-fMRI) have provided a powerful tool to investigate functional coordination between brain areas (Biswal et al., 1995, 2010; Fox and Raichle, 2007; Smith et al., 2009). Low frequency signal fluctuations are coherently detected in large-scale systems such as sensory and motor systems (Biswal et al., 1995; De Luca et al., 2005), and in systems participating in attention (Fox et al., 2006) and memory (Vincent et al., 2006). Several studies have applied rs-fMRI to investigate age related changes in functional brain organization. Normal aging causes changes in functional connectivity between distributed brain networks and changes in activity within network nodes of highly functionally connected networks such as the default mode network (DMN) (Damoiseaux et al., 2008; Wu et al.,...
2007). Andrews-Hanna et al. (2007) found age-related disruptions in the functional integrity of the dorsal attention network and the DMN. Furthermore, disruptions in functional connectivity were significantly associated with changes in executive functions, cognitive processing speed, and memory (Andrews-Hanna et al., 2007).

Functional connections between the spatially distributed signal sources in rs-fMRI are dependent on structural connections, supporting the notion that these resting state networks (RSNs) reflect the underlying anatomical connectivity (Greicius et al., 2009; Hagmann et al., 2008; Skudlarski et al., 2008), and providing a basis for further research combining structural and functional imaging. While direct cortico-cortical connections have been found for some distributed RSNs (Honey et al., 2009; Teipel et al., 2009), the subcortical nuclei (i.e. the thalamus and basal ganglia) are known to be structurally connected to virtually all cortical areas of the brain (Postuma and Dagher, 2006). These regions were also recently identified to be among the most globally functionally connected regions of the brain in the resting state (Cole et al., 2009).

Here we hypothesize that structural connections from the subcortical nuclei may provide integral routes of communication for cortical RSNs, and that changes in the structural integrity of connections between subcortical nuclei and certain RSNs play a role in cognitive aging. We applied multi-modal MRI to identify distinct subcortico-cortical ber tracts correlating with age-related cognitive decline, such as the DMN and the dorsal attention network. The current results show that age related cognitive function is associated with connections to specific RSNs, and indicate that subcortico-cortical connections play an important role in cortical RSN communication that needs to be further explored.

Materials and methods

Subjects

The present study included 100 healthy individuals (mean age = 64 yrs., range 49–80, 64 females) recruited through advertisement in local newspapers as part of a larger study on cognitive aging (see also Andersson et al., 2008; Wehling et al., 2010; Ystad et al., 2010). All participants were interviewed before inclusion, and participants with present or previous neurological or psychiatric disorders, a history of substance abuse, or other significant medical conditions were excluded. All participants underwent a neuropsychological assessment and participated in a multi-modal MRI examination. Interviews and neuropsychological test scores were evaluated by an experienced neuropsychologist, and none of the included participants was diagnosed with dementia or had symptoms on mild cognitive impairment (MCI) (Petersen, 2004) at inclusion. All subjects provided their informed consent to participate in the study. The study was approved by the Regional Committee for Medical and Health Research Ethics of Southern Norway.

Neuropsychological assessment

All subjects were assessed according to a neuropsychological test battery including the official Norwegian translation of the California Verbal Learning Test—Second Version (CVLT-II) (Delis DC and Kaplan, 2001) – a variation of the more well known Stroop test (Stroop, 1935) – the Digit Symbol Substitution Task from WAIS-R (Wechsler, 1981), and the Mini Mental State Exam (MMSE) (Folstein et al., 1975). Raw scores from CVLT-II (short and long delayed recall, total learning, and total recognition discrimination), CWIT (subtests 1 through 4), and Digit Symbol Substitution Task were standardized by calculating the z-scores on all the tests. Z-scores from the CVLT test were inverted to obtain the same ordinal order as in the other two tests (higher score = better function). All z-scores were then combined in a principal components analysis (PCA) to reduce the dimensionality and to obtain stable composite scores for separate cognitive faculties suitable for analysis across the age range. The Kaiser Measure of Sampling Adequacy (Kaiser, 1974) was >0.8 and Bartlett’s test of sphericity was highly significant, confirming that the data were suitable for PCA. Selected components were transformed using a Varimax orthogonal rotation to reveal the pattern of component loadings (Table 1). MATLAB 2009a scientific software package was used for these analyses.

MR imaging

Multimodal MRI examinations were performed on a 1.5 T GE Signa Echospeed scanner with a standard 8-channel head coil. All recordings, i.e. 3D anatomy, DTI, and BOLD fMRI, were acquired during the same imaging session so that the positional information in the DICOM file headers could be used in subsequent multimodal image registration. We acquired two consecutive T1-weighted 3D volumes using a fast spoiled gradient echo (FSPGR) sequence (TR/TE/TA/FA = 9.11 ms/1.77 ms/450 ms/90°; 124 axial slices; and voxel size = 0.94 x 0.94 x 1.4 mm³). This was done in order to obtain a good signal-to-noise ratio (SNR) for the following semi-automated brain segmentation procedure (see later). Diffusion tensor image (DTI) acquisitions were obtained with a spin-echo echo planar sequence (TE/FA = 7900 ms/104.9 ms/90°, acquisition matrix 64 x 64, x–y–z resolution 1.8 x 1.8 x 4 mm³). For BOLD fMRI measurements during the resting state condition, a total of 256 volumes were recorded with a temporal resolution of 2 s using a gradient echo echo planar imaging (GRE-EPI) sequence with 25 axial slices per volume (TR/TE/FA = 2000 ms/50 ms/90°, acquisition matrix 64 x 64, field of view...
240 mm, slice thickness 5 mm, and slice gap 0.5 mm). The participants were instructed to lie still with their eyes closed during this examination. Cushions and earmuffs were used to reduce subject motion and scanner noise.

Anatomical image segmentation

Whole-brain and subcortical image segmentation was performed with the FreeSurfer image analysis suite, Ver 4.2 (http://surfer.nmr.mgh.harvard.edu). For each subject, the two consecutive T1 anatomical image volumes were averaged after coregistration to improve signal to noise ratio before skull stripping (Segonne et al., 2004), intensity normalization, and Talairach registration (Talairach and Tournoux, 1988). Subcortical segmentation produces segments for a number of subcortical structures, including the thalamus and basal ganglia, by applying manual labels from a training set to determine the most probable tissue class for each voxel in the current volume (Caviness et al., 1989; Kennedy et al., 1989; Seidman et al., 1999). This automated procedure has been shown to be comparable in accuracy to manual procedures (Fischl et al., 2002; Klauschen et al., 2009).

Functional MRI feature extraction

As previously reported in Ystad et al. (2010), each resting state fMRI volume in the time series from a given subject was registered to the first image volume to correct for head motion, and then normalized to Montreal Neurological Institute (MNI) standard space. The images were then resliced to a voxel size of 3 mm³ and smoothed using a 6 mm FWHM Gaussian kernel. The data was decomposed using the group spatial ICA rationale proposed by Calhoun et al. (2001), see Ystad et al. (2010) for details. We used the subcortical components from our previous study and identified matches to cortical and cerebellar RS-task-fMRI-pairs presented in Smith et al. (2009). The corresponding RSN components were then selected for further analysis with subcortical RSNs.

Functional ICA component subsegmentation. In the segmentation of the ICA components, the aim was to obtain a representative segmentation map for each subject. This was obtained by applying an adaptive thresholding procedure at 99% histogram intensity in each ICA component, extracting target voxels above this value only. The 99% threshold was chosen since this value yielded segmentations representative for active brain regions for each ICA component in each subject. Individual components were then spatially intersected with group t-statistic maps of the corresponding component, restricting individual components to its group-level definition, and allowing for individual variations within the latter. Group t-statistic map threshold was empirically adjusted to t ≥ 13, as this provided the most informative basis for analysis in all components.

DTI reconstruction and fiber tracking

From the DTI acquisitions, combining 750 image files from each participant, the eigenvectors and eigenvalues of the diffusion tensor were constructed voxel-wise (Basser et al., 1994), using the Diffusion Toolkit software package (www.trackvis.org). Fractional anisotropy (FA) maps were then created for each individual brain volume. After reconstruction of the diffusion tensor, fiber assignment by continuous tracking (FACT) was applied in the fiber tracking procedure (Mori et al., 1998; Mori and van Zijl, 2002) using the Trackvis software package.

Integrated multimodal white matter analysis

All analyses were carried out in the anatomical domain to which the DTI and functional images had been transformed (see later). Fractional anisotropy (FA) values were calculated in fiber connections between the basal ganglia and thalamic ICA components and the selected cortical RSNs. To limit the extent of the independent components to the true anatomical region, the intersection between the regions defined in the anatomical segmentation and the ICA component was computed for the basal ganglia and thalamus. An in-house MATLAB program was developed to extract specific tracts running between the basal ganglia and selected RSNs. This algorithm uses the tracts from the entire volume and selects those fulfilling the criteria of running between the desired regions of interest (ROIs). A threshold of minimum of 10 continuous fibers was set to avoid artificial fibers and to reduce the variability in extracted fiber bundles. The mean FA value of a fiber bundle was computed as the mean over all track points inside the tracts.

MR image registration. An affine registration between the calculated fractional anisotropy (FA) image and the high-resolution 3D anatomical image was used in this study. Voxel positioning information was extracted from the DICOM file headers, providing a high-quality initial approximation to the spatial transformation used in later steps, as all images for a given subject were recorded during the same imaging session without repositioning the subject in the scanner. A linear registration algorithm (http://www.fmrib.ox.ac.uk/fs) was used to find an initial affine transformation for the FA image to the T1 anatomical image. A second affine registration was applied to eliminate residual inconsistencies from movement. Fibers from the fiber tracking procedure were then transformed into the anatomy domain using the extracted affine transformation.

Resting state fMRI volumes were transformed to Montreal Neurological Institute standard space (MNI), using an affine transformation, prior to the extraction of the ICA activation maps. The MNI template was then coregistered to each subject’s anatomical T1 image as described earlier, providing an affine transformation that was later applied to each ICA activation map (see Supplementary Fig. 1 for an overview).

Results

Neuropsychological feature extraction

Three components were retained in the principal components analysis (PCA), each displaying an eigenvalue >1 after Varimax rotation, explaining 80% of the total variance. One component loaded highly on all the CVLT variables, while another loaded highly on the speed of word reading and color naming subtests from CWIT. The third component loaded most heavily on highly demanding tasks (the inhibition and the inhibition/switching subtests from CWIT, and Digit Symbol Substitution Test) used to measure the aspects of executive function. We thus identified three components/composite scores which we hereby denote (verbal) memory function, cognitive processing speed, and executive function, respectively (Table 1). Memory and executive function correlated significantly with age (r = −0.26 and r = −0.4, respectively, p < 0.01). Women scored higher than men on all three components (two sample t-tests, p < 0.01).

Resting state network components

Among the 49 extracted RSN components from the independent components analysis, five were identified as parts of the thalamus and basal ganglia (labeled IC1, ..., IC5; Fig. 1; Suppl. Fig. 2). Component IC1 occupied the bulk of the thalamus, while IC2 was located in the dorsomedial nucleus of the thalamus. Component IC3 was confined to the superior part of the putamen, while IC4 occupied the inferior-medial part. Both components spanned the entire posterior–anterior extent of the putamen. The caudate nucleus component, IC5, was clearly confined to the head of the caudate nucleus. All components

1 Available by request. To be published in a separate communication.
were bilateral and symmetric. See Ystad et al. (2010) for further details.

The cortical components were compared to the RS-task-fMRI pairs in Smith et al. (2009) and corresponding pairs were found for 15 of the cortical components (Fig. 1). Two components were identified as belonging to the default mode network (DMN) (labeled IC6 and IC7; Fig. 1); IC6 composing the anterior-inferior part in the medial and orbital prefrontal cortex, and IC7 the posterior part, mainly localized in the precuneus. IC8 is identified as an “executive control network” that covers several medial–frontal areas, such as the anterior cingulate and paracingulate gyri (Smith et al., 2009). Two components were found in areas corresponding to the dorsal attention network (IC9 and IC10; Fig. 1), corresponding to parietal areas around the intraparietal sulcus (IPS). The ventral attention network, IC11, consists of right-lateralized activity in the right temporal–parietal junction (TPJ) and the right ventral frontal cortex (VFC). The contralateral mirror image was also found (IC12; Fig. 1). A “sensorimotor” RSN, including bilateral sensory–motor cortices, was represented by three components in our material. IC13 and IC14 accounted for the sensory–motor cortices on the left and right sides respectively, while IC15 accounted for the medial parts of the sensory–motor cortex, bilaterally. IC16 includes the superior temporal gyrus, Heschl’s gyrus, and posterior insular, and the corresponding RS was labeled as an “auditory” RSN in Smith et al. (2009). Three components were found in the occipital/lingual/calcarine cortices, areas which are involved in early visual perception and (written) language processing, all labeled “visual” in Smith et al. (2009). IC17 spanned the cuneus, lingual–, and calcarine cortices. Components IC18 and IC19 mainly occupied the posterior occipital lobe and lingual gyrus, respectively. One cerebellar component, IC20, corresponded to the one reported in Smith et al. (2009). Finally, three components, IC21, IC22, and IC23 (see Suppl. Fig. 3), were found in the bilateral inferior temporal lobe, left- and right lateral occipital lobe, respectively. IC21–23 had overlapping relations to two components presented in Smith et al. (2009).

Extracted white matter fiber bundles

Fiber tracking revealed distinct cortical RSN fiber bundle connections for all the individual subcortical RSNs. The putamen exhibited the highest number of connections to the other RSNs, while the thalamus, dorsomedial nucleus of the thalamus, superior part of the putamen, and the caudate nucleus had progressively fewer connections (Fig. 1). Five cortical RSNs, IC10, IC14, and ICs 21–23 (Suppl. Fig. 3), did not display fiber bundle connections to any of the subcortical nuclei (Fig. 1). Due to differences in group t-map distributions and individual variability within each component, the number of subjects in which individual fiber bundles were found varied (from 0 to 98). Fiber bundles that were found in less than 25% of the subjects were not included in further analysis.
Fiber integrity and cognitive functions

Fig. 2 displays correlations between the fiber bundle structural integrity (FA values) and the cognitive function composite scores (threshold \( p = 0.01 \)). Only the fiber bundles connecting the thalamus and the putamen to cortical RSNs correlated with these scores. The mean FA of the connection from the thalamus (IC1) to the frontal part of the DMN (IC6) correlated moderately with executive function (\( r = 0.43, p < 0.001 \)). For the putamen (IC3 and IC4), several remarkable correlations were found. Fiber bundles connecting the inferior putamen (IC4) to the frontal part of the DMN, correlated moderately with executive function (\( r = 0.40, p < 0.001 \)). Fiber bundles connecting the former to the dorsal attention network (IC9) correlated strongly with both executive function (\( r = 0.73, p < 0.001 \)) and cognitive processing speed (\( r = 0.58, p = 0.002 \)). Cognitive processing speed was also correlated to connections between the putamen and IC17 (calcarine/visual/lingual cortices, \( r = 0.49, p < 0.001 \)). Finally, the connection between the superior part of the putamen and the left sensorimotor-cortex (IC13) correlated with cognitive processing speed (\( r = 0.46, p = 0.007 \)). All of the aforementioned correlations with executive function and cognitive processing speed were significant after controlling for age and gender.
located around the central sulcus (Fig. 1), while the inferior putamen had connections to superior cortical components. The latter would include areas involved in the subcortical nuclei to sub-regional IC-maps, we identified five individual IC maps within the subcortical nuclei, in addition to 39 cortical-, and 5 cerebellar IC maps. The components in the subcortical nuclei appeared to reflect subdivisions of the corresponding anatomical structures (Postuma and Dagher, 2006). Our IC1 component occupied the bulk of the thalamus, while the peak t-values of IC2 were located in the dorsomedial nucleus of the thalamus bilaterally. One component was found in the head of the caudate nucleus (IC5). Topographical models of corticostriatal projections have revealed orientations along the medial–lateral, superior–inferior, and anterior–posterior directions (Haber et al., 2000; Selemon and Goldman-Rakic, 1985). Moreover, fMRI studies have revealed different coactivation patterns in the superior versus inferior striatum (Postuma and Dagher, 2006). Hence, the separation of the head of the caudate nucleus and the superior- and inferior parts of the putamen in resting state fMRI are probable outcomes. Among the cortical and cerebellar components, we identified analogues to all components presented in Smith et al. (2009). As the latter was a large meta-analysis, we regarded the components identified here as thoroughly founded in the fMRI literature. Many of the selected components can be ascribed a functional relevance through their analogues in task-fMRI, while others, such as the DMN, ventral-, and dorsal attention networks, are also found to have functional relevance through resting state fMRI studies (Andrews-Hanna et al., 2007; Fox et al., 2005, 2006).

Subcortical–cortical fiber bundle connections

In this study we identified structural connections between subcortical and cortical IC maps from resting state fMRI. By limiting the involvement of the subcortical nuclei to sub-regional IC-maps, we identified more functionally relevant fiber bundles than would be produced by tracking from purely anatomically defined areas. The latter would include fibers from regions that were not active in the resting state, and fail to appreciate the functional segregation discussed earlier. The current approach thus allows for an interpretation of findings within a resting state framework. Cortico-striatal fibers involving the putamen dominated the findings in this study. Corresponding to topological models of organization of corticostriatal projections (Haber et al., 2000; Lawrence et al., 1998), the superior putamen had connections to superior cortical components located around the central sulcus (Fig. 1), while the inferior putamen had numerous frontal, temporal, and dorsal connections (Fig. 1). The connection between the head of the caudate nucleus to the frontal part of the DMN, is also in line with anatomical models (Haber et al., 2000). In the widely acknowledged parallel loop model of subcortical connections (Lawrence et al., 1998), the thalamus projects to all areas of cortex. Correspondingly, thalamo-cortical connections were found to frontal, superior, and dorsal cortical regions, as well as cerebellar regions (Fig. 1). Although individually consistent with anatomical predictions, a number of cortico-subcortical fiber tracts in this study are limited by design. Due to inter-individual variability in IC components, in affine registration, and in DTI fiber analysis, individual reproducibility of fiber tracts are also subject to variability. In particular, smaller, more peripheral fiber tracts are more prone to partial volume effects and faulty registration than are larger, more central fiber pathways (Vollmar et al., 2010). Major white matter tracts are reliably reproduced across a majority of subjects, while thinner, more elongated tracts have a lower reproducibility rate.

Discussion

Resting state components

In this study, we applied a high-model-order ICA on a large sample of resting state fMRI data to extract reproducible subcortical and cortical RSN components. According to Elseoud et al. (2009), model orders of 70±10, extracted detailed independent component (IC) signal maps of structures like the putamen, anterior and posterior sections of the DMN, and visual signal sources, while model orders <60 showed variable reproducibility. Consequently, we identified five individual IC maps within the subcortical nuclei, in addition to 39 cortical-, and 5 cerebellar IC maps. The components in the subcortical nuclei appeared to reflect subdivisions of the corresponding anatomical structures (Postuma and Dagher, 2006). Our IC1 component occupied the bulk of the thalamus, while the peak t-values of IC2 were located in the dorsomedial nucleus of the thalamus bilaterally. One component was found in the head of the caudate nucleus (IC5). Topographical models of corticostriatal projections have revealed orientations along the medial–lateral, superior–inferior, and anterior–posterior directions (Haber et al., 2000; Selemon and Goldman-Rakic, 1985). Moreover, fMRI studies have revealed different coactivation patterns in the superior versus inferior striatum (Postuma and Dagher, 2006). Hence, the separation of the head of the caudate nucleus and the superior- and inferior parts of the putamen in resting state fMRI are probable outcomes. Among the cortical and cerebellar components, we identified analogues to all components presented in Smith et al. (2009). As the latter was a large meta-analysis, we regarded the components identified here as thoroughly founded in the fMRI literature. Many of the selected components can be ascribed a functional relevance through their analogues in task-fMRI, while others, such as the DMN, ventral-, and dorsal attention networks, are also found to have functional relevance through resting state fMRI studies (Andrews-Hanna et al., 2007; Fox et al., 2005, 2006).

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Fiber integrity and cognitive functions

Principal components analysis extracted a composite score that loaded heavily on measures of different aspects of executive function, i.e. Digit Symbol Substitution Test, and the Inhibition and Inhibition/ Switching subtests from CWIT. This executive function composite score correlated positively with the white matter fiber integrity of three cortico-subcortical fiber bundles: thalamus (IC1) to frontal DMN (IC6), putamen (IC4) to frontal DMN, and putamen to the dorsal attention network (IC9, Fig. 2). While both the putamen and the thalamus had fiber connections to the dorsal DMN (IC7), no significant correlations to executive function were found for these in our sample. This corresponds to the findings in Damoiseaux et al. (2008), where reduced activity in the anterior DMN, but not the posterior DMN, correlated with reduced executive function score in a cohort of healthy elderly. The dorsal attention network is involved in the top-down control of attention and is believed to interact with several other brain areas including those comprising the ventral attention network (IC1) (Corbetta and Shulman, 2002; Dosenbach et al., 2006). The distributed fashion of its known functional connections (Cole et al., 2009) may be provided by its fiber connection to the putamen, thus explaining the strong positive correlation between fiber bundle integrity and executive function in this particular connection (Fig. 2). Although cognitive processing speed and executive function were separated as two components, the two functions are related in that both depend on visual attention, known to rely on overlapping brain areas (Corbetta, 1998; Wojciulik and Kanwisher, 1999). Cognitive processing speed correlated strongly with the integrity of the fiber connection from the dorsal attention network to the putamen, indicating that this pathway serves the communication needed for several related cognitive functions. As the cognitive processing speed component loaded heavily on speed of reading and color naming, visual and lingual cortices would be expected to contribute significantly. Consequently, fiber connections between the Putamen and the cuneus/lingual/calcarine (IC17) correlated significantly with cognitive processing speed. Furthermore, both tests required subjects to vocalize the correct answer, invariably involving the motor system. The fiber integrity and cognitive processing speed correlation in the connection between the superior putamen (IC3) and the left motor cortex (IC13) provide a solid and intuitive relation between function and fiber bundle integrity in the extracted connections.

By observing the marginal histograms provided in Fig. 1, it is clear that the cumulated number of connections for each IC is not necessarily predictive of its fiber connections’ relation to the cognitive measures included here (see Fig. 2). Apart from the regional specificity of connected ICs discussed earlier, another possible explanation can be found by noting that the number of subjects displaying inter-IC connections in Fig. 2 is inversely related to the correlation strength between FA and cognitive functions (mostly). It is possible that the global pruning algorithm applied to fibers and ICs was too tolerant in some instances, while too restrictive in other. This would reduce the specificity of extracted fiber bundles in the former case, and extract only the most central and direct fiber connections in the latter. As FA values are averaged across whole fiber bundles, this provides a partial explanation to the observed trend.

No correlations were found between the fiber bundle integrity and the fPCA-extracted memory component. An age related memory change has traditionally been ascribed to regional changes in medial
temporal lobe (MTL) structures such as the hippocampus. This view is however, changing towards a more integrated view, focusing on connectivity changes throughout the brain (O’Sullivan et al., 2001). We recently found that the global number of functional connections from the thalamus and the putamen was significantly associated with episodic memory function in the present sample of healthy elderly (Ystad et al., 2010), adding support to the distributed nature of this cognitive function. Memory may therefore prove to rely on a more distributed array of cortical areas than other cognitive functions, making specific cortico-subcortical fiber bundles less sensitive to subtle age related changes.

In light of the findings in previous DTI studies on cognitive decline in aging, we note some novel contributions from this study. While the definition of regions of interest in DTI analysis can be derived from anatomical knowledge or task-fMRI, the immense complexity of the structural and functional wiring of the human brain provides a significant challenge to any manual methodology. Here, we present an entirely data-driven approach to address this problem. By using resting state fMRI, the approach largely eliminates potential subject- and entirely data-driven approach to address this problem. By using resting state fMRI, the approach largely preserves individual variability in the extracted fMRI. Furthermore, the present methodological approach largely preserves individual variability in the extracted fMRI, while identifying unique cortico-subcortical fiber bundles shared by multiple subjects. We thereby propose an intuitive approach in the integration of two modalities, expanding contributions from DTI into the ever more important domain of resting state fMRI. The current investigation of the structure–function relationship between white matter- and resting state functional network connectivity. While several studies have reported close correspondence between structural and resting state functional network connectivity between cortical areas (Hagmann et al., 2008; Skudlarski et al., 2008), the inclusion of subcortical nuclei in such analyses may prove valuable in the understanding of whole-brain functional network connectivity, and expand on existing on subcortico-cortical connectivity models. As such analyses were out of the scope of the present study, but still relevant in the current setting, a section commenting on the structure–function relationship is provided in the Supplementary material along with the results from preliminary analysis.

Conclusion

In this study, we investigated the possible role of fiber bundle connections between the subcortical nuclei and distributed resting state networks in mediating cognitive functions associated to cortical areas defined by RSNs, and thus whether structural integrity changes in these bundles may contribute to age related cognitive decline. By using IC maps from resting state fMRI as regions of interest in the fiber identification process rather than manually defined ROIs, we employed a data-driven approach better suited to account for inter-individual variability in the exact spatial localization of the resting state networks. Our findings show that an age-related decline in executive function and cognitive processing speed is correlated to the fiber integrity between subcortical nuclei and cortical RSNs of known specific functional importance. This suggests that the subcortical nuclei and their widely distributed cortical connections provide an important hub for distributed resting state network connectivity. Supplementary materials related to this article can be found online at doi:10.1016/j.neuroimage.2010.11.016.

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