NeuroImage 55 (2011) 277–286

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Contribution of chronic pain and neuroticism to abnormal forebrain gray matter in patients with temporomandibular disorder

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ARTICLE INFO

Article history:
Received 22 September 2010
Revised 30 November 2010
Accepted 5 December 2010
Available online 13 December 2010

Keywords:
Cortical thickness analysis
Voxel-based morphometry
MRI
Chronic pain
Neuroticism
TMD
Prefrontal cortex
Cingulate cortex
Sensorimotor cortex
Thalamus

ABSTRACT

Cortical plasticity is thought to occur following continuous barrage of nociceptive afferent signals to the brain. Hence, chronic pain is presumed to induce anatomical and physiological changes in the brain over time. Inherent factors, some pre-dating the onset of chronic pain, may also contribute to brain abnormalities present in patients. In this study we used structural MRI to examine whether patients with chronic temporomandibular (TMD) pain have abnormalities in gray matter (GM) within brain areas implicated in pain, modulation and sensorimotor function. We found that patients with TMD have cortical thickening in the primary somatosensory cortex (S1), frontal polar and the ventrolateral prefrontal cortex (PFC). These findings provide a structural basis for previous findings of TMD pain and cognitive sluggishness in TMD. We then examined the contribution of TMD characteristics to GM abnormalities. We found that 1) GM in the sensory thalamus positively correlated to TMD duration, 2) cortical thickness in the primary motor (M1) and the anterior mid-cingulate cortices (aMCC) were negatively correlated to pain intensity, and 3) pain unpleasantness was negatively correlated to cortical thickness in the orbitofrontal cortex (OFC). These findings suggest that an individual's TMD pain history contributes to GM in the brain. Lastly, we examined the contribution of a potential pre-existing vulnerability due to neuroticism. In the TMD patients, we found that there was an abnormal positive correlation between neuroticism and OFC thickness, in contrast to the negative correlation found in the healthy controls. Therefore, neuroticism may contribute to TMD pathophysiology. In sum, our data suggest that GM in the brain of patients with chronic TMD pain can be shaped by both personality and pain characteristics.

Introduction

Temporomandibular disorder (TMD) is a common chronic orofacial pain that is more prevalent in women than in men (Ramírez et al., 2005). TMD can be idiopathic in that there may not be any clear peripheral etiological factors identifiable (Dworkin, 1994; Dworkin and Massoth, 1994; Dworkin et al., 1994; Ohrbach and Dworkin, 1998). In this scenario, it is thought that the CNS may initiate and/or maintain the pain (Sarlani and Greenspan, 2005).

Although a clear pattern of change has yet to be determined, previous structural MRI studies of chronic pain populations have found both increases and decreases in gray matter (GM). For instance, some studies of headache and chronic facial pain populations have found that patients with chronic pain had GM increases in regions likely associated with pain perception (DaSilva et al., 2007; May, 2008; Obermann et al., 2009; Younger et al., 2010). Additionally, most studies of chronic pain patients have found reduced GM in cortical regions likely associated with pain modulation and limbic function (Blankstein et al., 2010; Geha et al., 2008; May, 2008). Interestingly, some studies have also reported GM loss in cortical and subcortical motor areas (Apkarian et al., 2009; May, 2008; Schmidt-Wilcke et al., 2010). However, the increases are not

Abbreviations: TMD, temporomandibular disorder; CTA, cortical thickness analysis; VBM, voxel-based morphometry; S1, primary somatosensory cortex; S2, secondary somatosensory cortex; M1, primary motor cortex; ACC, anterior cingulate cortex; MCC, mid-cingulate cortex; aMCC, anterior mid-cingulate cortex; OFC, orbitofrontal cortex; PFC, prefrontal cortex; VPM, ventroposterior medial nucleus of the thalamus; VL, ventrolateral nucleus of the thalamus; Po, posterior nucleus of the thalamus.

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doi:10.1016/j.neuroimage.2010.12.013

limited to regions thought by some to be associated with pain perception, and the decreases are not limited to regions typically associated with pain modulation. Although the role of motor regions in pain is not fully established, there is evidence suggesting these areas play a role in pain modulation (Adachi et al., 2008; Brown and Barbaro, 2003; Craig and Dostrovsky, 1997; Garcia-Larrea et al., 2009, 1999; Lima and Fregni, 2008). In support of this concept are the motor abnormalities that can accompany chronic pain (Chen et al., 2009; Juottonen et al., 2002; Kirveskari et al., 2010; Svensson and Graven-Nielsen, 2001; Weissman-Fogel et al., 2011), possibly related to nocifensive behaviour (Murray and Peck, 2007).

There are two main routes by which the CNS may contribute to the development and/or maintenance of chronic pains such as TMD. One possibility is that long-term nociceptive input into the brain induces maladaptive brain plasticity, which may play a role in maintaining pain (Albanese et al., 2007; Woolf and Salter, 2000). For example, a recent study demonstrated that experimental pain that increased GM in nociceptive regions (Teutsch et al., 2008), induced pain habituation over time that was accompanied by decreased activity within nociceptive areas and increased activity within the antinociceptive system (Bingel et al., 2007). Chronic pain patients, however, may not be able to adapt in this way to nociceptive activity. For example, neuroimaging studies of chronic pain have shown hyperactivity in nociceptive regions, and hypoactivity in antinociceptive regions (Apkarian et al., 2005; Lev et al., 2010). Chronic pain patients' inability to habituate to increased nociceptive activity may be related to a reduced capacity of the brain to dampen pain by descending (top–down) controls (Bingel and Tracey, 2008). Indeed, many structural MRI studies have found GM differences in chronic pain populations associated with pain-related characteristics (intensity, unpleasantness, or duration) (Apkarian et al., 2004; Blankstein et al., 2010; May, 2008; Rodriguez-Raecke et al., 2009; Younger et al., 2010).

The second route by which the CNS may contribute to the development and/or maintenance of chronic pain relates to inherent personality-related factors that reduce the brain's capacity to modulate nociceptive input. This poor pain control represents a vulnerability to develop chronic pain. For example, there is evidence that neuroticism may be associated with pain-related suffering (Harkins et al., 1989), pain sensitivity (Costa, 1987; Goubert et al., 2004; Wade et al., 1992), nerve injury outcomes and neuropathic pain (Taylor et al., 2010) and inhibition of negative thoughts (Costa and McCrae, 1992). However, not all chronic pain patients have high neuroticism scores, and not all persons with neuroticism have chronic pain (Costa et al., 1986). Therefore, neuroticism alone is not sufficient to develop chronic pain. Rather, the normal relationship between neuroticism and brain structure and function may be disrupted within regions involved in pain modulation, such as the orbitofrontal cortex (OFC) (Wright et al., 2006) or the medial prefrontal cortex (mPFC) (DeYoung et al., 2010; Haas et al., 2008) and this could facilitate or maintain chronic pain.

Thus, in the current study we examined GM abnormalities in patients with idiopathic TMD and focused our investigation on the contribution of pain-related characteristics and neuroticism. Towards this goal, we measured GM in patients who had suffered from TMD over a range of pain intensities, unpleasantness and for varying durations, and neuroticism scores. Based on the aforementioned behavioural and neuroimaging studies, we specifically tested the hypotheses that TMD patients will have: 1) increased GM in areas associated with pain perception; 2) reduced GM in areas associated with pain modulation and motor function; 3) GM positively correlates with pain intensity, unpleasantness and TMD duration within areas associated with pain perception areas and negatively correlates with GM in areas associated with antinociception; 4) negative correlation between neuroticism and GM in regions implicated in pain modulation, and positive correlation in regions implicated in the affective dimension of pain, because of the interaction between affective processing and pain modulation in TMD (Turner et al., 2001).

Materials and methods

Subjects

A group of 17 females with idiopathic TMD (mean age ± SD: 33.1 ± 11.9 years) and 17 healthy females (mean age ± SD: 32.2 ± 10.1 years) provided informed written consent to procedures approved by the University Health Network and Mount Sinai Hospital Research Ethics Boards. All subjects were right-handed. Patients with TMD were screened using TMD research diagnostic criteria (TMD-RDC) (Dworkin and Leresche, 1992) by dentists at the Mount Sinai Hospital Dental Clinic. Inclusion criteria included: 1) TMD pain masticatory muscle region greater or equal to 4/10 for at least 3 months or pain that is aggravated by mandibular function; and 2) moderate pain to palpation and/or persisting pain after examination in at least 3 muscle sites and/or moderate pain to palpation of the temporomandibular joint (TMJ) region and/or limitation in the mandibular movement (opening less than 40 mm). Patients were asked to remain analgesic-free for 24 h prior to scanning, as functional data was also being collected during the scanning session. For both patients and control subjects, exclusion criteria included: 1) serious metabolic, rheumatoid or vascular disorders and other diseases; 2) other craniofacial pain disorders, previously diagnosed psychiatric disorders (e.g., depression, schizophrenia and ADHD) or self-reported history of an abnormal neurological examination; 3) any contraindication to MRI scanning (e.g., claustrophobia and metal); and 4) use of psychotropic drugs. In addition, healthy controls were not eligible for the study if they had a history of chronic pain.

Questionnaires

Each participant completed the NEO-Five Factor Inventory (NEO-FFI) (Costa and McCrae, 1992). The NEO-FFI is a self-report questionnaire comprising of 60 statements. Participants were asked to indicate the degree to which they agree with a statement on a five-point scale (strongly disagree, disagree, neutral, agree and strongly agree), each of which is coded to a number (0–4). A total of 15 of 60 questions probe for aspects of neuroticism in this questionnaire.

Prior to scanning, patients were interviewed. They were asked to verbally provide a numerical pain score for their current pain intensity and pain unpleasantness and their average pain intensity and unpleasantness over the last month before scanning. They were specifically asked the following questions: “Please rate your current/average pain/unpleasantness rating over the last month on a scale of 0 to 10 (0 = no pain, 10 = worst pain imaginable)”. The duration of the patients' TMD was also recorded for each patient.

Imaging parameters

Brain imaging data were acquired using a 3T GE MRI system fitted with an eight-channel phased array head coil. Subjects were placed supine on the MRI table and each subject's head was padded to reduce movement. A whole brain three dimensional (3D) high-resolution anatomical scan was acquired with a T_1-weighted 3D IR-FSPGR sequence: 128 axial slices, $0.94 \times 0.94 \times 1.5$ mm^3 voxels, 256×256 matrix size, field of view = 24×24 cm, one signal average, flip angle = 20°, TE = 5 ms, TR = 12000ms, TI = 300 ms.

Structural brain imaging analysis

We used the analysis approaches best suited to measure GM cortically and subcortically from high-resolution MRI images. At the cortical level, we evaluated differences in cortical thickness (measured in mm) with cortical thickness analysis (CTA) (Fischl and Dale, 2000; Lerch and Evans, 2005; MacDonald et al., 2000), and subcortically we used voxel-based morphometry (VBM) (Ashburner and Friston, 2000) to measure subcortical GM volume. To verify the