The Cortical Signature of Central Poststroke Pain: Gray Matter Decreases in Somatosensory, Insular, and Prefrontal Cortices

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It has been proposed that cortical structural plasticity plays a crucial role in the emergence and maintenance of chronic pain. Various distinct pain syndromes have accordingly been linked to specific patterns of decreases in regional gray matter volume (GMV). However, it is not known whether central poststroke pain (CPSP) is also associated with cortical structural plasticity. To determine this, we employed T1-weighted magnetic resonance imaging at 3 T and voxel-based morphometry in 45 patients suffering from chronic subcortical sensory stroke with (n = 23) and without CPSP (n = 22), and healthy matched controls (n = 31). CPSP patients showed decreases in GMV in comparison to healthy controls, involving secondary somatosensory cortex (S2), anterior as well as posterior insular cortex, ventrolateral prefrontal and orbitofrontal cortex, temporal cortex, and nucleus accumbens. Comparing CPSP patients to nonpain patients revealed a similar but more restricted pattern of atrophy comprising S2, ventrolateral prefrontal and temporal cortex. Additionally, GMV in the ventromedial prefrontal cortex negatively correlated to pain intensity ratings. This shows for the first time that CPSP is accompanied by a unique pattern of widespread structural plasticity, which involves the sensory-discriminative areas of insular/somatosensory cortex, but also expands into prefrontal cortex and ventral striatum, where emotional aspects of pain are processed.

Keywords: cortical plasticity, MRI, pain, stroke

Introduction

Any ischemic or hemorrhagic stroke affecting the somatosensory pathway can result in a chronic regional neuropathic pain syndrome located within a distribution corresponding to the cerebrovascular lesion. This central poststroke pain (CPSP) has a prevalence of ∼8% in stroke patients (Klit et al. 2011), often refractory to medical treatment and can severely impair quality of life (Andersen et al. 1995; Klit et al. 2009, 2011). It is known that the underlying pathophysiological mechanisms. It has been proposed that a lesion of the spinothalamic tract (STT) or its target regions is a necessary prerequisite for CPSP (Boivie et al. 1989). Accordingly, we and others have demonstrated that in thalamic sensory strokes, CPSP occurs in those patients whose lesions are located in more postero-lateral parts of the thalamus where STT is known to terminate (Krause et al. 2012; Sprenger et al. 2012). However, apart from specific lesion locations, other factors may also contribute to the emergence and maintenance of CPSP (Klit et al. 2009). There is growing evidence from recent magnetic resonance imaging (MRI) studies using voxel-based morphometry (VBM) that chronic pain syndromes are associated with maladaptive cortical structural plasticity. Most of these studies found decreases in regional gray matter volume (GMV) in diverse pain syndromes such as chronic back pain (Apkarian et al. 2004; Schmidt-Wilcke et al. 2006), complex regional pain syndrome (Geha et al. 2008), osteoarthritis (Rodriguez-Raecke et al. 2009), different types of headache (Schmidt-Wilcke et al. 2005, 2008), trigeminal facial pain (Gustin et al. 2011; Henderson et al. 2013), and even in individuals from the general population with ongoing pain of variable origin (Ruscheweyh et al. 2011). Gray matter atrophy usually comprised multiple areas which are known to be involved in the processing of pain, that is, somatosensory cortices, thalamus, insular cortex, cingulate cortex, and prefrontal cortex. Remarkably, clinically distinct chronic pain syndromes exhibit specific anatomical patterns of atrophy, and it has been proposed that these patterns reflect some of the maladaptive mechanisms unique to each chronic pain condition (Baliki et al. 2011).

Whether CPSP also is associated with maladaptive structural cortical plasticity is not known to date. For this purpose, we examined 45 patients with a somatosensory stroke at a chronic stage. Out of these, 23 patients suffered from CPSP and were compared with those chronic sensory stroke patients without pain. Both patient groups were also compared with 31 healthy matched controls. We hypothesized that

1. compared with controls, CPSP-patients show gray matter atrophy in somatosensory as well as insular and frontal cortical areas which are known to be involved in pain processing,
2. the pattern of atrophy is also evident when comparing CPSP-patients to nonpain stroke patients,
3. GMV in pain-related areas negatively correlates with intensity and/or duration of pain in CPSP patients.

Methods

Subjects

Forty-five patients were recruited retrospectively from our in-house stroke database (n = 32), as well as from a still ongoing prospective study in a period from 2009 to 2012 (n = 13). Inclusion criteria was a solitary and chronic subcortical ischemic or hemorrhagic stroke (thalamus, internal capsule, brainstem, or medulla oblongata) accompanied by contralateral somatosensory symptoms. Exclusion criteria were: lesions in other parts of the somatosensory pathway, moderate-to-
severe leucencephalopathy, moderate-to-severe paresis, any other chronic pain syndrome, and any other musculoskeletal, internal, or neurological disorder potentially confounding the aetiology of their pain syndrome (i.e., including other entities of poststroke pain such as shoulder pain or spasticity). Six of these patients were included in a previous study using lesion-to-symptom mapping in patients with thalamic sensory stroke (Krause et al. 2012).

Each patient underwent detailed history taking and neurological examination with emphasis on testing of positive and negative somatosensory symptoms, as described before (Krause et al. 2012). CPSP was defined as spontaneous pain, allodynia or hyperpathia which emerged within months after stroke, located within a distribution corresponding to a vascular lesion confirmed by MRI. Based on these criteria, patients were assigned either to the CPSP (n = 23, 41% female) or to the nonpain sensory stroke group (n = 22, 43% female). We additionally examined MR images of a group of healthy controls (n = 31, 42% female), drawn from another database derived from a previous study of our group (Witte et al. 2014), in order to match the whole-patient group as well as both patient subgroups with respect to age and sex.

To evaluate neurological deficits the National Institute of Health Stroke Scale (NIHSS) were used. Depressive symptoms were rated using the Geriatric Depression Scale (GDS). CPSP patients were asked to rate mean as well as maximum pain intensity during the 4 weeks prior to study visit on the Visual Analogue Scale (VAS; 0 = no pain at all; 10 = maximum imaginable pain). To allow for an analysis regarding the impact of pain medication on GMV, drug consumption was quantified using the Medication Quantification Scale (Harden et al. 2005). In the case of binary data, statistical tests were performed using the exact Fisher test. For all other purposes, the non-parametric Mann–Whitney U test was used (with z-transformed data as dependent variables). All statistical tests were performed by means of the Statistical Package for the Social Sciences software (SPSS, Version 15.0).

Written informed consent was obtained from each patient and subject prior to study inclusion. The study was approved by the local ethics committee.

MRI Data Acquisition
In all subjects, MRI was performed on a clinical 3 T Scanner (TIM Trio; Siemens). To screen for acute or chronic ischemic or hemorrhagic cerebral lesions, diffusion weighted imaging, T2*-weighted imaging and a FLAIR sequence were acquired. In all subjects, a 3-dimensional T1-weighted dataset at high resolution using a magnetization prepared rapid gradient echo (MPRAGE) imaging sequence was acquired (spatial resolution 1.0 × 1.0 × 1.0 mm3; time repetition = 1900 ms, time echo = 2.5 ms, flip angle = 98°).

Data Analysis
Lesion volumes were delineated manually from raw T1-weighted images by means of the MRICro software (http://www.mricro.com) as described previously (Krause et al. 2012). T1-weighted images were then preprocessed using the Statistical Parametric Mapping software version 8 (SPM8, Wellcome Trust Centre for Neuroimaging, University College London, London, UK; http://www.fil.ion.ucl.ac.uk/spm) running under Matlab version 7.11 (Mathworks Inc., Natick, MA, USA; www.mathworks.com/matlabcentral). Anatomical datasets had to be flipped from right to left in 20 of the patients to ensure that all lesions were located on the same (left) side of the brain. Standard routines and default parameters of the VBM8 analysis toolbox including DARTEL (Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra) were applied (http://dbm.neuro.uni-jena.de/vbm.html). For preprocessing, images were bias-field corrected, then segmented and registered to standard Montreal Neurological Institute (MNI) space using the unified segmentation approach (Ashburner and Friston 2005). Cost function masking (Brett et al. 2001) was employed during normalization procedures using the models established with MATLAB in order to minimize deformations due to chronic stroke lesions (Ander sen et al. 2010). Gray matter segments were modulated with non-linear components to allow for comparison of the absolute amount of tissue corrected for individual brain sizes (volume of gray matter; (Good et al. 2001)). Subsequently, the resulting images were smoothed with an isotropic Gaussian kernel of 8 mm3 full width at half maximum (FWHM). The resulting gray matter images were statistically analysed by voxel-wise comparison of intensity values employing a 2-sample t-test. The group comparisons contrasts tested were “CPSP patients versus healthy controls”, “CPSP patients versus nonpain sensory stroke patients”, and “nonpain sensory strokes versus healthy controls”. An additional subanalysis using the same contrasts was calculated for patients with permanent CPSP (pCPSP, n = 18), since we assumed that cortical plasticity is presumably more pronounced in patients with permanent neuropathic pain than in those patients with mere pain attacks, mere allodynia, or hyperpathia, respectively. To test whether specific lesion location leads to different patterns of cortical atrophy, we also compared a subgroup of CPSP patients with thalamic stroke to healthy controls (“thalamic CPSP patients vs. healthy controls”). Finally, a whole-brain multiple regression analysis was conducted on all CPSP subjects using maximum pain intensity, mean pain intensity, and pain duration (as well as their interaction), Medication Quantification Scale (MQS) and lesion volume as covariates of interests. Age, sex, and total intracranial volume were always used as nuisance variables.

To ensure that analysis was restricted to gray matter segments, thresholding with an absolute value of 0.2 was applied to the data. The statistical threshold for the T-Maps was first set to P < 0.001, uncorrected for multiple comparisons at the voxel level. To control for multiple comparisons, T-maps were then thresholded at P < 0.05 using a family-wise error correction at cluster size level, and an additional non-stationary cluster correction was employed (Hayasaka et al. 2004). The resulting T-maps were allocated to the Brodmann areas by means of the WFU PickAtlas tool version 3.0 (Maldjian et al. 2003). Based on data from previous VBM studies on pain patients, we expected prefrontal areas to be involved in gray matter changes. Anatomical subdivisions of prefrontal cortex were therefore predefined as follows: orbitofrontal cortex (BA10/11), ventrolateral prefrontal cortex (VLPFC) (BA 44/45/47), dorsolateral prefrontal cortex (DLPFC, BA46/9), VMPFC (BA 14) (Kringlelback 2005; Badre and Wagner 2007). Insular cortex was separated into anterior and posterior parts by the macroanatomical landmark of the insular central sulcus as described by Nieuwenhuys (2012).

Results
Twenty-three of the 45 patients suffered from CPSP, out of which 5 had pure allodynia accompanied by short lasting pain attacks, while all others reported permanent spontaneous pain. The remaining 22 nonpain stroke patients did not report any pain symptoms at all (Table 1). Mean age (±standard deviation; SD) was 65.3 (±10.2) in CPSP, 63.45 (±9.1) in nonpain stroke, and 63.8 (±13) years in healthy controls. CPSP and nonpain patients did not differ with respect to age and sex (P = 0.39 and P = 0.99, respectively). In comparison to healthy controls, CPSP and nonpain groups also did not differ with respect to age (P = 0.83 and P = 0.32, respectively) or sex (P = 0.99 for both comparisons). When compared with each other, patients subgroups differed with respect to mean NIHSS (1.9 ± 1.2 for CPSP vs. 0.9 ± 0.7 for nonpain patients; P = 0.0022) and GDS (9.2 ± 6.6 for CPSP vs. 5.1 ± 9.1 for nonpain patients; P = 0.022), while they did not differ with respect to average lesion volume: 186.5 mm3 (SD 184.1 mm3) for CPSP patients, and 108.5 mm3 (SD 123.9 mm3) for nonpain stroke patients, respectively (P = 0.13). For the CPSP group, mean pain duration was 20.6 months (SD 19), mean pain intensity was 4.5 (VAS score; SD 1.9), mean maximum pain intensity was 6.3 (VAS score; SD 2.2). Mean time from stroke onset to study visit was 25.5 months (SD 26.6) for CPSP patients and 22 months (SD 26.2) for nonpain stroke patients (P = 0.82).

As compared with healthy controls, patients with CPSP showed significant decreases in GMV in bilateral somatosensory cortex.
cortex (S2), in bilateral anterior insular cortex (aIC), in ipsilesional posterior insular cortex (pIC), in ipsilesional VLPFC, in contralesional orbitofrontal cortex (OFC), nucleus accumbens (NAc), and in contralesional temporal cortex along the superior temporal sulcus, in superior temporal as well as middle temporal gyrus, respectively ($P < 0.05$, FWE-corrected). In comparison to nonpain patients, decreases were found in contralesional S2 and superior temporal gyrus.

A further analysis based on those CPSP patients with permanent pain ($n = 18$) revealed the same areas as significantly decreased compared with healthy controls (Fig. 1A). The contrast “permanent CPSP < nonpain sensory stroke patients” showed decreases in contralesional S2, contralesional superior temporal as well as middle temporal gyrus, and ipsilesional VLPFC (Fig. 1B). The opposite contrasts did not show any significant differences (i.e., there were no significant GMV increases in CPSP nor in nonpain patients as compared with controls).

MNI coordinates of significant clusters and their $T$-values for the of both groups of CPSP patients versus healthy controls are given in Table 2.

In Figure 2, the 3 contrasts “permanent CPSP < healthy controls”, “permanent CPSP < nonpain stroke patients”, and “nonpain stroke patients < healthy controls” are given compared at a less conservative threshold ($P < 0.001$, uncorrected for multiple comparisons).

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**Table 1**

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<th>Pain duration (m)</th>
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Note: CPSP, central post stroke pain; y, years; m, months; f, female; m, male; NIHSS, National Institute of Health Stroke Scale; GDS, Geriatric Depression Scale; VAS, Visual Analogue Scale; thal, thalamus; med obl, medulla oblongata; int caps, internal capsule; C, hand; F, face; L, lower limb; T, trunk; d.m., data missing; allodyn, allodynia; GBP, gabapentin; BCL, baclofen; PGB, pregabalin; CBZ, carbamazepine; CLP, clomipramin; APZ, alprazolam.
When comparing the subgroup patients with CPSP and thalamic strokes to healthy controls, significant decreases of gray matter were found in ipsilesional VLPFC and anterior insula, as well as in contralesional OFC, NAc and middle temporal gyrus (see Supplementary Fig. 1).

Results of the whole-brain multiple regression analysis are depicted in Figure 3. Significant negative correlations of mean pain intensity are found in contralesional ventromedial prefrontal cortex (VMPFC). All other variables of interests (maximum pain intensity, pain duration (as well as their

Figure 1. Significant decreases in GMV in patients with permanent CPSP as compared with healthy controls and with nonpain sensory stroke patients. T-maps of group comparisons were thresholded at $P<0.05$ using a familywise error correction at cluster size level and an additional non-stationary cluster correction (Hayasaka et al. 2004). GMV changes are overlaid onto axial, sagittal, and coronal slices of an individual patient’s $T$-weighted anatomical image set. Slice locations are indicated by $x/y/z$ coordinates for each plane. In (A) significant decreases are found in bilateral S2, in bilateral aIC, in ipsilesional posterior insular cortex, in ipsilesional ventrolateral prefrontal cortex (VLPFC), contralesional orbitofrontal cortex (OFC), contralesional Nucleus accumbens, contralesional temporal gyrus (TG). In (B) (CPSP < nonpain patients) significant decreases are found in VLPFC, contralesion S2 and contralesional TG. Brain slices are depicted in neurological convention, and parts of the datasets were horizontally flipped to provide that all lesions are located on the same (i.e., left) side of the brain. In one of the axial slices ($z = +2$), the thalamic infarction can be seen.
pain syndromes exhibit distinct patterns of structural plasticity, possibly reflecting distinct pathophysiological processes in each condition (Baliki et al. 2011). And indeed, the pattern of gray matter decreases we found in CPSP patients differs from those previously reported in other pain syndromes.

In particular, we found gray matter decreases in posterior insular cortex and secondary somatosensory cortex (S2). Studies using functional imaging and transcranial magnetic stimulation have linked these areas to a sensory-discriminative role (e.g., intensity coding) during painful stimulation (Peyron et al. 1999; Bornhovd et al. 2002; Mazzola et al. 2012). Intraoperative electrical stimulation of posterior insula leads to painful sensations in contralateral hemisiby (Ostrowsky et al. 2012), and stroke lesions in this area can even result in a distinct central pain syndrome termed “operculo-insular pain” (Garcia-Larrea 2012).

Cortical atrophy in aIC has also been found in a variety of pain syndromes (DaSilva et al. 2008; Gustin et al. 2011; Absinta et al. 2012; Henderson et al. 2013). Beyond its involvement in pain processing as observed in functional imaging studies (Brooks et al. 2005; Kong et al. 2006; Peltz et al. 2011), aIC is also activated during a wide range of interoceptive conditions including sexual arousal, thirst, dyspnea, or itch (Craig 2009). It is also sometimes referred to as “visceroceptive” cortex, because intraoperative cortical stimulation of aIC leads to nausea and epigastric sensations (Ostrowsky et al. 2000). Strong functional connections of aIC to areas known for affective and cognitive processing such as anterior cingulum have led to the assumption that aIC integrates interoceptive information with emotional salience to form a subjective image of our body (Taylor et al. 2009; Peltz et al. 2011). The VLPCF is activated during experimentally induced allodynia (Witting et al. 2001), and it is thought to be involved in both the generation and regulation of emotion in appraisal processes (Wager et al. 2008). The adjacent lateral orbitofrontal cortex is regarded to monitor and evaluate negative reinforcers such as pain in behavioural decision tasks (Kringelbach and Rolls 2004). It is accordingly activated by painful more than by pleasant or neutral touch (Rolls et al. 2003). Both frontal areas show enhanced activation during placebo analgesia as compared with opioid analgesia and exert a top-down influence on activity in anterior cingulate cortex (Petronic et al. 2010).

We also found decreases in subcortical gray matter of the ventral striatum, that is, NAc, as reported in patients with trigeminal (Gustin et al. 2011) and persistent subacute back pain (Baliki et al. 2012). In the latter longitudinal study, the most accurate predictor for a later transition from subacute to chronic pain was functional connectivity between medial prefrontal cortex and NAc (Baliki et al. 2012). Complementary to the traditional view of NAc as an area signaling reward and positive reinforcement, there is growing evidence that it also processes aversive stimuli such as pain, as shown in human imaging studies (Becerra and Borsook 2008; Roitman et al. 2008). NAc can be anatomically divided into 2 subunits (i.e., shell and core), which have been recently shown to differentially respond to stimuli depending on their hedonic value (Baliki et al. 2013): the NAc shell was activated by impending pain, while the core signaled anticipation of cessation of pain (i.e., the reward value of analgesia). Both structures were also activated by cues signaling monetary reward, but in a reverse fashion. When comparing these findings to the MNI coordinates of the most significant voxels in NAc in our CPSP
patients, we found that the center of NAc atrophy in CPSP is located within the boundaries of the NAc shell (which mediates impending pain) as reported by Baliki and coworkers. It fits to this data that a recent single case study suggests NAc as a promising therapeutic target for deep brain stimulation in CPSP (Mallory et al. 2012).

Temporal cortex is also frequently observed to show gray matter decreases: superior temporal gyrus was affected in patients with chronic back pain (Baliki et al. 2011) and fibromyalgia (Schmidt-Wilcke et al. 2007), while middle temporal gyrus showed atrophy, for example, in cluster headache and migraine (Absinta et al. 2012). Within the cognitive neuroscience literature, the region of the superior temporal sulcus (which separates superior from middle temporal gyrus) has been ascribed a decisive role for language comprehension as well as social perception and attention (Redcay 2008). It is assumed to...
constitute the main region for audiovisual integration, and plays an important role in biological motion perception and processing of faces (Hein and Knight 2008). However, despite these findings and in contrast to the aforementioned areas, little is known about the underlying functional role of temporal cortex in pain processing, and a comprehensive theory of how these temporal areas contribute to the emergence or the maintenance of chronic pain is lacking (Holle et al. 2011).

A negative correlation of mean pain intensity with gray matter volume was found in VMPFC. This is strikingly similar to findings reported by Geha et al. (2008) who reported that VMPFC atrophy was associated with the interaction of pain intensity and pain duration in patients with complex regional pain syndrome. The authors related this phenomenon to the patients' impaired performance in emotional-decision tasks (Apkarian et al. 2004). Also, VMPFC is activated during states of sustained and high spontaneous pain intensity in chronic back pain patients, which has been interpreted as a sustained emotional suffering signaling (Baliki et al. 2006). VMPFC is known to encode the emotional value of somatosensory stimuli (Kringelbach 2005), and lesions of VMPFC lead to severe emotional dysregulation (Anderson et al. 1999, 2006). Against this background, it has been proposed that VMPFC “constitutes the emotional motivational and hedonic components that may influence the quality of perceived pain” (Apkarian et al. 2011).

Taken together, cortical atrophy in CPSP patients encompasses a wide range of prefrontal, insular and subcortical regions which are involved not only in the sensory discrimination of pain but also in its affective and cognitive aspects and which modulate pain perception and emotion.

The potential mechanisms underlying such decreases in cortical gray matter as revealed by VBM include amongst others cell atrophy, decreased cell size or decrease in glial cells, changes in interstitial fluids, or a combination of these (Apkarian et al. 2011). For example, a reduction of N-acetyl-aspartate as a marker of decreased cell density (Grachev et al. 2000) has been linked to cortical atrophy in DLPCF as revealed by VBM in patients with chronic back pain (Apkarian et al. 2004). Geha et al. (2008) showed that regional decreases in gray matter density in CRPS patients are accompanied by regional changes in white matter connectivity, also suggesting neuronal loss as a probable cause. However, there is growing evidence which points to synaptic plastic changes as the most likely mechanism of gray matter decreases in pain syndromes (Apkarian et al. 2011): decreases in cortical volume of chronic pain patients have been repeatedly shown to be reversible within a time-period of 4–12 months when pain is relieved (Obermann et al. 2009; Rodriguez-Raecke et al. 2009; Ruscheweyh et al. 2011). Interestingly, repetitive painful stimulation leads to gray matter decreases in pain-processing brain regions of healthy subjects who show a lack of habituation to these stimuli (Stanekowitz et al. 2013).

One might speculate whether the changes seen in CPSP patients are due to somatosensory symptoms in general, irrespective of pain. If that was the case, one should expect similar changes in both nonpain and CPSP patients. But comparison of nonpain sensory stroke patients to healthy controls did not reveal any significant cortical changes. Additionally, at a less conservative threshold the emerging pattern of gray matter decreases in nonpain patients differed clearly from that of CPSP patients, whereas the contrasts “CPSP patients versus healthy controls” and “CPSP patients versus nonpain sensory stroke patients” resembled each other. This finding strongly argues in favor of CPSP as the main contributor to the decreases in gray matter.

CPSP and nonpain patients differed with respect to their Geriatric Depression Score, which might also have contributed to the changes in GMV. However, the results of 2 meta-analyses of VBM studies do not overlap with our findings and show that cortical atrophy in depression is pronounced in anterior cingulate gyrus and limbic areas (Du et al. 2012; Lai 2013). Besides, as opposed to subjective pain intensity ratings, the GDS scores here did not show any significant correlation to regional GMV.

Patients’ subgroups showed some differences in terms of lesion location. For example, lesions of medulla oblongata were more frequent in CPSP patients than in nonpain patients. Yet, the subanalysis focusing on CPSP patients with thalamic strokes revealed gray matter atrophy in areas also found in the analysis comprising all CPSP patients. This argues against a differential impact of lesion location in our data. Although it cannot be ruled out that such effects might be traceable in larger patient groups. Beyond this, it has to be taken into account that there might still be subtle spatial differences on a smaller scale. It has been concluded from clinical studies that a lesion of the STT is a necessary prerequisite for the development of CPSP (Boivie et al. 1989). Correspondingly, we and others have recently shown that lesions in thalamic stroke patients with CPSP tend to be located more lateral, ventral and posterior as compared with thalamic stroke patients without pain, and thereby affecting a thalamic subregion where spinothalamic afferents predominantly terminate (Krause et al. 2012; Sprenger et al. 2012).

**Limitations**

A limitation to our study is that differences between groups with respect to handedness or education as confounding factors cannot be excluded, since we did not have consistent data on these topics. One might expect associations of handedness and GMV in cortical (pre-) motor or sensory areas, but, to our knowledge, such evidence is lacking so far. Moreover, a VBM study on 465 healthy adults failed to show any effect of handedness on regional cortical volume (Good et al. 2001). An influence of pain medication on cortical morphology cannot be completely ruled out. We quantified drug consumption using the MQS (Harden et al. 2005), and performed a whole-brain voxel-wise multiple regression analysis. In good accordance with other VBM studies on pain patients this did not reveal any correlation of pain medication and gray matter volume (Apkarian et al. 2004; DaSilva et al. 2008; Geha et al. 2008). However, it might still be speculated that drugs with distinct mechanisms of action in the central nervous system may differentially influence gray matter volumes, for example, as shown for antipsychotic drugs (Moncrieff and Leo 2010). Studies combining a much larger cohort stratified for drug subcategories are needed to clarify this issue.

**Conclusions**

In summary, chronic CPSP is accompanied by a unique and widespread pattern of cortical atrophy involving secondary somatosensory cortex, insular cortex, ventrolateral prefrontal, and orbitofrontal cortex, temporal cortex and NAC. The pattern of plasticity indicates that in CPSP not only the sensory-
discriminative aspects but also the affective evaluation of pain are disturbed. Such maladaptive changes might at least partially account for the resistance of CPSP to medical treatment. Our results may provide targets for new therapeutic approaches (e.g., specific training, psychotherapy, and noninvasive stimulation techniques) as well as possible future markers for measures of therapeutic interventions.

Supplementary Material
Supplementary material can be found at: http://www.cercor.oxfordjournals.org/

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References


