White matter organization in relation to upper limb motor control in healthy subjects: exploring the added value of diffusion kurtosis imaging

J. Gooijers, A. Leemans, S. Van Cauter, S. Sunaert, S. P. Swinnen & K. Caeyenberghs

Brain Structure and Function

ISSN 1863-2653

Brain Struct Funct

DOI 10.1007/s00429-013-0590-y

Your article is protected by copyright and all rights are held exclusively by Springer-Verlag Berlin Heidelberg. This e-offprint is for personal use only and shall not be self-archived in electronic repositories. If you wish to self-archive your article, please use the accepted manuscript version for posting on your own website. You may further deposit the accepted manuscript version in any repository, provided it is only made publicly available 12 months after official publication or later and provided acknowledgement is given to the original source of publication and a link is inserted to the published article on Springer's website. The link must be accompanied by the following text: "The final publication is available at link.springer.com".

White matter organization in relation to upper limb motor control in healthy subjects: exploring the added value of diffusion kurtosis imaging

J. Gooijers · A. Leemans · S. Van Cauter ·
S. Sunaert · S. P. Swinnen · K. Caeyenberghs

Received: 23 January 2013 / Accepted: 31 May 2013
© Springer-Verlag Berlin Heidelberg 2013

Abstract Diffusion tensor imaging (DTI) characterizes white matter (WM) microstructure. In many brain regions, however, the assumption that the diffusion probability distribution is Gaussian may be invalid, even at low b values. Recently, diffusion kurtosis imaging (DKI) was suggested to more accurately estimate this distribution. We explored the added value of DKI in studying the relation between WM microstructure and upper limb coordination in healthy controls ($N = 24$). Performance on a complex bimanual tracking task was studied with respect to the conventional DTI measures (DKI or DTI derived) and kurtosis metrics of WM tracts/regions carrying efferent (motor) output from the brain, corpus callosum (CC) substructures and whole brain WM. For both estimation models, motor performance was associated with fractional anisotropy (FA) of the CC-genu, CC-body, the anterior limb of the internal capsule, and whole brain WM (r_s range

0.42–0.63). Although DKI revealed higher mean, radial and axial diffusivity and lower FA than DTI ($p < 0.001$), the correlation coefficients were comparable. Finally, better motor performance was associated with increased mean and radial kurtosis and kurtosis anisotropy (r_s range 0.43–0.55). In conclusion, DKI provided additional information, but did not show increased sensitivity to detect relations between WM microstructure and bimanual performance in healthy controls.

Keywords Bimanual motor control · Diffusion tensor imaging · Excess kurtosis · Non-Gaussian diffusion

Introduction

Diffusion tensor imaging (DTI) is a widely used non-invasive, in vivo magnetic resonance (MR) imaging technique for characterizing the microstructural organization of white matter (WM) bundles (Basser et al. 1994; Basser and Pierpaoli 1996; Le Bihan et al. 2001; Tournier et al. 2011;

Electronic supplementary material The online version of this article (doi:10.1007/s00429-013-0590-y) contains supplementary material, which is available to authorized users.

J. Gooijers (✉) · S. P. Swinnen · K. Caeyenberghs
Motor Control and Neuroplasticity Research Group, Department of Kinesiology, Group Biomedical Sciences, KU Leuven, Tervuursevest 101, Bus 1501, 3001 Heverlee, Belgium
e-mail: Jolien.Gooijers@faber.kuleuven.be

S. P. Swinnen
e-mail: Stephan.Swinnen@faber.kuleuven.be

K. Caeyenberghs
e-mail: Karen.Caeyenberghs@UGent.be

A. Leemans
Image Sciences Institute, University Medical Center Utrecht, Heidelberglaan 100, Location AZU-Room Q.S.4.300, 3584 CX Utrecht, The Netherlands
e-mail: Alexander@isi.uu.nl

S. Van Cauter · S. Sunaert
Department of Radiology, University Hospital, KU Leuven, Herestraat 49, 3000 Leuven, Belgium
e-mail: vancautersofie@gmail.com

S. Sunaert
e-mail: Stefan.Sunaert@uz.kuleuven.ac.be

K. Caeyenberghs
Department of Physical Therapy and Motor Rehabilitation, Faculty of Medicine and Health Sciences, University of Ghent, De Pintelaan 185, 9000 Ghent, Belgium

Jones and Leemans 2011). Over the last decade, this technique has been introduced to investigate the potential contribution of variation in WM microstructure with respect to motor indices. For example, previous clinical studies on patients with chronic stroke, with hemiplegia and traumatic brain injury have revealed relationships between DTI metrics of efferent motor pathways and upper limb function (Bleyenheuft et al. 2007; Schaechter et al. 2009; Caeyenberghs et al. 2010b; Qiu et al. 2011; Song et al. 2012). Moreover, several studies revealed that in healthy adults the microstructure of the corpus callosum (CC) is related to bimanual performance in both simple (Sullivan et al. 2001; Johansen-Berg et al. 2007; Muetzel et al. 2008) and more complex (Gooijers et al. 2013) movement conditions. In these studies, increases in the WM coherence, as expressed by fractional anisotropy (FA), have been associated with better motor performance. Notwithstanding the impact of these findings, it is well known that DTI assumes a Gaussian approximation of the displacement probability distribution, represented by a mono-exponential MR signal decay (Basser and Jones 2002; Lu et al. 2006). This assumption may not be valid due to the presence of barriers, which may induce restricted rather than hindered diffusion components (Kärger 1985; Lu et al. 2006). As such, DTI may not be optimal to capture the relation between tissue microstructure and behavioral measures.

Several other models were suggested to characterize the non-Gaussian diffusion behavior. Some of these models go beyond the angular model of DTI, i.e., models that can better deal with the presence of two or more fiber populations. Examples of such models are the generalized diffusion tensor model (Liu et al. 2004; Minati et al. 2007), diffusion spectrum imaging (Wedeen et al. 2005), constrained spherical deconvolution (Tournier et al. 2007; Dell'Acqua et al. 2010), and Q-space imaging (Callaghan 1991). The main disadvantages of these techniques are, however, longer scan times and higher hardware demands. In addition, models exist that can describe the diffusion-weighted signal attenuation more accurately compared to the DTI model. The bi-exponential model (Niendorf et al. 1996; Clark and Le Bihan 2000; Maier et al. 2004; Kiselev and Il'yasov 2007; Maier and Mulkern 2008; Mulkern et al. 2009), for example, describes the MR signal decay as the superposition of two signals arising from rapidly and slowly decaying components, showing a better fit to the experimental data. However, the true attribution of these two compartments remains ambiguous. Another upcoming approach, which suffers less from acquisition constraints, is diffusion kurtosis imaging (DKI) (Jensen et al. 2005; Lu et al. 2006). This model utilizes a non-mono-exponential decay of the MR signal (Jensen and Helpert 2010), which allows the quantification of the degree of non-Gaussian diffusion by adding an excess kurtosis term (Jensen et al.

2005; Lu et al. 2006; Fieremans et al. 2008; Veraart et al. 2011), resulting in a more accurate assessment of the brain tissue complexity compared to DTI (Fieremans et al. 2008). Moreover, Lazar et al. (2008) suggested that DKI can be used for tracking crossing fibers. Since DKI is an extension of the conventional DTI method (Jensen and Helpert 2010), all the typical diffusion parameters [mean (MD), radial (RD), and axial (AD) diffusivity, and FA] as well as several kurtosis metrics [being kurtosis anisotropy (KA) and mean (MK), radial (RK), and axial (AK) kurtosis] are acquired (Poot et al. 2010). This provides us with the opportunity to directly compare the typical diffusion parameters obtained via the conventional DTI method and the more recently proposed DKI approach. In this context, previous pilot studies on rodents and patient populations have already demonstrated that the DTI-derived diffusivities are generally lower than those estimated with DKI (Veraart et al. 2011; Rosenkrantz et al. 2012).

Recent studies have shown that the additional kurtosis metrics of DKI indeed provide more sensitive and complementary information concerning microstructural changes in healthy aging (Falangola et al. 2008) and pathologies, such as tumors (Jansen et al. 2010; Raab et al. 2010; Rosenkrantz et al. 2012; Van Cauter et al. 2012), cerebral infarction (Jensen et al. 2011), Parkinson's disease (Wang et al. 2011), attention-deficit hyperactivity disorder (Helpert et al. 2011), traumatic brain injury (Grossman et al. 2012), Alzheimer's disease (Vanhoutte et al. 2013; Falangola et al. 2013), multiple sclerosis (Raz et al. 2013) and lung dysfunction (Trampel et al. 2006). To date, DKI has not yet been applied to study the relation between WM diffusion parameters and behavioral measures in healthy young adults or patients. The present study is the first, to our knowledge, to explore potential relationships in healthy controls, while quantifying the non-Gaussian behavior of diffusion with both the DTI and the DKI model. The main goal was to investigate the added value of the full kurtosis framework in relating WM organization to bimanual coordination in a number of tracts, each demonstrating a different microstructural architecture. The visuomotor tracking task included in this work is a computerized version of the "Etch-a-Sketch" device (Sisti et al. 2011; Gooijers et al. 2013), allowing manipulation of the key behavioral principles of bimanual coordination. In line with previous findings, we hypothesized that the typical DTI-based diffusivity measures (FA, MD, RD, AD) obtained via the DKI model estimation method would be associated with bimanual performance. In addition, we investigated whether there would be any differences between the results derived from DTI and DKI. Finally, we explored the benefit of the additional kurtosis measures in terms of offering valuable new information for detecting relations between WM structures and motor performance.

Materials and methods

Subjects

Twenty-four undergraduate students of the KU Leuven (20 females, 4 males, mean age 20.8, SD = 1.4 years, range 19.3–25.3) participated in the experiment. Subjects were all right-handed as determined by the Oldfield Handedness scale (Oldfield 1971) (mean laterality score 94.2 ± 9.0 , range 70–100) and had no history of neurological or psychiatric disorders. They were naive with respect to the task and had normal or corrected-to-normal vision. Informed written consent was obtained from each participant prior to testing according to the Declaration of Helsinki. The experimental protocol received approval from the local ethical committee of the University of Leuven.

Bimanual tracking task

The equipment, paradigm parameters, and dependent variables were similar to our previous studies (Sisti et al. 2011; Gooijers et al. 2013). Specifically, the task was to follow a specified pathway with a certain angle, presented on a screen, by moving two dials, one with each hand (see Fig. 1). The left and right dial controlled the movement of the subject's cursor along the vertical and horizontal axis, respectively. When the left dial was rotated to the right [clockwise (CW)], the cursor moved up; when turned to the left [counterclockwise (CCW)], the cursor moved down. When the right dial was rotated to the left, the cursor moved to the left (CCW); when rotated to the right (CW), the cursor moved to the right. The goal of each trial was to generate the correct direction and speed by turning the dials, producing a line equivalent to the target line presented on the display (see Fig. 1). The target moved at a constant rate for a total duration of 7 s. After 7 s, the screen turned black, regardless of the subject's location on the screen, and the next target line would appear after a random interval of 4–6 s. Four coordination patterns were introduced: two in which the left and right dial moved in the same direction, either clockwise (CW) or counterclockwise (CCW), and two in which the left and right dial moved toward (IN) or away (OUT) from each other. The coordination patterns were performed according to one of the following frequency ratios between the left and right hand (L:R): 1:1, 1:3, 2:3, 3:1 and 3:2 (see Fig. 1). All trials were performed in the presence of online visual augmented feedback, showing the subject's actual performance, as represented by a red cursor on the screen (see Fig. 1).

Subjects performed six trial blocks, each consisting of 20 distinctive target lines (see Fig. 1), with 3 min of rest between blocks. The entire task typically lasted 45 min. Similar to our previous study (Gooijers et al. 2013), the

Fig. 1 Experimental set-up. (Left) Subject seated in front of a computer screen displaying the task. The target pathway (blue line), a target cursor (white dot) and visual feedback of actual performance (red cursor with a 1-cm long tail) appeared on the display during a single trial. (Right-Top) The hands were covered with a table-top bench during the experiment. (Right-Bottom) Schematic representation of the bimanual tracking task. Twenty possible target pathways are represented: five frequency ratios between the left and right hand (L:R): 1:1, 1:3, 2:3, 3:1, 3:2 and four different coordination patterns: both hands move in the same direction, either clockwise (CW) or counterclockwise (CCW), both hands move towards (IN), or away from each other (OUT)

Slope Error was used as a measure of accuracy per trial. For this dependent variable the slope produced by the subject relative to the target line was calculated. To determine whether subjects generally met the task requirements, all data were transformed into z scores $[(X - \text{mean})/\text{SD}]$, where X is defined as the actual value. A trial was classified as an outlier and discarded from the analysis when z values were greater than $|3|$. In the present study, 0.8 % of the data points were removed from the dataset (range 0–3.3 %, SD 1.1) because of not complying with the task demands. One participant was not able to perform the task correctly and was discarded from the analyses. Therefore, data analysis was performed on 23 of 24 participants. Computer programming and analyses were done using both LabView (version 8.5) software (National Instruments, Austin, Texas, USA) and MATLAB R2008a.

Image acquisition

A scanning session (including diffusion images and anatomical scan) was followed within a week of the behavioral session. A Siemens 3T Magnetom Trio MRI scanner (Siemens, Erlangen, Germany) with an eight-channel standard head coil was used for image acquisition. For all subjects, a high resolution T1-weighted structural image was acquired using magnetization prepared rapid gradient echo [MPRAGE; TR = 2300 ms, echo time (TE) = 2.98 ms,

$1 \times 1 \times 1.1 \text{ mm}^3$ voxel size, field of view (FOV) $240 \times 256 \text{ mm}^2$, 160 sagittal slices] for anatomical detail. Diffusion-weighted images were acquired using the following parameters: single-shot spin-echo; slice thickness = 2.5 mm, TR = 8700 ms, TE = 116 ms, number of diffusion directions = 150, number of sagittal slices = 58, voxel size = $2.5 \times 2.5 \times 2.5 \text{ mm}^3$. Implemented b values were 700, 1000, and 2800 s/mm^2 , applied in 25, 40, and 75 uniformly distributed directions, respectively. In addition, 10 images without diffusion weighting were obtained.

Image processing

The diffusion data were analyzed and processed in *ExploreDTI* (version 4.8.1) (Leemans et al. 2009), using a multi-step procedure as described previously (Caeyenberghs et al. 2010a; Jones and Leemans 2011). In summary, the following steps were taken: (1) we visually checked the separate diffusion-weighted imaging volumes at high frame rate to spot any obvious artifacts in the data, such as large signal dropouts and geometric distortions. The images were inspected from different “orthogonal” views to detect any interslice and intravolume instabilities (Tournier et al. 2011). (2) The diffusion-weighted data sets were corrected for subject motion and eddy current-induced geometrical distortions with the appropriate reorientation of the b matrix (Leemans and Jones 2009). (3) The diffusion tensor was estimated with a weighted linear least squares estimator for both the DTI model (two b values included: 0 and 1000 s/mm^2) and the DKI model (all b values included) (Veraart et al. 2012). Subsequently, the conventional diffusion parameters, fractional anisotropy (FA), radial (RD), axial (AD), and mean diffusivity (MD) were calculated (Jones and Basser 2004). The estimation procedure for DKI also provided the kurtosis tensor, from which the kurtosis anisotropy (KA) and mean (MK), radial (RK), and axial (AK) kurtosis parameters were derived (Poot et al. 2010). Analogous to the diffusivity indices in DTI, the KA represents the degree of anisotropy of the kurtosis along different orientations, the MK is the average kurtosis, the AK is defined as the kurtosis estimated along the orientation of the principal eigenvector, and RK is the average kurtosis in the directions orthogonal to the principal eigenvector (Poot et al. 2010; Fieremans, Jensen, Helpert 2011), and (4) the DTI data were transformed to MNI space for subsequent analyses. In this last step, the transformation matrices were concatenated to minimize smoothing due to data interpolation.

ROIs definition

The WM parcellations, developed by Mori et al. (2005), were applied to the normalized images and the

corresponding diffusion and kurtosis metrics were averaged across the 3D ROI labels. We have also used the add-ons to the analysis software package FSL, which provide other atlases in MNI space, such as a digitized version of the original Talairach atlas (Lancaster et al. 2000, 2007). In doing so, the following eight WM tracts and regions were defined: three subregions of the corpus callosum (genu, body, and splenium), the corticospinal tract (CST), the anterior limb of the internal capsule (ALIC), the cerebral peduncles (CP), the superior cerebellar peduncles (SCP) and whole brain WM. Given the lack of hemispheric differences for the motor tracts, diffusion parameters for left and right were combined. A more detailed description of this analysis procedure can be found in Caeyenberghs et al. (2010a).

The rationale for proposing the corpus callosum was based on previous research, demonstrating its importance for upper limb coordination tasks (Johansen-Berg et al. 2007; Muetzel et al. 2008; Fling et al. 2011). Because we were, strictly speaking, not specifically interested in the relation between bimanual performance and WM microstructure in the functionally segmented CC, as has been studied widely by now, subdivision into three CC subregions (genu, body, splenium) has been made primarily to focus on the comparison of the DKI and DTI estimation methods and the resulting metrics in relation to behavior. Moreover, we investigated the WM tracts that are mainly concerned with motor function (Bleyenheuff et al. 2007; Schaechter et al. 2009; Caeyenberghs et al. 2010a, 2010b, 2011; Qiu et al. 2011; Song et al. 2012), and we selected the whole brain WM label of the Talairach atlas, excluding gray matter (GM, cortex, and nuclei) or cerebral spinal fluid.

For visualization purposes, tracts and regions were reconstructed and presented on the white-matter atlas of Mori et al. (2005) in Fig. 2.

Statistical analysis

Both behavioral and diffusion measures violated the assumption of normality as tested by the Shapiro–Wilks normality test. Therefore, non-parametric tests were used. Because of the minor impact of the four coordination patterns reported in earlier studies by our group (Sisti et al. 2011; Gooijers et al. 2013), they were combined in the subsequent analyses. For the outcome measure of the bimanual tracking task, a Friedman test was performed to compare the Slope Error on the different Frequency Ratios (i.e., 1:1, 1:3, 3:1, 2:3 and 3:2). Significant main effects were further explored using post hoc Wilcoxon signed-rank tests. Bonferroni corrections for multiple comparisons were made, hence $p < 0.005$ was considered significant following correction for the 5 frequency ratios.

Fig. 2 Example regions of interest masks. Regions are depicted on fractional anisotropy maps of the white-matter atlas of Mori et al. (2005): *a* Sagittal view of the genu of the corpus callosum (orange). *b* Sagittal view of the body of the corpus callosum (red). *c* Sagittal

view of the splenium of the corpus callosum (purple). *d* Coronal view of the corticospinal tract (green). *e* Axial view of the cerebral peduncle (light blue). *f* Axial view of anterior limb of internal capsule (gold). *g* Sagittal view of the superior cerebellar peduncle (dark blue)

Statistical comparisons of all diffusion parameters FA, MD, RD and AD between kurtosis and diffusion model estimation were performed using Wilcoxon signed-rank tests. We applied Bonferroni correction for eight comparisons whereby p values ≤ 0.006 were considered significant.

To determine whether diffusion metrics were correlated with performance on the bimanual tracking task, we calculated Spearman correlation coefficients of the diffusion (DKI and DTI derived) and kurtosis values against slope error for both the DKI and DTI model estimations. The Spearman's rank correlation was used here because it is a useful tool for exploratory data analysis.

Finally, Steiger's Z statistic for dependent correlations (Steiger 1980) was used to evaluate potential differences between the correlation coefficients of the DTI and DKI model estimations. Statistical analyses were performed with Statistica 10 (StatSoft, Inc. Tulsa). Unless otherwise stated, the p value was set at 0.05.

Results

Bimanual coordination

The behavioral results showed a significant effect of Frequency Ratio on Slope Error, $\chi^2(4) = 40.70$, $p < 0.001$. Post hoc tests (Wilcoxon signed-rank tests) revealed that the error of the slope angle was significantly lower for the 1:1 ratio than for all non-1:1 ratios (all $p_{\text{corr}} < 0.001$) and the Slope Error for the ratio 3:1 was higher than for the

ratio 3:2 ($p_{\text{corr}} < 0.005$). These results imply that the 1:1 ratio was less difficult than the non-1:1 ratios and that the integer ratio of the left-hand leading condition (3:1) resulted in a higher error score than the non-integer left-hand leading condition (3:2). In the remainder of the paper, the 1:1 ratio is referred to as the isofrequency ratio and the non-1:1 ratios will be collapsed without consideration of all frequency ratios separately, and denoted as the non-isofrequency ratios. Accordingly, this strategy reduces the likelihood of type I errors.

Diffusion parameter estimation with DKI versus DTI model

A significant effect for model estimation (DTI vs. DKI) was seen on the diffusion parameters. Specifically, higher values of diffusion (MD, RD and AD) were found for DKI for all WM tracts and regions (all $p_{\text{corr}} < 0.001$). A significant effect of model was also found for FA values. DKI showed significantly lower values of FA in all ROIs (all $p_{\text{corr}} < 0.001$), except for the CST ($p > 0.05$). Mean diffusion and FA parameter values computed by the two different diffusion models in eight WM structures are shown in Fig. 3.

Association between “typical” diffusion parameters and bimanual performance

To gain insight into the relation between the microstructural organization of specific WM regions and motor

Fig. 3 Average diffusion parameter values (FA, MD, RD and AD) for DTI (*striped bars*) and DKI (*full bars*) and the average kurtosis parameter values (KA, MK, RK, AK). The diffusion parameter values (**a** FA, **b** MD, RD and AD) in eight brain structures [anterior limb of internal capsule (ALIC), genu of CC (GENU_CC), body of CC (BODY_CC), splenium of CC (SPLENIUM_CC), cerebral peduncles (CEREBR_PED), superior cerebellar peduncles (SUP_CER_PED), corticospinal tract (CST), and whole brain white matter (WM)] calculated using DTI (*striped bars*) and DKI (*full bars*). **c** KA, MK, RK and AK values in similar eight brain structures. The *error bars* indicate the standard deviation

performance, while quantifying the non-Gaussianity of diffusion, we performed correlations between the bimanual tracking task scores and the typical DTI metrics estimated with either the DTI or DKI model. In the following section, we will report the correlation results for both models, per diffusion metric. Correlations following exclusion of the male subjects did not alter our findings significantly. A summary of the correlation analyses is reported in Online Resource 1.

Fractional anisotropy

For the DTI model estimation, correlational analyses demonstrated significantly negative correlations of FA with Slope Error on the non-isofrequency ratios for the genu ($r_s = -0.46$, $p = 0.027$) and the body of the CC ($r_s = -0.50$, $p = 0.016$), the CST ($r_s = -0.44$, $p = 0.037$), the ALIC ($r_s = -0.42$, $p = 0.046$) and whole brain WM ($r_s = -0.43$, $p = 0.041$), indicating that higher anisotropy

values in these ROIs coincided with a better performance on the bimanual tracking task (i.e., lower Slope Error scores) (see Fig. 4).

As shown in Fig. 4, correlations obtained with the DKI model also revealed that performance level on the bimanual tracking task increased (i.e., lower Slope Error scores on the non-isofrequency ratios) with increasing FA values in several ROIs: genu of the CC ($r_s = -0.42$, $p = 0.047$), body of the CC ($r_s = -0.52$, $p = 0.011$), the ALIC ($r_s = -0.43$, $p = 0.039$) and whole brain WM ($r_s = -0.51$, $p = 0.012$). Moreover, for the isofrequency ratio, FA values of the ALIC correlated negatively with bimanual performance ($r_s = -0.63$, $p = 0.001$).

Mean diffusivity

No significant relations emerged between MD of any of the WM structures and bimanual performance, for both the DTI and DKI model estimates.

Radial diffusivity

Analyses of the values obtained using the DTI model showed that an increase in RD in the body ($r_s = 0.47$, $p = 0.023$) and genu of the CC ($r_s = 0.53$, $p = 0.010$) was associated with poorer performance on the non-isofrequency ratios of the bimanual tracking task.

When the RD values were estimated using the kurtosis model, only the body of the CC appeared to be positively correlated with bimanual performance on the non-isofrequency ratios ($r_s = 0.42$, $p = 0.046$). Thus, subjects with higher RD values in this WM region showed poorer bimanual performance.

Axial diffusivity

Higher AD values in the splenium of the CC, as obtained with the DTI model, coincided with a lower error score on the isofrequency ratio of the bimanual tracking task, i.e., a better performance ($r_s = -0.47$, $p = 0.024$).

Comparable results were found for the DKI estimates. Negative associations revealed that subjects with lower error scores, i.e., better performance on the isofrequency ratio, had higher AD values in the genu ($r_s = -0.42$, $p = 0.049$) and the splenium of the CC ($r_s = -0.53$, $p = 0.009$).

Association between diffusion parameters and bimanual performance; DTI versus DKI

To determine whether the correlations between the typical diffusion metrics (FA, MD, RD and AD) and bimanual performance were different between DKI and DTI

estimates, we calculated the Steiger's Z statistic for dependent correlations. Findings revealed no significant differences in correlation coefficients between both model estimations for any of the diffusion metrics (all $p_{\text{corr}} > 0.01$).

Association between the kurtosis parameters and bimanual performance

Mean kurtosis parameters are shown in Fig. 3. Negative associations between the typical kurtosis parameters (MK, KA, RK and AK) and bimanual performance revealed that subjects demonstrating a better performance on the non-isofrequency ratios showed increased kurtosis values (particularly MK, KA and RK) in the body (MK: $r_s = -0.51$, $p = 0.013$, RK: $r_s = -0.48$, $p = 0.021$, KA: $r_s = -0.54$, $p = 0.008$) and the genu of the CC (RK: $r_s = -0.46$, $p = 0.026$, KA: $r_s = -0.43$, $p = 0.039$), the ALIC (MK: $r_s = -0.46$, $p = 0.027$, RK: $r_s = -0.43$, $p = 0.040$, KA: $r_s = -0.45$, $p = 0.031$) and the whole brain WM (MK: $r_s = -0.49$, $p = 0.018$, RK: $r_s = -0.44$, $p = 0.035$). Furthermore, KA values of the ALIC correlated negatively with bimanual performance on the isofrequency ratio ($r_s = -0.53$, $p = 0.010$), whereas positive correlations were found for the AK values ($r_s = 0.55$, $p = 0.007$). See Online Resource 2 for a summary of the correlation analyses.

Discussion

This is the first paper that uses DKI to investigate potential relations between WM diffusion parameters and motor performance in a group of healthy young adults. Our results indicate that (1) with respect to the bimanual tracking task, the isofrequency movements were performed more successfully than the non-isofrequency movements, completely in line with previous research (Sisti et al. 2011); (2) consistent with previous findings (Veraart et al. 2011), DKI model estimates of the diffusion indices were increased and FA values decreased as compared to the DTI estimates; (3) the correlations between the typical diffusion metrics and motor performance were comparable for both diffusion methods; and (4) being dependent on the WM structure, kurtosis indices correlated significantly with motor performance.

Although DTI is a routinely used non-invasive imaging technique to investigate the contribution of the WM microstructure of the CC to bimanual coordination, recent work has shown that there are many brain regions where the Gaussian assumption for DTI may not be valid (Vos et al. 2012; Jeurissen et al. 2012), possibly leading to heterogeneity across previous DTI work on bimanual coordination. For example, significant associations

Fig. 4 Relationship between the behavioral task scores and average FA values. Scatterplots with best-fit lines showing Spearman correlations between the behavioral task scores and average values for fractional anisotropy (FA) of the CC-genu, CC-body, corticospinal tract (CST), anterior limb of internal capsule (ALIC) and whole brain white matter (WM) for both the diffusion kurtosis imaging (DKI) (black triangles) and diffusion tensor imaging (DTI) (gray circles) model estimates

between bimanual performance and FA values in the pre-frontal region of the CC in a population of MS patients (Bonzano et al. 2008) and the anterior midbody of the CC

in healthy controls have been identified (Johansen-Berg et al. 2007), whereas other studies point to the more posterior regions of the CC as predictors for bimanual

coordination (Sullivan et al. 2001; Pfefferbaum et al. 2007; Muetzel et al. 2008; Gooijers et al. 2013). Although this discrepancy can be partly explained by differential features of the task as well as differences in the population under study (healthy/pathological), it is also possible that a more accurate estimation of the white matter microstructure by means of DKI, as done in the present study, may alleviate these inconsistencies to a certain degree. More specifically, with the DKI model and in regions with a non-Gaussian diffusion distribution, diffusion parameters are estimated more accurately, rendering subsequent analyses more reliable (Veraart et al. 2011).

In this study, the conventional diffusion parameters were estimated with both the DTI and the DKI model. The kurtosis model, compared to the diffusion model, showed increased values for mean, axial and radial diffusivity and decreased FA values for almost all WM structures. These findings are largely in line with two earlier studies on rats (Hui et al. 2008; Cheung et al. 2009; Veraart et al. 2011). Cheung et al. (2009) studied whether DKI would be more sensitive in detecting tissue microstructural changes with age and found that indeed the DTI-derived diffusivity values were generally underestimated in several WM tracts and regions. A more methodological study on rats by Veraart et al. (2011) also revealed that the typical diffusivity measures are dependent on the selected model, i.e., values obtained by DKI are higher as compared to DTI. No discrepancy was found between the DTI and DKI approach for FA values. Besides animal studies, there is also one pilot study in a small sample of four healthy human participants (Lu et al. 2006), in whom the diffusion kurtosis model was introduced. It was shown that apparent diffusion coefficient values estimated by the DTI approach were repeatedly lower than those obtained by the kurtosis model. They concluded that, using the second-order polynomial model instead of the mono-exponential model, one can estimate the true apparent diffusion coefficient more accurately. Finally, a recent study on prostate cancer, in which the feasibility of the DKI model for detecting and assessing the aggressiveness of the cancer was tested, revealed that diffusivity values derived from DKI were approximately twice as large as those obtained with DTI (Rosenkrantz et al. 2012). The present study is the first report confirming the abovementioned results in a large group of healthy human participants.

From a theoretical point of view, DKI is more *accurate* than DTI in terms of estimating the diffusion tensor measures (Jensen et al. 2005; Jensen and Helpert 2010). The question now arises whether this increase in accuracy would also affect the sensitivity in relating diffusion parameters to performance on behavioral tasks, such as bimanual skills. Hence, we explored the relationship between bimanual performance and DKI-derived diffusivity estimates on the

one hand, and the relationship between bimanual performance and DTI-derived diffusivity estimates on the other hand. We hypothesized that with the expected increase in accuracy, we would find stronger correlations between performance on the bimanual tracking task and diffusion measures with DKI than with DTI. Contrary to these expectations, this study showed that the association trends between motor performance and diffusivity indices, estimated with either the DKI or DTI model, were not significantly different.

In this study, several associations were observed between performance and diffusion measures. First, higher FA values of the body and genu of the CC, the ALIC, and the whole brain WM were associated with lower error scores on the non-isofrequency ratios, i.e., a better performance. Second, lower RD values of the body and the genu of the CC corresponded with better performance on the non-isofrequency ratios. Third, the AD of the splenium and the genu of the CC correlated negatively with performance on the isofrequency ratio. By contrast, there were no correlations between performance and the MD (derived with DKI or DTI). These results indicate that both diffusion methods were sensitive enough to relate diffusion parameters of essential WM structures with the ability to perform a bimanual tracking task. Subsequent analyses revealed that the nature and the strength of the correlations between the diffusion metrics and bimanual performance were very similar for the DKI and DTI parameter estimations. This suggests that for a group of healthy young adults, demonstrating dense WM fibers with a relatively low level of complexity, DKI did not significantly influence the relationship between WM integrity and bimanual performance. Hence, for the present experimental design, the DTI model does not have to be discarded.

In other circumstances, DKI-based measures might be more sensitive and informative than DTI-based measures. For example, several recent studies have demonstrated that DKI parameters are especially advantageous when investigating microstructural alterations and complexity in both gray and white matter structures (Falangola et al. 2008; Hui et al. 2008; Veraart et al. 2011). Moreover, in a study by Lazar et al. (2008), fiber tractography based on DKI has shown to resolve crossing fibers in white matter bundles with high complexity levels, which is not possible with the conventional DTI model. In addition, correlations with DKI possibly depend on the anatomical location studied (Szczypankiewicz et al. 2013). Furthermore, we believe that the DKI model can be of added value in multiple clinical research questions, as discussed next (Trampel et al. 2006; Raab et al. 2010; Jansen et al. 2010, 2011; Wang et al. 2011; Helpert et al. 2011; Rosenkrantz et al. 2012; Grossman et al. 2012; Van Cauter et al. 2012). We know from several recent DKI studies that besides the

conventional diffusion measures, additional kurtosis parameters are highly sensitive and provide complementary information, especially in detecting pathological conditions (Trampel et al. 2006; Jansen et al. 2010, 2011; Raab et al. 2010; Wang et al. 2011; Helpert et al. 2011; Van Cauter et al. 2012; Grossman et al. 2012). For example, Van Cauter et al. (2012) demonstrated that kurtosis parameters, in contrast to the conventional diffusion parameters, were very accurate in classifying gliomas as high or low grade, resulting in better diagnostics and improved clinical management. Therefore, we also studied the kurtosis measures as these could offer superior sensitivity in detecting significant relations between WM microstructural properties and motor performance. In the genu and body of the CC, the ALIC, and for the whole brain WM, all kurtosis measures, except the AK, were correlated negatively with performance on the (non-) isofrequency ratios of the bimanual tracking task. These results reinforce previous findings using the conventional DTI-based metrics, namely the contribution of the more anterior regions of the CC to bimanual performance. The prefrontal region of the CC is known to exchange information between prefrontal and medial wall motor areas of both hemispheres and is involved in the integration of sensorimotor information and for preparation of a motor response (Schulte et al. 2005; Johansen-Berg et al. 2007; Bonzano et al. 2008). In this context, a coherent microstructural organization of these anterior callosal connections has been shown to be crucial for bimanual coordination (Preilowski 1972; Serrien et al. 2001; Sisti et al. 2012). Moreover, it is not surprising that the generic whole brain WM measure correlated with bimanual performance, because the CC takes a substantial share in the latter measure. Our results also indicate that bimanual performance was correlated with FA in the ALIC. Although no previous studies have reported such a relation, it is known that supplementary motor pathways pass through the ALIC and that fibers controlling upper limb movement are found in the anterior part of the internal capsule (Shelton and Reding 2001). The diffusion parameters of the CST, SCP and cerebral peduncles, however, were not predictive of bimanual performance. Although these structures are principal pathways to convey motor commands, the microstructural organization is less crucial for bimanual performance than the CC, which is critical for interhemispheric interactions.

In summary, we have shown that using DKI for estimating DTI-based measures does not alter the relationships between WM microstructural properties and bimanual performance in a group of young healthy controls. In addition, the diffusion measures obtained with DKI, i.e., the kurtosis parameters, provided novel information, which is promising for future neuropathology studies.

Acknowledgments This work was supported by a grant from the Research Programme of the Research Foundation—Flanders (Fonds Wetenschappelijk Onderzoek—FWO) (G.0482.010, G0483.10, G.A114.11, G0721.12), from the Research Fund of the Katholieke Universiteit Leuven, Belgium (OT/11/071), and Grant P7/11 from the Interuniversity Attraction Poles program of the Belgian federal government, awarded to S.P. Swinnen. J. Gooijers is funded by an aspirant fellowship of the Research Foundation—Flanders (FWO).

Conflict of interest There are no conflicts of interest.

References

- Basser PJ, Jones DK (2002) Diffusion-tensor MRI: theory, experimental design and data analysis - a technical review. *NMR Biomed* 15:456–467
- Basser PJ, Pierpaoli C (1996) Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. *J Magn Reson B* 111:209–219
- Basser PJ, Mattiello J, LeBihan D (1994) MR Diffusion tensor spectroscopy and imaging. *Biophys J* 66:259–267
- Bleyenheuft Y, Grandin CB, Cosnard G, Olivier E, Thonnard JL (2007) Corticospinal dysgenesis and upper-limb deficits in congenital hemiplegia: a diffusion tensor imaging study. *Pediatrics* 120:E1502–E1511
- Bonzano L, Tacchino A, Roccatagliata L, Abbruzzese G, Mancardi GL, Bove M (2008) Callosal contributions to simultaneous bimanual finger movements. *J Neurosci* 28:3227–3233
- Caeyenberghs K, Leemans A, Geurts M, Taymans T, Vander Linden C, Smits-Engelsman BCM, Sunaert S, Swinnen SP (2010a) Brain-behavior relationships in young traumatic brain injury patients: DTI metrics are highly correlated with postural control. *Hum Brain Mapp* 31:992–1002
- Caeyenberghs K, Leemans A, Geurts M, Taymans T, Vander Linden C, Smits-Engelsman BCM, Sunaert S, Swinnen SP (2010b) Brain-behavior relationships in young traumatic brain injury patients: fractional anisotropy measures are highly correlated with dynamic visuomotor tracking performance. *Neuropsychologia* 48:1472–1482
- Caeyenberghs K, Leemans A, Geurts M, Vander Linden C, Smits-Engelsman BCM, Sunaert S, Swinnen SP (2011) Correlations between white matter integrity and motor function in traumatic brain injury patients. *Neurorehabil Neural Repair* 25:492–502
- Callaghan PT (1991) Principles of nuclear magnetic resonance microscopy. Oxford University Press, Oxford
- Cheung MM, Hui ES, Chan KC, Helpert JA, Qi LQ, Wu EX (2009) Does diffusion kurtosis imaging lead to better neural tissue characterization? A rodent brain maturation study. *Neuroimage* 45:386–392
- Clark CA, Le Bihan D (2000) Water diffusion compartmentation and anisotropy at high b values in the human brain. *Magn Reson Med* 44:852–859
- Dell'Acqua F, Scifo P, Rizzo G, Catani M, Simmons A, Scotti G, Fazio F (2010) A modified damped Richardson-Lucy algorithm to reduce isotropic background effects in spherical deconvolution. *Neuroimage* 49:1446–1458
- Falangola MF, Jensen JH, Babb JS, Hu C, Castellanos FX, Di Martino A, Ferris SH, Helpert JA (2008) Age-related non-gaussian diffusion patterns in the prefrontal brain. *J Magn Reson Imaging* 28:1345–1350
- Falangola MF, Jensen JH, Tabesh A, Hu C, Deardorff RL, Babb JS, Ferris S, Helpert JA (2013) Non-Gaussian diffusion MR assessment of brain microstructure in mild cognitive impairment and Alzheimer's disease. *Magn Reson Imaging* 31:840–846

- Fieremans E, De Deene Y, Delpitte S, Ozdemir MS, D'Asseler Y, Vlassenbroeck J, Deblaere K, Achten E, Lemahieu I (2008) Simulation and experimental verification of the diffusion in an anisotropic fiber phantom. *J Magn Reson* 190:189–199
- Fieremans E, Jensen JH, Helpert JA (2011) White matter characterization with diffusional kurtosis imaging. *Neuroimage* 58:177–188
- Fling BW, Walsh CM, Bangert AS, Reuter-Lorenz PA, Welsh RC, Seidler RD (2011) Differential callosal contributions to bimanual control in young and older adults. *J Cogn Neurosci* 23:2171–2185
- Gooijers J, Caeyenberghs K, Sisti HM, Geurts M, Heitger MH, Leemans A, Swinnen SP (2013) Diffusion tensor imaging metrics of the corpus callosum in relation to bimanual coordination: effect of task complexity and sensory feedback. *Hum Brain Mapp* 34:241–252
- Grossman EJ, Ge YL, Jensen JH, Babb JS, Miles L, Reaume J, Silver JM, Grossman RI, Inglese M (2012) Thalamus and cognitive impairment in mild traumatic brain injury: a diffusional kurtosis imaging study. *J Neurotrauma* 29:2318–2327
- Helpert JA, Adisetiyo V, Falangola MF, Hu CX, Di Martino A, Williams K, Castellanos FX, Jensen JH (2011) Preliminary evidence of altered gray and white matter microstructural development in the frontal lobe of adolescents with attention-deficit hyperactivity disorder: a diffusional kurtosis imaging study. *J Magn Reson Imaging* 33:17–23
- Hui ES, Cheung MM, Qi LQ, Wu EX (2008) Towards better MR characterization of neural tissues using directional diffusion kurtosis analysis. *Neuroimage* 42:122–134
- Jansen JFA, Stambuk HE, Koutcher JA, Shukla-Dave A (2010) Non-Gaussian analysis of diffusion-weighted MR imaging in head and neck squamous cell carcinoma: a feasibility study. *AJNR* 31:741–748
- Jensen JH, Helpert JA (2010) MRI quantification of non-Gaussian water diffusion by kurtosis analysis. *NMR Biomed* 23:698–710
- Jensen JH, Helpert JA, Ramani A, Lu HZ, Kaczynski K (2005) Diffusional kurtosis imaging: the quantification of non-Gaussian water diffusion by means of magnetic resonance imaging. *Magn Reson Med* 53:1432–1440
- Jensen JH, Falangola MF, Hu CX, Tabesh A, Rapalino O, Lo C, Helpert JA (2011) Preliminary observations of increased diffusional kurtosis in human brain following recent cerebral infarction. *NMR Biomed* 24:452–457
- Jeurissen B, Leemans A, Tournier JD, Jones DK, Sijbers J (2012) Investigating the prevalence of complex fiber configurations in white matter tissue with diffusion magnetic resonance imaging. *Hum Brain Mapp*. doi:10.1002/hbm.22099
- Johansen-Berg H, Della-Maggiore V, Behrens TEJ, Smith SM, Paus T (2007) Integrity of white matter in the corpus callosum correlates with bimanual co-ordination skills. *Neuroimage* 36:T16–T21
- Jones DK, Basser PJ (2004) “Squashing peanuts and smashing pumpkins”: how noise distorts diffusion-weighted MR data. *Magn Reson Med* 52:979–993
- Jones DK, Leemans A (2011) Diffusion tensor imaging. *Methods Mol Biol* 711:127–144
- Kärger J (1985) Nmr self-diffusion studies in heterogeneous systems. *Adv Colloid Interface Sci* 23:129–148
- Kiselev VG, Il'yasov KA (2007) Is the “biexponential diffusion” bilinear? *Magn Reson Med* 57:464–469
- Lancaster JL, Woldorff MG, Parsons LM, Liotti M, Freitas ES, Rainey L, Kochunov PV, Nickerson D, Mikiten SA, Fox PT (2000) Automated Talairach Atlas labels for functional brain mapping. *Hum Brain Mapp* 10:120–131
- Lancaster JL, Tordesillas-Gutierrez D, Martinez M, Salinas F, Evans A, Zilles K, Mazziotta JC, Fox PT (2007) Bias between MNI and talairach coordinates analyzed using the ICBM-152 brain template. *Hum Brain Mapp* 28:1194–1205
- Lazar M, Jensen JH, Xuan L, Helpert JA (2008) Estimation of the orientation distribution function from diffusional kurtosis imaging. *Magn Reson Med* 60:774–781
- Le Bihan D, Mangin JF, Poupon C, Clark CA, Pappata S, Molko N, Chabriet H (2001) Diffusion tensor imaging: concepts and applications. *J Magn Reson Imaging* 13:534–546
- Leemans A, Jones DK (2009) The B-matrix must be rotated when correcting for subject motion in DTI data. *Magn Reson Med* 61:1336–1349
- Leemans A et al (2009) ExploreDTI: A graphical toolbox for processing, analyzing, and visualizing diffusion MR data. In: 17th annual meeting of Intl Soc Mag Reson Med, p 3537. Hawaii, USA
- Liu CL, Bammer R, Acar B, Moseley ME (2004) Characterizing non-Gaussian diffusion by using generalized diffusion tensors. *Magn Reson Med* 51:924–937
- Lu HZ, Jensen JH, Ramani A, Helpert JA (2006) Three-dimensional characterization of non-Gaussian water diffusion in humans using diffusion kurtosis imaging. *NMR Biomed* 19:236–247
- Maier SE, Mulkern RV (2008) Biexponential analysis of diffusion-related signal decay in normal human cortical and deep gray matter. *Magn Reson Imaging* 26:897–904
- Maier SE, Vajapeyam S, Mamata H, Westin CF, Jolesz FA, Mulkern RV (2004) Biexponential diffusion tensor analysis of human brain diffusion data. *Magn Reson Med* 51:321–330
- Minati L, Aquino D, Rampoldi S, Papa S, Grisoli M, Bruzzone MG, Maccagnano E (2007) Biexponential and diffusional kurtosis imaging, and generalised diffusion-tensor imaging (GDTI) with rank-4 tensors: a study in a group of healthy subjects. *Magn Reson Mater Phys* 20:241–253
- Mori S, Wakana S, Van Zijl PCM, Nagae-Poetscher LM (2005) MRI atlas of the human white matter. Elsevier, Amsterdam
- Muetzel RL, Collins PF, Mueller BA, Schissel AM, Lim KO, Luciana M (2008) The development of corpus callosum microstructure and associations with bimanual task performance in healthy adolescents. *Neuroimage* 39:1918–1925
- Mulkern RV, Haker SJ, Maier SE (2009) On high b diffusion imaging in the human brain: ruminations and experimental insights. *Magn Reson Imaging* 27:1151–1162
- Niendorf T, Dijkhuizen RM, Norris DG, Campagne MV, Nicolay K (1996) Biexponential diffusion attenuation in various states of brain tissue: implications for diffusion-weighted imaging. *Magn Reson Med* 36:847–857
- Oldfield RC (1971) Assessment and analysis of handedness—Edinburgh inventory. *Neuropsychologia* 9:97–113
- Pfefferbaum A, Rosenbloom MJ, Adalsteinsson E, Sullivan EV (2007) Diffusion tensor imaging with quantitative fibre tracking in HIV infection and alcoholism comorbidity: synergistic white matter damage. *Brain* 130:48–64
- Poot DHJ, den Dekker AJ, Achten E, Verhoye M, Sijbers J (2010) Optimal experimental design for diffusion kurtosis imaging. *IEEE Trans Med Imaging* 29:819–829
- Preilowski B (1972) Possible contribution of anterior forebrain commissures to bilateral motor coordination. *Neuropsychologia* 10:267–277
- Qiu MG, Darling WG, Morecraft RJ, Ni CC, Rajendra J, Butler AJ (2011) White matter integrity is a stronger predictor of motor function than BOLD response in patients with stroke. *Neurorehabil Neural Repair* 25:275–284
- Raab P, Hattingen E, Franz K, Zanella FE, Lanfermann H (2010) Cerebral gliomas: diffusional kurtosis imaging analysis of microstructural differences. *Radiology* 254:876–881
- Raz E, Bester M, Sigmund EE, Tabesh A, Babb JS, Jaggi H, Helpert J, Mitnick RJ, Inglese M (2013) A better characterization of

- spinal cord damage in multiple sclerosis: a diffusional kurtosis imaging study. *Am J Neuroradiol*. doi:[10.3174/ajnr.A3512](https://doi.org/10.3174/ajnr.A3512)
- Rosenkrantz AB, Sigmund EE, Johnson G, Babb JS, Mussi TC, Melamed J, Taneja SS, Lee VS, Jensen JH (2012) Prostate cancer: feasibility and preliminary experience of a diffusional kurtosis model for detection and assessment of aggressiveness of peripheral zone cancer. *Radiology* 264:126–135
- Schaechter JD, Fricker ZP, Perdue KL, Helmer KG, Vangel MG, Greve DN, Makris N (2009) Microstructural status of ipsilesional and contralesional corticospinal tract correlates with motor skill in chronic stroke patients. *Hum Brain Mapp* 30:3461–3474
- Schulte T, Sullivan EV, Muller-Oehring EM, Adalsteinsson E, Pfefferbaum A (2005) Corpus callosal microstructural integrity influences interhemispheric processing: a diffusion tensor imaging study. *Cereb Cortex* 15:1384–1392
- Serrien DJ, Nirkko AC, Wiesendanger M (2001) Role of the corpus callosum in bimanual coordination: a comparison of patients with congenital and acquired callosal damage. *Eur J Neurosci* 14:1897–1905
- Shelton FDAP, Reding MJ (2001) Effect of lesion location on upper limb motor recovery after stroke. *Stroke* 32:107–112
- Sisti HM, Geurts M, Clerckx R, Gooijers J, Coxon JP, Heitger MH, Caeyenberghs K, Beets IAM, Serbruyns L, Swinnen SP (2011) Testing multiple coordination constraints with a novel bimanual visuomotor task. *Plos One* 6:e23619
- Sisti HM, Geurts M, Gooijers J, Heitger MH, Caeyenberghs K, Beets IAM, Serbruyns L, Leemans A, Swinnen SP (2012) Microstructural organization of corpus callosum projections to prefrontal cortex predicts bimanual motor learning. *Learn Mem* 19: 351–357
- Song F, Zhang F, Yin DZ, Hu YS, Fan MX, Ni HH, Nan XL, Cui X, Zhou CX, Huang CS, Zhao Q, Ma LH, Xu YM, Xia QJ (2012) Diffusion tensor imaging for predicting hand motor outcome in chronic stroke patients. *J Int Med Res* 40:126–133
- Steiger JH (1980) Tests for comparing elements of a correlation matrix. *Psychol Bull* 87:245–251
- Sullivan EV, Adalsteinsson E, Hedehus M, Ju C, Moseley M, Lim KO, Pfefferbaum A (2001) Equivalent disruption of regional white matter microstructure in ageing healthy men and women. *NeuroReport* 12:99–104
- Szczepankiewicz F, Latt J, Wirestam R, Leemans A, Sundgren P, Van Westen D, Stahlberg F, Nilsson M (2013) Variability in diffusion kurtosis imaging: impact on study design, statistical power and interpretation. *Neuroimage* 76:145–154
- Tournier JD, Calamante F, Connelly A (2007) Robust determination of the fibre orientation distribution in diffusion MRI: non-negativity constrained super-resolved spherical deconvolution. *Neuroimage* 35:1459–1472
- Tournier JD, Mori S, Leemans A (2011) Diffusion tensor imaging and beyond. *Magn Reson Med* 65:1532–1556
- Trampel R, Jensen JH, Lee RF, Kamenetskiy I, McGuinness G, Johnson G (2006) Diffusional kurtosis imaging in the lung using hyperpolarized ³He. *Magn Reson Med* 56:733–737
- Van Cauter S, Veraart J, Sijbers J, Peeters RR, Himmelreich U, De Keyser F, Van Gool SW, Van Calenbergh F, De Vleeschouwer S, Van Hecke W, Sunaert S (2012) Gliomas: diffusion kurtosis mr imaging in grading. *Radiology* 263:492–501
- Vanhoutte G, Pereson S, Delgado y Palacios R, Guns P, Asselbergh B, Veraart J, Sijbers J, Verhoye M, Van Broeckhoven C, Van der Linden A (2013) Diffusion kurtosis imaging to detect amyloidosis in an APP/PS1 mouse model for Alzheimer's Disease. *Magn Reson Med* 69:1115–1121
- Veraart J, Poot DHJ, Van Hecke W, Blockx I, Van der Linden A, Verhoye M, Sijbers J (2011) More accurate estimation of diffusion tensor parameters using diffusion kurtosis imaging. *Magn Reson Med* 65:138–145
- Veraart J, Rajan J, Peeters RR, Leemans A, Sunaert S, Sijbers J (2012) Comprehensive framework for accurate diffusion MRI parameter estimation. *Magn Reson Med*. doi:[10.1002/mrm.24529](https://doi.org/10.1002/mrm.24529)
- Vos SB, Jones DK, Jeurissen B, Viergever MA, Leemans A (2012) The influence of complex white matter architecture on the mean diffusivity in diffusion tensor MRI of the human brain. *Neuroimage* 59:2208–2216
- Wang JJ, Lin WY, Lu CS, Weng YH, Ng SH, Wang CH, Liu HL, Hsieh RH, Wan YL, Wai YY (2011) Parkinson disease: diagnostic utility of diffusion kurtosis imaging. *Radiology* 261: 210–217
- Wedeen VJ, Hagmann P, Tseng WYI, Reese TG, Weisskoff RM (2005) Mapping complex tissue architecture with diffusion spectrum magnetic resonance imaging. *Magn Reson Med* 54: 1377–1386