

The Brain and Chronic Pain

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Abstract

Objective: To review investigations into an association between brain changes and chronic pain; to synthesize the findings in the hope of generating interest among psychiatrists and casting some light on the road ahead.

Conclusions: There is good evidence that chronic pain is associated with changes in brain function. It is possible that these brain changes compound chronic pain and future agents may be able to prevent such complications. Psychiatrists have knowledge of the brain and brain active medication, and are well placed to contribute to the field of pain medicine (*German J Psychiatry* 2003; 6: 8-15)

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Introduction

Chronic pain has been reported in 17.1% of males and 20.0% of females in Australia (1), and probably elsewhere. It is the cause of personal suffering and growing public health costs.

It is well established that peripheral nerve injury may result in neuroplastic change not only in the axon but also in the dorsal horn of spinal cord (2). The questions that naturally follow are, 1) whether chronic pain from external insult (eg, amputation, herpes infection) can also result in plastic change in brain? and 2) whether the chronic pain conditions with no known history of external insult (eg, fibromyalgia (FM), atypical facial pain) are associated with brain changes?

The aim of this paper was to review and synthesize reported findings, in the hope that this may be of interest to psychiatrist, and give an indication of the lie of the land ahead.

Method

Research reports were sought using PubMed and the libraries of colleagues. A special search was made of the work of leaders in the field and a hand search was conducted of specialist journals. Reports were selected in which the brains of healthy volunteers or chronic pain patients were imaged or otherwise monitored using quantitative techniques, while rest, or responding to acute (experimental) pain.

Preliminary reading supported the notion of two broad groups of chronic pain conditions, one in which there was a history of external insult, and another, in which there was no such history. The studies generally employed one of two approaches, either quantified regional cerebral blood flow (rCBF), or some other quantitative approach. A first step in examining findings was to become familiar with the effects of experimental pain on the brain of healthy individuals.

There was variation in the methodology in the studies. Those that were sufficiently methodologically dissimilar as

to make categorization impossible were not considered in detail.

The identified studies were grouped under the following headings:

1. regional cerebral blood flow (rCBF) of healthy individuals exposed to experimental pain
2. resting state rCBF of patients with post external insult chronic pain
3. other quantitative brain studies in patients with post external insult chronic pain
4. brain studies in chronic pain without history of external insult
5. brain responses to experimental pain of people with chronic pain

Results

rCBF of healthy individuals exposed to experimental pain

Experimental pain is associated with activity and increased rCBF in the primary somatosensory cortex (SI), secondary somatosensory cortex (SII), anterior cingulate

cortex (ACC), thalamus, frontal cortex and insula (3-12). Other structures in which perfusion increased in at least one study include the lenticular nucleus (3, 9), the periaqueductal grey, and cerebellum (6, 8), the supplementary motor cortex, putamen, and superior colliculus (8), the posterior parietal cortex (10), the periventricular grey (11) and the amygdala (12). See Table 1 for details.

In only one study (8) was there a decrease in rCBF, and this was observed in only one region, the primary somatosensory area, contralateral to the side of the painful stimulus. The authors suggested that this unexpected effect may have been a response to the anticipation of pain, rather than to the actual stimulus.

With increasing conceptual and technological sophistication, attempts have been made to identify the brain structures involved in different dimensions of pain. Perhaps because of methodological differences, some opposing findings have been reached. For example, Iadarola et al (7) concluded that activation of the thalamus reflected a “sensation-perception” function, while Peyron et al (8) found activation of this structure reflected a “non-specific arousal component”.

It is sufficient for present purposes that a wide range of authors have found that experimental pain is associated with increased perfusion in the structures listed in Table 1. In particular, it is important to note that experimental pain administered to healthy individuals is associated with increased perfusion of the anterior cingulate gyrus and the

Table 1. rCBF of healthy individuals exposed to experimental pain

SI = primary somatosensory cortex, SII = secondary somatosensory cortex, ACC = anterior cingulate cortex, Thal = thalamus, FrCx = frontal cortex, Ins = insula, Oth = other, LN = lenticular nucleus (putamen + globus pallidus), PAG = periaqueductal grey, SMC = supplementary motor cortex, Put = putamen (see LN), Cer = cerebellum (anterior lobe and vermis), SC = superior colliculus, PPC = posterior parietal cortex, PVG = periventricular grey, Amg = amygdala, inject caps = injection of capsaicin

Reference	SI	SII	ACC	Thal	FrCx	Ins	Oth	Method
(3) 1991	+	+	+				LN	PET heat pain
(4) 1991			+	+				PET heat pain
(5) 1994	+	+	+	+	+			PET heat pain
(6) 1994	+	+	+	+		+	PAG, Cer	PET heat pain
(7) 1998		+		+		+		fMRI heat pain
(8) 1998	+		+	+		+	PAG, SMC, Put, Cer, SC	PET inject caps
(9) 1998			+	+	+	+	LN, Cer	PET heat pain
(10) 1999		+	+	+	+	+	PPC	PET heat pain
(11) 1999			+	+	+		PVG	PET heat pain
(12) 2002	+	+	+		+	+	Amg	fMRI heat pain

thalamus.

Resting state rCBF of patients with post external insult chronic pain

Five resting state rCBF studies of patients suffering post insult chronic pain were identified (13-17). All described decreased perfusion (therefore reduced activity) of the thalamus. See Table 2 for details.

One study (14) of neuropathic pain, in which sharp stabbing pains are a feature, also described increased perfusion in cortical regions similar to those described in experimental pain in healthy individuals. The consistent feature, however, in post external insult chronic pain was decreased perfusion in the thalamus. This was in stark contrast to the increased perfusion of that structure observed in experimental pain in healthy individuals.

Other quantitative brain studies in post external insult chronic pain

Three magnetoencephalogram (MEG) studies of brain function of post external insult chronic pain patients (phantom limb, back pain and complex regional pain syndrome (CRPS)) were located (18-20). All observed abnormalities of function and concluded there was of reorganization of SI.

Rommel et al (21) intensively studied CRPS using bedside neurological and quantitative sensory testing. They

found abnormal patterns of sensory impairment and conclude that the processing of noxious events was disturbed at the thalamus.

Three magnetic resonance spectroscopy (MRS) studies of the chemical composition of brain in post external insult chronic pain were located (22-23). In two (22, chronic back pain; 23, CRPS) the composition of a range of cortical areas and the thalamus was explored. In both the levels of N-acetyl aspartate were found to be reduced in the dorso-lateral prefrontal cortex (DLPFC) bilaterally. In the third (24, neuropathic pain after spinal cord injury) attention was focused on the thalamus. N-acetyl aspartate was significantly reduced and myo-inositol was increased.

These studies indicate altered physiological function and altered chemical composition of regions of the cortex (SI and DLPFC) and the thalamus. This is consistent with the rCBF findings. See Table 3 for details.

Brain studies in chronic pain without history of external insult

Under this heading have been grouped FM and burning mouth syndrome (BMS). While it cannot be stated with certainty that peripheral insult has not occurred in these conditions, any insult which may have commenced a process has been relatively slight.

Two groups (25, 26) have studied rCBF in people with FM, using single photon emission tomography (SPECT). They found reduced blood flow to the thalamus. One (25) also found reduced blood flow to the caudate and cerebral

Table 2. Resting state rCBF in post external insult chronic pain

Ref	Condition	Subjects	Controls	Technique	Findings
(13) 1991	Chronic cancer pain (unilateral)	5 patients before cordotomy	Same 5 after cordotomy Also, a group of healthy volunteers	Positron emission tomography (PET)	Before cordotomy patients compared to controls, significantly less blood to hemithalamus contralateral to pain. Before compared to after cordotomy, significantly less blood to hemithalamus contralateral to pain. Cordotomy abolished differences between sides.
(14) 1995	Neuropathic pain, lower limbs	8 total 4, left 4, right	Patients were their own controls	PET before and after regional nerve block	Increased activity, regardless of side of pain, bilateral anterior insula, posterior parietal, lateral inferior prefrontal, posterior cingulate cortex, anterior cingulate cortex (ACC) and right posterior ACC. Decreased activity in posterior thalamus contralateral to pain.
(15) 1995	Neuropathic pain	5 total 4 post-traumatic 1 post-herpetic	13 healthy volunteers	PET	Decrease thalamic activity contralateral to symptomatic side
(16) 1995	Central pain in the leg: spinal intramedullary cyst	Single case before surgery	Same case after surgery	Single photon emission computed tomography (SPECT)	Hypoperfusion of the thalamus contralateral to pain, which returned to normal after evacuation.
(17) 2001	Chronic pain	12 patients	12 healthy volunteers	SPECT	Significantly less perfusion in thalamus bilaterally

Table 3. Other quantitative brain studies in post external insult chronic pain

Ref	Condition	Subjects	Controls	Technique	Findings
(18) 1995	Phantom limb pain	13 patients 8 with pain 5 without pain	Contralateral versus ipsilateral	Magneto-electroencephalography (MEG)	Significant reorganization of SI. Intensity of pain positively correlated with extent of reorganization
(19) 1997	Chronic back pain	10 patients	9 healthy volunteers	MEG	Results suggestive of reorganization of SI cortex.
(22) 2000	Chronic back pain	9 patients	11 healthy volunteers	Magnetic resonance spectroscopy (MRS)	Reduction in N-acetyl aspartate and glucose bilaterally in dorsolateral prefrontal cortex (DLPFC).
(20) 2001	Complex regional pain syndrome (CRPS) of Upper limb	6 affected sides	6 unaffected sides of same patients	MEG	SI responses, 25-55% stronger to tactile stimuli on the painful side. Reactivity of 20Hz motor cortex rhythm altered. Indicating reorganization of cortex.
(21) 2001	CRPS, with hemisensory deficits	40 affected sides	40 unaffected sides of same patients	Bed-side and quantitative sensory testing	Hemisensory impairment in of CRPS is probably related to disturbed processing at the thalamus.
(23) 2002	CRPS	10 patients	10 healthy volunteers	As for Grachev et al (22)	Reduction in N-acetyl aspartate bilaterally in DLPFC. Increased myoinositol, left orbitofrontal cortex.
(24) 2002	Neuropathic pain after spinal cord injury (SCI)	7 patients with SCI and pain	10 healthy controls 9 patients with SCI and no pain	MRS	In thalamus, concentration N-acetyl acetate negatively correlated with pain intensity, significantly reduced, compared to controls and patients without pain. Myo-inositol was increased.

cortex, and the other (26) found reduced blood flow to the inferior pontine tegmentum. See Table 4 for details.

Salerno et al (27) studied people with FM, using transcranial magnetic stimulation (TMS) to trigger cortical responses. They found people with FM manifested significant cortical dysfunction, when compared to healthy individuals. However there was no difference between the results of people with FM and a comparison group with rheumatoid arthritis. This suggested that the observed cortical dysfunction may be a general feature of chronic pain.

Drawing on their research experience in related fields, Jaaskelainen et al (28) used PET to examine dopaminergic function of patients with BMS. They found significantly reduced function in the right caudate. In reconciling this study with the others, kept in mind that dopamine is distributed in discrete areas of the brain, and as mentioned above, Montz et al (25) found involvement of the caudate in chronic pain.

This batch of studies suggests that one type of chronic pain without history of external insult (FM) may be characterized by reduced rCBF, particularly to the thalamus, and disturbance of cortical neurophysiology. Another (BMS), may manifest neurotransmitter abnormality in a subcortical structure.

Brain responses to experimental pain of people with chronic pain

Six groups (29, atypical facial pain; 30 cluster headache; 31 and 34, irritable bowel syndrome (IBS); 32, FM; 35 low back pain) have compared the responses to experimental pain of people with chronic pain and healthy volunteers. Another group (33) compared the responses to experimental pain of people with sympathetically mediated pain (SMP), before and after the chronic pain was temporarily relieved by sympathetic block.

Derbyshire et al (29) and Silverman et al (31) found distinctly different results. Compared to healthy volunteers, Derbyshire et al (29) found patients with atypical facial pain to have significantly more activation of the ACC and significantly less in the ipsilateral frontal cortex. Compared to healthy volunteers, Silverman et al (31) found patients with IBS to have significantly less activation of the ACC and significantly more activation of the left frontal cortex. Both groups were studying chronic pain, but different primary disorders, which may help to explain the different findings. They both, however, found the response of a group with chronic pain to be different to that of healthy volunteers.

Gracely et al (32) studied the rCBF response to experimental pain of patients with FM. They applied pressure to the thumb nail bed of 16 people suffering FM, and the

Table 4. Quantitative brain studies in chronic pain without history of external insult

Ref	Condition	Subjects	Controls	Technique	Findings
(25) 1995	Fibromyalgia (FM)	10 female patients	7 healthy females	SPECT	Significantly reduced blood to thalamus, left and right caudate and cerebral cortex of patient group.
(26) 2000	FM	17 female patients	22 healthy females	SPECT and magnetic resonance imaging (MRI) to enable anatomic localization.	Significantly reduce blood flow in the right but not the left thalamus, and in the inferior pontine tegmentum.
(27) 2000	FM	13 female patients	13 healthy female volunteers 5 females with rheumatoid arthritis (RA)	Motor evoked potentials triggered by single and double transcranial magnetic stimulations	Comparison of FM patients and healthy controls revealed significant cortical dysfunction. No difference between RA and FM patients suggests a mechanism common to chronic pain.
(28) 2001	Burning mouth syndrome (BMS)	10 patients	14 healthy volunteers	PET arranged to study dopaminergic function.	Dopamine function significantly reduced in right caudate in BMS group.

same number of healthy volunteers. When the same pressure was applied to the groups, there was more widespread brain activation in the FM group, but when the pressure was modified to produce the same pain in the two groups, there was more widespread brain activation in the healthy group. The authors concluded that FM augments pain processing.

Apkarian et al (33) found the rCBF of the resting brain in SMP to be an increased prefrontal cortex and ACC perfusion and a decrease in the contralateral thalamus. This is

very similar to the picture described by Hsieh et al (14) who were examining neuropathic pain, an overlapping condition.

Only one group (35) failed to find significant differences between patients and controls. They studied 16 patients with “non-specific chronic low back pain” using PET and heat pain. While they observed some differences, these did not reach statistical significance.

Thus, six (29-34) of seven studies (29-35) found that the brain of people with chronic pain responds differently to healthy volunteers when exposed to experimental pain.

Discussion and conclusions

The shortcomings of this review include that some papers have been overlooked. All papers which could be identified using PubMed, or were known to colleagues, were obtained. A special search was made of the work of leaders in the field and a hand search was conducted of specialist journals. While some papers have doubtless not been examined, it is unlikely they would contain sufficient material to negate the modest conclusions reached. Another shortcoming could be that statistical methods have not been em-

ployed. However, such resources were unavailable to the authors and useful observations can be made without them.

Shortcomings of the examined body of studies include that researchers used different numbers of subjects, different technology (eg rCBF was estimated by both SPECT and PET), and different experimental designs (some compared patients with control subjects, some compared one side of the patient with the other side, some compared the patient before and after analgesic treatment), making comparisons difficult.

Studies were arranged in groupings and the following general conclusions appear justified by the evidence.

1. Experimental pain applied to healthy individuals is associated with increased perfusion in a set of structures. In particular, increases occur in the thalamus and ACC.
2. rCBF in the resting patient with post external insult chronic pain is dissimilar to that of the healthy individual exposed to experimental pain. In particular, there is decreased rather than increased perfusion of the thalamus.
3. In addition to the perfusion studies, a range of studies of post external insult chronic pain indicate altered physiological function and chemical composition of the cortex and thalamus.
4. Some evidence suggests that chronic pain without a history of external insult (particularly FM) is also associated with brain changes. The reduced perfusion of the thalamus which is described in post external insult chronic pain may also be present where there is chronic pain but no history of external insult.
5. The brain responses to experimental pain of people with chronic pain appear to be different to those of healthy volunteers. It has been impossible to character-

ize the difference, as a variety of methods have been used, but only one of seven studies failed to find substantial differences.

6. Thus, a substantial body of evidence indicates that chronic pain is associated with changes in brain structure and function. This is stronger for post external insult chronic pain, but some evidence indicates that chronic pain without a history of external insult may also be associated with similar changes.

One interpretation of these findings is that chronic pain leads to changes in brain structure and function. In the case of post external insult chronic pain, an important question to be decided is whether destructive process becomes established in which the brain changes exaggerate contribute to the intensity or the chronicity of pain. In the case of chronic pain without a history of external insult, a possibility to be excluded is that the brain change precedes the pain.

Many patients with chronic pain struggle with self-doubt,

concerned that the existence of their pain or their failure to live as they did prior to onset, is the result of weakness of character. Such patients may be encouraged by knowing that evidence indicates that chronic pain is associated with changes to the highest level of the nervous system. Of course, caution is necessary in discussing this information with patients as those particularly prone to self-criticism may be able interpret these findings as proof, not of the existence and potency of chronic pain, but as proof of weakness and impotence of their character.

The brain is the substrate of psychiatry. The information that chronic pain changes brain function may encourage psychiatrists to become involved in this important field of suffering. They have knowledge of the antidepressants and mood stabilizers which act supratentorially, as well as on damaged the peripheral nerves and dorsal horn cells. Psychiatrists are also well placed to prescribe drugs of addiction.

If the brain changes that are associated with chronic pain contribute to the unpleasantness of the experience, prevention would be desirable. This may mean that in addition to

Table 5. Brain responses to experimental pain of people with chronic pain

Ref	Condition	Subjects	Controls	Technique	Findings
(29) 1994	Chronic atypical facial pain (AFP)	6 female patients. Painful and non-painful thermal stimuli	6 healthy female volunteers. Painful and non-painful thermal stimuli	Positron emission tomography (PET) Before and during stimuli	For painful heat, AFP patients demonstrate greater activation in the anterior cingulate cortex (ACC) and significantly less in the ipsilateral prefrontal cortex.
(30) 1994	Cluster headache	12 patients	10 healthy volunteers	SPECT Before and during cold pain	Changes in rCBF significantly less in patient group S1 and thalamus.
(31) 1997	Irritable bowel syndrome (IBS)	6 patients	6 healthy volunteers	PET Before and during rectal distention via balloon	Healthy subjects, rectal pain was associated with activation of the ACC. IBS patients, ACC failed to respond, but significant activation of the left prefrontal cortex.
(33) 2001	Sympathetically mediated pain (SMP)	7 patients.	29 healthy volunteers. Same 7 patients. Heat pain, before and after sympathetic blockade.	Functional magnetic resonance imaging (fMRI) before and after blockade	Chronic state, increased prefrontal and anterior cingulate activity, and decreased contralateral thalamic activity.
(34) 2001	IBS	12 patients	12 healthy volunteers	PET before and during rectal distention	Patients, altered brain responses to rectal stimuli
(35) 2002	Non-specific back pain	16 patients	16 healthy volunteers	PET Before and during heat pain	Differences not sufficient to indicate abnormal nociceptive processing
(32) 2002	FM	16 patients	16 healthy volunteers	fMRI during painful pressure thumb-nail bed	Similar pressure, greater distribution of activation in FM group. Pressure applied to Produce similar pain, wider activation in the healthy group.

current and future analgesics, future management of trauma may include agents aimed at prevention of the compounding of chronic pain. There is current interest in the idea that the administration of an N-methyl-d-aspartate agonist concomitant with opioids may prevent opioid tolerance (36). It is not too great a stretch of the imagination then, to hope for agents which will prevent the exaggeration of chronic pain.

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