Morphing voxels: the hype around structural imaging of headache patients

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Neuroimaging analysis using structural data has begun to provide insights into the pathophysiology of headache syndromes. Several independent studies have suggested a decrease in grey matter in pain-transmitting areas in migraine patients. Most of these data are discussed as damage or loss of brain grey matter, reinforcing the idea of migraine as a progressive disease. However, given what we know about the nature of morphometric changes detectable by the methods we have to date, this interpretation is highly speculative and not supported by the data. It is likely that these changes are the consequence and not the cause of the respective headache syndromes, as they are probably not irreversible and only mirror the proportion or duration of pain suffered. Moreover, structural changes are not headache specific and have to be seen in the light of a wealth of pain studies using these methods. The studies in cluster headache patients prompted the use of stereotactic stimulation of the hypothalamic target point identified by functional and structural neuroimaging. Due to the nature of the methods used and due to a high anatomical variance it is more than questionable to use this point as a definite answer to the source of the headache in clusters and even more so when it is uncritically used in individuals. We need a way to study each patient individually using the functional imaging method with the highest spatial and temporal resolution available to enable us to target the seed point for deep brain stimulation on this individual basis. One of the major future challenges is to understand the behavioural consequences and cellular mechanisms underlying neuroanatomic changes in pain and headache.

Keywords: headache; migraine; morphometry; brain; VBM; functional imaging

Introduction

Traditionally, studies of brain morphology completely depended on autopsy material. This situation changed with the advent of modern in vivo imaging methods, in particular magnetic resonance (MR) imaging. While early imaging studies of the brain provided a qualitative description of normal brain morphology and its deviations in disease states, more recently developed MR-based methods allow a quantitative evaluation of brain morphology (Draganski and May, 2008). The whole assortment of these MR-based methods comes under the heading of MR morphometry of the brain. One of the immense advantages is the in vivo observation of temporal changes in brain morphology and the correlation of brain morphology with brain function (Ashburner et al., 2003). Normally, three-dimensional, high-resolution, T1-weighted MRI images acquired with conventional 1.5 T MR scanners and 1 mm3 voxels provide sufficient detail and contrast. One of the widely spread and validated morphometric techniques used to capture structural alterations in the brain is voxel-based morphometry (VBM). VBM is a whole brain method for analysis of automatically pre-processed structural high-resolution MRI data treating images as continuous scalar...
measurements (Draganski and May, 2008). VBM is relatively simple to use, has moderate demands on computational resources and is available in common software packages like FSL or SPM. This technique relies on the segmentation of MR images into different tissue types (grey matter, white matter and CSF) using information derived from image intensity. The grey matter map, as a result of this segmentation, thus describes the spatial distribution for each individual at the level of every voxel. Additional a priori knowledge about the spatial distribution of different tissue types can be applied to refine this segmentation process. To take advantage of this approach, MR data have to be registered to the same stereotactic space as the a priori images—making the segmentation accuracy sensitive to registration errors. Because of this dependency of registration errors, several approaches have been developed to improve registration accuracy, such as the use of segmented images for registration rather than MR images (Good et al., 2001b), a combined model of image registration, tissue classification and bias correction (Ashburner and Friston, 2005), or the application of high-resolution registration methods (Shen and Davatzikos, 2003). These solutions have been implemented in advanced VBM protocols, which then allow voxel-wise statistical testing of grey matter volume in each voxel.

Morphometric studies in headache syndromes

Cluster headache

The pioneering study using VBM to find possible brain differences between headache patients and healthy volunteers found a significant structural difference in grey matter density, a ‘lesion’ coinciding with the inferior posterior hypothalamus, in cluster headache (May et al., 1999), which showed a co-localization of morphometric alterations and functional activation in cluster headache patients (May et al., 1999). These studies prompted the use of stereotactic stimulation (DBS) of this target point identified by functional and structural neuroimaging (May, 2008b). Until now, nearly 50 successfully operated intractable chronic cluster headache patients have been reported (Leone et al., 2008). However, the method of hypothalamic DBS is not without risk (Schoenen et al., 2005) and it does only work in about 50% of patients (Bartsch et al., 2008; Leone et al., 2008). One of the reasons why it only works in some patients and not in others could be the fact that the target point is not exactly defined in patients where higher voltage is needed and is simply wrong in those patients where hypothalamic DBS does not work. This target point was taken directly from the structural and functional studies mentioned above. It needs to be pointed out that these studies are the result of group studies and that the original data needed to be normalized into a stereotactic space and additionally, are smoothed with a filter kernel of at least 10 mm. It is more than questionable to use this point as a definite answer to the source of the headache in cluster and even more so when it is uncritically used in individuals. The anatomy is different (the simple reason why normalization is used in functional neuroimaging) and these subtle differences are corrected in the normalization process (Ashburner and Friston, 1999, 2000). Although the original work by Franzini and Leone (Leone et al., 2001) is ingenious in that it is the first and only time that functional imaging was directly translated into a treatment, which in turn proved to be effective. This work definitely opened new avenues in cluster headache treatment. However, the more we learned about this method over the last 8 years, the more we have to ask ourselves whether the discussion about the target region should be exhausted by discussing the correct name (e.g. hypothalamic grey versus ventral tegmentum, etc.) of this anatomical point which is undoubtedly crucial for the pathogenesis of the trigeminal autonomic syndromes (May, 2005). We need more and better studies and, above all, we need to address the question of individual anatomy and possible anomalies. We need a way to study each patient individually using the functional imaging method with the highest spatial and temporal resolution available to enable us to target the seed point for deep brain stimulation on this individual basis.

Chronic tension type headache

Recently, 20 patients with chronic tension type headache (CTTH) were compared to healthy volunteers and showed a significant decrease in grey matter in the dorsal rostral and ventral pons, the perigenual cingulate cortex, the middle cingulate cortex and the right posterior cingulate cortex, the anterior and posterior insulae bilaterally, the right posterior temporal lobe, the orbitofrontal cortex and parahippocampus bilaterally and the right cerebellum. Interestingly, this decrease in grey matter correlated positively with increasing headache duration in years, i.e. patients with longer history had less grey matter in these regions (Schmidt-Wilcke et al., 2005). In the same paper, patients with medication overuse showed a non-significant decrease in the left orbitofrontal cortex and the right midbrain. As the change in grey matter in chronic tension type headache patients was restricted to structures involved in pain processing, the authors concluded that these data may be interpreted as the consequence of central sensitization, generated by prolonged nociceptive input from the pericranial myofascial tissues (Schmidt-Wilcke et al., 2005).

Migraine

Regarding migraine, a pioneering study by Matharu et al. did not find any significant morphometric changes in grey or white matter in patients suffering from episodic migraine (Matharu et al., 2003). However, five more recent studies question this negative finding. The first one was published by Rocca et al. who investigated 16 migraine patients with T2-visible abnormalities and 15 matched controls using VBM and reported an increased density of the PAG and of the dorsolateral pons in migraine patients (Rocca et al., 2006). The authors also found a decrease in grey matter in the anterior cingulate cortex (ACC) and both insulae in migraine patients. One possibility why this study found structural changes in migraine, whereas an earlier study did not, may be the fact that the study by Rocca et al. used a scanner with higher field strength (3T) whereas the former studies were done on a 1.5T scanner. However, the migraine cohort was rather small
(16 patients) and comprised of patients with T2-visible brain lesions, a finding which is not part of the IHS criteria (Headache Classification Committee of the International Headache Society, 2004). Population-based findings suggest that some patients with migraine (with and without aura) are at an increased risk for sub-clinical lesions in certain brain areas (Kruit et al., 2004; Tietjen, 2004), which was also suggested by a meta-analysis (Swartz and Kern, 2004). Although it is more than questionable that these white matter changes are true vascular infarcts, given that they can vanish spontaneously (Rozen, 2007; Agarwal et al., 2008), it has been shown that they are independent of right-to-left shunts (Adami et al., 2008) and therefore cannot simply be attributed to the occurrence of a patent foramen ovale (PFO) (Dowson et al., 2008), as has been discussed before (Wilmshurst et al., 2000, 2006). In any case, studying only migraine patients with visible MR-lesions may imply a significant bias. Nevertheless, the findings of this study were, in essence, replicated by four other independent studies so far (Kim et al., 2008; Schmidt-Wilcke et al., 2008; Schmitz et al., 2008; Valfre et al., 2008). All of these studies reported a decrease in grey matter in the frontal and temporal cortex. The first one was published by Valfre et al., who investigated 27 migraine patients and 27 healthy controls (Valfre et al., 2008). In comparison with controls, migraineurs presented a significant focal grey matter reduction in the right superior temporal gyrus, right inferior frontal gyrus and left precentral gyrus. Dividing the patients into episodic and chronic migraine (n=11), chronic migraine patients showed a focal grey matter decrease in the bilateral anterior cingulate cortex. Other clusters were found in the amygdala, the parietal operculum, the frontal gyrus and bilateral insula. Comparing all the migraine patients with controls, a significant correlation between grey matter reduction in the anterior cingulate cortex and the frequency of migraine attacks was found (Valfre et al., 2008). The authors concluded that this study supports the concept that migraine is a progressive disorder (Valfre et al., 2008). The same conclusion was drawn by another study investigating 28 patients and demonstrating less grey matter in the frontal lobes, brainstem and the cerebellum in migraineurs. In this study, both the attack frequency and the disease duration correlated with the extent of grey matter reduction and the authors interpreted this finding as an indicator for ‘brain damage’ in migraine. The third study was published by Kim et al., who compared grey matter volume between 20 migraine patients (5 with and 15 without aura) with 33 healthy controls matched for age and sex (Kim et al., 2008). Although the statistics have to be seen with caution, given the different sample size per cohort, the findings are remarkably similar to the ones above: migraine patients had significant grey matter reductions in the bilateral insula, motor/premotor, prefrontal, cingulate cortex, right posterior parietal cortex and orbitofrontal cortex (Fig. 1). Moreover, all of these regions were negatively correlated with headache duration and lifetime headache frequency. The authors interpret their findings—they ‘suggest that repeated migraine attacks over time result in selective damage to several brain regions involved in central pain processing’.

The biggest study so far was published by Schmidt-Wilcke et al., who compared 35 patients suffering from migraine with 31 healthy controls with no headache history. They found a decrease in grey matter in the anterior and middle cingulate cortex in migraineurs (Schmidt-Wilcke et al., 2008). The authors discussed their findings in context with recent findings in chronic pain states, such as chronic phantom pain (Draganski et al., 2006b) and chronic back pain (Apkarian et al., 2004) and suggested that the grey matter change in migraine patients is the consequence of frequent nociceptive input and should thus be reversible when migraine attacks cease (Schmidt-Wilcke et al., 2008). In summary, all but the last study in migraine interpreted their finding—a focal reduction in grey matter—as a damage of the brain or as an indicator that migraine is a progressive disease. This argumentation disregards the point that migraine is a self-remitting disease which usually resolves with age. Until longitudinal studies, which assess whether these changes also recede, have been conducted, we should not over-interpret these data as ‘brain damage’. In this context it is interesting that chronic tension type headache does not always resolve with age and that morphometric changes seen in these patients may theoretically be more functionally relevant.

**Morphometric changes in chronic pain**

Any morphometric findings in headache patients have to be seen in the light of a wealth of morphometric studies in chronic pain.
In the last 2 or 3 years, several studies have been published, which demonstrated structural brain changes in chronic pain syndromes. A striking feature of all of these studies is the fact that the grey matter changes were not randomly distributed but concerned defined and functionally highly specific brain areas—namely, involvement in supraspinal nociceptive processing. The most prominent findings were different for each pain syndrome, but overlapped in the insula and dorsal pons (May, 2008a). Further structures comprise the thalamus, basal ganglia and parahippocampal cortex bilaterally. All of the studies conducted so far in chronic pain syndromes, including fibromyalgia (Kuchinad et al., 2007), irritable bowel syndrome (Davis et al., 2008), phantom pain (Draganski et al., 2006b), chronic back pain (Apkarian et al., 2004; Schmidt-Wilcke et al., 2006) and thoracic spinal cord injury (Wrigley et al., 2008) showed a decrease in some of the above-mentioned areas. Nevertheless, all available clinical MR morphometric studies have their limitations. One of the major drawbacks is the poor comparability of studies from different research centres. In addition, many studies were done in small patient samples and did not analyse the temporal dynamics and the determinants of brain morphological changes. Consequently, routine clinical application of MR-based morphometry is currently not feasible. However, the fact that the above mentioned findings in migraine and tension type headache have been replicated by nearly all studies investigating brain changes in patients suffering from all sorts of chronic pain, suggest that these findings are not specific to head pain but to the chronicity of pain. If it is true that chronic pain patients have a common ‘brain signature’ in areas known to be involved in pain control, the question arises whether the central reorganization processes in chronic pain syndromes could involve a ‘degeneration’ of specific brain areas. This question is not redundant as a degenerative process is irreversible. Although some of these studies in chronic pain also fall for the assumption that a decrease in brain grey matter must mean a damage to the brain (Apkarian et al., 2004; Kuchinad et al., 2007), the crucial question is what do we measure when we measure grey matter?

The neurobiological basis of structural alterations (increase or decrease in grey matter demonstrated by VBM) on a microscopic level are not well defined. VBM detects changes in grey matter concentration per voxel as well as changes in the classification of individual voxels, e.g. from white to grey matter (Good et al., 2001a) and probably a combination of both. In general, a decrease in grey matter could be due to a simple decrease in cell size, atrophy of neurons or glia, inactivation of spine density or even changes in blood flow or interstitial fluid. Unfortunately, all available studies compared cohorts of patients and therefore no statement regarding dynamic changes can be made. In some respects, this situation resembles that in the functional MRI-field some years ago, when its use for our understanding of brain function was not debated, yet the long-supposed physiological correlate of the BOLD-signal was not yet proven (Logothetis and Pfeuffer, 2004). As long as the causes of these changes on a histological–anatomical level remain unresolved, the clinical relevance of MR morphometric results is limited.

In vivo demonstrations of a change in brain structure could represent a neuroanatomical substrate for the respective disease (Reiss et al., 2004) or just an epiphenomenon or even an artefact. In this respect, any data that demonstrate a population difference between patients and controls must be regarded with caution as long it is not known whether such changes are the cause or the consequence of the disease (Weiller and Rijntjes, 1999). It is unquestionable that changes in the periphery, i.e. loss of afferent input due to unilateral amputation of an extremity, may change the brain structure of individuals (Draganski et al., 2006a). Recent studies also suggested that abnormalities in the cerebral cortex of subjects with ambylophia (Mendola et al., 2005), strabismus (Chan et al., 2004) and even amaurosis (Noppeney et al., 2005) exist, possibly as a result of experience-dependent neuronal plasticity (Draganski and May, 2008). As a non-invasive procedure, MR morphometry is the ideal tool for the quest to find the morphological substrates of diseases, deepening our understanding of the relationship between brain structure and function and even to monitor therapeutic interventions. One of the great challenges in the future is the validation of morphometric methods as well as the development of a reliable means that allows the pooling of data from several scanners and centres. With the application of these methods, MR-based morphometry will become an extremely powerful tool for multi-centre and therapeutic trials of several brain diseases.

The brain in pain: dynamic alterations and neuronal plasticity

Considering that activation-dependant brain plasticity in humans on a structural level has already been demonstrated in adults (Draganski et al., 2004; Boyke et al., 2008), it is an interesting question whether repeated painful stimulation may lead to structural changes of the brain. In a very recent study, 14 healthy subjects were stimulated daily with a 20-min pain paradigm for 8 consecutive days, using structural MRI performed on Days 1, 8, 22 and again after 1 year. Using voxel-based morphometry, it was demonstrated that repeated painful stimulation resulted in a substantial increase of grey matter in classical somatosensory areas, including the mid-cingulate and somatosensory cortex (Teutsch et al., 2008). These data are in line with most morphometric studies investigating structural brain plasticity as a result of exercise and learning (Gaser and Schlaug, 2003; Draganski et al., 2004; May et al., 2007). The changes in brain structure are usually exclusively demonstrated in brain areas which are ascribable to the task, just as in the present study, where changes are only seen in somatosensory areas. Moreover, the finding of structural changes follows the previously described functional pattern (Bingel et al., 2007) precisely, i.e. a significant change during the protocol which reverses to pre-stimulation levels at the fourth time-point, i.e. after 1 year. It is an intriguing fact that chronic pain patients suffer constant pain, but seem not to develop an increase in grey matter in somatosensory areas, although several studies showed that exercise is accompanied by an increase of grey matter in the
regions which are specific for the respective task (for review see May and Gaser, 2006). One explanation for this lack of grey matter increase in chronic pain patients is that they do not have a significant noxious input (any more). In that case, the experience of constant pain is mostly driven by the brain itself and the afferent (peripheral noxious) input is no longer needed for this experience. Another possibility is that a given task-specific exercise will only increase grey matter in corresponding brain areas until the task is learned and that this change recedes once the task is learned sufficiently.

It is not understood why only a relatively small proportion of humans develop a chronic pain syndrome, considering that pain is a universal experience. The question arises whether in some humans a structural difference in central pain transmitting systems may act as a diathesis for chronic pain. In the course of chronicity, numerous modulatory mechanisms have been postulated and altogether addressed as ‘neuronal plasticity’ (Woolf and Salter, 2000) and structural changes of the brain may be added to this list (May, 2008b). There is no conclusive data regarding the cause or the consequence of the different cortical and subcortical morphological changes that have been observed in chronic pain states, although the correlation of pain duration and the degree of grey matter decrease in most studies suggests that the morphological changes are, at least in part, secondary to constant pain.

**Which structural changes are specific for headache?**

Given that nearly all studies investigating structural changes in different headache syndromes found similar results and given that these results have been found in most studies of chronic pain as well, one has to address these changes, namely a decrease of grey matter in pain transmitting structures, as non-specific for a given headache or pain syndrome and further studies will be required to definitively address this issue. As most changes correlate to pain duration, it seems plausible to argue that the alteration of this region is a consequence, rather than a cause, of frequent nociceptive input. The nature of chronic pain makes it difficult to prove this point. Regarding headache, however, it is not known why migraine usually remits with age. It is a very interesting question for future studies whether the morphological changes reverse when migraine, and hence the disproportionate amount of nociceptive stimulation, stops.

Two studies reported structural changes which may be specific for the respective disease: the hypothalamus in cluster headache (May et al., 1999) and the brainstem in migraine (Rocca et al., 2006). The data on cluster headaches describe an increase in grey matter which follows the functional pattern during the acute headache attack (May et al., 1998). The study in migraine patients reported an increased density of grey matter in the dorsal pontine region, at virtually the same location as the activation reported in the migraine PET studies. The anatomical co-localization of functional and structural changes raises the possibility that the observed changes may be causal rather than a consequence of the pain. In both cases the question arises whether these changes (an increase of regional grey matter rather than a decrease) reflect the above mentioned morphometric studies investigating structural brain plasticity as a result of exercise and learning. Further studies need to be done and as migraine has a strong genetic component, the ideal inclusion criteria for future studies to render groups as homogenous as possible could be based on genotype (cohort study) or response to treatment (longitudinal study including controls). However, any data of a decrease in grey matter in headache syndromes need to be seen in the light of all the intelligence which has been gathered in the last 10 years and probably do not justify the discussion of brain damage or whether or not the disease is progressive.

**Limitations of VBM**

As a non-invasive procedure, MR Morphometry has the potential to be the ideal tool for the quest to find the morphological substrates of diseases, deepening our understanding of the relationship between brain structure and function and even to monitor therapeutic interventions. VBM is for research purposes only and requires groups of at least 20 subjects per group to produce stable results (May and Gaser, 2006). However, headache and pain studies thus far suffer relatively often from small sample sizes and selected patient samples (e.g. cases from specialized centres rather than population cases). Given that the groups which are to be compared need to be highly homogenous, an excellent and scrupulous matching of cases and controls is mandatory. However, who is the proper control for a migraine study: volunteers who claim to never have experienced a headache in their life or volunteers who just have no migraine and no first-grade family member with migraine? Both choices make this very challenging due to recall issues, and the long-term nature of the disorder. Perhaps structural studies of a condition that is potentially genetically heterogenous, such as migraine, miss subtle changes that might segregate with a more homogenous genotype (Matharu et al., 2003). The advantage of VBM is that it is fully automated and allows for changes elsewhere in the brain and thus avoids observer bias, and moreover, it incorporates a voxel-wise estimation of variance. However, differences in imaging modalities/equipment/analysis and, above all, image pre-processing steps such as smoothing, registration, choice of small volume correction, etc. may well account for differences in VBM-findings. Until there is a better standardization between different studies and centres (Magis et al., 2007; May and Gaser, 2006) we need to be cautious not to overinterpret morphometric data in headache patients.

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**References**


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