EJN fens European Journal of Neuroscience

European Journal of Neuroscience, Vol. 35, pp. 1481–1487, 2012 doi:10.1111/j.1460-9568.2012.08048.x

COGNITIVE NEUROSCIENCE

Perceived helplessness is associated with individual differences in the central motor output system

Tim V. Salomons,[1,*] Massieh Moayedi,[1,2,*] Irit Weissman-Fogel,[1] Michael B. Goldberg,[3,4] Bruce V. Freeman,[3,4] Howard C. Tenenbaum[2,3,4] and Karen D. Davis[1,2,4,5]

[1]Division of Brain, Imaging and Behaviour – Systems Neuroscience, Toronto Western Research Institute, Toronto, ON, Canada
[2]Institute of Medical Science, University of Toronto, Toronto, ON, Canada
[3]Faculty of Dentistry, University of Toronto, Toronto, ON, Canada
[4]Mount Sinai Hospital, Department of Dentistry Toronto, ON, Canada
[5]Department of Surgery, University of Toronto, Toronto, ON, Canada

Keywords: cortical thickness, fractional anisotropy, MRI, temporomandibular disorder, tractography

Abstract

Learned helplessness is a maladaptive response to uncontrollable stress characterized by impaired motor escape responses, reduced motivation and learning deficits. There are important individual differences in the likelihood of becoming helpless following exposure to uncontrollable stress but little is known about the neural mechanisms underlying these individual differences. Here we used structural MRI to measure gray and white matter in individuals with chronic pain, a population at high risk for helplessness due to prolonged exposure to a poorly controlled stressor (pain). Given that self-reported helplessness is predictive of treatment outcomes in chronic pain, understanding such differences might provide valuable clinical insight. We found that the magnitude of self-reported helplessness correlated with cortical thickness in the supplementary motor area (SMA) and midcingulate cortex, regions implicated in cognitive aspects of motor behavior. We then examined the white matter connectivity of these regions and found that fractional anisotropy of connected white matter tracts along the corticospinal tract was associated with helplessness and mediated the relationship between SMA cortical thickness and helplessness. These data provide novel evidence that links individual differences in the motor output pathway with perceived helplessness over a chronic and poorly controlled stressor.

Introduction

From the mundane stress of a traffic jam to a battle with serious illness, uncontrollable stress is an inevitable aspect of modern life. An organism's adaptation to its environment depends on its ability to cope with uncontrollable stress, yet little is known about why some individuals are resilient while others become easily overwhelmed.

Prolonged exposure to uncontrollable stress can lead to increased stress responses and deficits in learning and motivation (as demonstrated by reduced motor escape behaviors), a pattern of behavior known as learned helplessness (Maier & Seligman, 1976; Weiss *et al.*, 1994). These effects are reliably elicited at the group level but there are notable individual differences, with up to half of subjects exposed to uncontrollable stress showing no signs of helplessness (Hiroto, 1974; Maier & Seligman, 1976; Minor *et al.*, 1994). Given that individual differences in perceived helplessness are associated with both mental and physical health, understanding the mechanisms of these individual differences might be of tremendous clinical benefit.

Correspondence: Karen D. Davis, [1]Division of Brain, as above.
E-mail: kdavis@uhnres.utoronto.ca

*These authors contributed equally to this work.

Received 16 January 2012, accepted 23 January 2012

One approach to studying susceptibility to helplessness is to examine individual differences in persons exposed to a persistent and quantifiable stressor such as chronic pain. Changes in self-reported helplessness have been associated with treatment outcomes (Keefe *et al.*, 1990; Smith *et al.*, 1994; Burns *et al.*, 2003; Samwel *et al.*, 2006) in chronic pain. These relationships are not a simple function of disease severity (Keefe *et al.*, 1990; Smith *et al.*, 1994; Burns *et al.*, 2003; Samwel *et al.*, 2006). Taken together, these findings support the use of chronic pain as a model for understanding individual differences in susceptibility to helplessness. Furthermore, they suggest that understanding such differences can provide insight into successful coping with long-term health-related stressors.

This study examines structural correlates of individual differences in helplessness. Subcortical regions such as the dorsal raphe nucleus (Maier & Watkins, 2005) and locus coeruleus (Weiss *et al.*, 1994) have been implicated in helplessness, but recent data suggest that operations necessary for distinguishing between controllable and uncontrollable stress are dependent on cortical input (Amat *et al.*, 2005). One approach to understanding cortical mechanisms of helplessness is to examine the relationship between self-reported helplessness and cortical morphometry. Recent evidence suggests that susceptibility to helplessness in this population may be related to

cortical structure. Repeated exposure to pain can alter cortical structure (Teutsch *et al.*, 2008), and successful treatment can resolve structural abnormalities (Seminowicz *et al.*, 2011), suggesting that a treatment-relevant variable such as helplessness might also be associated with cortical morphometry. In support of this hypothesis, cortical structure has been linked to individual differences in behavior and cognition (Kanai & Rees, 2011), including the ability to cope with chronic pain (Schweinhardt *et al.*, 2008; Blankstein *et al.*, 2010).

We investigated these individual differences by conducting a cortical thickness analysis (Fischl & Dale, 2000) to locate areas that were correlated with helplessness in chronic pain patients. We then investigated the white matter (WM) connectivity of these regions using probabilistic tractography and examined whether structural characteristics of these WM tracts were associated with helplessness.

Materials and methods

Subjects

Seventeen females with temporomandibular disorder (TMD; mean age ± SD, 33.1 ± 11.9 years) and 17 pain-free females (mean age ± SD, 32.2 ± 10.1 years) provided written informed consent to procedures approved by the University Health Network and Mount Sinai Hospital Research Ethics Boards. Subjects were right-handed. Patients were diagnosed with TMD by dentists based on the following inclusion criteria: (i) TMD pain in the masticatory muscle region ≥ 4/10 for at least 3 months or pain that is aggravated by mandibular function; and (ii) moderate pain to palpation and/or persisting pain after examination in at least three muscle sites and/or moderate pain to palpation of the temporomandibular joint (TMJ) region and/or limitation in the mandibular movement (opening < 40mm). Exclusion criteria for all subjects included: (i) serious metabolic, rheumatoid, neurological or vascular disorders and other diseases; (ii) other pain disorders in the craniofacial region; (iii) any contraindication to MRI scanning (e.g., claustrophobia, metal); or (iv) previously diagnosed psychiatric disorders (e.g., depression, schizophrenia, ADHD) or self-report of the use of psychotropic drugs.

Three individuals reported that their pain was primarily in the masticatory muscle, six reported the TMJ region and eight reported pain in both sites. Thirteen subjects reported bilateral pain, three primarily on the right and one primarily on the left. Six individuals reported taking no medication for their pain. Eight reported daily use of non-steroidal anti-inflammatory drugs (NSAIDs, e.g. naproxen, arthrotec), three reported use of NSAIDS as needed. Five reported using muscle relaxants (e.g. flexaril) and one reported use of a narcotic (hydromorphone). Four subjects reported using more than one class of these drugs. Subjects were asked to not use pain medication for 24 h prior to their scan.

Self-report measures

Helplessness was assessed from the helplessness subscale of the Pain Catastrophizing Scale (PCS; Sullivan *et al.*, 1995), a well-validated measure of maladaptive thinking patterns related to pain. The full measure consists of thirteen items measured on a five-point Likert scale (1 = 'not at all', 5 = 'all the time'). The helplessness subscale consists of six items measuring the degree to which individuals feel defeated and overwhelmed by their pain (sample item: 'There is nothing I can do to reduce the intensity of the pain').

This investigation focused on relationships between helplessness and cortical structure in the chronic pain group rather than on correlations with helplessness across groups. Due to our interest in linking clinical and experimental literature on helplessness, we were interested in studying self-reported perceived helplessness in the presence of a chronic quantifiable stressor. This was not the case in the control group, as subjects were excluded if they had any chronic pain condition and were presumably referring to low perceived control over acute painful stressors, which were neither chronic nor quantifiable. Given the substantial differences in the stressor the two groups referred to with the questionnaire, we did not expect or look for linear relationships between helplessness and brain structure across subjects.

Patients were also asked to provide verbal numerical pain scores for their current and their average (over the last month) pain intensity and pain unpleasantness. The scale was anchored at 0 and 10 with 'no pain' and 'the worst pain imaginable', respectively. The patients also provided the duration of TMD symptoms.

Imaging parameters

Imaging data were acquired using a 3-T GE Signa HDx MRI system fitted with an eight-channel phased array head coil. A whole-brain 3-D high-resolution anatomical scan was acquired with a T1-weighted 3-D IR-FSPGR sequence: 128 axial slices, TI = 300 ms, TR = 12 ms, TE = 5 ms, $0.94 \times 0.94 \times 1.5$ mm^3 voxels, field of view (FOV) = 24×24 cm^2, 256×256 matrix size, flip angle = 20°, one signal average.

Diffusion-weighted scans (TR = 14 500 ms, FOV 24×24 cm^2, 128×128 matrix, $1.875 \times 1.875 \times 3$ mm voxels) were acquired for each subject along 23 non-colinear directions (b = 1000 s/mm^2). Two non-diffusion weighted scans (b = 0 s/mm^2) were also acquired. Two runs of diffusion-weighted scanning were acquired for each subject.

Analysis

Cortical thickness analysis

Cortical thickness (CT) analysis was performed using the FreeSurfer software (http://surfer.nmr.mgh.harvard.edu). Briefly, pre-processing included intensity normalization, skull stripping, separation of the hemispheres, and gray matter segmentation. The WM–gray matter border and gray matter–CSF border were identified and modeled as surfaces. The software then calculated the distance between the two surfaces at every point on the cortex, for each hemisphere. Each individual subject's cortex underwent automatic anatomical parcellation, and each sulcus and gyrus was labeled during pre-processing (Fischl *et al.*, 2004). Each subject's gray matter (cortical) surface was then warped such that homologous gyri and sulci were aligned to the FreeSurfer standard cortical surface (fsaverage). Given that we were examining structural correlates of pain-related beliefs, we restricted our search to cortical regions implicated in cognitive and/or affective modulation of pain (prefrontal, cingulate and insular cortices; Wiech *et al.*, 2008; Wiech & Tracey, 2009) using the cortical parcellations map implemented into FreeSurfer. A 6-mm full-width half-maximum spatial smoothing kernel was applied to the data prior to statistical analysis. The distance between two vertices was 0.71 mm.

We searched for regions of the cortex where thickness was associated with helplessness in patients by running a vertex-wise correlation within the cortical mask. We corrected for multiple comparison using a Monte Carlo simulation (5000 iterations) in AlphaSim (http://afni.nimh.nih.gov/afni/doc/manual/AlphaSim). We calculated that to obtain a corrected ($P < 0.05$) cluster, a cluster of 168 contiguous vertices at an image-wide $P < 0.01$ was required for significance. Because of developmental progression of cortical

thickness, age was modeled as a covariate of no interest (Good *et al.*, 2001; Sowell *et al.*, 2003; Bergfield *et al.*, 2010).

In regions where helplessness was significantly correlated with cortical thickness in the patient group, we compared thickness in corresponding regions in the control group to determine whether CT values were abnormal in patients.

Diffusion-weighted imaging analysis

Diffusion-weighted images were imported into DTiStudio v.2.4.01 (https://www.mristudio.org/) for quality control. Scans underwent eddy current and motion artifact correction using the automatic image registration tool within DTiStudio. This tool uses the first non-diffusion-weighted scan as a template for registration of all subsequent acquisitions. Images were visually inspected for alignment and data corruption, and corrupt slices were discarded. The scans were then imported into FSL (FMRIB software library v.4.1; http://www.fmrib.ox.ac.uk/fsl/) for further processing.

To attain isotropic voxels for tractography, we downsampled our scans to $3 \times 3 \times 3$ mm^3 in FSL. A diffusion model was then fitted to each voxel within the brain (Behrens *et al.*, 2007). Probabilistic modeling of diffusion parameters was carried out using methods described in detail elsewhere. We used a two-fibre model to increase resolution of crossing fibres (Behrens *et al.*, 2007). Then, affine registration transformation matrices between T1, diffusion tensor images (DTI) and MNI152 standard spaces were created using the FLIRT (FMRIB's linear image registration tool) tool in FSL. Seeds for tractography were based on our gray matter (cortical thickness) findings. Masks of our significant findings were transformed from each individual's FreeSurfer cortical surface space to each individual's high-resolution T1-weighted scan. Masks were then converted to each individual's diffusion space, and used as a seed for tractography.

In order to create a connectivity mask of regions where cortical thickness was associated with helplessness, we conducted probabilistic tractography in each individual's diffusion space within the patient group using the supplementary motor area (SMA) and PCC as seeds. Given the physical proximity and documented connectivity between midcingulate cortex (MCC) and the other two regions (Shackman *et al.*, 2011), we used the MCC mask as a waypoint such that tracts included in the connectivity masks of the other two regions had to pass through the MCC on their way to the rest of the brain (Figs 1 and 2). Consistent with previously published work, each individual's tractograms were thresholded by excluding voxels receiving < 10 samples (i.e., 0.02%) from the target, and the group map was thresholded such that at least 25% ($n \geq 5$) of subjects show common tracts (Beckmann *et al.*, 2009).

Fractional anisotropy (FA) of tracts within this connectivity mask was examined. First, brain masks were created using the Brain Extraction Tool (Smith, 2002). FA maps from the DTI scans were then constructed with DTIFIT in the FSL Diffusion Toolbox v. 2.0 (FDT). The FA maps were processed using Tract-Based Spatial Statistics v.1.2 (TBSS; Smith *et al.*, 2006). Briefly, FA maps underwent non-linear registration to a $1 \times 1 \times 1$ mm standard space. A mean image derived from all the subjects in the patient group was then created, and then thinned to a 1-mm-thick skeleton to represent major WM tracts common to all subjects. Each subject's peak FA value perpendicular to the thinned tract was then projected onto the skeleton. To examine regions where WM was associated with helplessness in patients, a voxel-wise *t*-test was performed and restricted to the tractography mask. Age was included as a covariate of no interest. Statistical significance ($P < 0.05$, corrected for multiple comparisons) was determined using AlphaSim (image-wide *P*-value of 0.05, cluster threshold of 8 voxels).

Analyses were conducted to determine whether WM FA of regions along the corticospinal tract (CST) mediated the relationship between cortical thickness in the seed regions and helplessness (Baron & Kenny, 1986). We formed a composite variable of the regions where FA was negatively correlated with helplessness and correlated with cortical thickness in MCC and SMA (see Supporting Information Tables S1 and S2). Mediation was tested using the Sobel test to evaluate the difference between the total effect (i.e. the zero-order correlation between independent and dependent measure) and that same effect once the indirect effect through the mediator has been accounted for (Sobel, 1982). We also tested alternative models using FA as both mediator (of the helplessness–CT relationship) and independent variable (with CT as the mediator).

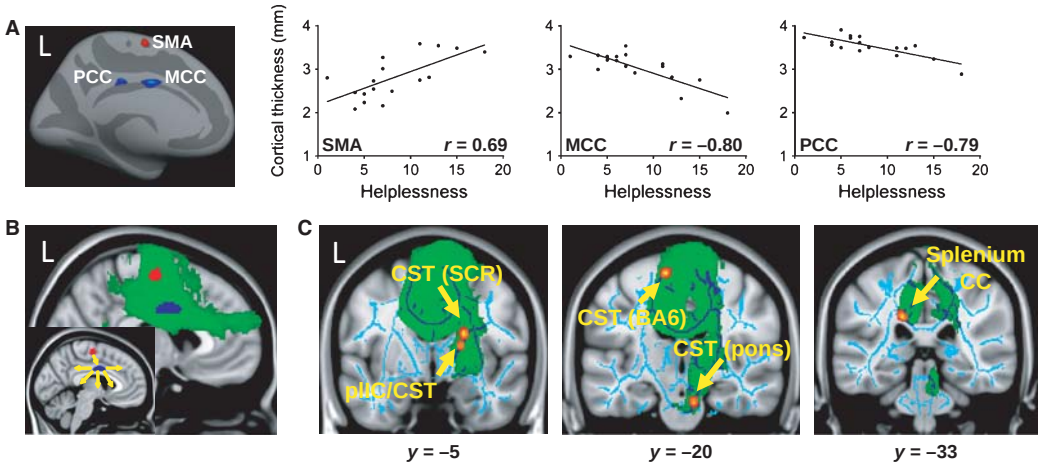

FIG. 1. Helplessness associated with structure of gray and white matter. (A) Regions where cortical thickness significantly correlated with helplessness in patients. The SMA (red) was positively correlated with helplessness, while the MCC and PCC (blue) were negatively correlated with helplessness. (B) Connectivity masks (green) of these regions were formed using probabilistic tractography. Here SMA was used as a seed and MCC as a waypoint, such that all tracts traced from the SMA origin had to go through MCC. (C) Within these masks we searched for regions of the WM skeleton (blue) where fractional anisotropy was correlated with helplessness as well as cortical thickness in the seed regions. BA6, Brodmann Area 6; CST, corticospinal tract; plIC; posterior limb of internal capsule; SCR, superior corona radiata.

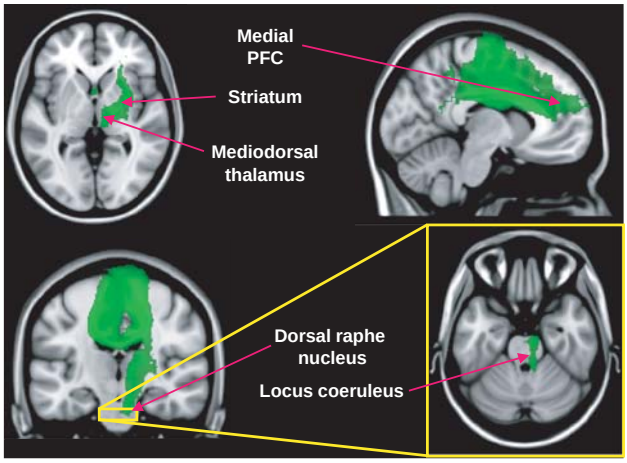

FIG. 2. SMA–MCC connectivity mask. Regions connected with both SMA and MCC as determined by probabilistic tractography.

Results

Self-report data

Details of the individual TMD patient's pain characteristics have been described previously (Moayedi *et al.*, 2011). Briefly, in the patient group, the mean TMD duration was 9.8 years (SD 8.3, range 1–30 years), mean pain intensity out of 10 was 4.3 (SD = 1.8, range 2–7) and mean pain unpleasantness out of 10 was 5.4 (SD = 2.1, range 1–8). Helplessness scores were not significantly correlated with patients' age ($r = 0.07$, $P = 0.8$), TMD duration ($r = 0.26$, $P = 0.31$), pain intensity ($r = 0.17$, $P = 0.52$) or pain unpleasantness ($r = 0.28$, $P = 0.27$).

Group differences in helplessness approached significance (mean ± SD; patients, 8.24 ± 4.48; controls, 5.74 ± 4.04; $F = 3.41$, $P = 0.07$). These values are highly similar to those observed in a larger trial of chronic pain patients and healthy controls, where a significant difference was observed (Osman *et al.*, 2000).

Cortical thickness analysis

In individuals with TMD, cortical thickness was significantly correlated with helplessness in three brain regions. In the supplementary motor area (SMA; BA6, peak = −9, −10, 55; all coordinates MNI) cortical thickness was positively correlated, and in the MCC (BA24, peak = −5, −2, 31) and posterior cingulate cortex (PCC; BA31, peak = −5, −23, 32) cortical thickness was negatively correlated with helplessness (Fig. 1A).

To determine whether abnormal CT in the chronic pain patients drove these correlations, we examined differences in CT in these regions between the patient and pain-free controls. We found no differences between thickness values in MCC, PCC or SMA (one-way ANOVA, $F_{1,31} = 0$ for MCC, 0.4 for PCC and 0.01 for SMA, all P = ns). Pain intensity, unpleasantness and duration did not correlate significantly with cortical thickness findings. Fisher r-to-z tests were used to compare correlations between cortical thickness and helplessness in the patient and control groups. For all three regions (SMA, MCC and PCC), correlations between cortical thickness and helplessness in the control group were non-significant (SMA: $r = 0.03$, $P = 0.99$; MCC $r = -0.25$, $P = 0.34$; PCC: $r = 0.13$, $P = 0.64$) and lower than the equivalent correlations in the patient group ($P < 0.05$). In a *post hoc* analysis in pain-free subjects, we found no significant associations between helplessness and CT.

As our *a priori* interest was in helplessness, we did not conduct a search for regions associated with overall scores on the PCS. *Post hoc* analysis of PCS scores indicated that overall scores on the PCS were highly correlated with helplessness ($r = 0.72$, $P < 0.05$). PCS scores were significantly correlated with cortical thickness in SMA, MCC and PCC ($r = 0.65$, −0.52 and −0.58, respectively; all $P < 0.05$) but these correlations were no longer significant after controlling for scores on the PCS helplessness subscale ($r = 0.31$, 0.14 and −0.04 respectively; all ns).

Given consistent findings of motor deficits following prolonged exposure to uncontrollable stress, the association of both SMA and MCC were of particular interest and these regions were therefore the focus of subsequent analysis and discussion.

Probabilistic tractography

To examine the connectivity of SMA and MCC with other regions subserving behavioral aspects of helplessness (cognitive, affective and motivational deficits), we mapped their WM connectivity using probabilistic tractography (Behrens *et al.*, 2003). SMA was used as a seed regions and MCC as a waypoint, such that tracts traced from the seed regions had to pass through MCC on the way to the rest of the brain (see Materials and methods). We found that the WM tracts seeded from the SMA connected with the medial prefrontal cortex thalamic and striatal regions (medial dorsal nucleus and pallidum, respectively) and brainstem (Figs 1b and 2).

Fractional anisotropy

To test whether WM tracts are, along with our gray matter findings, part of a neural circuit involved in the instantiation of helplessness we identified the specific WM regions within our connectivity mask where FA correlated with self-reported helplessness (see Supporting Information Table S1). To focus on regions that were part of the same circuit as our gray matter findings, we also required that FA in these regions correlated with CT in the SMA and MCC seed regions and was within the connectivity mask corresponding to these regions. We found that FA along the cingulum ($r = 0.61$, $P < 0.05$; all comparisons corrected for multiple comparisons), superior corona radiata ($r = 0.8$, $P < 0.05$) and WM adjoining primary somatosensory and premotor cortices ($r = 0.61$ and 0.73 respectively, $P < 0.05$) was positively correlated with helplessness. FA was negatively correlated with helplessness along the corpus callosum ($r = -0.60$ and −0.58, $P < 0.05$) and at four points along the CST: superior corona radiata ($r = -0.63$, $P < 0.05$) and the posterior limb of the internal capsule ($r = -0.69$, $P < 0.05$), and adjacent to the premotor cortex ($r = -0.69$, $P < 0.05$) and pons ($r = -0.67$, $P < 0.05$); Fig. 1C). Correlations between FA regions along the CST (included in the CST composite used in the mediation analysis; see below) and helplessness, SMA and MCC CT and TMD characteristics are given in Supporting Information Table S2.

DTI does not have the resolution to delineate the CST from other corticofugal tracts, including the corticopontine and corticobulbar tracts. However, two factors strongly indicate that in fact the tracts that were identified are related to motor function. First, the cortical seed (i.e., in the SMA) used to delineate the WM mask used for TBSS encompassed a cognitive–motor region. Second, many of the WM tracts identified were adjacent to motor regions, or within WM regions known to be related to motor function, including the posterior limb of the internal capsule. We therefore refer to findings along this pathway as CST herein. Nevertheless WM analysis can never absolutely rule

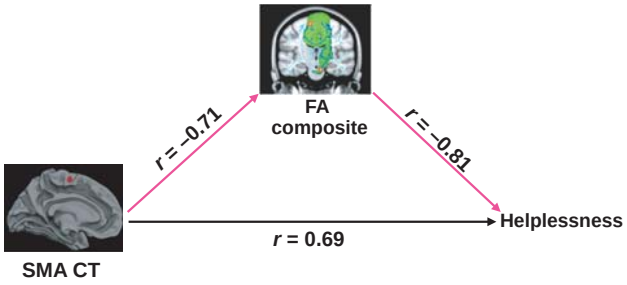

FIG. 3. CST WM mediates the relationship between SMA thickness and helplessness. The relationship between cortical thickness and helplessness (black arrow) was significantly mediated by the indirect pathway by way of CST WM (pink arrows; Sobel statistic = 2.44, $P < 0.05$). The inverse meditational model was not significant (Sobel statistic = 0.7, $P = 0.48$), suggesting that the gray matter–helplessness relationship occurs by way of a descending circuit; *r*, Pearson's correlation coefficient.

out the contribution of effects on axons belonging to other systems that are known to course through this region.

Mediation analysis

Many of our FA findings coincided with the CST, suggesting that the relationship between our gray matter regions (SMA and MCC) and helplessness occurs by way of this descending motor pathway. If this were the case, we would expect that WM findings along that pathway would account for the relationship between cortical thickness of SMA and helplessness, but that the inverse mediational model (that gray matter findings would account for the relationship between WM and helplessness) would not be the case. Therefore, we tested whether the relationship between helplessness and cortical thickness was mediated through the WM or vice versa (Baron & Kenny, 1986). We constructed a composite variable of the CST regions (posterior limb of the internal capsule, superior corona radiata and along the brainstem–pons and premotor cortex; see Supporting Information Tables S1 and S2) that were significantly correlated with helplessness and both SMA and MCC, and tested whether this composite variable mediated the relationship between cortical thickness in SMA and helplessness. This mediational relationship was significant (Sobel statistic = 2.44, $P < 0.05$). Importantly, the inverse mediational model (SMA gray matter mediating the relationship between WM and helplessness) was not significant (Sobel statistic = 0.7, $P = 0.48$), supporting the directional hypothesis that the relationship between cortical thickness of the SMA and helplessness occurs by way of descending WM tracts along the CST (Fig. 3).

Discussion

Here we investigated whether individual differences in neural structure were associated with self-reported helplessness in persons with chronic pain. We found that cortical thickness of SMA and MCC were correlated with helplessness. Tractography analysis demonstrated that these regions are connected to medial prefrontal, striatal and brainstem regions associated with cognitive, emotional and motivational functions impaired in states of learned helplessness. Within these connected WM tracts, we found regions where FA was associated with helplessness as well as cortical thickness in the seed regions. Of particular interest were findings along the CST, suggesting that the association between cortical regions and helplessness may occur by way of a descending motor circuit. Consistent with this possibility, we found that FA of these CST regions mediated the relationship between SMA thickness and helplessness.

The SMA has been implicated in motor planning (Nachev *et al.*, 2008) and the MCC has been associated with the selection of optimal motor responses under conditions of uncertainty and affective salience (Shackman *et al.*, 2011). Furthermore, both of these regions are preferentially involved in processing pain when it is perceived to be uncontrollable (Salomons *et al.*, 2004). In the context of these findings, our results suggest that these regions are involved in cognitive aspects of motor behavior, including altering motor responses on the basis of whether a stressor is perceived to be controllable or not. The association between the structure of these regions and helplessness is therefore unsurprising, but how these regions contribute to the belief that one's actions will have no beneficial effect on pain remains to be elucidated. Several lines of evidence have demonstrated the involvement of SMA in preemptively inhibiting motor responses based on cognitive and motivational factors (Chen *et al.*, 2010; Scangos & Stuphorn, 2010; Wardak, 2011), suggesting that individuals with thicker gray matter in this region might demonstrate a pattern of inhibiting therapeutically beneficial motor responses to pain and that such inhibition might obviate more immediate context-dependent processing in MCC. Such an account would explain why helplessness was positively correlated with cortical thickness in SMA and negatively correlated with MCC thickness but is subject to further testing, particularly considering ambiguities inherent in interpreting structural findings in terms of their underlying function (Kanai & Rees, 2011). Nevertheless, the involvement of regions associated with cognitive aspects of motor behavior could provide a link between observations of reduced behavioral activity and escape responses in animals exposed to uncontrollable stress (Maier & Seligman, 1976; Weiss *et al.*, 1994) and maladaptive behavioral responses (increased disability and behavioral depression) in chronic pain populations.

One potential explanation for the association between cortical thickness and self-reported helplessness in the patient group is that both are simply reflections of the cumulative effects of living with pain. Self-reported helplessness might be an accurate reflection of a state of poorly controlled pain, which could in turn be associated with pain-driven alterations in cortical thickness. If this were the case, we would expect that persons with chronic pain would have abnormal cortical thickness values in these regions. Furthermore, we would expect both helplessness and correlated cortical thickness values would be associated with chronic pain characteristics such as pain intensity, unpleasantness and duration. The fact that cortical thickness in these regions neither differed between groups nor correlated significantly with pain characteristics therefore suggests that the association between helplessness and cortical thickness in SMA and MCC is not due to the cumulative effects of pain. Rather, our data suggest the possibility that structural characteristics of neural pathways subserving motor planning and function may predispose some individuals to helplessness within the context of an uncontrollable stressor such as chronic pain. Thus, helplessness in a chronic pain population would be a function of the interaction between predisposing factors and exposure to chronic pain. Such a framework would be consistent with individual differences in the propensity to become helplessness in the presence of chronic stress, but would be considerably strengthened by corroborative longitudinal study.

The involvement of SMA and MCC in helplessness is further supported by their connectivity with regions involved in functions impaired in learned helplessness. We found that the WM tracts seeded from the SMA connected with the medial prefrontal cortex (Figs 1b and 2). This region is involved in contingency learning (Balleine &

Dickinson, 1998) and may be a human analog to an area found to be necessary for the neural and behavioral effects of helplessness in rodents (Amat *et al.*, 2005), suggesting a possible link between our findings and observed cognitive deficits in helplessness. Tracts originating in SMA largely coincided with the CST, consistent with the known contribution of SMA and MCC to CST (Nachev *et al.*, 2008). FA of CST regions was negatively correlated with helplessness, suggesting the possibility that impaired transmission in motor tracts connected to these regions may underlie some of the motor deficits commonly associated with helplessness. The SMA connectivity mask also reached thalamic and striatal regions (medial dorsal nucleus and pallidum, respectively) known to be involved in corticostriatal motivational loops (Haber & Knutson, 2010). Furthermore, the SMA–MCC connectivity map extended to the brainstem and included the dorsal raphe nucleus and locus coeruleus, regions that are necessary for the instantiation of helplessness (Weiss *et al.*, 1994; Maier & Watkins, 1998). Thus, these WM findings provide a plausible route for interaction between the cortical regions implicated here and regions such as medial PFC and brainstem previously involved in processing the behavioral deficits associated with helplessness.

The data reported here are consistent with involvement of SMA and MCC in cognitive and motor responsivity characteristic of helplessness. Furthermore, we have demonstrated patterns of WM connectivity through which these regions may contribute to helplessness. Nevertheless, some limitations of the present data need to be noted. First, there is significant overlap between helplessness and symptoms of depression and anxiety (Weiss *et al.*, 1994; Maier & Watkins, 1998). While current diagnoses of depression and/or anxiety were exclusion criterion in the study, further quantification of depression and anxiety symptoms would have allowed for a more complete analysis of the contribution of depression and anxiety to the present findings. Second, the link between the present findings and animal literature on helplessness need to be further validated through studies of behavioral deficits corresponding to self-report. This will build on previous studies in chronic pain patients that demonstrated associations between self-reported helplessness and deficits in cognition, motivation and emotional response consistent with helplessness (Keefe *et al.*, 1990; Smith *et al.*, 1994; Samwel *et al.*, 2006). Based on the functionality of SMA and MCC, we have hypothesized that the role of these regions in helplessness might be changes in cognitive aspects of motor planning within the context of chronic pain. Direct behavioral testing of this hypothesis would represent a logical next step towards understanding the neural and behavioral mechanisms of clinically relevant individual differences in self-reported helplessness.

How an individual responds to uncontrollable stress is critical to their ability to adapt to their environment. The experimental literature has demonstrated that when exposed to uncontrollable stress a proportion of animals become listless and fail to learn new ways of adapting to their environment, a phenomenon known as learned helplessness. Several lines of evidence indicate that there are individual differences in the tendency to become helpless when confronted with uncontrollable stress, a finding which might provide significant insight into the ability to cope with stress, yet little is known about the neural factors that might contribute to these individual differences. Here we demonstrated that structural characteristics of a descending motor circuit are associated with self-reported helplessness in individuals with chronic pain. These characteristics did not differ between chronic pain patients and matched healthy controls, and did not correlate with chronic pain characteristics, suggesting that these correlations are not driven by abnormalities caused by pain *per se*. Rather, our data suggest the possibility that structural characteristics of neural pathways subserving motor planning and function may predispose some individuals to helplessness within the context of an uncontrollable stressor such as chronic pain and therefore provide a framework for understanding why some individuals become helpless while others are able to cope with seemingly uncontrollable stressors.

Supporting Information

Additional supporting information may be found in the online version of this article:

Table S1. Regions where FA was correlated with helplessness.

Table S2. Correlations between helplessness, TMD characteristics and structural findings.

Please note: As a service to our authors and readers, this journal provides supporting information supplied by the authors. Such materials are peer-reviewed and may be re-organized for online delivery, but are not copy-edited or typeset by Wiley-Blackwell. Technical support issues arising from supporting information (other than missing files) should be addressed to the authors.

Acknowledgements

This work was supported by the Canadian Institutes of Health Research (Grant Number MOP 53304). T.V.S. was funded by a Clinician-Scientist Award from the University of Toronto Centre for the Study of Pain. M.M. was funded by a CIHR Banting and Best Canada Graduate Scholarship, an Ontario Graduate Scholarship and the CIHR Pain: M2C and Cell Signals Strategic Training in Health Research grants. The authors declare no conflict of interest.

Abbreviations

CST, corticospinal tract; CT, cortical thickness; DTI, diffusion tensor image; FA, fractional anisotropy; MCC, midcingulate cortex; PCC, posterior cingulate cortex; PCS, Pain Catastrophizing Scale; SMA, supplementary motor area; TMD, temporomandibular disorder; TMJ, temporomandibular joint; WM, white matter.

References

Amat, J., Baratta, M.V., Paul, E., Bland, S.T., Watkins, L.R. & Maier, S.F. (2005) Medial prefrontal cortex determines how stressor controllability affects behavior and dorsal raphe nucleus. *Nat. Neurosci.*, **8**, 365–371.

Balleine, B.W. & Dickinson, A. (1998) Goal-directed instrumental action: contingency and incentive learning and their cortical substrates. *Neuropharmacology*, **37**, 407–419.

Baron, R.M. & Kenny, D.A. (1986) The moderator–mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J. Pers. Soc. Psych.*, **51**, 1173–1182.

Beckmann, M., Johansen-Berg, H. & Rushworth, M.F.S. (2009) Connectivity-based parcellation of human cingulate cortex and its relation to functional specialization. *J. Neurosci.*, **29**, 1175–1190.

Behrens, T.E.J., Johansen-Berg, H., Woolrich, M.W., Smith, S.M., Wheeler-Kingshott, C.A.M., Boulby, P.A., Barker, G.J., Sillery, E.L., Sheehan, K., Ciccarelli, O., Thompson, A.J., Brady, J.M. & Matthews, P.M. (2003) Non-invasive mapping of connections between human thalamus and cortex using diffusion imaging. *Nat. Neurosci.*, **6**, 750–757.

Behrens, T.E.J., Berg, H.J., Jbabdi, S., Rushworth, M.F.S. & Woolrich, M.W. (2007) Probabilistic diffusion tractography with multiple fibre orientations: what can we gain? *Neuroimage*, **34**, 144–155.

Bergfield, K.L., Hanson, K.D., Chen, K., Teipel, S.J., Hampel, H., Rapoport, S.I., Moeller, J.R. & Alexander, G.E. (2010) Age-related networks of regional covariance in MRI gray matter: reproducible multivariate patterns in healthy aging. *Neuroimage*, **49**, 1750–1759.

Blankstein, U., Chen, J., Diamant, N.E. & Davis, K.D. (2010) Altered brain structure in irritable bowel syndrome: potential contributions of pre-existing and disease-driven factors. *Gastroenterology*, **138**, 1783–1789.

Burns, J.W., Kubilus, A., Bruehl, S., Harden, R.N. & Lofland, K. (2003) Do changes in cognitive factors influence outcome following multidisciplinary treatment for chronic pain? A cross-lagged panel analysis. *J. Consult. Clin. Psych.*, **71**, 81–91.

Chen, X., Scangos, K.W. & Stuphorn, V. (2010) Supplementary motor area exerts proactive and reactive control of arm movements. *J. Neurosci.*, **30**, 14657–14675.

Fischl, B. & Dale, A.M. (2000) Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proc. Natl. Acad. Sci. USA*, **97**, 11050–11055.

Fischl, B., van der Kouwe, A., Destrieux, C., Halgren, E., Ségonne, F., Salat, D.H., Busa, E., Seidman, L.J., Goldstein, J., Kennedy, D., Caviness, V., Makris, N., Rosen, B. & Dale, A.M. (2004) Automatically parcellating the human cerebral cortex. *Cereb. Cortex*, **14**, 11–22.

Good, C.D., Johnsrude, I.S., Ashburner, J., Henson, R.N., Friston, K.J. & Frackowiak, R.S. (2001) A voxel-based morphometric study of ageing in 465 normal adult human brains. *Neuroimage*, **14**, 21–36.

Haber, S.N. & Knutson, B. (2010) The reward circuit: linking primate anatomy and human imaging. *Neuropsychopharmacology*, **35**, 4–26.

Hiroto, D.S. (1974) Locus of control and learned helplessness. *J. Exp. Psych.*, **102**, 187–193.

Kanai, R. & Rees, G. (2011) The structural basis of inter-individual differences in human behaviour and cognition. *Nat. Rev. Neurosci.*, **12**, 231–242.

Keefe, F.J., Crisson, J., Urban, B.J. & Williams, D.A. (1990) Analyzing chronic low back pain: the relative contribution of pain coping strategies. *Pain*, **40**, 293–301.

Maier, S.F. & Seligman, M.E. (1976) Learned helplessness: theory and evidence. *J. Exp. Psych.*, **105**, 3–46.

Maier, S.F. & Watkins, L.R. (1998) Stressor controllability, anxiety, and serotonin. *Cog. Ther. Res.*, **22**, 595–613.

Maier, S.F. & Watkins, L.R. (2005) Stressor controllability and learned helplessness: the roles of the dorsal raphe nucleus, serotonin, and corticotropin-releasing factor. *Neurosci. Biobehav. Rev.*, **29**, 829–841.

Minor, T.R., Dess, N.K., Ben-David, E. & Chang, W.C. (1994) Individual differences in vulnerability to inescapable shock in rats. *J. Exp. Psychol. Anim. Behav. Process.*, **20**, 402–412.

Moayedi, M., Weissman-Fogel, I., Crawley, A.P., Goldberg, M.B., Freeman, B.V., Tenenbaum, H.C. & Davis, K.D. (2011) Contribution of chronic pain and neuroticism to abnormal forebrain gray matter in patients with temporomandibular disorder. *Neuroimage*, **55**, 277–286.

Nachev, P., Kennard, C. & Husain, M. (2008) Functional role of the supplementary and pre-supplementary motor areas. *Nat. Rev. Neurosci.*, **9**, 856–869.

Osman, A., Barrios, F.X., Gutierrez, P.M., Kopper, B.A., Merrifield, T. & Grittmann, L. (2000) The Pain Catastrophizing Scale: further psychometric evaluation with adult samples. *J. Behav. Med.*, **23**, 351–365.

Salomons, T.V., Johnstone, T., Backonja, M.M. & Davidson, R.J. (2004) Perceived controllability modulates the neural response to pain. *J. Neurosci.*, **24**, 7199–7203.

Samwel, H.J.A., Evers, A.W.M., Crul, B.J.P. & Kraaimaat, F.W. (2006) The role of helplessness, fear of pain, and passive pain-coping in chronic pain patients. *Clin. J. Pain*, **22**, 245–251.

Scangos, K.W. & Stuphorn, V. (2010) Medial frontal cortex motivates but does not control movement initiation in the countermanding task. *J. Neurosci.*, **30**, 1968–1982.

Schweinhardt, P., Kuchinad, A., Pukall, C.F. & Bushnell, M.C. (2008) Increased gray matter density in young women with chronic vulvar pain. *Pain*, **140**, 411–419.

Seminowicz, D.A., Wideman, T.H., Naso, L., Hatami-Khoroushahi, Z., Fallatah, S., Ware, M.A., Jarzem, P., Bushnell, M.C., Shir, Y., Ouellet, J.A. & Stone, L.S. (2011) Effective treatment of chronic low back pain in humans reverses abnormal brain anatomy and function. *J. Neurosci.*, **31**, 7540–7550.

Shackman, A.J., Salomons, T.V., Slagter, H.A., Fox, A.S., Winter, J.J. & Davidson, R.J. (2011) The integration of negative affect, pain and cognitive control in the cingulate cortex. *Nat. Rev. Neurosci.*, **12**, 154–167.

Smith, S.M. (2002) Fast robust automated brain extraction. *Hum. Brain Mapp.*, **17**, 143–155.

Smith, T.W., Christensen, A.J., Peck, J.R. & Ward, J.R. (1994) Cognitive distortion, helplessness, and depressed mood in rheumatoid arthritis: a four-year longitudinal analysis. *Health Psych.*, **13**, 213–217.

Smith, S.M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T.E., Mackay, C.E., Watkins, K.E., Ciccarelli, O., Cader, M.Z., Matthews, P.M. & Behrens, T.E.J. (2006) Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *Neuroimage*, **31**, 1487–1505.

Sobel, M.E. 1982. Asymptotic intervals for indirect effects in structural equation models. In Leinhart, S. (Ed.), *Sociol. Methodol*. Jossey-Bass, San Francisco, pp. 290–312.

Sowell, E.R., Peterson, B.S., Thompson, P.M., Welcome, S.E., Henkenius, A.L. & Toga, A.W. (2003) Mapping cortical change across the human life span. *Nat. Neurosci.*, **6**, 309–315.

Sullivan, M.J.L., Bishop, S.R. & Pivik, J. (1995) The Pain Catastrophizing Scale: development and validation. *Psych. Assess.*, **7**, 524–532.

Teutsch, S., Herken, W., Bingel, U., Schoell, E. & May, A. (2008) Changes in brain gray matter due to repetitive painful stimulation. *Neuroimage*, **42**, 845–849.

Wardak, C. (2011) The role of the supplementary motor area in inhibitory control in monkeys and humans. *J. Neurosci.*, **31**, 5181–5183.

Weiss, J.M., Stout, J.C., Aaron, M.F., Quan, N., Owens, M.J., Butler, P.D. & Nemeroff, C.B. (1994) Depression and anxiety: role of the locus coeruleus and corticotropin-releasing factor. *Brain Res. Bull.*, **35**, 561–572.

Wiech, K. & Tracey, I. (2009) The influence of negative emotions on pain: behavioral effects and neural mechanisms. *Neuroimage*, **47**, 987–994.

Wiech, K., Ploner, M. & Tracey, I. (2008) Neurocognitive aspects of pain perception. *Trends Cogn. Sci.*, **12**, 306–313.

Supporting Information Table S1: Regions where FA was correlated with helplessness

Regions within the combined PCC and SMA connectivity mask where FA was correlated with helplessness. All correlations with helplessness (*r*) are significant at $P<0.05$ (corrected). Coordinates are in MNI space. Voxels are $1mm^3$. Reported GM regions are the nearest labels to the WM cluster identified.

Region	*r*	*X*	*Y*	*Z*	No. of voxels
Regions negatively correlated with helplessness					
CST – plIC*†	–0.69	23	–5	19	134
CST	–0.60	25	–20	39	101
Body of CC*	–0.58	20	–31	36	88
CST (GM: BA6)‡	–0.69	15	–19	59	63
PCR	–0.62	27	–32	24	41
Splenium of CC*	–0.60	–17	–33	30	38
CST (GM: BA6)‡*†	–0.69	–10	–21	65	36
CST (pons) *†	–0.67	9	–20	–25	30
CST (midbrain)	–0.58	15	–18	–11	27
SCR	–0.51	19	–51	54	25
SLF*	–0.54	23	–40	39	19
CST	–0.57	25	–22	25	17
ACR	–0.55	27	12	21	17
CST (midbrain)*†	–0.63	17	–10	–4	17
SCR (GM: BA6)	–0.71	–16	9	49	16
CST	–0.67	25	–21	23	15
SCR (GM: BA6)	–0.57	–16	18	45	13
ACR/forceps minor of CC	–0.6	14	47	28	13
CST/cerebral peduncle (midbrain)	–0.54	10	–16	–17	12
ACR	–0.49	23	24	2	10
ACR‡	–0.59	–12	28	45	9
PCR (GM: BA7)	–0.69	20	–59	48	8
Splenium of CC	–0.51	15	–31	29	8
Regions positively correlated with helplessness					
Body of CC	0.63	3	1	25	112
Cingulum	0.58	–8	19	25	83
ACR	0.57	–15	30	37	64
SLF/PCR	0.64	20	–47	41	40
Forceps minor of CC	0.54	21	37	21	34
Genu of CC	0.56	5	20	17	31
Body of CC	0.55	6	13	22	29
Fornix	0.71	2	–9	15	29
Forceps minor of CC‡	0.77	–18	45	19	28
CST/SLF	0.61	–19	–13	44	26
Body of CC	0.54	–7	–4	28	26
SCR (GM: BA5)*	0.8	15	–49	61	25
Forceps minor of CC‡	0.61	–9	50	32	24
Cingulum‡	0.63	9	7	33	22
ExC/EC/IFO	0.66	35	2	–3	22
Cingulum*	0.61	10	–33	40	21
Body of CC	0.54	9	–6	28	20
ACR	0.53	18	19	33	19
Inferior cerebellar peduncle	0.58	10	–45	–33	16
CST (GM: BA6)*‡	0.73	–10	–27	53	15
Cingulum‡	0.6	9	15	30	15
Body of CC	0.54	9	–15	28	15
CST	0.61	–11	–31	55	14
Fornix (amygdala)	0.58	20	–8	–10	14
Tectospinal/medial lemniscus (dorsal raphe)	0.64	4	–26	–19	14
SCR (GM: BA6)	0.56	11	–1	62	12

SCR (GM: BA6)‡	0.62	–13	14	51	12
SCR	0.5	18	0	39	12
Thalamus (VPL)	0.54	15	–23	3	12
Body of CC	0.52	–5	12	22	11
Medial lemniscus	0.59	16	–22	–3	11
Thalamus (lateral dorsal nucleus)	0.53	12	–17	13	10
Adjacent to BA44	0.53	47	4	16	9
SCR (GM: BA6)‡	0.67	9	11	61	8
SCR (GM: BA2)*	0.61	18	–46	58	8
Body of CC	0.5	0	12	22	8
Body of CC	0.5	4	16	19	8
Adjacent to BA44	0.53	43	12	15	8

*Specifies a region within the SMA mask and correlated with cortical thickness in SMA and MCC; ‡specifies a region within the PCC mask and correlated with thickness in PCC and MCC; †specifies regions included in the CST composite variable for mediation analysis. Abbreviations: GM, gray matter; BA, Brodmann's area; CST, corticospinal tract; ACR, anterior corona radiata; SCR, superior corona radiata; PCR, posterior corona radiata; CC, corpus callosum; IFO, inferior fronto-occipital fasciculus; EC, external capsule; ExC, extreme capsule; plIC, posterior limb of the internal capsule; SLF, superior longitudinal fasciculus; VPL, ventroposterior lateral nucleus of the thalamus.

Supporting Information Table S2: Correlations between helplessness, TMD characteristics and structural findings

	Help	Dur	Int	Unp	SMA	MCC	plIC FA	BA6 FA	Pons FA
Help	--								
Dur	0.26	--							
Int	0.17	0.06	--						
Unp	0.28	0.27	0.4	--					
SMA	-0.8*	-0.04	-0.38	-0.12	--				
MCC	0.69*	0.28	0.19	0.21	-0.56*	--			
plIC FA	-0.69*	0.03	-0.42	-0.43	0.62*	-0.64*	--		
BA6 FA	-0.69*	-0.19	-0.31	-0.25	0.57*	-0.69*	0.6*	--	
Pons FA	-0.67*	-0.08	-0.36	-0.26	0.64*	-0.60*	0.65*	0.52*	--
Midbrain FA	-0.63*	0.07	0.13	-0.09	0.53*	-0.53*	0.47	0.55*	0.55*

FA values listed are those along the corticospinal tract which were included in the composite variable for the mediation analysis. * $P<0.05$ (two-tailed).
Abbreviations: BA, Brodmann's area; MCC, midcingulate cortex; SMA, supplementary motor area; FA, fractional anisotropy; Help, helplessness; Dur, duration; Int, intensity; Unp, unpleasantness.