TECHNICAL REPORT

Tract-Based Magnetic Resonance Spectroscopy of the Cingulum Bundles at 7 T

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Abstract: The cingulum bundle is a white matter fiber bundle in the human brain that is believed to be implicated in various neurological and psychiatric diseases. Subtle disease-related differences in metabolite concentrations in the cingulum tracts that may underlie these diseases may be detected using MR spectroscopic information. However, to date, limited signal to noise and lack of spatial resolution have prevented a reliable and reproducible measurement of metabolites in the cingulum bundle in vivo. Here we propose a new method that combines MR spectroscopic imaging at 7 T with fiber tracking to select only those MR spectroscopy voxels that are actually part of the cingulum bundles. The spectra of the selected spectroscopy voxels are processed per voxel and then combined yielding one spectrum at high spectral resolution for each cingulum bundle. In this way sensitivity is increased, as large parts of the cingulum are included while partial volume effects with both gray matter and white matter from other tracts is kept to a minimum. Three healthy volunteers were scanned to assess the feasibility of the method. For all three healthy volunteers spectra for the left and right cingulum tracts were computed, partial volume fractions calculated and metabolite fractions were quantified yielding similar results suggesting that tract-based MR spectroscopy allows us to study metabolic concentrations of individual white matter fiber bundles with high sensitivity and high specificity. *Hum Brain Mapp* 33:1503–1511, 2012. © 2011 Wiley Periodicals, Inc.

Key words: neural pathways; diffusion tensor imaging; fiber tracking; human brain; ultra high-field MR

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INTRODUCTION

The cingulum tract is an elongated and curved white matter fiber bundle that connects the cingulate gyrus with the hippocampal gyri in each of the two hemispheres of the human brain (see Fig. 1). The cingulum bundle plays a key role in the so-called default mode network [Fox and Raichle, 2007; Greicius et al., 2003; van den Heuvel et al., 2008] and is believed to be implicated in various neurological [Liu et al., 2009; Rocca et al., 2010; Senda et al., 2009]

Figure 1.

Example of the reconstructed left cingulum bundle seen from the left (**A**) and top (**B**).

and psychiatric diseases [Bloemen et al., 2010; Cullen et al., 2010; Voineskos et al., 2010; Wang et al., 2010], including schizophrenia. Numerous studies investigated the role of the cingulum bundles in schizophrenia using diffusion tensor imaging (DTI) [Basser et al., 1994; Le Bihan and Breton, 1985] in combination with fiber tracking showing disease-related changes in the microstructure of the tract [Kanaan et al., 2005; Kubicki et al., 2003; Mori et al., 2007; Rosenberger et al., 2008]. In particular, the application of a technique named tract-based analysis (where the measurements are averaged over complete fiber tracts) allows for the detection of very subtle changes and/or differences in microstructural properties that span the whole cingulum tract. However, to obtain detailed information on possible disease-related changes in metabolic concentrations underlying or accompanying these microstructural changes, a technique like magnetic resonance spectroscopy (MRS) is needed. But using conventional single-voxel MRS to obtain spectral information from the complete (or at least large parts of the) cingulum tract is not straightforward. Single-voxel MRS requires the sampling of relatively large volumes (typically $10 \times 10 \times 10 \text{ mm}^3$, or larger, at 3 T main field strength) as compared to the diameter of the cingulum bundle to obtain acceptable signal-to-noise (SNR) levels. This would result in extensive partial volume effects (i.e., the mixture of 2 or more different tissue types in the sample) of white matter tissue of the cingulum bundle with the surrounding gray matter tissue and/or surrounding white matter tissue from other tracts because large parts of the cingulum bundle are only a few millimeters wide. The use of a higher main magnetic field strength (e.g., 7 T) can partly solve the problem as a higher magnetic field strength not only leads to an increase in spectral resolution but also to an increase in SNR, which can be utilized to reduce the volume size of

the sample and therefore to potentially increase the specificity of the measured signal due to a reduction of partial volume effects. However, to detect subtle disease-related differences in the spectra, the volume of the sample should be chosen as large as possible to maximize SNR and hence the sensitivity of the acquisition method. A possible solution is found in a technique named segmented spectroscopy [Hanson et al., 2000; Hanson and Paulson, 1998; Hetherington et al., 1996], which combines high-resolution chemical shift imaging (CSI) with the definition of a region of interest (ROI). With this technique, fractions of gray and white matter as well as the metabolite fractions are computed separately for all voxels that are part of the ROI. These CSI voxel metabolite and tissue fractions are then fitted in a linear model yielding one estimate of the metabolite fractions for gray and white matter in the ROI.

Here we propose to extend the idea of segmented spectroscopy by combining a novel two-dimensional high-resolution CSI scan [Boer et al., 2011] acquired at ultra-high field strength (7 T) with DTI and fiber tracking. The key idea behind this new method—which we dubbed tract-based MR spectroscopy—is that white matter should not be considered a homogeneous substance but actually consists of tracts, which are separate structural and functional units that can be individually affected and should therefore be studied accordingly. We start with the acquisition of a DTI scan and use this scan to perform on-the-fly fiber tracking of the left and right cingulum bundles during the actual acquisition. The resulting tracts are then displayed on the console of the MRI scanner and used to plan the CSI scan in such a way that the CSI scan coincides with (large parts of) the reconstructed cingulum tracts. In the postprocessing step the reconstructed cingulum tracts are used to select those voxels from the CSI scan that are part of the left or right cingulum bundle after which the spectra of the selected individual CSI voxels are combined. In this way, we obtain a high specificity due to the usage of a small CSI voxel size and we obtain high sensitivity by combining the information from all voxels that are part of the cingulum thereby effectively increasing the sampled volume (and hence the SNR). Similar to segmented spectroscopy, we use model fitting to estimate the contributions of different tissue types to the measured signal of the ROI. However, in contrast to segmented spectroscopy we take into account that white matter consists of separate structural and functional units (i.e., the fiber bundles). Therefore, we distinguish between three tissue types instead of two namely: white matter from the cingulum, noncingulum white matter and gray matter, which increases the sensitivity for cingulum-specific changes. Also, with segmented spectroscopy the metabolite concentrations are estimated first for each separate CSI voxel and then (linear) model fitting is used to combine these metabolite concentrations. This approach requires that one has to decide beforehand on which metabolites are studied. In contrast, with tract-based MR spectroscopy, we use a

linear model to fit the full spectra from each of the CSI voxels to determine the spectrum from white matter in the cingulum tract. The major advantage is that, in addition, this approach allows for analysis methods that operate on full spectra (e.g., Relief-F [Kononenko, 1994], PCA [Pearson, 1901], ICA [Comon, 1994]) and is therefore well suited for more explorative purposes. To demonstrate the feasibility of this new tract-based MR spectroscopy method, we tested it in three healthy participants and assessed the two different ways of combining the CSI voxel signals (i.e., the segmented spectroscopy approach versus the tract-based MR spectroscopy approach).

MATERIALS AND METHODS

These experiments were approved by the Dutch medical ethical committee (METC). Three right-handed adult healthy volunteers were scanned after they signed written informed consent.

Acquisition

All data were acquired using a Philips 7 T whole body scanner (Philips, Best) equipped with a quadrature transmit head coil and a 16-channel parallel receive coil. A sagittal three-dimensional TFE T1-weighted scan was acquired (450 overcontiguous slices, slice thickness = 0.8 mm; slice gap = -0.4 mm; TR = 7 ms; TE = 3 ms; flip angle = 8°; FOV = $251 \times 200 \times 180 \text{ mm}^3$; 312×312 acquisition matrix; SENSE factor 2.7; scan duration = 408 s) for gray and white matter tissue classification and anatomical reference.

Two single shot echo planar imaging (EPI) DTI scans were acquired (60 slices; no gap; 104×104 acquisition matrix; FOV = $231 \times 231 \text{ mm}^2$; slice thickness 2 mm; flip angle = 90°; TR = 7,184 ms; TE = 75 ms; 30 different diffusion-weighted gradient directions; $b = 1,000 \text{ s/mm}^2$; five diffusion-unweighted scans; SENSE factor = 3; scan time per DTI set = 273 s) in transverse direction. The second DTI scan was identical to the first DTI scan but was acquired with a reversed k-space readout allowing the application of a susceptibility correction step during post-processing [Andersson et al., 2003]. The first DTI set was used to perform on-the-fly fiber tracking of the left and right cingulum tract using the FiberTrack software package, which is part of the Philips acquisition software. These reconstructed tracts were then used to plan the high-resolution CSI scan [Boer et al., 2011] (32×32 matrix; TR/TE = 517.6 ms/1.4 ms; slice thickness 7.5 mm; voxel size = $5 \times 5 \times 7.5 \text{ mm}^3$; total acquisition time 12.5 min). Maximum chemical shift artifact in the slice direction was $\pm 3.3\%$ /ppm yielding a maximum displacement between NAA (2.0 ppm) and myo-inositol (4.0 ppm) of $\pm 0.5 \text{ mm}$ in the slice direction. Accurate shimming for the CSI-scan was obtained using cost-function based shimming [Siero et al., 2009]. Additionally, a water scan was acquired with

the same acquisition parameters as the CSI scan, which served as a reference for frequency alignments and signal normalization.

Postprocessing

Gray and white matter tissue classification was performed on the high-resolution T1-weighted scan using SPM8 (www.fil.ion.ucl.ac.uk/spm) yielding detailed fractional maps for gray and white matter.

The two DTI data sets were combined and corrected for susceptibility artifacts [Andersson et al., 2003] followed by a correction for gradient-induced distortions [Andersson and Skare, 2002]. Next, for each voxel, the tensor model was fitted using M-estimators [Chang et al., 2005]. Whole brain fiber tracking was carried out using the fiber assignment by continuous tracking (FACT) algorithm [Mori et al., 1999] (minimum fractional anisotropy = 0.2, maximum tract angle = 45°). A two ROI approach [Mori et al., 2005] was used to select the left and right cingulum tracts from this complete set of reconstructed tracts.

These reconstructed cingulum tracts were then used to select those voxels from the CSI-scan that overlap with the left or right cingulum. All computations were done using MATLAB (MathWorks). The individual spectra of the selected CSI voxels were automatically processed using the freely available Simulation Package on In vitro Databases (SPID) software (<http://homes.esat.kuleuven.be/%7Ebiomed/software.php#SpidGUI>) as follows. For each CSI voxel, the signal was subjected to a Lorentz-to-Gauss apodization [de Graaf, 2007] before time domain phase correction was applied [Klose, 1990]. Next an automatic zero- and first-order phase correction was performed using the ACME method [Chen et al., 2002] taking into account the 1.4 ms sample delay of the FID-CSI acquisition. The water signal was filtered out [Pouillet et al., 2007b] followed by a baseline correction. Finally, eretic normalization [Laudadio et al., 2002; Pouillet et al., 2007a] was applied on all spectra simultaneously to correct for small displacements in frequencies due to possible intervoxel B_0 inhomogeneities.

Instead of defining two types of tissue [Hanson et al., 2000], namely gray matter and white matter, with tract-based MR spectroscopy we define three types of tissue distinguishing between white matter inside the cingulum bundle and white matter outside the cingulum bundle as we are only interested in signal from the white matter of the cingulum bundle itself. For each of the selected CSI voxels, we computed these three fractions and used them in a linear model fit approach to estimate the signal from the white matter of the cingulum bundle as follows. For each separate frequency point f in the spectrum a linear model is used to estimate the contribution of white matter inside the cingulum bundle to the measured signal in the n CSI voxels that are part of the cingulum tract using:

Figure 2.

Tract-based MR spectroscopy. The spectrum (y) is automatically computed for each of the n CSI voxels from the cingulum [depicted in red in (A)]. For each frequency f a model (B) was fitted to estimate the contribution of white matter from the cingulum (represented by a in the model) to the measured signal. The fractions of the different tissue types in the selected CSI voxels used in the model namely white matter in the cingulum, white matter outside the cingulum, and gray matter are represented by WMC, WME, and GM. The resulting spectra for the different tissue types are shown in (C).

$$\begin{bmatrix} y_1 \\ y_2 \\ \vdots \\ y_n \end{bmatrix} = a \cdot \begin{bmatrix} WMC_1 \\ WMC_2 \\ \vdots \\ WMC_n \end{bmatrix} + b \cdot \begin{bmatrix} WME_1 \\ WME_2 \\ \vdots \\ WME_n \end{bmatrix} + c \cdot \begin{bmatrix} GM_1 \\ GM_2 \\ \vdots \\ GM_n \end{bmatrix} + \bar{\epsilon}$$

where y is a vector of size n containing the measured signal for all n cingulum voxels at frequency f , and a , b , and c are the signal intensity estimators. WMC, WME, and GM are vectors of size n representing the fractions of white matter inside the cingulum bundle, white matter outside the cingulum bundle and gray matter, respectively, as determined on the T1-weighted scan. The distinction between cingulum white matter and external white matter is made by computing the overlap with the DTI voxels that are part of the reconstructed cingulum bundles. Thus, a represents the estimated signal from white matter of the cingulum bundle for frequency f (see Fig. 2).

Comparing tract-based MR spectroscopy with segmented MR spectroscopy

To compare the tract-based MR spectroscopy approach with the conventional segmented spectroscopy approach

metabolite concentrations of choline, creatine, glutamate, myo-inositol, and *N*-acetyl-aspartate (NAA) were estimated using AQSES [Pouillet et al., 2007a].

We note that for this comparison the same CSI voxels were used in the segmented spectroscopy approach as in the tract-based MR spectroscopy approach because here we want to study the possible differences due to the application of two ways to fit the metabolite concentrations, namely averaging spectra followed by fitting versus fitting followed by averaging. For tract-based MR spectroscopy, the fitting of the metabolite concentrations was performed only once namely for the estimated spectrum for the white matter of the cingulum bundle (Fig. 3A). For the segmented spectroscopy approach, the fitting of the metabolite concentrations was performed separately for each CSI voxel. The linear model was then fitted to these metabolite concentrations (instead of fitting the model per frequency as with tract-based MR spectroscopy) to estimate the metabolite concentrations in the white matter of the cingulum bundle.

One may question if possible differences, in for instance metabolite concentrations between left and right cingulum bundles, could not simply be detected by selecting one proper CSI white matter voxel for each subjects left and right cingulum bundle and then compare their concentrations at a group level. To illustrate the increased sensitivity of the tract-based approach as compared to such a single CSI voxel approach, we computed the distribution of average left and right estimated glutamate concentrations (i.e., averaged over subjects) computed over 10,000 combinations of those CSI voxels that contain at least 50% cingulum bundle tissue.

To assess the specificity of the tract-based approach, we also computed the metabolite concentrations for white matter outside the cingulum bundles separately for the left and right hemisphere. CSI voxels were included if the full-width-at-half-maximum of the water peak was smaller than 10 Hz and did not contain cingulum bundle tissue. Here we considered only two tissue classes (i.e., white matter and gray matter). For each subject average white matter spectra were computed for the left and right hemisphere.

RESULTS

The results of the spectra for the white matter in the left and right cingulum of the three participants are shown in Figure 3B. The mean (SD) full-width-at-half-maximum of the water peaks for participants 1, 2, and 3 were for the left CSI cingulum voxels 8.1 Hz (0.8), 6.3 Hz (0.9), and 8.4 Hz (1.2), and 9.6 Hz (1.0), 7.7 Hz (2.3), and 8.6 Hz (4.2) for the right CSI cingulum voxels, respectively. The estimated totals of white matter in the CSI voxels that are part of the cingulum tracts are shown in Table I. The estimated metabolite fractions for left and the right cingulum tracts for all three subjects computed in the two different ways

Figure 3.

Example of metabolite estimation and spectra results for all healthy participants. The results of fitting simulated metabolite spectra using AQSES to the measured spectrum of the white matter from the left cingulum tract from Subject 1 are shown in (A). The measured spectra for the white matter of the left and right cingulum tracts for all three healthy participants are shown in (B).

(i.e., tract-based MR spectroscopy and segmented spectroscopy) are shown in Figure 4.

Figure 5 shows the distributions for the estimated glutamate concentrations averaged over subjects for 10,000 randomly selected CSI voxels for the left (blue) and right (green) cingulum bundles. Application of the Kruskal-Wallis test for each of these 10,000 combinations showed that for 45% of possible CSI voxel combinations

no significant difference was found in average estimated glutamate concentrations between left and right cingulum CSI voxels.

DISCUSSION

In this feasibility study, we combine a novel two-dimensional CSI MR scan at ultra high field MRI (7 T)

TABLE I. Cingulum fractions

Subject no.	Total cingulum left	CSI	GM	WM	WM CSI	Total cingulum right	CSI	GM	WM	WM CSI
1	3.6 cc	2.6 cc	0.6 cc	2.0 cc	1.2 cc	4.5 cc	4.3 cc	0.9 cc	3.4 cc	1.7 cc
2	5.6 cc	3.6 cc	0.7 cc	2.9 cc	2.3 cc	5.0 cc	5.1 cc	0.9 cc	4.2 cc	2.5 cc
3	5.0 cc	4.9 cc	1.4 cc	3.5 cc	2.1 cc	4.8 cc	5.3 cc	1.3 cc	4.0 cc	1.4 cc

Total cingulum, total white matter volume of complete reconstructed cingulum bundles; CSI, volume of all CSI voxels part of the cingulum bundle; GM, total gray matter in CSI; WM, total white matter in CSI; WM CSI, volume of measured white matter of cingulum in CSI voxels.

Figure 4.

with DTI and fiber tracking to obtain spectral information from the left and right cingulum bundles with both a high sensitivity and a high specificity. The results presented in Figure 3B show similar spectra for the left and the right cingulum bundles of the three participants indicating that the proposed tract-based MR spectroscopy method is a robust method that can be used in patient-control studies. Moreover, the way of combining spectral information from the CSI-voxels from the cingulum tracts as with tract-based MR spectroscopy (i.e., using a model to combine the full spectra followed by an estimation of the metabolite concentration) yields results which are very similar to the results obtained with the conventional segmented spectroscopy approach (i.e., first an estimation of the metabolite concentrations for each voxel and then use a model to combine these per voxel estimations). Both approaches show a significant difference in glutamate concentrations between the left and right cinguli using the Kruskal-Wallis test ($\chi^2 = 3.86$, $P < 0.05$; uncorrected for multiple comparisons) but not for the other estimated other metabolite concentrations (see Fig. 4). The tract-based MR spectroscopy approach is therefore favorable as it yields full spectra for the white matter of the cingulum tracts, and therefore it also allows for

analysis methods (e.g., Relief-F, PCA, ICA) that do not require explicit estimation of specific metabolite concentrations.

Figure 5.

The cingulum bundle plays a crucial role in the default-mode network and various studies suggest that the cingulum bundle is implicated in schizophrenia. The glutamate hypothesis in schizophrenia [Chang et al., 2007; Choe et al., 1994; Coyle, 1996; Gordon, 2010] predicts altered levels of glutamate in various brain regions—including white matter—of patients with schizophrenia. In addition, there is evidence that one of the hemispheres is more affected than the other (the so-called lateralization hypothesis [Crow et al., 1996; Oertel et al., 2010; Ribolsi et al., 2009]). For instance, the left over right asymmetry of fractional anisotropy values of the cingulum bundles found in healthy subjects [Gong et al., 2005; Park et al., 2004; Takao et al., 2010] is attenuated in patients with schizophrenia [Fujiwara et al., 2007]. The tract-based MR spectroscopy method in its current configuration allows us to measure (large parts of) the cingulum bundle in each hemisphere. In this way, we cannot only detect possible disease-related alterations in (among others) glutamate levels but also possible differences in lateralization of various metabolite concentrations. Interestingly, differences in glutamate concentrations were found between the left and right cingulum indicating that tract-based MR spectroscopy is at least sensitive enough to detect possible lateralization differences in various metabolite concentrations. To assess the specificity of the tract-based approach, we computed the average metabolite concentrations for white matter outside the cingulum voxels separately for the left and right hemisphere. Here, no differences were found between any of the average metabolite concentrations computed for the left and right hemisphere (for glutamate the Kruskal–Wallis test yielded $\chi^2 = 0.43$, $P = 0.51$). These results suggest that differentiation between white matter within the fiber tract and external white matter (i.e., the tract-based approach) indeed increases specificity.

One may question if such lateralization differences could not simply be detected by selecting one proper CSI white matter voxel for each subjects left and right cingulum bundle and then compare their concentrations at a group level. The results shown in Figure 5 show that the distribution for the average glutamate concentrations of the left cingulum tract (blue) clearly overlaps with the

average glutamate concentrations of the right cingulum tract (green). Moreover, application of the Kruskal–Wallis test for each of these 10,000 combinations showed that for 45% of possible CSI voxel combinations no significant difference was found in estimated glutamate concentrations between left and right cingulum CSI voxels. Thus the tract-based approach not only allows us to differentiate between inter- and intracingulum white matter but also increases sensitivity as compared to a single voxel approach.

Tract-based MR spectroscopy as applied here includes large parts of the cingulum bundle, but it does not completely encompass the cingulum bundle (see Table I). The reason for this is that we want to obtain information from both cingulum bundles within one CSI-scan because of time constraints. However, if necessary the method can be extended in two ways to increase the volume of the sample. The first option is to use one slice per cingulum (left or right) and position the CSI slice in such a way that it completely comprises the reconstructed cingulum tract. A second option is to add a second (or even third) consecutive CSI slice. Both cases however result in an increase in acquisition time.

In this study, fiber reconstruction was used at two different stages. First, during acquisition it was used to position the two-dimensional CSI slice in such a way that it captured most of the cingulum tracts. Second, during post-processing the reconstructed tracts were used to estimate the amount of cingulum tissue present in the CSI voxels. For other white matter fiber bundles, the use of on-the-fly fiber tracking (Stage 1) may not be necessary if other reliable landmarks are available to plan the CSI-scan. In that case, the presented method may also be used with alternative white matter delineation techniques (e.g., manual or automatic white matter segmentation) to estimate the amount white matter tissue in the tracts of interest (Stage 2).

Finally, we note that the use of tract-based MR spectroscopy is not limited to studying various neurological and psychiatric diseases but may also be used in a functional setting [Boucard et al., 2005; Mostert et al., 2005] to obtain more information on previously reported task-related FA changes in white matter [Mandl et al., 2008].

Figure 4.

Metabolite fractions computed using tract-based MR spectroscopy and segmented spectroscopy approach. The results of estimating metabolite concentrations using AQSES for the left and right cingulum tracts for all three subjects using the tract-based MR spec-

troscopy approach (A) and the segmented spectroscopy approach (B). For both approaches, a significant difference ($P < 0.05$, uncorrected for multiple comparisons) in estimated glutamate concentrations was found between left and right cingulum tracts.

Figure 5.

Distributions of left and right glutamate mean values at a CSI voxel level. For each subject, one voxel was randomly selected from the set of CSI voxels that contain at least 50% of cingulum tissue. For the left and right cingulum CSI voxels, the average

estimated glutamate concentrations were computed over all three subjects. This procedure was repeated 10,000 times yielding a distribution of average estimated glutamate concentrations for the left (blue) and right cingulum tract (green).

In conclusion, the results show very similar spectra for all three subjects suggesting that the reliable acquisition of spectral information of the cingulum using tract-based MR spectroscopy is feasible. When studying the cingulum bundles one CSI slice can be used to obtain information on metabolic concentrations for both left and right cingulum bundle with minimal partial volume effects allowing us to search for possible disease-related lateralization effects.

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