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Originalartikel

Magnetic Resonance Imaging-Based Neuromorphometry in Single Patients – A Proposal for its Usefulness

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Abstract: The usefulness of MRI-based neuromorphometry for the investigation of single patients is described. A longitudinal cortical thickness analysis in a patient revealed lateral temporal lobe atrophy, suggesting rather semantic than frontotemporal dementia. A boy with the diagnosis of ADHD and control boys were compared and showed cortical thickness increases in the patient in the orbitofrontal cortex contradicting ADHD and suggesting disturbed social behaviour. The multiple synaesthetes E. S. was compared with control groups and showed hyperconnectivity between auditory and gustatory brain regions suggesting that interval-taste synaesthesia is rooted in anatomical alterations. McLeod syndrome patients were investigated and revealed severe atrophy of the caudate nucleus bilateral across time. Additionally, statistical recommendations for the comparison of MRI data of single patients are provided.

Keywords: Magnetic resonance imaging, neuromorphometry, grey matter, cortical thickness, fractional anisotropy, single patients, diagnosis, monitoring, semantic dementia, attention deficit hyperactivity disorder, disturbed social behaviour, synaesthesia, McLeod syndrome

Magnet-Resonanz-Tomographie-basierte Neuromorphometrie in einzelnen Patienten – ein Exposé für ihre Nützlichkeit

Zusammenfassung: Die Nützlichkeit MRT-basierter Neuromorphometrie zur Untersuchung einzelner Patienten wird beschrieben. Eine longitudinale, kortikale Dickeanalyse in einem Patient zeigte Atrophie im lateralen Temporallappen, welche eher eine semantische als eine frontotemporale Demenz suggeriert. Ein Knabe mit der Diagnose ADHS und Kontrollknaben wurden verglichen und der Patient zeigte erhöhte kortikale Dicke im orbitofrontalen Kortex. Dieser Befund spricht gegen ADHS und legt eher ein gestörtes Sozialverhalten nahe. Die multiple Synästhetin E. S. wurde mit zwei Kontrollgruppen verglichen und zeigte Hyperkonnektivität zwischen auditorischen und gustatorischen Hirnregionen, was nahelegt, dass ihre Interval-Geschmacks-Synaesthesie in diesen anatomischen Veränderungen wurzelt. Patienten mit McLeod-Syndrom wurden untersucht und zeigten starke Atrophie im Nucleus caudatus bilateral über die Zeit. Statistische Empfehlungen zum Vergleich von MRT-Daten von einzelnen Patienten werden zusätzlich gegeben.

Schlüsselwörter: Magnet-Resonanz-Tomographie, Neuromorphometrie, graue Substanz, kortikale Dicke, fraktionale Anisotropie, einzelne Patienten, Diagnose, Überwachung, semantische Demenz, Aufmersamkeitsdefizit-Hyperaktivitätsstörung, gestörtes Sozialverhalten, Synästhesie, McLeod Syndrom

Introduction

The functional and structural neuroimaging methodologies are powerful tools that are frequently used in basic and clinical neuroscientific research to investigate physiological and morphological features of the brain at different temporal and spatial scales. Typical structural brain imaging methods are the computer (assistant) tomography and magnetic resonance imaging (MRI). For the investigation of the brain at a system level, MRI is the preferred structural and functional neuroimaging methodology due to its non-invasive nature, good spatial resolution, broad applicability, and high availability. Commonly used structural MRI modalities in neuroscientific research are T1-weighted and diffusion-weighted images. T1-weighted pulse sequences provide informations about grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF) and are therefore well suited for the investigation of the cortical, subcortical, and cerebellar GM architecture (i. e. the neurons). T1-weighted MRI scans are characterised by high contrast-to-noise ratios of the different brain tissue types (GM, WM, CSF) and their spatial resolution (voxel-size) is in the range of 0.5 to 1.5 mm^3. Among the diffusion-weighted MRI techniques, diffusion tensor imaging (DTI) is the most frequently applied method and can be used to investigate

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the WM architecture (i.e. the fibre bundles). DTI scans encode information about the brain tissues' diffusion characteristics that can be used to gain information about the organisation and integrity of axonal fibres and their spatial resolution is in the range of 1.5 to 3.0 mm^3.

The most frequently reported measure of the GM architecture in the MRI literature is cortical volume, also referred to as cortical "density" or "concentration" in probabilistic morphometric approaches such as implemented in a classical voxel-based morphometry (VBM) analysis. Further frequently used measures are cortical thickness, cortical surface area, and subcortical volumes. Measurements of cortical curvature, cortical shape, and gyrification indices are less frequently reported. Morphological measures can be assessed at the global level (e.g. whole cortical GM, whole supratentorial WM, or whole subcortical GM), at the regional level (e.g. precentral gyrus, corpus callosum, or thalamus), at the subregional level (e.g. primary motor hand area, rostrum of corpus callosum, or corpus geniculatum laterale) and at the local level, also called voxel or vertex level, the smallest building elements of MRI-derived digital brain images.

There is a vast number of cross-sectional structural imaging studies in clinical research that revealed patterns of neuromorphological differences between patients and healthy control subjects (Baur et al., 2011; DaSilva, Granziera, Snyder & Hadjikhani, 2007; Etgen et al., 2005; Hänggi, Streffer, Jäncke & Hock, 2011) as well as in basic research that revealed anatomical alterations between experts and non-experts (Bengtsson et al., 2005; Bermudez, Lerch, Evans & Zatorre, 2009; Gaser & Schlaug, 2003; Hänggi, Koeneke, Bezzola & Jäncke, 2010; Jäncke, Koeneke, Hoppe, Rominger & Hänggi, 2009). In addition, longitudinal studies using computational neuromorphometric methods in healthy subjects revealed changes in brain structures as a result of learning and experience (Bezzola, Merillat, Gaser & Jäncke, 2011; Draganski et al., 2004; Draganski et al., 2006; Haier, Karama, Leyba & Jung, 2009; Scholz, Klein, Behrens & Johansen-Berg, 2009). Although there are no doubts about the usefulness of these methodologies when investigating samples of a given size, little is known about the power and usefulness of these methods for the investigation of single patients in isolation as well as in comparison with normative brain data.

Several reports exist in the literature that all used the method of VBM for the investigation of single patients. Mühlau and colleagues investigated 16 patients with Huntington disease (HD) and compared each of them separately (by means of independent sample t-tests with pooled variance estimates) with a control group of 133 healthy control subjects and found that 15 of 16 HD patients showed decreased GM density in the head of the caudate nucleus (Mühlau et al., 2009). In contrast, only 1 of 22 healthy control subjects who were pair-wise matched to the 16 HD patients with respect to age and gender showed decreased GM density in the head of the caudate nucleus when compared with the other 111 control subjects and this was the expected false positive rate when using a statistical height threshold of $p < 0.05$ (corrected). In another study, Colliot and colleagues investigated 27 patients with focal cortical dysplasia and compared each of them separately with 39 healthy matched control subjects (by means of z-score maps) and showed that VBM was able to detect focal cortical dysplasia in a majority of patients (Colliot et al., 2006). Additional encouraging findings when applying VBM in single patients were revealed for children with autism (Salmond, de Haan, Friston, Gadian & Vargha-Khadem, 2003) and in patients with semantic dementia (Mummery et al., 2000). However, in the presence of brain lesions with aberrant MRI signal intensities such as hypo- and hyperintensities the preprocessing steps of VBM (mainly spatial normalisation and tissue class segmentation) are adversely influenced by these lesions (Mehta, Grabowski, Trivedi & Damasio, 2003), although this problem is neither specific nor restricted to single patients VBM analyses.

Visual inspection is the neuroradiologists' method of choice when assessing brain images from single patients. Inspection often causes the vague impression of a "borderline finding" that cannot be interpreted in more detail because no statistical measures of the "suspicious brain region" are available (Mühlau et al., 2009). However, it is possible to apply statistics to imaging data of single patients compared with healthy control subjects by means of z-score transformations, one-sample t-tests, and two-sample t-tests with pooled variance estimates (Henson, 2006). In the present study, I try to further elucidate the usefulness of computational neuromorphometric procedures in the assessment of single patients and suppose how these imaging methods can support the radiologist's assessment and help in diagnosing and monitoring in clinical daily routine. For that aim, several cases are presented including a patient who was suspected to suffer from frontotemporal lobar degeneration, a 14 years old boy who was diagnosed to suffer from an attention deficit hyperactivity disorder (ADHD), the famous multiple synaesthete E.S. (Beeli, Esslen & Jäncke, 2005; Hänggi, Beeli, Oechslin & Jäncke, 2008), and three brother suffering from a genetic condition called McLeod syndrome (Valko, Hänggi, Meyer & Jung, 2010).

Structural neuromorphometry methods applied in single patients

The aim of the present study is neither to provide a comprehensive summary of structural neuromorphometry methods nor to describe in detail the preprocessing steps implemented in these methods. The purpose of this paragraph is to provide a short overview of the methods applied to the patients and control subjects reported in the Application section below and it is directed towards readers who are not familiar with structural neuroimaging

methods and the measures that these methods provide. More information about these methods and its different preprocessing steps can be found in my Ph.D. thesis (http://www.juergenhaenggi.ch) as well as on the websites of the different tools (see below).

Structural neuromorphometric methods applied to the cases and control subjects reported in the current study are: (1) voxel-based morphometry (VBM), the most frequently used tool in MRI-based neuromorphometrics. VBM is based on T1-weighted MRI scans and provides information about GM (and also WM) volume and "probabilistic density". The preprocessing steps of the MRI data for VBM analyses were done with the VBM toolbox (VBM5; http://dbm.neuro.uni-jena.de/vbm/) that uses the statistical parametric mapping software (SPM; http://www.fil.ion.ucl.ac.uk/spm/) running under MATLAB (http://www.mathworks.com/). (2) Surface-based morphometry (SBM) based on T1-weighted MRI scans is a more sophisticated method providing, beside others, measures of cortical thickness and cortical surface area separately. The FreeSurfer software (http://surfer.nmr.mgh.harvard.edu/fswiki) was used to reconstruct surface-based brain models in order to measure cortical thickness. (3) Subcortical volumetric segmentations provide volumetric measures of subcortical structures such as the amygdala, hippocampus, and thalamus. Subcortical volumetric segmentation is also implemented in the FreeSurfer software suite. (4) Fractional anisotropy (FA) analysis based on DTI data provides measures of WM organisation and integrity. These methods are implemented in the FSL's diffusion toolbox (FDT) and in the tract-based spatial statistics tool (TBSS; http://www.fmrib.ox.ac.uk/fsl/tbss/index.html) and both are freely available in the Oxford centre of functional magnetic resonance imaging of the brain (FMRIB) software library (FSL; http://www.fmrib.ox.ac.uk/fsl/fsl/).

Statistics of neuromorphometric data in single patients

The following paragraph was drawn from a draft written by Dr. R. Henson that is available online (www.mrc-cbu.cam.ac.uk/people/rik.henson/personal/Henson_Singlecase_06.pdf). In order to compare a single patient versus a group of control subjects several statistical tests are appropriate: Z-score transformation, one-sample t-test, and two-sample t-test with pooled variance estimates (Henson, 2006). If we knew the mean μ and the standard deviation σ of the control "population", we can construct the z-score:

$$Z_p = \frac{x_p - \mu}{\sigma}$$

where x_p is the score of the single patient. We can then determine the probability of obtaining a z-score of this size or larger from the "Z-distribution". In practice, z-scores are often tested this way when the group of control subjects is large and therefore one has very reliable estimates of μ and σ. However, when we estimate μ and σ from a small sample of the population, we need to take into account that the values of μ and σ are estimated quantities that have associated errors. The distribution of the mean ($\hat{\mu}$) can be estimated and it is approximately Gaussian according to the central limit theorem. Its standard deviation (standard error of mean) σ_μ is dependent on σ and can be estimated. In small samples, the distribution of the estimated $\hat{\sigma}$ is not Gaussian, but has a positive, skewed distribution and therefore testing against a Z-distribution is no longer appropriate (Henson, 2006). But, we can construct a t-score:

$$t_p = \frac{x_p - \hat{\mu}}{\hat{\sigma}_\mu}$$

This t-score has a known T-distribution, which is a function of the degrees of freedom (df), and replacing $\hat{\sigma}_\mu$ by $\hat{\sigma}/\sqrt{N}$ leads to the formula:

$$t_{p(df)} = \frac{x_p - \hat{\mu}}{\hat{\sigma}/\sqrt{N}}$$

In the SPM software, such a t-test is equivalent to creating contrast images of the patient image by subtracting each control subject image from it and entering the resulting difference images into an one-sample t-test.

When there are two independent samples, we can construct the classical t-statistic and the common variance can be estimated with two different approaches: "unpooled" and "pooled" variance estimates (Henson, 2006). In the case of unpooled variance estimates, the formula of the t-statistic is:

$$t_{p(df)} = \frac{\hat{\mu}_p - \hat{\mu}_c}{\sqrt{(\hat{\sigma}_p^2/N_p) + (\hat{\sigma}_c^2/N_c)}}$$

where p and c subscripts denote patients and controls, respectively. For the pooled variance estimates, the t-statistic is:

$$t_{p(df)} = \frac{\hat{\mu}_p - \hat{\mu}_c}{\sqrt{\hat{\sigma}^2((1/N_p) + (1/N_c))}}$$

$$\hat{\sigma}^2 = \frac{(N_p - 1)\hat{\sigma}_p^2 + (N_c - 1)\hat{\sigma}_c^2}{N_p + N_c - 2}$$

In the pooled approach, the number of observations in each sample is weighted when estimating the common variance, i.e. giving more weight to larger samples because they are better estimates. If the patient group consists only of one patient, then there is no variance and the unpooled two-

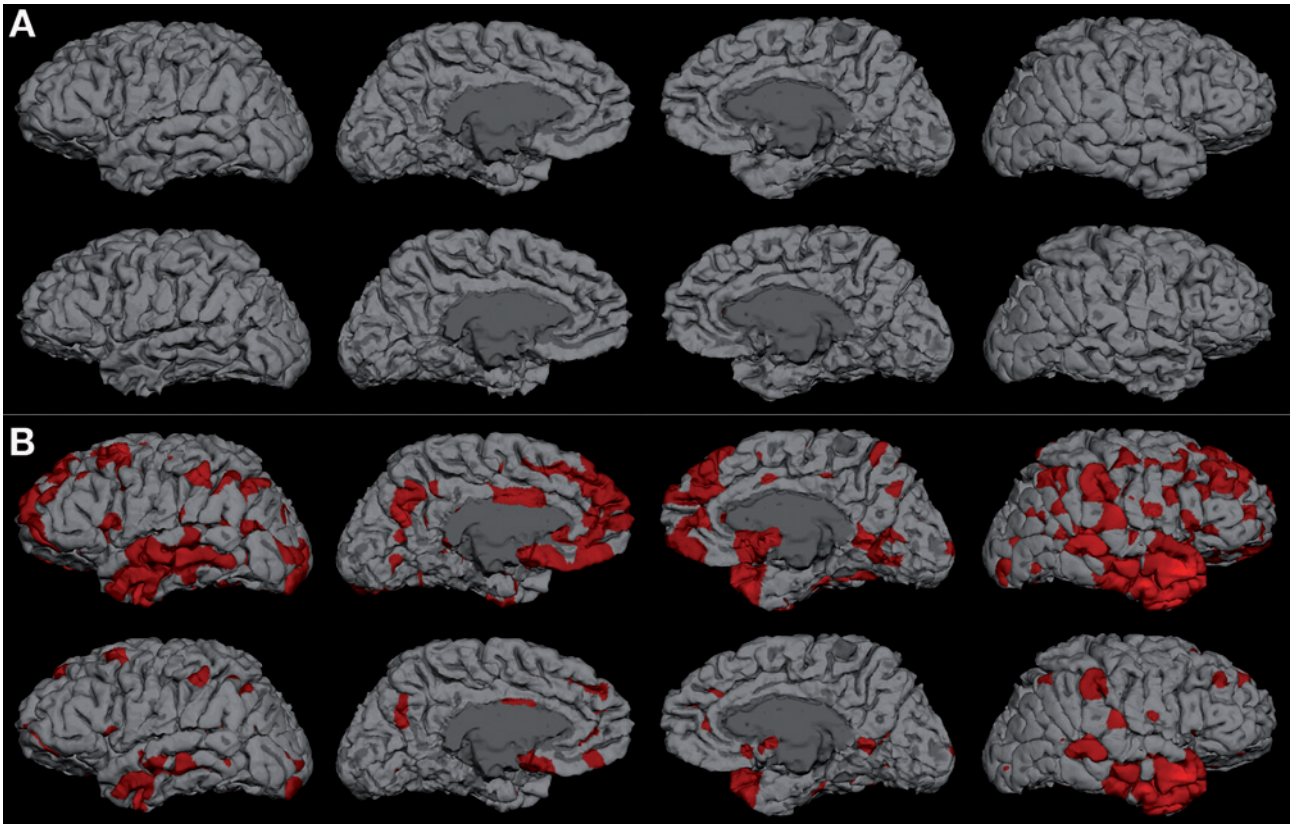

Figure 1. A) Shown are views of the patient's grey matter surface models for the left (left side) and right hemisphere (right side) in October 2005 (first row) and in February 2010 (second row). A clear atrophy is visible in both temporal lobes that is more pronounced in the anterior compared with the posterior portion of the temporal lobe. B) Shown is the cortical thickness difference map between October 2005 and February 2010 overlaid on the patient's grey matter surface models for the left (left side) and right hemisphere (right side) derived from the data acquired in October 2005. Red colours indicate clusters with cortical thickness decreases between the two time points that were larger than 0.25 mm (first row) or larger than 0.5 mm (second row). Atrophy between the two time points is stronger in the right compared with the left temporal pole.

sample t-test reduces to a one-sample t-test. However, in this case the pooled two-sample t-test reduces to the formula:

$$t_{p(df)} = \frac{x_p - \hat{\mu}_c}{\sqrt{\hat{\sigma}_p^2((1/N_c)+1)}} = \frac{x_p - \hat{\mu}}{\hat{\sigma}\sqrt{(1/(N)+1))}}$$

This kind of t-test is also called Crawford's modified t-test (Crawford, Garthwaite & Howell, 2009). When comparing the equations, it is obvious that the one-sample t-test and the two-sample t-test with pooled variance estimates can give different results (the latter being much more conservative). Note that the SPM software always uses pooled estimates of the (error) variance (Henson, 2006) and FreeSurfer software as well (personal communication).

For small sample sizes of the control group, a t-transformation rather than a z-transformation have to be used. Whether the one- or two-sample t-test should be applied depends on the question one is asking. If the patient is regarded as a unique, single case (assuming that the measurement error associated with the patient's score is negligible), then one might prefer the one-sample t-test, in which the patient's score is regarded as a fixed effect. If, however, one regards the patient as a representative example of a population of similar patients (even if that population is hypothetical), then one might prefer the two-sample t-test with pooled error variance estimates. Indeed, statisticians often recommend the pooled two-sample t-test (Crawford et al., 2009; Henson, 2006; Mühlau et al., 2009).

Applications

I will present four different applications that, in my opinion, illustrate the power and usefulness of MRI-based computational neuromorphometric procedures in single patients and single extraordinary subjects. I provide practical examples of single patients, who were assessed neuropsychologically at our institute, but were also investigated by MRI-based structural neuromorphometric procedures such as VBM, SBM, subcortical segmentation as well as voxel-wise analysis of FA derived from DTI data.

A patient with the suspicion of frontotemporal lobar degeneration

In 2010, a 50 years old male subject with the suspicion of frontotemporal lobar degeneration was assessed neuropsychologically at our division. The main reason for the assessment was to evaluate whether he can keep his driving license. He and his relatives reported progressive word-finding problems and impairments in memory functions since about ten years. Due to his long medical history, a bunch of diagnoses were made by clinicians including a somatoform disorder of different organs, hypochondriac disorder, Morbus Menière (a disease of the inner ear), reactive depression, Ganser syndrome (also called pseudo-dementia), combined personality disorder with anancastic, schizoid, and histrionic traits, as well as a dissociative personality disorder. Our own neuropsychological assessment revealed mild to moderate to severe impairments in attention, executive functions, and in the domain of language and semantics. In the domain of language and semantics, word-finding problems and the naming of common objects were more impaired than other language-related functions such as repeating words after and written language. However, several neuropsychological tests could not be applied and a lot of subtest that were started had to be aborted due to the patient's tiredness and incompliance. Besides his impairments in the domain of language and semantics, he was somewhat disinhibited, sometimes impulsive, and showed a high degree of distractibility. He repetitively uttered the "order" that we should rather have "a look into his brain than asking questions that he does not understand".

However, two clinicians who have already assessed this patient indicated structural MRI and recognized a mild to moderate atrophy of his left temporal lobe with an accentuation in the temporal pole. Therefore, the patient provided us two T1-weighted MRI scans from two different time points, one from October 2005 and one from February 2010. These two MRI scans were subjected to a longitudinal SBM using the FreeSurfer software suite to measure cortical thickness alterations within this five years time interval. I focused on the temporal and prefrontal cortex and expected stronger cortical atrophy in temporal than prefrontal regions in case of semantic dementia and stronger atrophy in prefrontal than temporal regions in case of frontotemporal dementia. The cortical surface models of both hemispheres at both time points and the corresponding cortical thickness difference maps between the two time points are shown in Fig. 1.

As can be seen from Figure 1 A (first row), the left temporal lobe and especially its pole is more atrophic than the right temporal lobe in 2005. Five years later, the atrophy of the left and the right temporal lobe can be recognized by visual inspection (second row) and still more pronounced in the left compared with the right temporal lobe.

However, cortical thickness reductions between 2005 and 2010 were more pronounced in the right temporal pole compared with the left one (Fig. 1B). In Figure 1B, red colours indicate clusters with cortical thickness decreases between the two time points that were larger than 0.25 mm (first row) or larger than 0.5 mm (second row). Besides the temporal lobes, medial and lateral prefrontal brain regions also revealed reduced cortical thickness in 2010 compared with 2005.

The pattern of predominantly frontotemporal brain atrophy with a clear accentuation in the temporal pole bilateral as revealed by cortical thinning in these regions is rather compatible with a semantic dementia (Krueger et al., 2010; Mummery et al., 2000; Rosen et al., 2002) than with a frontotemporal dementia (Rosen et al., 2002).

A young patient with the diagnosis of an attention deficit hyperactivity disorder

In 2010, a 14 years old boy with the suspicion of an ADHD visited our institute accompanied by his parents with the aim of a neuropsychological assessment. As reported by his parents and child physicians, the boy was behaviourally conspicuous since his birth because he frequently cried, was often hyperactive, worried his two younger brothers, was painlessness, and showed an increased muscle tone. His rough-motor skills were developed in advance compared with age-matched children, whereas the development of his fine-motor skills was delayed. At four years of age, an ADHD was diagnosed and one year later he went to the kindergarten. Main problems were hyperactivity, concentration problems, impulsivity, problems with fine-motor skills and severe deficits in social behaviour. Before put to school, Ritalin was prescribed by a physician and it improved the symptoms in the short term. Later, this improvement diminished and Ritalin was replaced by Concerta 36 mg that again improved the situation, but not sustainable. He then went to an external school, where aggressive behaviour, aggressive and sexual fantasies, as well as a sexual attack on one of his younger brothers were the most important problems. He also developed several tics (arm, hand, and finger movements, beating, leaping, to make noise, to cough, to shout) that were diagnosed as a Tourette's syndrome in 2004. He was sent to an internal school and due to an increase in aggression and an intensification of the tics, he was treated with Risperdal (0.5 mg) that reduced the aggression and the tics. Concerta was later replaced by Ritalin LA 30 mg and the tics diminished. Therefore, Risperdal was dropped and the tics came back. They tested Dexamphetamine that only temporarily helped. In 2006, he had to leave the internal school and was hospitalised in a child station for about one year. He was then treated with Strattera (18, 25, and 40 mg) during hospitalisation. Due to the fact that no school was willing to enrol him again, he was educated at home by his parents between 2007 and 2010 and his medical history during that time is comparable with that reported from 2005 to 2007. His parents reported that the patient's younger brother suffers also from ADHD, whereas the youngest one suffers from a disturbed social behaviour. The focus in his medical history was on ADHD and it seems that the specialists involved in assessing

this patient did not consider any alternative diagnosis, even not after the numerous attempts to treat the patient with amphetamines or similar drugs that all seem to be failed, although classical ADHD cases respond very well to these kind of medication, although it is known that aggressive behaviour benefit from amphetamines. In my opinion, a disturbed social behaviour or even traits of an antisocial personality disorder might be equally probable as an ADHD and these conditions would be, at least in part, in line with his behavioural conspicuousness and the numerous reports about his aggressive behaviour in his medical history. It is important to remark that the patient was not solely treated pharmacologically as the report might imply. During the whole time of his medication, several attempts with behaviourally oriented therapies failed to improve the situation.

In 2010, a radiologist scanned his brain using different MRI modalities. The only reported prominence finding was a smaller volume of the hypophysis (277 mm^3) in the patient's brain compared with age-matched norms (423 ± 110 mm^3). I used the patient's T1-weighted MRI image provided by the radiologist and compared it with those derived from six age-matched healthy control boys, whose MRI scans were acquired on the same MRI system with a similar T1-weighted MRI sequence. I applied SBM using FreeSurfer software in order to compare the patient's regional cortical thickness with that derived from the six control boys. I used two-sample t-tests with pooled variance estimates and report statistical parametric maps that were height thresholded at $p < 0.05$ and $p < 0.01$ (uncorrected for multiple comparisons). In addition, a false discovery rate (FDR) of $q < 0.05$ was applied to the parametric maps as well as a non-parametric procedure that corrects for multiple comparisons at the cluster size by using 500 synthetic z-maps permutations (Monte Carlo simulations).

The aim was to compare the regions of cortical thickness peculiarities found in the contrast between the boy diagnosed with ADHD and age-matched control boys with the relevant literature about grey matter alterations in ADHD on one hand and in patients with disturbed social behaviour and antisocial personality disorder on the other hand. The results of this cortical thickness analysis are shown in Figure 2.

Regions with increased cortical thickness in the patient compared with the control boys are shown in red-yellow and were restricted to the medial and lateral orbitofrontal cortex bilateral, right medial superior prefrontal cortex, and right dorsolateral prefrontal cortex (Fig. 2 A-E). Several of the clusters showing increased cortical thickness in the patient survived corrections for multiple comparisons (Fig. 2D-E) including the lateral orbitofrontal ($p = 0.028$) and the medial superior frontal cluster ($p = 0.036$), whereas the medial orbitofrontal cluster showed almost a trend toward significance ($p = 0.12$). Regions with decreased cortical thickness in the patient compared with the control boys are shown in blue-lightblue and were found only on the lateral cortical surface in the superior parietal lobule bilateral, left angular gyrus, left supramarginal gyrus, left precentral gyrus and left middle frontal gyrus (Fig. 2 A-B). Note that none of the clusters showing decreased cortical thickness in the patient survived correction for multiple comparisons, although the right superior parietal lobule cluster (shown in blue in Fig. 2E) revealed a trend toward a statistically significant thinner cortex ($p = 0.066$) in the Monte Carlo simulations.

The multiple synaesthete E.S. – Neuroanatomical basis of interval-taste and tone-colour synaesthesia

In 2005, Beeli and colleagues published a study in Nature that describe the extraordinary case of a musician who experiences different tastes in response to hearing different musical tone intervals, i.e. she has an interval-taste synaesthesia (Beeli et al., 2005). In addition, she experiences different colours in response to hearing different musical tones (tone-colour synaesthesia) and she also possesses the absolute pitch ability and uses her synaesthetic sensations in the complex task of tone-interval identification. Although the study by Beeli and colleagues experimentally tested and corroborated her interval-taste synaesthesia by using a gustatory Stroop paradigm, there was no information about how this condition might be implemented in her brain. Therefore, we acquired T1-weighted and diffusion-weighted MRI scans of the multiple synaesthete E.S. and appropriate control subjects in order to analyze her grey matter and white matter architecture volumetrically by means of VBM. In addition, fibre bundle characteristics were investigated by means of FA measures as well. Based on theoretical considerations in grapheme-colour synaesthesia (GCS) (Hubbard, Brang & Ramachandran, 2011; Hubbard & Ramachandran, 2005; Jäncke, Beeli, Eulig & Hänggi, 2009; Rouw, Scholte & Colizoli, 2011), we expected alterations in brain regions associated with the synaesthetic inducer (musical interval or tone) and its concurrent (taste or colour) as well as differences in the pattern of structural connectivity between the inducer and concurrent area (Bargary & Mitchell, 2008). In GCS, it is assumed that the visual word form area (VWFA) and the colour area (V4), which are direct neighbours located on the fusiform gyrus, are hyperconnected and therefore activity in the VWFA is spread into the area V4 where it produces the colour sensation (Hubbard & Ramachandran, 2005). By adapting this concept to interval-taste synaesthesia, we hypothesised hyperconnectivity between auditory and gustatory areas, which are also direct neighbours in the perisylvian plane.

In 2008, we published strong evidence for the hypothesis that the interval-taste synaesthesia and tone-colour synaesthesia of the multiple synaesthete E.S. are rooted in anatomical grey and white matter differences in auditory and gustatory brain regions on one hand and in auditory and visual brain regions on the other hand. Most striking finding was that auditory (superior temporal gyrus and Heschl's gyrus) and gustatory (insula) regions were hyperconnected bilaterally in the

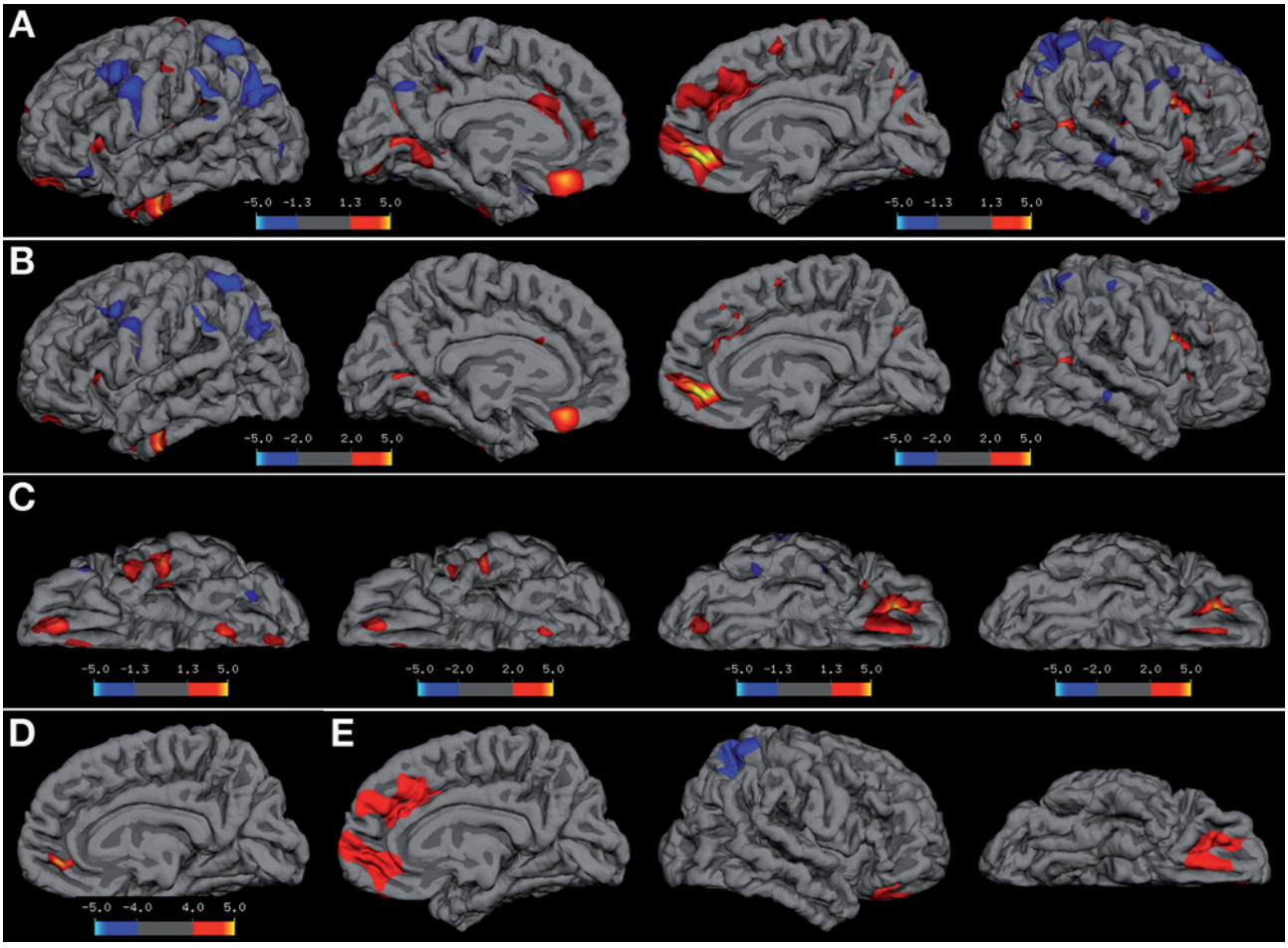

Figure 2. Shown are the statistical thickness difference maps between the patient with attention deficit hyperactivity disorder and six age-matched healthy control boys. Regions with increased cortical thickness in the patient compared with the control boys are shown in red-yellow and regions with decreased cortical thickness in the patient compared with the control boys are shown in blue-lightblue at a statistical height threshold (uncorrected for multiple comparisons) of $p < 0.05$ in A) and of $p < 0.01$ in B). Left lateral and medial view (first and second column, respectively) and right lateral and medial view (third and fourth column, respectively). C) Basal views of the statistical cortical thickness difference maps for the left hemisphere at $p < 0.05$ (first column) and at $p < 0.01$ (second column) and the right hemisphere at $p < 0.05$ (third column) and at $p < 0.01$ (fourth column). D) Statistical cortical thickness difference map of the right hemisphere (medial view) corrected with a false discovery rate (FDR) of $q < 0.05$. E) Statistical cortical thickness difference map of the right hemisphere corrected for the cluster size by 500 synthetic permutations (Monte Carlo simulations). Note that only the lateral orbitofrontal ($p = 0.028$) and the medial superior frontal ($p = 0.036$) cluster are statistically significant after permutations, whereas the medial orbitofrontal and superior parietal cluster show a trend toward significance ($p = 0.12$ and $p = 0.066$, respectively). The colour bars represent the statistical threshold indicated as the $-\log_{10}(p)$, so values of 1.3, 2, and 4 correspond to probabilities of $p < 0.05$, $p < 0.01$, and $p < 0.0001$, respectively.

brain of the multiple synaesthete E.S. as indexed by increased FA (Hänggi et al., 2008).

Volumetric GM differences were found in the hypothesised brain regions. In the multiple synaesthete E.S. compared with 20 normal controls (Fig. 3a–c) and also compared with 17 professional musicians (E.S. herself is a professional musician playing the alto flute) (Fig. 3d-f), increased GM volume was evident in occipital, temporo-occipital and thalamic regions and decreased grey matter volume was found in the left superior temporal gyrus and insula, left Heschl's gyrus extending into the planum temporale and insula, and in the right superior temporal gyrus, Heschl's gyrus, and planum temporale.

Volumetric WM changes and differences in FA were found in addition. There were clusters with increased FA and increased WM volumes in the planum temporale, Heschl's gyrus, insula and hippocampus bilateral in the multiple synaesthete E.S. compared with 20 normal controls (FA in green and WM volumes in yellow) and also compared with 17 professional musicians (FA in red and WM volumes in blue) (Fig. 4a-d).

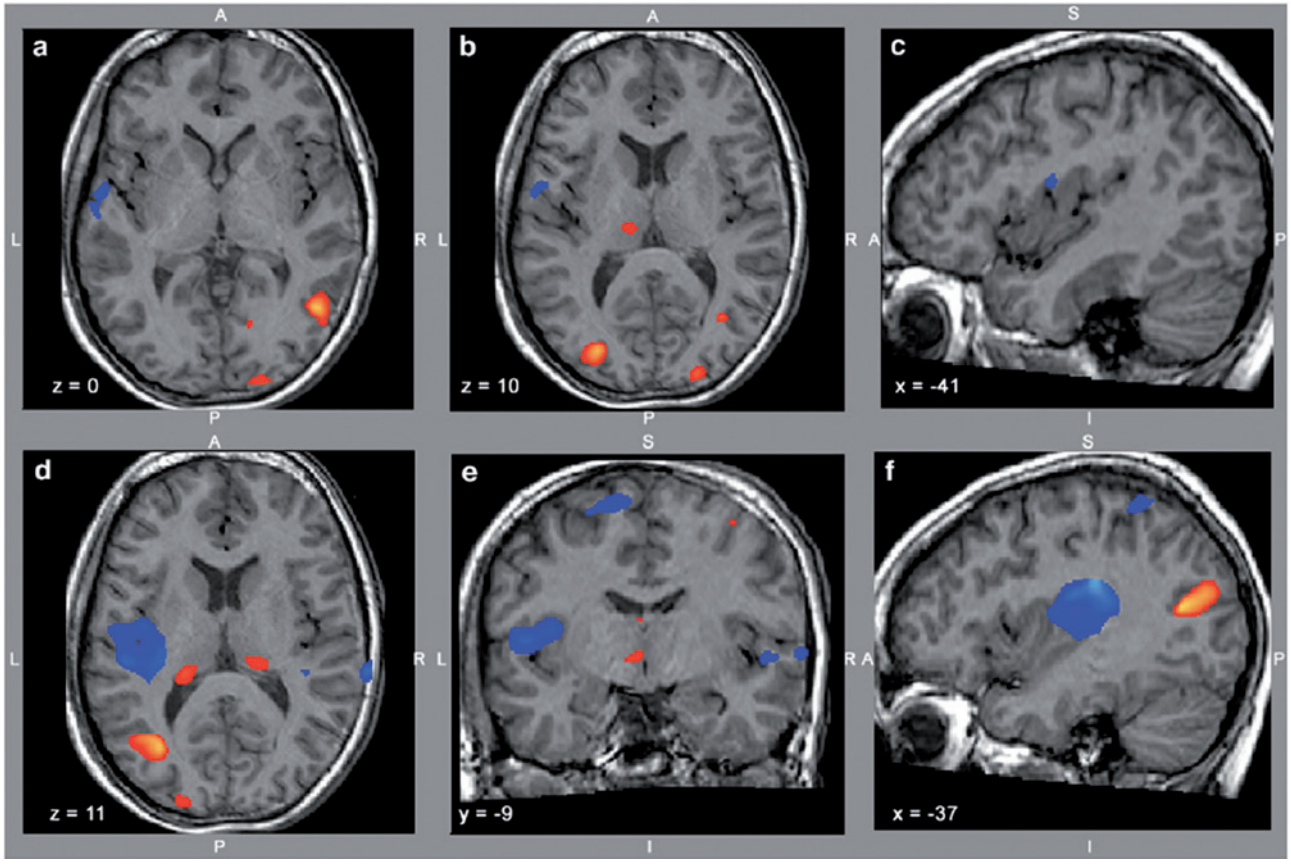

Figure 3. Increased (red-yellow, $z > 3.1$, $p < 0.001$) and decreased (blue-lightblue, $z < -3.1$, $p < 0.001$) grey matter (GM) volumes in the brain of the synaesthete E. S. compared with 20 normal control subjects (a–c) and 17 professional musicians (d–f). Increased GM volume was evident in occipital, temporo-occipital, and thalamic regions (a, b, d, f). Decreased GM volume was found in the left superior temporal gyrus and insula (a–c), left Heschl's gyrus/planum temporale/insula (d–f), and in the right superior temporal gyrus, Heschl's gyrus, and planum temporale (d, e). The GM volumes z-score maps are superimposed on the structural MR image of the synaesthete E. S. For further details see Tables 1 and 2 in the original publication (Hänggi et al., 2008). Reprint with the permission from Elsevier and ScienceDirect.

More detailed information about the clusters with morphological alterations can be found in the original publication (Hänggi et al., 2008).

Evolution of striatal degeneration in McLeod syndrome

McLeod neuroacanthocytosis syndrome is an X-linked multisystem disorder that is characterized by the association of erythrocyte acanthocytosis with central nervous system (CNS) symptoms resembling Huntington disease as well as neuromuscular and cardiac anomalies (Valko et al., 2010). CNS symptoms are caused by striatal dysfunction and neurodegeneration and include chorea, other hyperkinetic movement disorders, psychiatric abnormalities and cognitive decline as well as epileptic seizures. Neuropathological examinations revealed unspecific neuronal loss and astrocytic gliosis of the caudate nucleus, putamen and, to a lesser degree, of the globus pallidum but not of cortex, thalamus, subthalamic nucleus or brainstem (Valko et al., 2010).

We investigated the volumes of subcortical structures focussing on the striatum (caudate nucleus and putamen) in three brothers suffering from McLeod syndrome compared with healthy age-matched controls (cross-sectional comparison) as well as over a time interval of seven years (longitudinal comparison). The clinical characteristics of the three brothers reported in the current study can be found in Table 1 in our original publication (Valko et al., 2010). In line with the literature and our hypotheses, we found significant volume reductions of both caudate nuclei and putamina in all three patients when compared with the controls. In the longitudinal examination, we found decreases in the volumes of both caudate nuclei, but an increase in the volumes of the putamen and globus pallidus bilateral over the time interval of seven years (Fig. 5).

Figure 5 shows the results of the subcortical segmentation procedure of the MRI scans at the two time points in the two less affected brothers (IV-6 and IV-7). The results of the subcortical segmentation of the most affected brot-

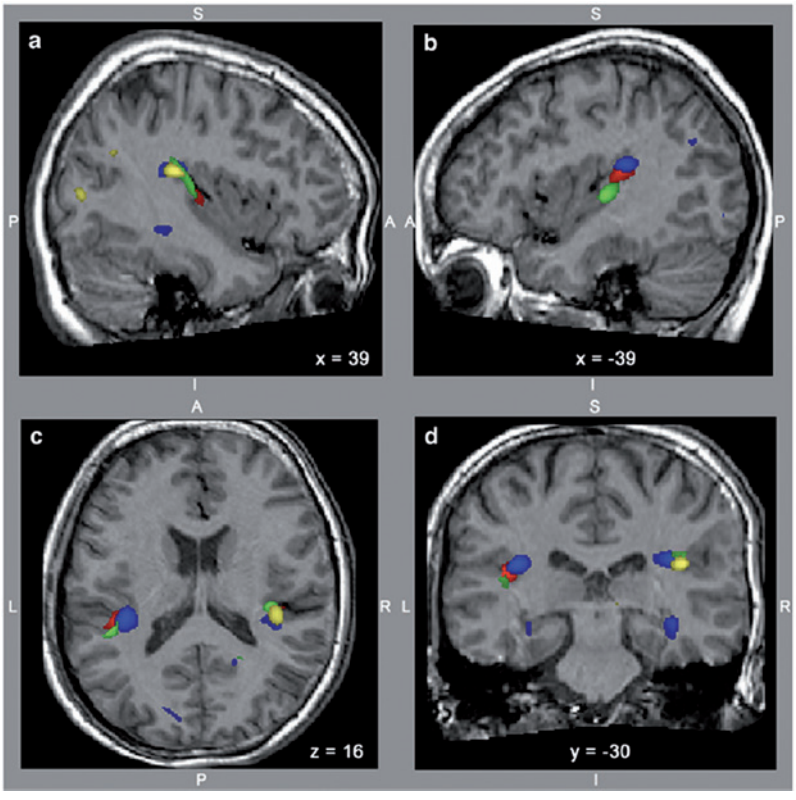

Figure 4. Clusters of significant increased fractional anisotropy (FA) (as shown in Fig.1 of the original publication (Hänggi et al., 2008)) and increased white matter (WM) volumes (as shown in Fig. 2 of the original publication (Hänggi et al., 2008)) in the brain of the synaesthete E. S. compared with 20 normal control subjects (FA in green; WM volumes in yellow) and 17 professional musicians (FA in red; WM volumes in blue). Shown are a right (a) and a left sagittal plane (b) through the perisylvian cortex and the insular region as well as the corresponding axial (c) and coronal (d) planes. The z-score maps are superimposed on the structural MR image of the synaesthete E. S. Reprint with the permission from Elsevier and ScienceDirect.

her (IV-4) can be found in Figure 1 in our original publication (Valko et al., 2010). The absolute volumes and error probabilities of subcortical and global brain volumes of the patients compared with the control subjects (cross-sectional comparison) are presented in Table 1 below.

With respect to the longitudinal analysis, Wilcoxon's signed ranks tests revealed a trend toward statistically significant volume reductions in McLeod patients over time ($p = 0.055$). More detailed information about the results of this study can be found in our original publication (Valko et al., 2010).

Discussion

The aim of the present proposal was to present some practical applications of structural MRI-based neuromorphometric procedures in single patients. I have reported four different applications: 1) a longitudinal, vertex-wise cortical thickness analysis (the patient with the suspicion of frontotemporal lobe degeneration; Fig. 1) that revealed cortical thinning in both temporal lobes with an accentuation of the temporal poles. In this application, I only reported cortical thickness reductions (atrophy) within the five years interval and did not apply any statistics. 2) A cross-sectional, vertex-wise comparison of cortical thickness between the patient diagnosed with ADHD and six healthy matched control boys (Fig. 2). Here I used t-tests with pooled variance estimates and reported statistical parametric maps that were thresholded at $p < 0.05$ and $p < 0.01$, both uncorrected for multiple comparisons. In addition, I applied a false discovery rate correction ($q < 0.05$) as well as a non-parametric cluster size correction by using 500 synthetic z-map permutations (Monte Carlo simulations). 3) A cross-sectional, voxel-wise comparison of differences in GM volume (Fig. 3) as well as differences in WM volume and in FA (Fig. 4) in the multiple synaesthete E. S. compared with two different control groups. The statistics in this application is based on voxel-wise z-score transformations. 4) A longitudinal, region of interest-based subcortical segmentation procedure and region-wise z-score transformations in the three patients suffering from McLeod syndrome compared with two different control groups. In the following, I will discuss the contributions that structural neuromorphometric procedures in single patients can provide for diagnosing and monitoring in clinical

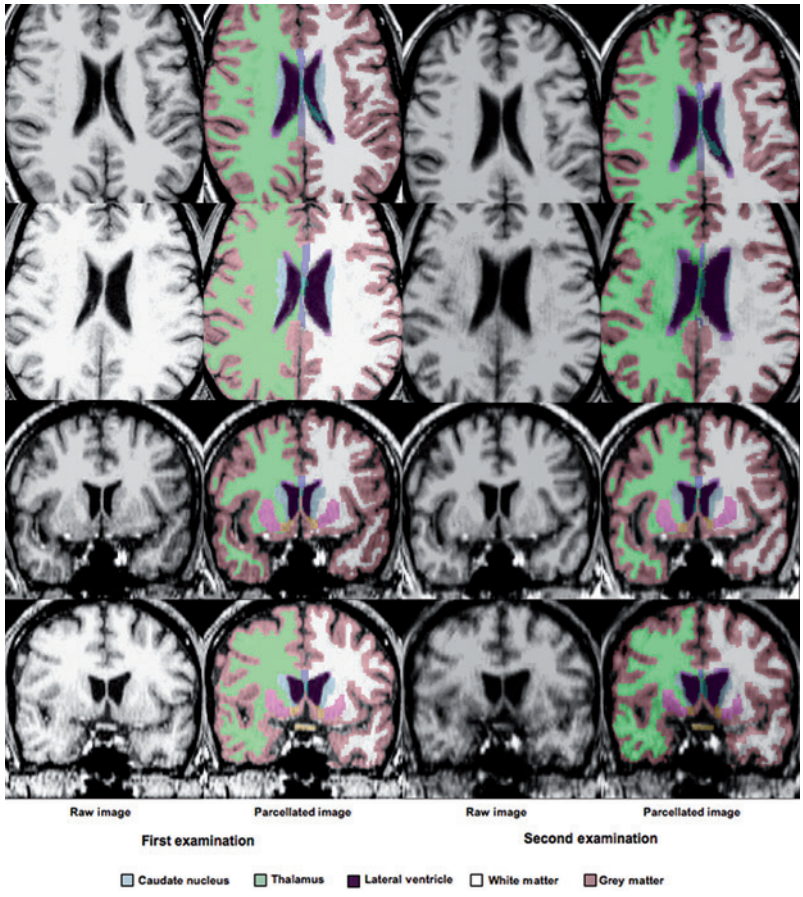

Figure 5. Automated subcortical segmentations. Raw structural T1-weighted MR images and the corresponding subcortical segmentations of the brain of patient IV-7 (first and third row) and of patient IV-6 (second and fourth row) demonstrate a normal aspect of the caudate nucleus and putamen at the time of the first examination (left panel) and moderate atrophy of the caudate nucleus 7 years later with consecutive enlargement of the lateral ventricles (right panel). The absolute volumes of the caudate nucleus and other subcortical structures can be found in Table 1. The MRI scans of the most affected patient (IV-4) is presented as Fig. 1 in our original publication (Valko et al., 2010).

settings. The medical history and the findings of the neuropsychological assessments are not the focus of this discussion. In the following discussion, I focus on the anatomical alterations found in the patients and compare these morphological peculiarities with the pattern of structural brain changes observed in the disorders under question and reported in the literature. In addition, the pros and cons of the statistics applied in single patients are presented together with some recommendation for its usage.

A patient with the suspicion of frontotemporal lobar degeneration – A case of semantic dementia

Conditions of frontotemporal lobar degeneration are frontotemporal dementia (FTD), semantic dementia (SD), nonfluent progressive aphasia, primary progressive aphasia, and progressive supranuclear palsy among others. The pattern of cortical atrophy in FTD is different from that observed in SD (Krueger et al., 2010; Rohrer et al., 2011; Rosen et al., 2002; Whitwell, Anderson, Scahill, Rossor & Fox, 2004). Rosen and colleagues revealed that the temporal pole is more strongly affected in SD compared with FTD, whereas the superior and middle lateral frontal areas are the primarily involved brain regions in FTD compared with SD. The patient reported in the present proposal showed a severe atrophy in the temporal poles and a less accentuated atrophy in the medial frontal cortices. But his lateral frontal regions, especially the middle frontal gyrus that is the most affected region in FTD (Krueger et al., 2010; Rohrer et al., 2011; Rosen et al., 2002; Whitwell et al., 2004), are almost entirely spared from atrophy. When one compares the pattern of atrophy of our patient with the patterns of atrophy in the six patients with SD published by Mummery and colleagues (Mummery et al., 2000), who each was compared in a cross-sectional manner against a group of controls, the striking congruencies of the atrophic brain regions is obvious. In my opinion, our patient is a classical case of SD and the pattern of atrophy found in his brain fits well with his behavioural profile that showed pronounced word finding and semantic impairments. But, if his prefrontal cortices atrophy further it might be

Table 1

Shown are the absolute volumes of the structures of interest in the three patients and the mean volumes of a control group consistent of 20 age-matched males. The z-scores and error probabilities (p) are derived from the cross-sectional comparison of the three patients' volumes at each time point with the mean volumes of these structures in the control group that was measured only once. These values are corrected for intracranial volume. Significant p-values are printed in bold and statistical trends toward significance ($0.05 < p < 0.10$) are printed in italic. Note that cortical grey and white matter does not include the cerebellar volumes. Reprint with the permission from Wiley and ScienceDirect.

			Patient IV-4			**Patient IV-6**			**Patient IV-7**			**Controls**	
Structure		Examination	Volume (cm^3)	z-score	p	Volume (cm^3)	z-score	p	Volume (cm^3)	z-score	p	Volume (cm^3)	SD
Caudate nucleus	Left	First	2.4	–3.07	**0.001**	2.3	–3.42	**0.0003**	2.7	–2.32	**0.01**	3.7	0.6
		Second	1.8	–4.08	**0.00002**	2.0	–4.16	**0.00002**	2.5	–2.72	**0.003**		
	Right	First	2.0	–2.96	**0.002**	2.0	–3.01	**0.001**	2.9	–1.51	*0.07*	3.6	0.6
		Second	1.6	–3.53	**0.0002**	1.8	–3.58	**0.0002**	2.6	–1.96	**0.02**		
Putamen	Left	First	3.1	–3.23	**0.0006**	4.7	–2.11	**0.02**	5.1	–1.46	*0.07*	6.2	0.9
		Second	3.4	–3.09	**0.001**	4.8	–2.33	**0.01**	5.2	–1.39	*0.08*		
	Right	First	3.4	–3.31	**0.0005**	3.9	–2.93	**0.002**	4.5	–1.94	**0.03**	5.8	0.9
		Second	3.6	–3.19	**0.001**	4.2	–3.01	**0.001**	4.8	–1.70	**0.04**		
Pallidum	Left	First	1.3	–1.89	**0.03**	1.6	–1.10	0.14	1.6	–0.52	0.30	1.6	0.3
		Second	1.7	–0.56	0.29	1.7	–1.24	0.11	1.8	0.17	0.43		
	Right	First	1.1	–2.10	**0.02**	1.5	–1.07	0.14	1.6	–0.43	0.33	1.6	0.3
		Second	1.2	–1.87	**0.03**	1.6	–1.23	0.11	1.7	–0.28	0.39		
Thalamus	Left	First	7.4	–1.00	0.16	8.0	–0.69	0.25	7.4	–0.70	0.24	7.3	0.8
		Second	6.5	–1.93	**0.03**	8.1	–1.29	0.10	7.2	–0.96	0.17		
	Right	First	7.2	–0.96	0.17	8.3	–0.16	0.44	7.0	–0.89	0.19	7.1	1.0
		Second	6.6	–1.76	**0.04**	8.0	–1.18	0.12	6.8	–1.16	0.12		
Lateral ventricle	Left	First	9.1	0.47	0.32	8.4	0.18	0.43	4.7	–0.65	0.26	7.1	2.9
		Second	14.8	1.92	**0.03**	10.6	0.51	0.31	5.3	–0.53	0.30		
	Right	First	8.5	0.18	0.43	5.5	–0.55	0.29	6.8	–0.13	0.45	7.3	3.2
		Second	14.2	1.42	*0.08*	7.5	–0.24	0.41	7.4	–0.002	0.50		
Cortical grey matter	Left	First	245	–1.49	*0.07*	242	–1.76	**0.04**	274	–0.53	0.30	269	37.9
		Second	208	–2.40	**0.008**	235	–2.35	**0.01**	255	–1.07	0.14		
	Right	First	234	–1.84	**0.03**	240	–1.90	**0.03**	28 2	–0.54	0.29	277	36.3
		Second	198	–2.66	**0.004**	240	–2.31	**0.01**	266	–0.99	0.16		
Cortical white matter	Left	First	246	–1.14	0.13	270	–0.56	0.29	251	–0.38	0.35	238	32.0
		Second	265	–0.52	0.30	283	–0.99	0.16	281	0.74	0.23		
	Right	First	257	–0.83	0.20	273	–0.58	0.28	256	–0.32	0.37	240	31.6
		Second	274	–0.24	0.41	291	–0.87	0.19	271	0.23	0.41		

expected that his disinhibited, impulsive and compulsive behaviours become more severe so that in the future he will show symptoms that could also justify the diagnosis of FTD or that of a mixed form between SD and FTD.

I am convinced that if the cortical thickness difference map (shown in Fig. 1B) were available to the clinicians that have already investigated this patient, they also would end up with the diagnosis that the patient is rather suffering from SD than having pseudo dementia, reactive depression or any personality disorder. In my opinion, this case report illustrates impressively the usefulness of structural neuromorphometric procedures in single patients and how these methods can contribute in diagnosing and monitoring in clinical daily routine.

A young patient with the diagnosis of an attention deficit hyperactivity disorder – A case with a disturbed social behaviour phenomenon

Based on the patient's medical history and the symptoms described therein, two general diagnoses are plausible. An ADHD, which seems to be pharmacologically untreatable, as already diagnosed by the physicians. But in my opinion, a disturbed social behaviour phenomenon such as a conduct disorder or an oppositional defiant disorder or even traits of an antisocial personality disorder might be equally possible solely based on the behavioural profile of the patient. Therefore, we have to look at the distribution of regions with cortical thickness differences to find evidence either for ADHD or for a disturbed social behaviour or maybe for both.

When consulting the ADHD literature that is most comparable with the results reported here, i.e. cortical thickness analyses between ADHD patients and healthy control subjects, decreased (but also increased) cortical thickness was found in ADHD patients in the dorsolateral prefrontal cortex (dlPFC) bilateral, inferior parietal lobule (IPL) bilateral, anterior cingulate cortex, anterior and posterior temporal cortex and precentral gyrus (Makris et al., 2007; Shaw et al., 2007; Sowell et al., 2003). Decreased cortical thickness in patients with ADHD in the dlPFC bilateral was found by two studies (Makris et al., 2007; Sowell et al., 2003) and delayed cortical thickness maturation in ADHD patients in these regions was found in another study (Shaw et al., 2007), but I did not found any evidence for an involvement of the dlPFC in the case presented in the present study. Although reduced cortical thickness is revealed in the patient's dlPFC bilateral at a less conservative threshold (Fig. 2 A), these differences were reduced or disappeared at a more conservative threshold (Fig. 2B) and did not survive corrections for multiple comparisons (Fig. 2D,E). With respect to the IPL, reduced cortical thickness was found mainly in the left IPL, which is in agreement with the findings by Makris and colleagues (Makris et al., 2007), but in contrast to the results by Sowell and colleagues who reported increased cortical thickness in both posterior temporal lobes and both IPL in ADHD patients compared with controls (Sowell et al., 2003). Again, this finding in the IPL also did not survive corrections for multiple comparisons in the present study. When focusing on VBM studies investigating cortical volume, additional cortical and subcortical structures were found to be associated with ADHD (Shaw & Rabin, 2009), but none of these additional structures correspond to the regions, which have been shown to be altered in the boy with the suspicion of ADHD in the present study. In my opinion, the cortical thickness alterations observed in the patient do not fit well with the pattern of cortical thickness changes revealed by the ADHD literature.

However, when comparing the finding in the boy with the results of a recently published study investigating the association between inattention symptoms and regional cortical thickness variation in healthy children, striking similarities are obvious (Ducharme et al., 2012). Ducharme and colleagues correlated the score of an inattention symptoms/attentive functioning questionnaire with cortical thickness in 6–18 years old individuals and revealed correlates of inattention in bilateral orbitofrontal cortex, right inferior frontal cortex, bilateral ventromedial prefrontal cortex, bilateral dlPFC and several additional attention network related regions. When these authors looked at different ages, cortical thickness variation in the right (and at younger ages also in the left) lateral orbitofrontal cortex was associated with attention between 6–10 years of age, but not between 11–18 years old individuals (Ducharme et al., 2012). This finding suggests that the right orbitofrontal cortex is especially involved in attentive functions as well as dysfunctions, and could imply that the attention deficit and, maybe in part, the hyperactivity observed in the young boy exists without necessarily implying the diagnosis of an ADHD. With respect to his behavioural profile – specifically his aggressive potential and disrupted social behaviour – I did not assume an isolated attention problem, rather I expected morphological evidence for a disturbed social behaviour phenomenon such as a conduct disorder or an oppositional defiant disorder.

The relevant literature about cortical thickness alterations in persons with disturbed social behaviour revealed cortical thickness decreases in the medial and lateral orbitofrontal cortex (Fahim et al., 2011; Narayan et al., 2007) and reduced orbitofrontal, lateral prefrontal, and temporal volumes in patients with antisocial personality disorder compared with healthy controls (Anderson & Kiehl, 2011; Ermer, Cope, Nyalakanti, Calhoun & Kiehl, 2011; Raine, Lencz, Bihrle, LaCasse & Colletti, 2000; Raine & Yang, 2006; Raine, Yang, Narr & Toga, 2011). In addition, there is evidence for the involvement of the orbitofrontal cortex in aggressive behaviour in healthy children (Ducharme et al., 2011). These effects were more pronounced in the right than in the left hemisphere. The findings of the case presented in the present study are in line with these studies insofar the locations of the effects are concerned. The most

affected regions in our patient are the right medial and lateral orbitofrontal cortex, right medial superior prefrontal cortex and the right superior parietal cortex. But with respect to the direction of the effects, our findings are contradictory because we found increased cortical thickness in these regions, whereas the relevant neuroscientific literature suggests that cortical thickness is decreased in these regions.

However, the literature is based, in part, on adult patients with antisocial personality disorder, whereas the patient I have described here is a 14 years old boy. But, it is known from the literature that cortical thickness decreased developmentally starting in early childhood and lasting into early adulthood (Shaw et al., 2007; Shaw et al., 2006; Shaw & Rabin, 2009; Sowell et al., 2007; Sowell et al., 2004; Sowell et al., 2003). Therefore, a thicker cortex in the boy is in line with slower regional cortical thinning rates and might suggest a delay in cortical maturation (Shaw et al., 2007; Shaw & Rabin, 2009; Sowell et al., 2003). It seems that the normal, developmentally driven thinning of the cortical sheet in this young patients did not take place in such an extent and magnitude as observed in normally developing children. It might be the case that the observed delay of cortical thinning in orbitofrontal and superior frontal regions will end up with a thinner cortex in these regions in adulthood similar to the findings reported by Shaw and colleagues for the relationship between cortical thickness trajectories and intellectual abilities (Shaw et al., 2006). In that study, it has been shown for the right medial and superior frontal cortex (among other regions) that individuals with superior intellectual abilities compared with average intellectual abilities showed a delayed peak of maximum cortical thickness (a marker of brain maturation) at age 11.2 years (compared with 5.6 and 8.5 years for subjects with average and high intellectual abilities, respectively). But then cortical thickness decreases stronger in the superior intellectual group compared with the two other groups into late adolescence. More information about the waxing and waning of grey and white matter in development and its relations to intellectual functioning can be found by Tamnes and colleagues (Tamnes et al., 2011).

The right hemispheric finding of a thicker lateral and medial orbitofrontal cortex as well as medial superior frontal cortex in the patient compared with age-matched control boys can be considered as a marker for delayed cortical maturation and might account for his disturbed social behaviour. The locations of the clusters with cortical thickness differences in the boy are in strong agreement with the clusters reporting anatomical peculiarities in conduct disorder, oppositional defiant disorder, antisocial personality disorder, and in psychopaths (Anderson & Kiehl, 2011; Ermer et al., 2011; Fahim et al., 2011; Narayan et al., 2007; Raine et al., 2000; Raine & Yang, 2006; Raine et al., 2011; Seguin, 2004). Additionally, it is well known from lesion studies that the disruption of the orbitofrontal cortex often leads to behaviours that are not desirable in the social context. The most famous case of such an orbitofrontally lesioned patients reported in the neuroscientific literature is the case of Phineas Gage (Damasio, Grabowski, Frank, Galaburda & Damasio, 1994).

The multiple synaesthete E.S. – Neuroanatomical basis of interval-taste and tone-colour synaesthesia

As hypothesised, the comparison of the brain of the synaesthete E.S. with the brains of 17 professional musicians and with the brains of 20 normal control subjects revealed large structural differences in areas involved in the processing of both the inducing stimulus (auditory cortices) and the concurrent perceptions (gustatory and visual areas). Our results derived from two different imaging modalities (diffusion- and T1-weighted) and from two different comparison populations (normal control subjects and professional musicians with absolute pitch) converge in that they show a consistent pattern of bilateral brain differences in auditory areas (planum temporale and Heschl's gyrus), insular cortex, and occipital regions. In these particular brain regions, the multiple synaesthete E.S. shows increased FA accompanied by increased WM volumes and decreased GM volumes in the same regions (Hänggi et al., 2008). Our results provide strong evidence for a neuroanatomical basis to synaesthetic experiences in the interval-taste and the tone-colour synaesthesia, hence corroborating the proposed theory of increased anatomical connections between relevant brain areas as originally formulated for grapheme-colour synaesthesia (Hubbard & Ramachandran, 2005; Ramachandran & Hubbard, 2001). Our results further show that in addition to alterations in the connections between the relevant areas in the brain of the synaesthete E.S., there are structural anomalies within these areas. These anomalies may reinforce proposed neurophysiological mechanisms such as local crossactivation, disinhibition of feedback, or re-entrant of feedback. The neurophysiological mechanism that is evoked by this hyperconnectivity might be different between the interval-taste and tone-colour synaesthesia and cannot be investigated by structural neuroimaging. For a more detailed description of the results and its interpretation, please read the results and discussion section in our original publication (Hänggi et al., 2008).

Evolution of striatal degeneration in McLeod syndrome

The natural progressive course of striatal atrophy in three patients with McLeod syndrome was described. Although only three individual patients were available for follow-up examinations, we were able to demonstrate a strong statistical trend ($p = 0.055$) toward significantly decreased caudate nucleus volumes over a time period of 7 years using a fully automated segmentation procedure based on

structural MRI scans. Several neuroimaging and pathological studies in McLeod syndrome revealed atrophy of caudate nucleus and putamen (Geser et al., 2008; Jung et al., 2001). A previous cross-sectional study showed an association of volume loss in the caudate nucleus and putamen with the disease duration (Jung et al., 2001). The volumetric analyses in the present study showed a significant volume loss of the caudate nucleus of the patients in comparison with 20 healthy age-matched control subjects scanned once on a different MRI system and also in comparison with 10 healthy elderly subjects scanned once on the same MRI system as used for the patients.

Furthermore, the longitudinal analysis revealed a statistical trend towards significant caudate volume reductions in the patients over the 7-year period. Although interpretation is limited because of the small number of patients examined, we observed that the patients with the more pronounced neurological signs and symptoms, i.e. the clinically more affected and older patients, had smaller volumes of the caudate nucleus compared to their younger and less affected brother.

Volumes of putamen and pallidum bilaterally were significantly smaller in the three patients when compared, at a single time point, to the 20 age-matched controls without a significant longitudinal volume change over the observation period of 7 years. In contrast to previous neuroimaging and pathological findings in McLeod syndrome, which did not demonstrate extrastriatal pathological alterations, we found evidence for a global volume reduction of grey matter (Geser et al., 2008; Jung et al., 2001). Also a previous MR spectroscopy study showed subtle metabolic alterations in cortical areas corresponding to the symptoms of the patients (Dydak et al., 2006). Therefore, minor extrastriatal pathology might be present in McLeod syndrome. Based on the neuropathological data available, however, these alterations seem to be much less pronounced compared to HD (Geser et al., 2008; Rinne et al., 1994; Vonsattel et al., 1985). Taken together and in line with the estimated disease duration of the McLeod syndrome ranging between 20 and 30 years, our findings reflect a slowly progressive neurodegenerative process affecting predominantly the caudate nucleus (Danek et al., 2001; Jung et al., 2001). For a more detailed description of the results and its interpretation, please read the results and discussion section in our original publication (Valko et al., 2010).

Statistical issues

With respect to methodological issues, one might criticize the fact that no control subjects were used for comparison of the patient with semantic dementia and that no statistics was applied at all. If I had longitudinal MRI data of age-matched healthy control males at hand, I would have used them in the comparison. However, in my opinion it is not so important to have a control group in this case, because I used a longitudinal study design to investigate whether there are neural correlates of the progressive impairments observed in the domain of language and semantics in this patient. Additionally, it is well known from the literature that the normal age-related atrophy rates associated with healthy aging are of a smaller magnitude than the atrophy rate observed in our patient (Fjell, Walhovd et al., 2009; Fjell, Westlye et al., 2009; Salat et al., 2004; Walhovd et al., 2011; Westlye et al., 2010).

With respect to the statistics applied in the investigation of the boy with the disturbed social beahaviour, following facts should be considered. As already outlined in the statistics section, z-score transformations are only recommended when the samples are large. As a rule of thumb, one can assume approximately a normal distribution when $N_p + N_c > 50$. If $N_p + N_c < 50$, the data are t-distributed. Therefore, in the present case, one has to use t-tests and not z-score transformations. But which kind of t-test do I have to use, a one-sample t-test or a two-sample t-test with pooled variance estimates, the later being more conservative than the former? This depends on the question one is asking, as already mentioned in the section: Statistics of neuromorphometric data in single patients (see above). Here, I preferred the more conservative two-sample t-test with pooled variance estimates as recommended by statisticians (Crawford et al., 2009; Henson, 2006).

With respect to the statistics applied in the multiple synaesthete E.S., it was suboptimal to apply z-score transformations in that case because the control samples were rather small ($n = 20$ and $n = 17$). As recommended by the statisticians, the two-sample t-test with pooled variance estimates would be more appropriate in such a situation (Crawford et al., 2009; Henson, 2006).

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