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MULTIMODAL MRI REVEALS MICROSTRUCTURAL BRAIN ALTERATIONS CORRELATING WITH PERSONALITY TRAITS IN CHRONIC PAIN

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Abstract
Extensive damage to this brain area is known to affect a person's personality. Subtle differences in the prefrontal cortex that are linked to lasting pain and have only become visible through advanced scans might also contribute to distinctive shifts in a person's personality. When a chronic neuropathic pain animal model was studied, minor changes in the prefrontal cortex such as differences in basal dendritic length, linked to difficulties in making decisions. Our studies combining various types of magnetic resonance imaging in living subjects showed that gray matter volume and brain signals were stable, yet chronic neuropathic pain decreased the movement of protons, reflecting subtle changes in the medial prefrontal cortex, anterior cingulate cortex and mediodorsal thalamus. Proton spectroscopy suggested that the medial prefrontal cortex had increased functional integrity in people who experience neuropathic pain and this change was strongly related to their degree of novelty seeking. The results indicate that very minor alterations in the prefrontal cortex can change personality in important ways.

Keywords: Chronic neuropathic pain, Magnetic resonance imaging (MRI), Personality temperament, Brain microstructure

Introduction

Extensive damage to the prefrontal cortex is known to cause changes in a person's personality. Yet, not as widely acknowledged is the possibility that small structural changes in the prefrontal cortex linked to chronic pain can result in minor changes in a person's personality. Not so many people were aware of this link before recently, mainly because seeing small brain anatomical changes in a live person was very hard. Sensitive neuroimaging methods have discovered relationships between chronic pain and slight changes to the thalamus, insular cortex and cingulate cortex [1], [2], [3]. Moreover, chronic pain appears to be related to slight cognitive problems. Chronic physical pain often leads to issues in decision-making, as people struggle to think in a helpful way [4], [5]. New research shows that these individuals display certain personality changes, with more harmful avoidance (by worrying a lot) and less interest in seeking out new and spontaneous activities [6]. It is possible that such thinking changes may happen because activity in the brain's cortex, particularly the prefrontal cortex, is altered [7], [8], [9], [10]. Metz and his coworkers found in an animal research of neuropathic pain that pyramidal cells in the medial prefrontal cortex had longer

and more branched dendrites than the control samples [11]. Greater dendritic spine density and stronger NMDA receptor responses at synapses were found where pain was present. If people undergo similar physical changes, they could help explain lower levels of novelty seeking and higher levels of harm avoidance in individuals with chronic pain. Here, we study how the structure and chemistry of regions like the medial prefrontal cortex change in those with chronic pain and look for relationships to their personality traits. Both DTI and T2-relaxometry were implemented to uncover early changes in the ways tissue is set up or matures in the brain [12], [13]. This connectivity analysis was supplemented by using proton spectroscopy to monitor N-acetyl aspartate (NAA), an indicator of how healthy the neurons are [14]. We suggest that chronic pain patients will have weaker DTI and T2 values and greater NAA levels in the medial prefrontal cortex and that these results will correlate with higher levels of novelty seeking and harm avoidance personality traits. Such results may show that changes happen in nerve cell shapes and numbers of their extensions, along with changes in their bodies.

Methods

Chronic neuropathic pain patients who participated were identified as having trigeminal neuropathy, according to the Liverpool criteria. Before any procedures were done, all volunteers were told about the study and agreed to participate on paper. The guidelines of the study were approved by the appropriate ethics committees. A few chronic pain participants had contributed to earlier projects similar to this one [1], [16–19]. Chronic pain subjects were asked to report their pain three times per day for a week with a 10 cm visual analogue scale before their MRI session. The average of all ratings was used to determine each person's total pain score. The evaluation of personality traits was done by means of the revised Temperament and Character Inventory (TCI-R). In all, 19 chronic pain patients (16 females; mean age ± SEM: 53 ± 1.8) and 30 healthy control participants (24 females; mean age ± SEM: 51 ± 1.0) completed the TCI-R and group differences were tested by checking the temperament scale scores between the groups.All neuroimaging was carried out using a 3 Tesla Philips Intera scanner. To obtain the imaging protocol, we used three sequences that took 3D T1-weighted images and four DTI series (TR = 8788 ms, flip angle = 90°, voxel size = 2 × 2×2.5 mm, 32 directions, b-values were 0 and 1000 s/mm²). Signal quality was improved by merging multiple T1 and DTI scans together. Out of the original group, 11 controls and 10 of the stacking pain patients came back for additional scans. In patients, we applied proton MRS in the medial prefrontal cortex on the opposite side of the pain and the same area was studied in control participants using ^{1}H-MRS. In the spectroscopy measurements, TR was set to 2000 ms, the echo time was 29 ms, spectral width was 2 kHz, 1024 points were collected, the scan took 9 minutes and the voxel size was 20 × 15 × 30 mm. Placement of spectroscopy voxels was influenced by previous diffusion and relaxometry findings. Image preparation and analysis were based on tested methods. To eliminate motion effects, all DTI data were adjusted, registered together, averaged and tensors computed using SPM8 and custom programs. Standard space was applied to mean diffusivity (MD) maps and a 6 mm Gaussian kernel was used to smooth them. The T2 relaxation values were found from multi-echo images and, much like the MPRAGE, were then normalized and smoothed. MD and T2 measurements for different groups were compared using random-effects models that use error correction and are adjusted for differences in age and sex ($p < 0.05$). VOI volume data was computed using VBM from T1 images and the findings were compared statistically between groups. Maps of cerebral blood flow (CBF) were made from quantitative arterial spin labelling (QASL) and placed next to the anatomical images. The data from ^{1}H-MRS was quantified for metabolites using jMRUI 4.1 and the QUEST algorithm, in turn giving the ratio of NAA to MI and to Cr. Relationships between imaging results, pain scores and temperament were explored using t-tests and Pearson correlations, at the significance level $p < 0.05$.

Result

Significant reductions in T2 relaxation times were observed in chronic pain patients compared to controls across all examined regions. Specifically, the contralateral medial prefrontal cortex

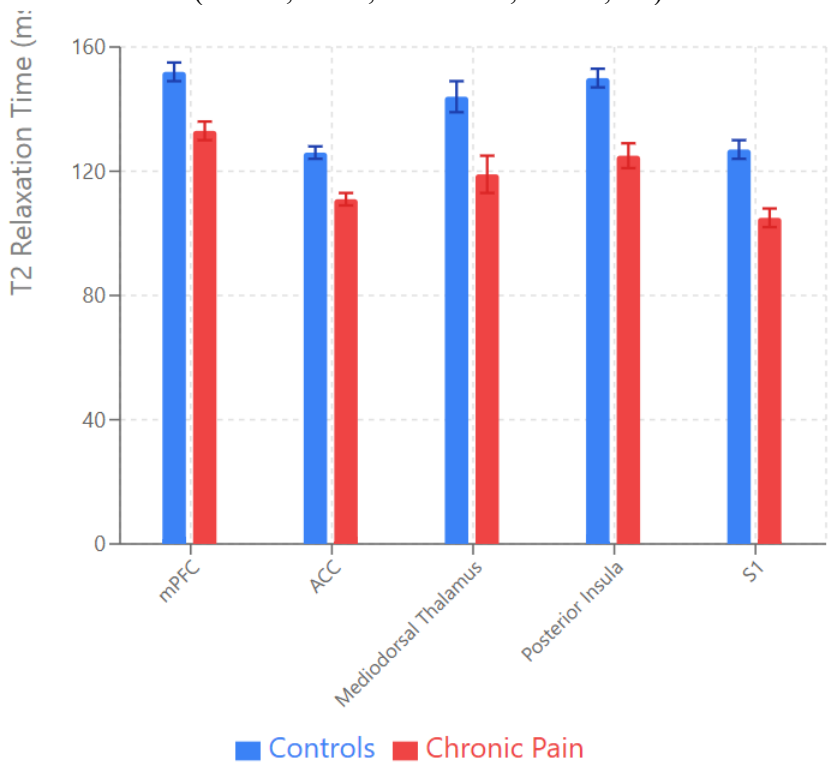
(mPFC) exhibited a mean T2 relaxation time of 133 ± 3 ms in chronic pain subjects, significantly lower than the 152 ± 3 ms recorded in controls ($p < 0.05$). Similar decreases were seen in the contralateral anterior cingulate cortex (ACC) (111 ± 2 ms vs. 126 ± 2 ms), contralateral mediodorsal thalamus (119 ± 6 ms vs. 144 ± 5 ms), ipsilateral posterior insula (125 ± 4 ms vs. 150 ± 3 ms), and contralateral primary somatosensory cortex (S1) (105 ± 3 ms vs. 127 ± 3 ms). These reductions in T2 values suggest subtle alterations in tissue microstructure consistent with changes in water content, myelination, or cellular density associated with chronic pain. Mean diffusivity (MD) values were also significantly decreased in the chronic pain group relative to controls across all regions. In the contralateral mPFC, MD was reduced from 1.30 ± 0.02 $\times 10^{-3}$ mm^2/s in controls to 1.15 ± 0.02 $\times 10^{-3}$ mm^2/s in chronic pain subjects ($p < 0.05$). Corresponding decreases were noted in the ACC (1.01 ± 0.01 vs. 1.14 ± 0.01), mediodorsal thalamus (1.35 ± 0.03 vs. 1.55 ± 0.04), posterior insula (1.13 ± 0.03 vs. 1.27 ± 0.05), and S1 (1.01 ± 0.02 vs. 1.15 ± 0.05). Lower MD values are indicative of restricted water diffusion, potentially reflecting microstructural reorganization or increased cellular packing density in these brain areas. Grey matter volume measurements did not differ markedly between groups. Values remained stable in the contralateral mPFC (0.46 ± 0.01 controls vs. 0.46 ± 0.01 chronic pain) and other regions, indicating that gross volumetric changes were not evident despite microstructural alterations. Cerebral blood flow analysis revealed modest, non-significant reductions in chronic pain subjects in several regions, including the ACC (30.0 ± 2.8 ml/min/g vs. 34.2 ± 1.8 ml/min/g) and S1 (34.5 ± 2.7 ml/min/g vs. 38.2 ± 2.5 ml/min/g). Interestingly, the mPFC showed a slight increase in CBF in chronic pain participants (33.1 ± 2.2 ml/min/g) compared to controls (31.0 ± 1.5 ml/min/g), although this difference did not reach statistical significance. Overall, these results highlight subtle yet widespread microstructural brain changes associated with chronic pain, particularly in regions implicated in pain processing and cognitive-emotional regulation. The combination of decreased T2 relaxation times and mean diffusivity, alongside preserved grey matter volume and largely unchanged cerebral blood flow, suggests that chronic pain may induce cellular and myelin alterations without overt volumetric loss. These findings contribute to understanding the neural substrates underlying chronic pain and its impact on brain integrity.

Table 1: Neuroimaging Metrics in Contralateral mPFC, ACC, Thalamus, Insula, and S1 in Controls vs. Chronic Pain

Parameter	**Group**	**Contralateral mPFC**	**Contralateral ACC**	**Contralateral Mediodorsal Thalamus**	**Ipsilateral Posterior Insula**	**Contralateral S1**
T2 Relaxation Time (ms ± SEM)	Controls	152 ± 3	126 ± 2	144 ± 5	150 ± 3	127 ± 3
	Chronic Pain*	133 ± 3	111 ± 2	119 ± 6	125 ± 4	105 ± 3
Mean Diffusivity ($\times 10^{-3}$ mm^2/s ± SEM)	Controls	1.30 ± 0.02	1.14 ± 0.01	1.55 ± 0.04	1.27 ± 0.05	1.15 ± 0.05
	Chronic Pain*	1.15 ± 0.02	1.01 ± 0.01	1.35 ± 0.03	1.13 ± 0.03	1.01 ± 0.02
Grey Matter Volume (probabilit	Controls	0.46 ± 0.01	0.47 ± 0.01	0.49 ± 0.01	0.64 ± 0.01	0.36 ± 0.01

y × volume ± SEM)						
	Chronic Pain	0.46 ± 0.01	0.45 ± 0.01	0.48 ± 0.01	0.64 ± 0.01	0.38 ± 0.01
Cerebral Blood Flow (ml/min/g ± SEM)	Controls	31.0 ± 1.5	34.2 ± 1.8	37.5 ± 2.5	29.0 ± 2.0	38.2 ± 2.5
	Chronic Pain	33.1 ± 2.2	30.0 ± 2.8	36.5 ± 2.9	28.5 ± 2.5	34.5 ± 2.7

Figure 1: Neuroimaging Metrics: Controls vs. Chronic Pain, Comparison across brain regions (mPFC, ACC, Thalamus, Insula, S1)



Discussion

Our results suggest that chronic pain is associated with structural changes in brain regions that affect aspects of personality such as the medial prefrontal cortex (mPFC), anterior cingulate cortex (ACC) and mediodorsal thalamus. Importantly, greater adjustments in the anatomy and biochemistry of the mPFC and ACC in people with chronic pain were related to a lower novelty seeking trait. Therefore, it appears that small changes in the brain may affect how a person's personality develops.In the past, Metz et al. found [11] that dendrites in the contralateral mPFC of pyramidal cells in a neuropathic pain condition were extended, had more branches and had more spines than dendrites from normal subjects. Should this happen in the brain of a human, it could limit the movement of protons and result in strong T2 effects from increased dendritic branches and increased binding of small molecules near macromolecules [13], [25] and [26]. Such patterns are consistent with visual findings from neuroimaging in our group with chronic pain. In addition, because of these tiny neuronal changes, the volume of grey matter in the mPFC, ACC and mediodorsal thalamus might not change noticeably which is consistent with our findings in chronic pain subjects. Both changes in mean diffusivity and T2 values could mean abnormalities in glial or vascular areas, but our NAA and myo-inositol results reveal no change. NAA mainly comes from

neurons and is often seen as an indicator of both healthy neurons and their synapses, since high levels are linked to improved cognition and low levels to certain neurodegenerative disorders [29], [30]. High levels of myo-inositol indicate that cells called glia are involved in the condition known as Alzheimer's [31], [32]. While spectroscopy samples were limited, the rise in NAA and continuing stability of myo-inositol argue that the detected changes in diffusion and T2 mostly indicate mild changes in neurons such as elongated dendrites and more spines in the mPFC. Many now believe that chronic pain includes sensory, emotional and thinking challenges. Chronic pain patients typically do poorly on the Iowa Gambling Task and prefer immediate cash rewards, despite the likelihood of losing more money in the future [4], [5]. Similar changes result from damage to the mPFC and amygdala such as problems with evaluating results and difficulties with tasks [7], [8], [33]. We found that our chronic pain individuals had fewer novelty-seeking qualities and more avoidance of harm, a pattern seen in bigger studies on chronic pain personalities [6].Novelty seeking refers to strong excitement from anything fresh which leads to a desire to find new experiences and avoid boredom or tough consequences [34]. This finding suggests that the individual appears less driven to act out to avoid repetition and was alienation which is compatible with lowered awareness of upcoming outcomes. This kind of temperament is related to the brain's behavioral activation system which needs a healthy mesolimbic dopaminergic connection between the mPFC and ACC [35], [36], [37]. Different studies have linked Parkinson's disease and other prefrontal cortical problems to having less interest in new things [38], [39]. The mPFC and ACC are influenced by dopaminergic neural fibers sent by the ventral tegmental area (VTA). It has been observed in animal studies that lesions in the VTA deter the animals' ability to explore and pay attention to what happens in their environments [40]. After depleting dopamine in the mPFC using a lesion in the VTA, there are shorter basal dendrites and fewer spines present on pyramidal cells [41]. Despite their opposite natures, these nerve changes show strong similarities with those reported in studies on animals with nerve pain and our findings from the human brain imaging confirm the similarities. Since both animal model findings and our imaging results are imbalanced, we suggest that these changes in mPFC, ACC and thalamus occur as a result of chronic pain rather than before. After an injury, it is possible that dopaminergic changes contribute to dendritic growth in mPFC, plus external inputs like those from the amygdala, to alter both cognition and emotions, for example by causing reduced decision-making and increased interest in new things. According to new evidence, many people with chronic pain lack the ability to direct their own behavior [6], [42], as this is predictive of personality disorders [20]. Future scientists should examine how novelty seeking and self-direction relate to brain anatomy, brain chemicals and brain function in the mPFC. Our analyses suggest there are small neural changes in the mPFC and ACC as people experience changes in their personality related to chronic pain. Although gross brain injuries in these regions can greatly change a person's personality, our results support the idea that less serious changes can also have some effect. Persistence is connected to the ACC, ventral striatum and both lateral and medial parts of the prefrontal cortex in those with healthy temperaments [43], [44]. It may be that the drop in novelty seeking and active avoidance in people with chronic pain which lacks associations, is simply an adaptation to pain-related changes in the brain. With the use of more sensitive brain imaging methods, we know that widespread medical diseases are linked to important changes in brain structures, particularly in the mPFC and ACC. Such events are found in respiratory disorders [45], diabetes [46], osteoarthritis [47] and obesity [48]. It appears that frequent, minimal brain anatomy changes can impact personality which may explain why adult personality is not always fixed over a lifetime.

Conclusion

This research reveals that chronic pain results in subtle but important changes to the mPFC, ACC and mediodorsal thalamus, parts of the brain responsible for personality and cognitive duties. We found that these changes in microstructure are related to decreased novelty seeking in personality temperament. This means that keeping the brain's structure very similar can still result in it structuring personality traits differently. Seeing that T2 relaxation times and mean diffusivity

dropped but grey matter volumes stayed the same, we believe that neuronal remodeling took place instead of a major decrease in grey matter cells. This interpretation is consistent with measurements showing higher NAA in the mPFC and no changes in glial markers. Changes in brain function probably help explain the reduced decision making and varying emotional patterns—higher fear of new situations and lower interest in exciting ones—often found in those with chronic pain. Novelty seeking and dopamin-related pathways through the mPFC and ACC might be the reason why these findings came about. A number of studies have shown that loss of dopaminergic tone can cause dendrite changes and memory problems, as observed in people with neuropathic pain. Our findings from only imaging the human brain agree with animal study outcomes which suggests that These brain changes are caused by the disease itself and not due to differences before the condition. Notably, shift in personality among chronic pain patients might suggest that they adapt to their pain and their brain is remodeling. A drop in novelty seeking may, in some cases, be a way to avoid additional pressures or stress. Actually, less self-control in these people seems to make them more at risk for personality disorders. Overall, discovering that brain changes occur in people with various chronic illnesses points out that personality features can be modified by factors including brain structure and chemicals. Future work might examine the link between brain variances, novelty seeking and self-directedness to understand better their contribution to ongoing pain and related emotional and cognitive difficulties.

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