Structural and functional cortical disconnection in Alzheimer's disease: A combined study using diffusion tensor imaging and transcranial magnetic stimulation

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ABSTRACT

We investigated the functional consequences of compromised white matter integrity in Alzheimer's disease by combining Diffusion Tensor Imaging (DTI) and Transcranial Magnetic Stimulation (TMS) in 19 patients with AD (Alzheimer's disease) and 19 healthy controls. We used a region of interest approach and correlated the ipsilateral silent period (ISP) and the resting motor threshold (RMT) from TMS with fractional anisotropy (FA) and mean diffusivity (MD) values of the corpus callosum and corticospinal tract. AD patients showed significant reductions of FA in intracortical projecting fibre tracts compared to controls and widespread increases in MD. TMS data showed increased latency of ISP in AD patients and a decreased RMT, indicating decreased motor cortical inhibition. Although both TMS and DTI metrics were prominently altered in AD patients, impaired white matter integrity was not associated with increased ISP latency or reduced RMT, as correlation of TMS parameters with FA and MD values in the a priori defined regions showed no significant effects. Therefore, we argue that the direct degeneration of the underlying fibre tracts, other pathophysiological mechanisms may account for the observation of decreased transcallosal inhibition and increased motor excitability in AD.

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1. Introduction

Alzheimer's disease (AD) is characterised by grey matter (GM) as well as white matter (WM) pathology (Brun and Englund, 1986; Bartzokis et al., 2003). Decreased axonal and dendritic integrity of white matter tracts has also been reported in AD (Brun and Englund, 1986; Kowall and Kosik, 1987) and can be measured by Diffusion Tensor Imaging (DTI) (Rose et al., 2000; Bozzali and Cherubini, 2007). DTI provides a measure of fibre tract integrity through fractional anisotropy (FA) and of mean diffusivity (MD), indicating the absolute amount of barriers to water diffusivity (Le Bihan et al., 2001). A number of studies have shown that FA is reduced in AD compared to controls in the cingulate cortex, hippocampus, corpus callosum and white matter of temporal, frontal and parietal lobes (Rose et al., 2000; Huang et al., 2007; Teipel et al., 2007). The measure of mean diffusivity has been recently shown to be among the most altered metrics in AD (Agosta et al., 2011; Pievani et al., 2010). Besides widespread decrease of fibre tract integrity, preserved (Rose et al., 2000) or even increased (Teipel et al., 2007) FA in the pyramidal and extrapyramidal system has been reported in AD, possibly due to disintegration of crossing fibres (Teipel et al., 2007).

Transcranial Magnetic Stimulation (TMS) is a tool for investigating patterns of functional connectivity (Ilmoniemi et al., 1997; Pascual-Leone et al., 1998) and can be used to test different facilitatory and inhibitory circuits in the brain (Chen et al., 2008). Furthermore, it is a powerful tool to investigate non-invasively transcallosal pathways in humans (Meyer et al., 1995). Several experimental approaches using TMS have provided strong evidence that transcallosal connections have mainly inhibitory effects. In normal subjects, firstly Meyer et al. (1995) found a suppression of tonic voluntary electromyographic (EMG) activity in hand muscles ipsilateral to motor cortex stimulation, with a latency of about 30 ms and a duration of about 20 ms before the voluntary EMG activity returned to its original size. ISP is considered to reflect the functional integrity of the transcallosal fibres connecting corresponding motor cortices (Ferbert et al., 1992; Meyer et al., 1995), and it is thought to be mediated by excitatory transcallosal output neurons projecting to contralateral
inhibitory interneurons modulating the neuronal network, which consists of the primary motor cortex layer III – the origin of transcallosal motor fibres and contralateral cortex layer V – the origin of the pyramidal tract (Meyer et al., 1995).

The iSP has been reported to be increased in its latency or absent altogether in a number of neurodegenerative diseases (Hoepner et al., 1999, 2000; Wolters et al., 2004). ISP is correlated with atrophy of the corpus callosum (Wolters et al., 2004) and corpus callosum agenesis or hypoplasia (Meyer et al., 1995). It has been suggested as a diagnostic tool for callosal function (Chen et al., 2008). Corpus callosum atrophy is a well-established finding in AD (Yamauchi et al., 2000; Teipel et al., 2002), raising the question whether decline of iSP in AD is related to callosal atrophy.

The resting motor threshold (RMT) can be used as a measure of corticospinal excitability (Kobayashi and Pascual-Leone, 2003). A number of studies have shown reduced RMT in AD patients (Di Lazzaro et al., 2004; Pennisi et al., 2011). This finding is in line with increased excitability of motor cortical circuits frequently reported in AD (Pennisi et al., 2011; Di Lazzaro et al., 2004). Furthermore, the cortical silent period (CSP) and intracortical inhibition and facilitation are of particular interest in AD patients (Pennisi et al., 2011). CSP, however, is described to be reduced in more severe AD and some of the results are not yet consistent, most likely due to different methodologies for the measurement procedure of the CSP (Pennisi et al., 2011).

Despite a wealth of studies focusing on either DTI or TMS measures alone in AD, the question whether the structural disconnection measured by DTI. We tested two main hypotheses: (i) Decreased FA and increased MD of the corpus callosum are associated with an increased latency and reduced duration of the iSP, as a measure of callosal fibre integrity. (ii) Increased FA and decreased MD in corticospinal tracts are associated with a reduced RMT, indicating increased cortical excitability.

2. Methods

2.1. Subjects

Nineteen patients with AD and 19 healthy comparison subjects underwent TMS, MRI and DTI examinations as well as neuropsychological assessment. The mean ages of the AD and comparison group upon MRI were similar: 71.8 ± 4.7 (S.D.), and 69.2 ± 3.7 (S.D.) years (two-tailed t-test AD vs. control subjects: t9m = 1.930; P = 0.0611). The groups showed a similar gender distribution: 12 women and seven men in the AD group, and 10 women and nine men in the control group (Pearson chi square test: χ² = 0.43; df = 1; P = 0.51). Both groups differed in years of education [AD 11.0 ± 2.8 (S.D.); controls 14.1 ± 2.4 (S.D.); P < 0.001; Mann–Whitney U = 65.5].

The AD patients fulfilled the NINCDS–ADRDA criteria for clinically probable AD (McKhann et al., 1984). The “Mini Mental State Examination” (MMSE) was used to assess the degree of overall cognitive impairment (Folstein et al., 1975). The MMSE score ranged between 10 and 27 with an average of 21.7 ± 4.9 (S.D.) for the AD patients, and between 26 and 30 with an average of 28.6 ± 1.0 (S.D.) for the controls. Groups differed significantly in MMSE scores (P < 0.001; Mann–Whitney U = 3.5). Controls did not have cognitive complaints and scored within ±1.5 standard deviations from the age-adjusted mean in all subtests of the CERAD cognitive battery (Morris et al., 1989). All healthy control subjects received a Shulman score of 1 in the clock drawing test (Shulman et al., 1986). All subjects included in the present sample have also been included and described in Hoepner et al. (2011).

The time frame between performing the DTI and the TMS measurement was 19.3 days (S.D. = 55.1) with a range of 107 to 162 days for the AD group and 51.1 days (S.D. = 49.6). The mean age for performing the TMS was 11.7 years (S.D. = 4.5) with a range of 5 to 20 years. The selection process included a semi-quantitative rating of T2-weighted MRI scans (Scheltens et al., 1993). Only subjects without subcortical white matter hyperintensities exceeding 10 mm in diameter or of three or more in number, were included.

Patients and control individuals were only included in the study if written consent was given. The study was approved by the Institutional Review Board of the Medical Faculty, University of Rostock.

2.2. Transcranial magnetic stimulation

Left motor cortex stimulation was performed over the hand motor area with a focal 8-shaped coil (MagPro 100 with MagOption, Medtronic Inc., Minneapolis, MN, USA). The coil was placed with the handle held posteriorly, laterally at an angle of 45° to the sagittal plane (Werhahn et al., 1999).

The resting motor threshold (RMT) of the right FDI muscle contralateral to TMS was defined as the lowest stimulation intensity to produce an EMG response of at least 50 μV measured peak to peak in at least six out of 10 stimuli (Rossini and Rossi, 1998). The presence or absence of muscle activation was monitored by both auditory feedback and high-gain display of EMG amplifier signals. The position of the coil at the skull at which the RMT of the right FDI was minimal was defined as the point of optimal excitability (POE) and marked at the skull with an ink pen.

The POE for the left hemisphere was used to determine the iSP (in ms) for the left FDI (Meyer, 1992). Elicited electromyographic responses were recorded ipsilaterally from the first dorsal interosseous muscle (FDI) using surface electrodes with a belly-tendon montage. Electromyographic signals were amplified and filtered (20–1500 Hz) by “brain vision amplifier” (MES, Germany). Voluntary isometric force of thumb and forefinger flexion (precision grip) was measured by a strain gauge (range ± 10 N, nonlinearity < 1%). Visual feedback of the force signal was given by means of an oscilloscope to enable the required force level to be kept constant. The voluntary activation of the left FDI was maximal to each individual condition, and the stimulus output was kept at 1.5 × RMT (S-max stimulus intensity) for investigation of the iSP (Meyer, 1995, 1998; Hoepner et al., 1999, 2000). Ten stimuli were applied in each subject for both conditions. The electromyographical (EMG) responses were recorded and the data were analysed off-line using standard software (Brain Vision Analyzer, ME/GERMANY). The EMG activity was sampled, rectified and averaged over a 200 ms prestimulus and 200 ms poststimulus period. iSP was calculated offline as means of the average of 10 single sweeps.

The onset latency of iSP (in ms) was defined as the time interval from transcranial stimulation to decline of tonic EMG activity of more than 70% of mean EMG activity assessed over 100 ms prior to stimulation. ISP duration was measured from the onset of the above-defined decrease of tonic EMG activity to recurrence of mean prestimulus EMG activity. The presence of iSP was assumed when tonic voluntary EMG activity was decreased over a time period of at least 10 ms (Meyer et al., 1995, 1998; Roericht et al., 1997; Hoepner et al., 1999, 2000; Wolters et al., 2004; Buchmann et al., 2007). Latency and duration were automatically analysed by using Brain Vision Software (MES, Germany) and manually corrected after that to exclude artifacts (for details see: Hoepner et al., 1999, 2000; Buchmann et al., 2007).

2.3. MRI acquisition

MRI acquisitions of the brain were conducted using a 1.5-Tesla MRI scanner with a 12-channel phased-array head coil and parallel imaging capabilities (Magnetom Avanto, Siemens, Erlangen, Germany). Parallel imaging was performed with a generalised auto-calibrating partially parallel acquisition reconstruction algorithm and an acceleration factor of 2. Subjects were scanned in a single session without changing their position in the scanner. The following sequences were used.

We acquired a sagittal high-resolution T1-weighted magnetisation prepared rapidly acquired gradient echo (MPRAGE) 3D-sequence, matrix size of 256 x 256, field of view of 250 x 250 mm², 176 slices with slice thickness of 1.0 mm (reconstial voxel size 1.0 x 1.0 x 1.0 mm³). T2-weighted images of 2.51 ms/1100 ms/1900 ms, flip angle 150°.

To identify white matter lesions a two-dimensional T2-weighted sequence was performed (fluid attenuation inversion recovery FLAIR, matrix size of 384 x 187, field of view 172 x 230 mm². 24 slices with slice thickness of 5.0 mm (resulting voxel size 0.4 x 1.2 x 5.0 mm³). T2/FLAIR of 123 ms/2500 ms/9000 ms, flip angle 150°)

Diffusion-weighted imaging was performed with an echo-planar-imaging sequence (TE/TR 85 ms/1100 ms). Diffusion gradients were applied in 30 different spatial directions. The b values were 0 and 1000 s/mm². The images had a matrix size of 114 x 114 with a FOV of 230 x 230 mm², slice thickness of 2.0 mm and slice spacing of 2.4 mm; the resulting voxel size was 2.0 x 2.0 x 2.0 mm³. Forty axially oriented slices were acquired for each scan. The diffusion-weighted imaging had a narrow FOV which did not cover the whole brain, omitting superior frontal-parietal parts.
2.4. MRI data processing

DTI data were pre-processed using the DTI toolbox of the FSL software [http://www.fmrib.ox.ac.uk/fsl/], FMRIB, Oxford, UK, Version 4.1] (Smith et al., 2004). We first applied corrections for eddy currents and head motion. The skull was stripped using Brain Extraction Tool and the diffusion tensors were fitted to the data with DTIIfm (FMRIB Image Analysis Group, Oxford, UK).

We performed a deformation based analysis using SPM8 (Wellcome Department of Imaging Neuroscience, London, UK, http://www.fil.ion.ucl.ac.uk/spm) implemented in Matlab 7 (Mathworks, Natwick). Diffeomorphic image registration was implemented in the DARTEL toolbox in SPM8. MPRAKE scans, FA- and MD-maps were manually aligned to place the anterior commissure at the origin of the three-dimensional Montreal Neurological Institute (MINI) coordinate system.

Then, the DTI maps were affine aligned to the Magnetisation Prepared Rapid Gradient Echo (MPRAGE) scans. The MPRAGE images were segmented into grey matter and white matter maps (Ashburner and Friston, 2000). The resulting grey and white matter maps were used to create flow fields by iteratively registering the images with their average (Ashburner, 2007). The FA and MD maps were transformed to MNI space without modulation. We used a binary mask to exclude voxels outside of the white matter and smoothed the normalised masked FA and MD maps using a Gaussian kernel with 8 mm FWHM.

2.5. Statistical analysis

As all TMS parameters showed a normal distribution, which was tested by the use of Kolmogorov Smirnov test (P > 0.1), the means and standard deviations of each variable were calculated. Differences in TMS parameters were compared between groups using Student's t-test.

We investigated group differences in fractional anisotropy and mean diffusivity using the general linear model on a voxel basis. For FA and MD maps, we used an explicit WM mask and no normalisation. Whole brain analyses were performed at P < 0.05 for multiple comparisons and applying an exact threshold of 50 contiguous voxels. If this yielded no results, an uncorrected threshold of P < 0.001 was applied.

Initially, an analysis of the data using tract based spatial statistics (TBSS; Smith et al., 2006) part of FSL, was performed as whole brain group comparisons and as regression of TMS parameters onto the DTI maps, but results are not reported in favour of a region of interest approach.

For analysis of correlation between TMS values and DTI measures, we performed a region of interest (ROI) analysis using MarsBar (Brett et al., 2002) to extract mean values from corpus callosum and left and right corticospinal tract, respectively. We differentiated the corticospinal tract hemispherically, since we assumed that the effects may be related more strongly to the left hemisphere where the TMS pulse was applied. The regions were defined anatomically on the basis of the JHU white matter atlas (Hua et al., 2008) implemented in FSL. The corpus callosum ROI was manually refined to match with the sample’s DARTEL template and the corticospinal tract, as defined in the JHU tract probability atlas (threshold at 0.25), was slightly dilated to produce a smoother shape. The raw mean voxel values of each subject were extracted from these ROIs and correlated with the TMS data in SPSS.

3. Results

3.1. TMS results

AD patients revealed a mean iSP latency of 44.11 ± 6.4 ms (S.D.) which was significantly longer than that of the healthy controls [M = 38.58 ± 3.9 ms (S.D.)] (t96 = 3.196; P = 0.003). No differences were found for the iSP duration between the AD patients [M = 18.37 ± 5.97 ms (S.D.)] and control subjects [M = 16.05 ± 4.43 ms (S.D.)] (t96 = 1.357; P = 0.183). AD patients showed a significantly lower mean RMT [M = 52.95 ± 8.8 (S.D.) %-max. stimulator output] compared to controls [M = 59.21 ± 7.6 (S.D.) %-max. stimulator output] (t96 = -2.349; P = 0.024).

3.2. Group differences in fractional anisotropy and mean diffusivity

Fig. 1 shows the regions where AD patients exhibited a significantly reduced FA-value compared to healthy controls (P < 0.001, uncorrected). The fibre tract integrity in AD was reduced in intracortical projecting pathways, including the inferior fronto-occipital fasciculus, superior longitudinal fasciculus, anterior thalamic radiation, genu of corpus callosum, cingulate and fornix. Fig. 2 shows regions of significantly increased mean diffusivity in AD patients as compared to healthy controls (P < 0.001, uncorrected) covering the same main fibre tracts as FA, but with a much broader spatial distribution.

There was no significant increase of FA or significant decrease of MD in AD patients compared to healthy controls at a corrected P-value of 0.05 or an uncorrected P-value of 0.001.

3.3. Correlation of TMS parameters with DTI measures

For estimating the correlation of TMS parameters with fibre tract integrity, first whole-brain analyses for the correlation of iSP latency and RMT with FA and MD at P < 0.05 corrected for multiple comparisons were compared to compute specificity of our subsequent region of interest analyses. Since there were no significant voxels at this threshold, we then extracted the mean values of FA and MD from our anatomically defined regions of interest. We determined correlations between iSP latency and FA and MD values in the corpus callosum and between RMT and FA and MD values in the corticospinal tract (left and right side analysed separately).

iSP duration was not considered for these analyses, as it did not exhibit significant group differences.

The mean values of FA in the corpus callosum did significantly differ between groups [AD patients 0.333 ± 0.02 (S.D.); controls 0.348 ± 0.02 (S.D.); t96 = -2.126; P = 0.040], as did the mean MD values [AD patients 0.00629 ± 0.00003 (S.D.); controls 0.00595 ± 0.000019 (S.D.); t96 = 4.272; P < 0.001]. Correlations between DTI parameters and iSP latency did not reach significance (all P > 0.4). We compared the correlation coefficients by converting them into Z-scores and using these values to calculate a Z-score of the differences which can be used to estimate the P-value, but differences between correlation coefficients in FA or MD did not reach significance (both P > 0.4) (Fig. 3).

The mean values of FA in the left CST did not significantly differ between groups [AD 0.416 ± 0.02 (S.D.); Controls 0.419 ± 0.02 (S.D.); Mann-Whitney-U = 179.0; P = 0.965], nor did mean values of MD [AD 0.006645 ± 0.00004 (S.D.); Controls 0.006065 ± 0.00005 (S.D.); Mann-Whitney-U = 1384.8; P = 0.175]. Correlations between DTI parameters and RMT did not reach significance (all P > 0.3) (Fig. 4).

The mean values of FA in the right CST did not significantly differ between groups [AD 0.397 ± 0.03 (S.D.); Controls 0.403 ± 0.03 (S.D.); Mann-Whitney-U = 776.0; P = 0.895], while mean MD values showed a tendency of higher MD values in the AD group which failed to reach significance [AD 0.006058 ± 0.00005 (S.D.); Controls 0.006068 ± 0.00005 (S.D.); Mann-Whitney-U = 1974.6; P = 0.056]. Correlations between DTI parameters and RMT did not reach significance (all P > 0.4) (Tables 1 and 2).

4. Discussion

In this study, we used DTI and TMS to determine the relationship between compromised white matter integrity and changes in cortical excitability. We found reduced FA in intracortical projecting pathways in AD, indicative of structural disconnection. Of note, MD values increased in AD were spatially more extended than were changes in FA values. Additionally, functional connectivity was altered in AD, with increased iSP latency and decreased RMT in TMS. Although TMS and DTI findings were both in accordance with the hypothesis of motor hyperexcitability and transcallosal disconnection in AD patients, we were not able to show the predicted relationships between DTI and TMS measures in the expected areas, namely corpus callosum and corticospinal tract.
We expected a negative relationship of FA and iSP latency, so that reduced fibre tract integrity would lead to a longer latency, but no significant results were found, which also hold true of the MD data.

For the corticospinal tract and RMT we expected a negative relationship with fibre tract integrity, so that a higher FA would be associated with a lower threshold, indicating a disinhibition in AD due to loss of fibres crossing the corticospinal tract. We also expected that the relationship of DTI measures and RMT would be larger in the left CST, as the TMS pulses were applied over the left motor cortex, but these assumptions were not confirmed by the data.

The pattern of reduced FA and increased MD in our analysis agrees with studies reporting significantly reduced FA in corpus callosum, anterior and posterior cingulate, hippocampus, superior longitudinal fascicle and frontal and temporal lobe white matter (Rose et al., 2000; Huang et al., 2007; Teipel et al., 2007). The similar, but stronger alteration of mean diffusivity in our patient group confirms results of recent studies (e.g. Agosta et al., 2011; Pievani et al., 2010). We were not able to reproduce the findings of increased fractional anisotropy in extracortical projecting pathways (Teipel et al., 2007), which we expected due to a combination of relatively well preserved pyramidal tracts (Rose et al., 2000; Ito, 2008) with a loss of crossing fibres (Douaud et al., 2010). This negative finding may be due to the univariate approach in the present study, as opposed to the multivariate approach previously used (Teipel et al., 2007). While it may seem counter-intuitive to focus on a region which is reported to be relatively preserved in AD, it has been recently acknowledged that there is a benefit in looking at regions where intact and affected fibre tracts are crossing, in order to measure early alterations of white matter that may not be detectable when looking at a fibre tract in isolation (Douaud et al., 2010).

Our TMS finding of decreased RMT is in accordance with previous reports. Increased motor cortex excitability has been reported in TMS studies even in AD patients presenting with no extrapyramidal or pyramidal signs (Pennisi et al., 2011; Di Lazzaro et al., 2004).

To our knowledge there is only one study investigating the interhemispheric inhibition in AD patients (Khedr et al., 2011). Contrary to our results, a significantly prolonged duration has been described. The differences to our results could be explained by methodological differences in iSP-measurements. In our study in mild to moderate affected AD patients a significantly longer iSP-latency was found, which indicates that the beginning of the inter-hemispheric inhibition is delayed in these patients. The prolonged iSP latency would agree with corpus callosum atrophy.
Fig. 2. Regions of significantly increased mean diffusivity in AD patients compared to healthy controls, $P < 0.001$, uncorrected; voxel extent threshold 50. Effects projected onto a normalised mean T1 image of the sample. Axial slices go from MNI coordinate $z = 25$ to $z = -30$ and are 5 mm apart in MNI space. Right of image is right of brain for axial and coronal slices.

Fig. 3. Correlations of mean values of fractional anisotropy and mean diffusivity in the corpus callosum with the iSP latency (ms). Left side of figure shows sample slice of the region of interest, extracted from the JHU white matter labels atlas and manually refined to match the DARTEL normalised mean T1 image of the sample. Left scatterplot shows correlation of fractional anisotropy with the iSP latency (ms) (AD, Pearson $R = 0.201$; $P = 0.409$; HC, Pearson $R = -0.076$; $P = 0.758$; difference between correlation coefficients, $Z = 0.792$; $P = 0.428$). Right scatterplot shows correlation of mean diffusivity with iSP latency (ms) (AD, Pearson $R = -0.167$; $P = 0.494$; HC, Pearson $R = -0.047$; $P = 0.848$); MD values on x-axis multiplied by $10^3$ for better readability AD, Alzheimer’s disease; HC, healthy controls; FA, fractional anisotropy, MD, mean diffusivity; iSP, ipsilateral silent period.
in AD (Yamauchi et al., 2000; Teipel et al., 2002), as the iSP is a measure of interhemispheric motor inhibition (Giovannelli et al., 2009) and the corpus callosum provides the morphological basis for inter-hemispheric connectivity (Meyer et al., 1995; Hoeppner et al., 1999, 2000; Wolters et al., 2004).

Only a few studies so far have investigated the relationship between TMS and DTI measures, and to our knowledge there is no other published study on combined DTI and TMS findings in AD. There are known relationships of iSP duration and FA of the corpus callosum in child development (Koerte et al., 2009) and of transcallosally mediated interhemispheric inhibition and the FA of callosal motor fibres in healthy subjects (Wahl et al., 2007). Two studies report findings linking decreased FA values of the corticospinal tract with impaired motor cortex excitability in neurological disorders (Yoo et al., 2008; Lindberg et al., 2007).

There were no significant associations between TMS and DTI parameters in our study, therefore our results can only serve to generate, but not to support or refute, hypotheses on the underlying substrate of motor cortex excitability and transcallosal inhibition. The lack of significant findings may also be related to a number of methodological limitations of our study: DBM analyses suffer from imperfect registration problems and may lead to artefactual results due to partial volume effects, even using the DARTEL-approach of high-dimensional normalisation (Smith et al., 2006). Also, the choice of smoothing kernel size for FA data has to be chosen rather arbitrarily, since its impact on the data is still poorly understood (Smith et al., 2006). Another limitation was that the time elapsed between DTI and TMS was often too long and has exceeded two months for five AD patients. This likely has increased the error variance and obscured correlations between DTI and TMS parameters that are due to disease progression.

Lack of significant findings may also point to alternative mechanisms underlying structural correlates of TMS measures. Synaptic degenerations of GABAergic inhibitory interneurones rather than only structural fibre deficits need to be discussed, since inhibitory gabaergic dysfunction may affect the complex balance of cortical excitability in AD patients (Pennisi et al., 2011). In addition, dopamine neurotransmission could be involved, since in AD patients, a strong correlation was found between reduced FA values of the corpus callosum in child development (Yoo et al., 2008; Lindberg et al., 2007). Two studies report findings linking decreased FA values of the corticospinal tract with impaired motor cortex excitability in neurological disorders (Yoo et al., 2008; Lindberg et al., 2007).

Most of the studies investigating the RMT in AD patients discuss a neuronal degeneration as the underlying pathophysiological mechanism (Pennisi et al., 2011). In detail, it was assumed that the decrease of RMT might be compensatory to the loss of motor cortex neurons (Pepin et al., 1999; Ferreri et al., 2003). The reduction of the RMT was not affected by a treatment with cholinesterase inhibitors (Pennisi et al., 2002), which suggests that treatment did not influence the neurophysiological progression of AD. Since previous TMS investigations did not find correlations between the RMT and intracortical inhibition (ICI, a marker of GABA-A activity) or short-latency afferent inhibition (SAI, a marker of cholinergic activity), the reduced RMT does not.
posterior commissure line (positive, superior); AD, Alzheimer’s disease; HC, superior to inferior distance relative to the anterior commissure (positive, anterior); z, anterior to posterior distance relative to the anterior commissure (positive, anterior); x, the medial to lateral distance relative to midline (positive, right hemisphere); y, the anterior to posterior distance relative to the anterior commissure line (positive, superior); AD, Alzheimer’s disease; HC, healthy control; MNI, Montreal Neurologic Institute.

Decrease in Fractional Anisotropy (FA) values in the AD patient group compared to healthy controls. The height threshold was set at P < 0.001, uncorrected for multiple comparisons. The cluster extension, representing the number of contiguous voxels passing the height threshold was set at > 50. Coordinates delineate a cluster and the peak T value (36 degrees of freedom) within the cluster. x, the medial to lateral distance relative to midline (positive, right hemisphere); y, the anterior to posterior distance relative to the anterior commissure line (positive, superior); z, superior to inferior distance relative to the anterior commissure-posterior commissure line (positive, superior); AD, Alzheimer’s disease; HC, healthy control; MNI, Montreal Neurologic Institute.

Increase in Mean Diffusivity (MD) values in the AD patient group compared to healthy controls. The height threshold was set at P < 0.001, uncorrected for multiple comparisons. The cluster extension, representing the number of contiguous voxels passing the height threshold was set at > 50. Coordinates delineate a cluster and the peak T value (36 degrees of freedom) within the cluster. x, the medial to lateral distance relative to midline (positive, right hemisphere); y, the anterior to posterior distance relative to the anterior commissure line (positive, superior); AD, Alzheimer’s disease; HC, healthy control; MNI, Montreal Neurologic Institute.

Unrelated reference

Freitas et al. (2011).

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