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DTI detects water diffusion abnormalities in the thalamus that correlate with an extremity pain episode in a patient with multiple sclerosis ☆

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ABSTRACT

Background: Various types of multiple sclerosis (MS) related pain have been discussed. One concept is that deafferentation secondary to lesions in the spino-thalamo-cortical network can cause central pain. However, this hypothesis is somehow limited by a lack of a robust association between pain episodes and sites of lesion location.
Objective: We tested the hypothesis that temporary tissue alterations in the thalamus that are not detectable by conventional magnetic resonance imaging (T1w, FLAIR) can potentially explain a focal, paroxysmal central pain episode of a patient with MS. For microstructural tissue assessment we employed ten longitudinal diffusion tensor imaging (DTI) examinations.
Results: We could demonstrate an abnormal, unilateral *temporary* increase of the fractional anisotropy (FA) in the thalamus contralateral to the affected body side. Before the pain episode and after pain relief the FA reached completely normal values as seen in identically investigated age and gender matched 100 healthy control subjects.
Conclusion: These findings suggest that: i.) frequently applied and *quantitatively* evaluated DTI could be used as a sensitive imaging technique for detection of pathological processes associated with MS not detectable with conventional imaging strategies, ii.) temporary pathological processes in the "normal-appearing" thalamus may explain waxing and waning symptoms like episodes of central pain, and iii.) cross-sectional case examinations on (MS) patients with central pain should be performed to investigate how often thalamic alterations occur together with central pain.

1. Introduction

Structural magnetic resonance imaging (MRI) is the most commonly used neuro-radiological tool in addition to clinical and laboratory data for diagnosis and monitoring of multiple sclerosis (MS), and has emerged as a key surrogate measure for treatment outcomes in clinical trials (Filippi et al., 2012). Because MS has been classically regarded as an inflammatory, demyelinating condition that primarily affects white matter (WM) tracts, the main focus of conventional MRI lies usually on WM plaques (lesions) that occur as signal hyperintensities on T2-weighted images. However, recent studies provide growing evidence of gray matter (GM) involvement in MS, e.g. GM atrophy having a predictive value for development of MS after clinically isolated syndromes (CIS) (Batista et al., 2012; Ceccarelli et al., 2008; Houtchens et al., 2007; Khaleeli et al., 2007; Mesaros et al., 2011; Neema et al., 2009; Rocca et al., 2010; Vercellino et al., 2009; Zivadinov et al., 2012). It has been shown, for example, that selective GM atrophy is relevant in patients with CIS who convert early to MS (Calabrese et al., 2011).

Despite the fast-paced development of imaging techniques there is still a lack of robust association between relapses, clinical symptoms, and sites of lesion location (Svendsen et al., 2011). In addition, methods to detect neurodegeneration or neuroprotection during the disease course in daily practice or clinical studies are still limited.

The microscopic spatial sensitivity of diffusion tensor imaging (DTI) might be one approach to bridge this gap due to its potential to *quantitatively* differentiate apparently normal brain tissue on conventional MRI (T1w, T2w, FLAIR) into tissue with normal and conspicuous water diffusion behavior (Deppe et al., 2007). DTI has recently been applied successfully to quantify structural WM disintegration in a neuroprotection study (Duning et al., 2011) and is capable to detect functionally relevant neurodegeneration even if conventional MRI is inconspicuous (Deppe et al., 2008; Stubbe-Dräger et al., 2012; Duning et al., 2010). These quantitative characteristics of DTI and the ability to detect functionally relevant microscopic alterations in "normal appearing" brain tissue (Reilmann et

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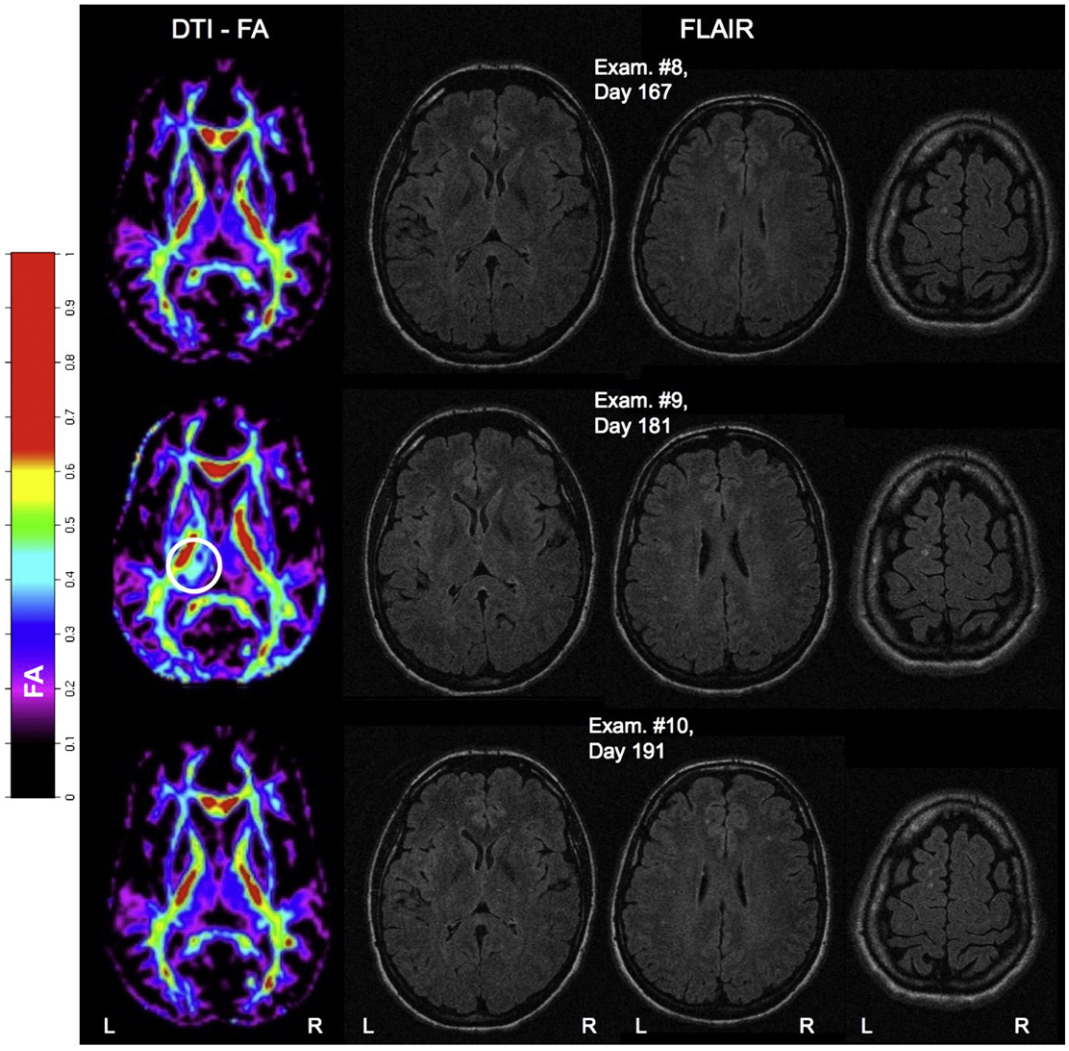

Fig. 1. Comparison of DTI (column 1) and FLAIR MRI (columns 2–4). The slices were taken on examination #8 (row 1), #9 (row 2), and #10 (row 3). The slice position of the FA image almost corresponds to the FLAIR section shown in column 2. While the FA image taken on examination 9 demonstrates increased FA in the left thalamus (white circle) during the episode of central pain, the corresponding FLAIR (column 2, row 2) appears completely inconspicuous. The three FLAIR slices include all lesions found in the patient's brain, including brain stem and whole spinal cord. The latter was imaged separately.

al., in press) promote DTI as an ideal tool for the clinical routine as well as for longitudinal studies on neurodegeneration and neuroprotection. The objective of the present study was to exploit this new imaging technique to investigate the origin of a pain episode in a patient with multiple sclerosis considered as central pain and to test the hypothesis whether the origin is associated with WM/GM plaques.

2. Methods

2.1. Patient

In context of a pilot examination for a clinical trial study[1] a 38-year-old female patient with early MS, diagnosed according to revised McDonald criteria (Polman et al., 2011), was admitted for MRI at 10 different time points (average inter-scan interval = 25.6 days +/− 13.1 days SD, total interval = 230 days), after obtaining written informed consent. The background of the pilot study was to examine the reproducibility of DTI parameters on MS patients. The patient presented with a first relapse of sensory symptoms of the left body side in 2011 and was diagnosed with relapsing remitting multiple sclerosis (RRMS) in 2012 according to McDonald criteria. At that time she showed dissemination in space (Swanton et al., 2006) and time in addition to oligoclonal bands, 6 lymphocytes/µl and intrathecal IgG production. This first relapse was contralateral (left) to the episode of central pain and sensory symptoms of the relapse described in the following. She was treated with immunomodulation (interferon ß 1a, once weekly i.m.) after the first relapse, and when she entered the series of DTI scans her expanded disability status scale (EDSS) was 2.0. Within the series of imaging scans she developed an episode of central pain and abnormal somatosensory and thermal sensations on the *right* hand side of her body. These symptoms occurred and disappeared simultaneously. Since this combination of symptoms developed over 2 days and remained for > 24 h we considered this episode as a relapse according to the international accepted definition of MS relapses. In addition, sensory symptoms and central pain very well responded to steroid therapy.

2.2. Control subjects

To prove the specificity and to quantitatively compare estimated diffusion parameters we compared the patient's data with data of identical DTI examinations, i.e. same scanner, same MRI sequences, same data analysis, of 100 well age matched healthy female control

[1] The background of the pilot study and the reason for the 10 consecutive MRI examinations was to examine the reproducibility of DTI parameters on MS patients. Similar reproducibility examinations have been performed on healthy control subjects.

subjects (mean age 38.05 y, SD 6.6 y, range 28 y–48 y). These subjects have been scanned in context of another, epidemiological study. The local ethics committee approved all examinations.

2.3. MR imaging acquisition

The patient underwent the longitudinal series of 10 DTI examinations in parallel to conventional imaging (T1w, FLAIR). All MRI scans were performed on a 3.0 T scanner (Gyroscan Intera T30, Philips Medical Systems, Best, The Netherlands) using a transmit–receive head coil. Slice orientation was reproduced as accurately as possible.

2.3.1. FLAIR

TE = 120 ms, optimized for lesion detectability at 3.0 T (Bachmann et al., 2006), TI = 2600 ms, TR = 11 s, slice thickness = 2 mm, no gap, FOV = 230 mm × 230 mm, image matrix = 512 × 512, number of slices = 54, voxel dimensions (X, Y, Z) = 0.449 mm × 0.449 mm × 2.5 mm.

2.3.2. DTI

Diffusion weighted images were acquired by using single-shot SE echo planar imaging (EPI) with 20 diffusion directions (two b-factors, 0 s/mm^2 and 1000 s/mm^2, TR = 9.8 s/TE = 95 ms, acquisition matrix = 128 × 128, voxel size = 1.8 mm × 1.8 mm × 3.6 mm (reconstructed to 2.0 mm × 2.0 mm × 2.0 mm for image processing), 2 averages, scanning time 7:46 min).

2.4. DTI data post-processing

All diffusion-weighted images were effectively corrected for eddy currents and head movements using a recently developed algorithm (Mohammadi et al., 2010) and a multi-contrast image registration algorithm for the optimum spatial pre-processing of DTI data (Mohammadi et al., 2012). The registration algorithm provided iterative multi-contrast registration steps based on FA contrasts and b0 contrasts (b = 0 s/mm^2). Prior to the iterative registration, the b0 EPI images were registered to the SPM EPI template using affine transformations. The multi-contrast registration was then iteratively applied to obtain normalized FA images. In addition to the FA we generated whole-brain maps of axial diffusivity (AD), radial diffusivity (RD), and mean diffusivity (MD). All registered diffusivity images corresponded to the MNI coordinate space. For quantitative analysis of the optimally spatially registered images, we generated ROIs for the left and right thalamus separately, from which mean values of FA, AD, RD, and MD were calculated (Fig. 2). These ROIs were automatically created on the output images from the registration toolbox for all patients and controls. All DTI image-processing steps (registration, eddy current correction, tensor estimation, diffusion parameter and ROI calculation) were performed in a fully automated processing pipeline ("Münster Neuroimaging Evaluation System" (EVAL)).

3. Results

During the longitudinal series of 10 MRI examinations, DTI #9 showed a remarkable obvious FA increase in the left thalamus (Fig. 1). This increase was further quantitatively investigated by a ROI analysis of thalamus FA in the 10 DTIs of the patient as well as in the 100 control subjects (Figs. 2 and 3). In the left and right thalamus ROIs the 100 control subjects had a mean FA value of 0.267 (SD: 0.016; range: 0.225–0.296; 95%-CI: 0.264–0.270, CV[2] = 6.0%) and 0.265 (SD: 0.015; range: 0.231–0.304; 95%-CI: 0.262–0.268, CV = 5.5%), respectively. The average FA over the first 8 images of the patient was 0.265 (SD: 0.004; range: 0.259–0.269; 95%-CI: 0.262–0.265, CV = 1.5%) for the left and 0.262 (SD: 0.005; range: 0.256–0.271; 95%-CI: 0.258–0.266, CV = 1.9%)

[2] CV = coefficient of variation = ratio of the standard deviation to the mean (×100%).

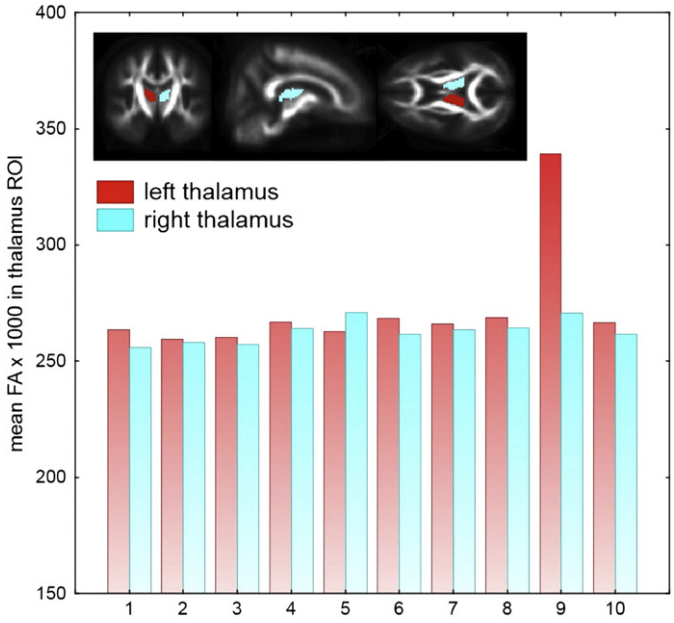

Fig. 2. Time course of mean FA in the left and right thalamus ROI over the 10 MRI examinations. The used two regions of interest (ROI) outlining the thalamus are overlaid to the employed FA template. The "outbreak" of thalamic FA occurred only in the left thalamus on examination #9 during the clinical episode of central pain.

for the right thalamus (Fig. 3) and thus well within the 95% confidence intervals for normal left and right thalamus FA. In the 9th image, which was acquired exactly during the clinical appearance of the episode of central pain in the right hand side of the body, the FA in the left ROI was increased significantly by 28% and far beyond the range of normal controls (FA(exam. #9, left) = 0.339, $p_{FA} < 0.00001$) while the right thalamus FA remained completely normal (FA(exam. 9, right) = 0.265, p = 0.69) (Figs. 1 and 2). After clinical amelioration the tenth DTI showed again completely normal FA in left and right thalamus (left 0.266, p = 0.99; right 0.262, p = 0.850). Left thalamus MD and AD were significantly increased in DTI #9 (+15.6%, $p_{MD} < 0.05$ and +25.4%, $p_{AD} < 0.005$) relative to the other 9 examinations. RD of DTI #9 showed only a tendency to increase (+9.9%, $p_{RD} = 0.18$). Of note, conventional imaging (FLAIR) failed to detect a thalamic lesion. White matter lesions could be detected on more superior FLAIR sections (Fig. 1, column 3 and 4). These lesions remained stable over all 10 MRI examinations.

4. Discussion

The main finding of the present case study is a temporary, local water diffusion affecting process in a MS patient's left thalamus that is correlated with an episode of central pain and sensory deficits of the contralateral body side. Changes in FA, AD, RD, or MD maps reflect alterations in local water diffusion but are not specific to any inflammatory or degenerative activity in the brain. Thus, they always must be interpreted in context of the clinical signs and the diagnosis of the patient. It is plausible (Chen et al., 2010; Quiton et al., 2010), but not a priori justified to assume, that in the present case the thalamic alteration plays a causative role. Potentially, the local diffusion change could be also a treatment effect. Up to now, the direct impact of corticosteroids on local tissue diffusion properties is not systematically investigated. Thus it cannot entirely be ruled out that the detected water diffusion alteration in the thalamus is an effect of corticosteroids. For example, Anneken et al. described a transient lesion in the splenium of an epilepsy patient that was related to antiepileptic medication (Anneken et al., 2008). This "lesion" *disappeared* in DTI as well as in conventional T1w and T2w images after the abrupt reduction of carbamazepine to half of the patient's regular dose. However, in the present case it would be far-fetched to explain a *directly related* effect of (any) medication that acts only on the left thalamus

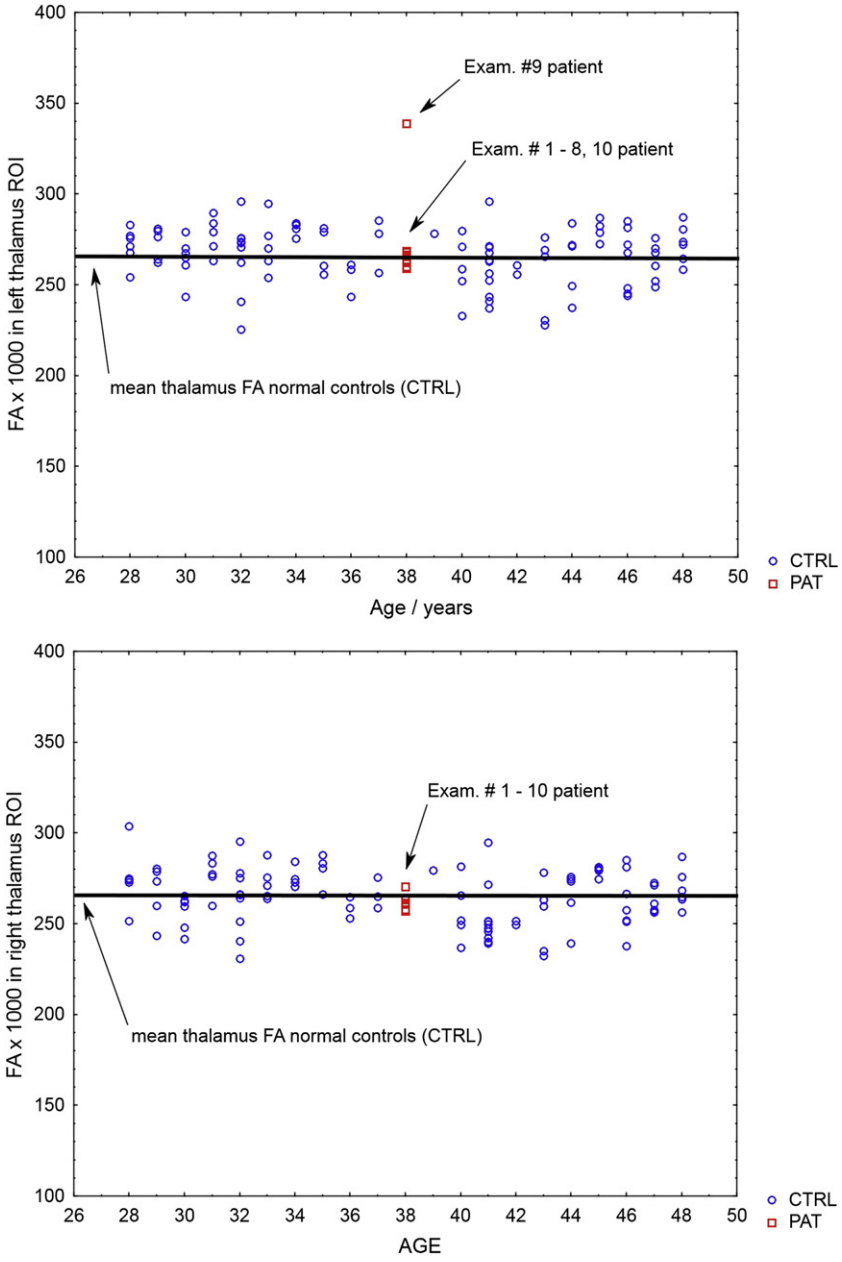

Fig. 3. Comparisons of thalamic left and right mean FA between the patient and 100 control subjects. Apart from one exception (left thalamus, exam. #9), the patient's thalamic FA was completely in the normal range. Each round symbol represents the mean FA in left or right thalamus of one examined control subject.

but not on the right one (Fig. 2). The strong temporal correlation of symptom on- and offset and the spatial congruency with the affected body side support a temporary pathological process in the thalamus as a more plausible explanation for the symptoms and DTI findings.

The thalamus plays not only a fundamental role in pain perception but also in processing of temperature, itch, and touch. Assuming a causative role of the thalamus here, it would not be surprising that the symptoms of central pain *and* sensory deficits of the right body side occurred and disappeared simultaneously after steroid treatment (Kim et al., 2007; LaBuda et al., 2000; Nandi et al., 2003). However, based on this interrelation it cannot be ruled out if actually both, the pain *and* the sensory deficits are caused by the thalamus.

Using voxel-based morphometry, previous studies suggest that thalamic degeneration is prominent even in the early course of the disease of RRMS and clinically isolated syndrome (CIS), and a direct relationship between white matter lesions and thalamic atrophy in CIS patients has been demonstrated recently (Henry et al., 2009). While decreased GM volumes suggest the presence of irreversible neuronal degeneration, microstructural tissue alterations as assessed by DTI can be interpreted as both, irreversible degeneration like axonal damage or temporary tissue alterations due to reversible processes like inflammation, edema or temporary changes of the blood–brain barrier (BBB).

Although the interpretation of DTI diffusivity parameters in GM is still a topic of debate, the massive FA increase in our patient was most probably due to an increase in axonal diffusivity, i.e. higher water mobility along the main diffusion direction and not due to restriction of water mobility orthogonal to the main direction.

It could be shown also in a different study that DTI is able to detect abnormalities in the thalamus of MS patients, even when conventional imaging techniques showed inconspicuous results (Tovar-Moll et al., 2009). In this study by Tovar-Moll and colleagues 24 MS patients showed higher thalamic FA and MD compared to 24 controls. The authors reported that the thalamic MD increase explained 55% of EDSS variance in their patients with RRMS. They also found a

trend between thalamic MD increase and the partial sensory score of the EDSS.

In our report the patient showed outside the pain episode FA and MD values in both thalami essentially *equivalent* to 100 age- and sex-matched controls. Parallel to the episode of central pain in the right hand side of the body, FA values of the contralateral left thalamus were increased by 28%, distinctly outside of the range of all 100 controls (Fig. 3, upper panel). This finding fits also to current hypotheses that central pain can be an important symptom in MS, which is putatively caused by pathological alterations in the spinothalamic tract (Osterberg et al., 2005) or in the spinothalamo-cortical network (Osterberg and Boivie, 2010).

A further, methodological point seems also noteworthy: the low *intra*- and *inter*-individual coefficients of variation of 1.9% and 5%, respectively, demonstrate that thalamic FA can be estimated to be highly reproducible by clinically suited DTI and a fully automated data processing pipeline. Thus, routine diffusion weighted MRI could principally provide sensitive structural markers for (pathological) tissue alterations not detectable by other non-invasive techniques. The high *intra*-individual reproducibility in combination with the low *inter*-individual variability of thalamic FA suggests cross-sectional case series on (MS) patients with central pain to investigate how frequent the thalamic alterations shown here can be found in patients with central pain.

5. Conclusion

We conclude from this report of a single case and 100 control subjects, that DTI offers a valuable and *quantitative* tool that might significantly add novel information to standard imaging techniques (T1w, FLAIR) in multiple sclerosis. The potential to detect the lesion location in paroxysmal symptoms like in a clinical episode of central pain seems appealing for the monitoring of the disease course; perhaps this technique might also offer a promising metric as marker of treatment response. Independent trials are warranted to prove these findings in larger cohorts of (MS) patients with central pain.

References

Anneken, K., Evers, S., Mohammadi, S., Schwindt, W., Deppe, M., 2008. Transient lesion in the splenium related to antiepileptic drug: case report and new pathophysiological insights. Seizure 17, 654–657.

Bachmann, R., Reilmann, R., Schwindt, W., Kugel, H., Heindel, W., Kramer, S., 2006. FLAIR imaging for multiple sclerosis: a comparative MR study at 1.5 and 3.0 Tesla. European Radiology 16, 915–921.

Batista, S., Zivadinov, R., Hoogs, M., Bergsland, N., Heininen-Brown, M., Dwyer, M.G., Weinstock-Guttman, B., Benedict, R.H., 2012. Basal ganglia, thalamus and neocortical atrophy predicting slowed cognitive processing in multiple sclerosis. Journal of Neurology 259 (1), 139–146.

Calabrese, M., Rinaldi, F., Mattisi, I., Bernardi, V., Favaretto, A., Perini, P., Gallo, P., 2011. The predictive value of gray matter atrophy in clinically isolated syndromes. Neurology 77, 257–263.

Ceccarelli, A., Rocca, M.A., Pagani, E., Ghezzi, A., Capra, R., Falini, A., Scotti, G., Comi, G., Filippi, M., 2008. The topographical distribution of tissue injury in benign MS: a 3 T multiparametric MRI study. NeuroImage 39, 1499–1509.

Chen, W.K., Liu, I.Y., Chang, Y.T., Chen, Y.C., Chen, C.C., Yen, C.T., Shin, H.S., Chen, C.C., 2010. Ca(v)3.2 T-type Ca2+ channel-dependent activation of ERK in paraventricular thalamus modulates acid-induced chronic muscle pain. Journal of Neuroscience 30, 10360–10368.

Deppe, M., Duning, T., Mohammadi, S., Schwindt, W., Kugel, H., Knecht, S., Ringelstein, E.B., 2007. Diffusion-tensor imaging at 3 T: detection of white matter alterations in neurological patients on the basis of normal values. Investigative Radiology 42, 338–345.

Deppe, M., Kellinghaus, C., Duning, T., Moddel, G., Mohammadi, S., Deppe, K., Schiffbauer, H., Kugel, H., Keller, S.S., Ringelstein, E.B., Knecht, S., 2008. Nerve fiber impairment of anterior thalamocortical circuitry in juvenile myoclonic epilepsy. Neurology 71, 1981–1985.

Stubbe-Dräger, B., Deppe, M., Mohammadi, S., Keller, S.S., Kugel, H., Gregor, N., Evers, S., Young, P., Ringelstein, E.B., Arendt, G., Knecht, S., Husstedt, I.W., 2012. Early microstructural white matter changes in patients with HIV: A diffusion tensor imaging study. BMC Neurology 12, 23. http://dx.doi.org/10.1186/1471-2377-12-23.

Duning, T., Kellinghaus, C., Mohammadi, S., Schiffbauer, H., Keller, S., Ringelstein, E.B., Knecht, S., Deppe, M., 2010. Individual white matter fractional anisotropy analysis on patients with MRI negative partial epilepsy. Journal of Neurology, Neurosurgery & Psychiatry 81, 136–139.

Duning, T., Schiffbauer, H., Warnecke, T., Mohammadi, S., Floel, A., Kolpatzik, K., Kugel, H., Schneider, A., Knecht, S., Deppe, M., Schabitz, W.R., 2011. G-CSF prevents the progression of structural disintegration of white matter tracts in amyotrophic lateral sclerosis: a pilot trial. PLoS One 6, e17770.

Filippi, M., Rocca, M.A., Barkhof, F., Bruck, W., Chen, J.T., Comi, G., DeLuca, G., De, S.N., Erickson, B.J., Evangelou, N., Fazekas, F., Geurts, J.J., Lucchinetti, C., Miller, D.H., Pelletier, D., Popescu, B.F., Lassmann, H., 2012. Association between pathological and MRI findings in multiple sclerosis. Lancet Neurology 11, 349–360.

Henry, R.G., Shieh, M., Amirbekian, B., Chung, S., Okuda, D.T., Pelletier, D., 2009. Connecting white matter injury and thalamic atrophy in clinically isolated syndromes. Journal of Neurological Sciences 282, 61–66.

Houtchens, M.K., Benedict, R.H., Killiany, R., Sharma, J., Jaisani, Z., Singh, B., Weinstock-Guttman, B., Guttmann, C.R., Bakshi, R., 2007. Thalamic atrophy and cognition in multiple sclerosis. Neurology 69, 1213–1223.

Khaleeli, Z., Cercignani, M., Audoin, B., Ciccarelli, O., Miller, D.H., Thompson, A.J., 2007. Localized grey matter damage in early primary progressive multiple sclerosis contributes to disability. NeuroImage 37, 253–261.

Kim, J.H., Greenspan, J.D., Coghill, R.C., Ohara, S., Lenz, F.A., 2007. Lesions limited to the human thalamic principal somatosensory nucleus (ventral caudal) are associated with loss of cold sensations and central pain. Journal of Neuroscience 27, 4995–5004.

LaBuda, C.J., Cutler, T.D., Dougherty, P.M., Fuchs, P.N., 2000. Mechanical and thermal hypersensitivity develops following kainate lesion of the ventral posterior lateral thalamus in rats. Neuroscience Letters 290, 79–83.

Mesaros, S., Rocca, M.A., Pagani, E., Sormani, M.P., Petrolini, M., Comi, G., Filippi, M., 2011. Thalamic damage predicts the evolution of primary-progressive multiple sclerosis at 5 years. AJNR. American Journal of Neuroradiology 32, 1016–1020.

Mohammadi, S., Keller, S.S., Glauche, V., Kugel, H., Jansen, A., Hutton, C., Floel, A., Deppe, M., 2012. The influence of spatial registration on detection of cerebral asymmetries using voxel-based statistics of fractional anisotropy images and TBSS. PLoS One 7, e36851.

Mohammadi, S., Moller, H.E., Kugel, H., Muller, D.K., Deppe, M., 2010. Correcting eddy current and motion effects by affine whole-brain registrations: evaluation of three-dimensional distortions and comparison with slicewise correction. Magnetic Resonance in Medicine 64, 1047–1056.

Nandi, D., Aziz, T., Carter, H., Stein, J., 2003. Thalamic field potentials in chronic central pain treated by periventricular gray stimulation — a series of eight cases. Pain 101, 97–107.

Neema, M., Arora, A., Healy, B.C., Guss, Z.D., Brass, S.D., Duan, Y., Buckle, G.J., Glanz, B.I., Stazzone, L., Khoury, S.J., Weiner, H.L., Guttmann, C.R., Bakshi, R., 2009. Deep gray matter involvement on brain MRI scans is associated with clinical progression in multiple sclerosis. Journal of Neuroimaging 19, 3–8.

Osterberg, A., Boivie, J., 2010. Central pain in multiple sclerosis — sensory abnormalities. European Journal of Pain 14, 104–110.

Osterberg, A., Boivie, J., Thuomas, K.A., 2005. Central pain in multiple sclerosis—prevalence and clinical characteristics. European Journal of Pain 9, 531–542.

Polman, C.H., Reingold, S.C., Banwell, B., Clanet, M., Cohen, J.A., Filippi, M., Fujihara, K., Havrdova, E., Hutchinson, M., Kappos, L., Lublin, F.D., Montalban, X., O'Connor, P., Sandberg-Wollheim, M., Thompson, A.J., Waubant, E., Weinshenker, B., Wolinsky, J.S., 2011. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Annals of Neurology 69, 292–302.

Quiton, R.L., Masri, R., Thompson, S.M., Keller, A., 2010. Abnormal activity of primary somatosensory cortex in central pain syndrome. Journal of Neurophysiology 104, 1717–1725.

Reilmann, R., Holtbernd, F., Bachmann, R., Mohammadi, S., Ringelstein, E.B., Deppe, M., in press. Grasping multiple sclerosis: do quantitative motor assessments provide a link between structure and function? Journal of Neurology. http://dx.doi.org/10.1007/s00415–012–6639–7 (Electronic publication ahead of print, http://www.ncbi.nlm.nih.gov/pubmed/22872165?dopt=AbstractPlus).

Rocca, M.A., Mesaros, S., Pagani, E., Sormani, M.P., Comi, G., Filippi, M., 2010. Thalamic damage and long-term progression of disability in multiple sclerosis. Radiology 257, 463–469.

Svendsen, K.B., Sorensen, L., Jensen, T.S., Hansen, H.J., Bach, F.W., 2011. MRI of the central nervous system in MS patients with and without pain. European Journal of Pain 15, 395–401.

Swanton, J.K., Fernando, K., Dalton, C.M., Miszkiel, K.A., Thompson, A.J., Plant, G.T., Miller, D.H., 2006. Modification of MRI criteria for multiple sclerosis in patients with clinically isolated syndromes. Journal of Neurology, Neurosurgery & Psychiatry 77, 830–833.

Tovar-Moll, F., Evangelou, I.E., Chiu, A.W., Richert, N.D., Ostuni, J.L., Ohayon, J.M., Auh, S., Ehrmantraut, M., Talagala, S.L., McFarland, H.F., Bagnato, F., 2009. Thalamic involvement and its impact on clinical disability in patients with multiple sclerosis: a diffusion tensor imaging study at 3 T. AJNR. American Journal of Neuroradiology 30, 1380–1386.

Vercellino, M., Masera, S., Lorenzatti, M., Condello, C., Merola, A., Mattioda, A., Tribolo, A., Capello, E., Mancardi, G.L., Mutani, R., Giordana, M.T., Cavalla, P., 2009. Demyelination, inflammation, and neurodegeneration in multiple sclerosis deep gray matter. Journal of Neuropathology and Experimental Neurology 68, 489–502.

Zivadinov, R., Brown, M.H., Schirda, C.V., Poloni, G.U., Bergsland, N., Magnano, C.R., Durfee, J., Kennedy, C., Carl, E., Hagemeier, J., Benedict, R.H., Weinstock-Guttman, B., Dwyer, M.G., 2012. Abnormal subcortical deep-gray matter susceptibility-weighted imaging filtered phase measurements in patients with multiple sclerosis: a case–control study. NeuroImage 59 (1), 331–339 (Jan 2).