Behavioural evidence for vestibular stimulation as a treatment for central post-stroke pain

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► Additional data (supplementary figs 1–3, supplementary table 1 and appendices 1–3) are published online only at http://jnnp.bmj.com/content/vol79/issue11

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ABSTRACT

Background: Central post-stroke pain (CPSP) is often resistant to treatment. We have previously proposed that caloric vestibular stimulation might alleviate it.

Methods: We conducted a single blind placebo controlled investigational study of caloric vestibular stimulation (CVS) in nine patients with CPSP. Participants rated their pain levels before and after the procedure on a 10 point scale.

Results: We found a significant immediate treatment effect of the cold water caloric stimulation with an average pain reduction of 2.58 points (SEM 0.52) for the experimental condition compared with 0.54 points (SEM 0.49) for the placebo conditions.

Conclusions: Participants who responded best to CVS had suffered strokes that spared and permitted activation of the dominant parieto-insular vestibular cortex (PIVC), which is known to be located in the non-dominant hemisphere. These findings tie in closely with the thermosensory disinhibition hypothesis for central pain, which leads us to propose that vestibular stimulation may alleviate CPSP from cross activation between the PIVC and the thermosensory cortex in the adjacent dorsal posterior insula. Alternatively, if one views vestibular function and thermoregulation as part of a larger interoceptive system that exists to maintain homeostasis, then it is possible they share a common integrative mechanism in the brainstem, which may act to reset the balance in central pain.

Central post-stroke pain (CPSP) is often treatment refractory.[1] We have suggested that caloric vestibular stimulation (CVS) may bring relief to individuals with this condition.[2 3] Here we present a placebo controlled single blind study of CVS in nine patients with CPSP. Our findings are best interpreted within the framework of the thermosensory disinhibition hypothesis for central pain.[4 5]

Interoception and the thermosensory disinhibition hypothesis

CPSP can develop from a lesion affecting any part of the lamina I layer of the spinothalamic tract or its projection via the lateral thalamus to the dorsal posterior insula (dpIns).[5–8] The lamina I layer carries the interoceptive senses (eg, itch, tickle and thermosensation) to the interoceptive cortex in the posterior insula and parietal operculum, which includes the thermosensory cortex in dpIns.[6 8] The role of these senses is to monitor the body's physiological condition and maintain homeostasis. They do so by conferring both a sensation and, when necessary, a motivation to take corrective action.

The basis of the thermosensory disinhibition hypothesis is that central pain is a thermoregulatory disorder that occurs from the loss of the central inhibition of pain by cooling.[4 5] This happens because non-painful cold temperatures below 25°C actually activate both cold thermoreceptors (Aδ fibres) and also C nociceptors. These inputs pass together in the lamina I layer to the thalamus, where the C fibre input travels via the ventral caudal part of the medial dorsal nucleus of the thalamus to the anterior cingulate cortex (ACC) and the Aδ fibre input passes via the posterior part of the ventromedial nucleus (VMpo) in the lateral thalamus to dpIns (supplementary fig 1, available online).

It is thought, from functional imaging, that it is the ACC which is selectively associated with the motivation to take corrective action that characterises thermoregulatory distress.[6 9 10] Normally, when Aδ fibres activate the dpIns it acts (via the parabrachial nucleus (PB) and periaqueductal grey (PAG)) to suppress the perception of pain at the ACC. However, when the temperature falls below 15°C, the C activity predominates over the Aδ activity.[6] Therefore, the ACC is no longer suppressed and potentially harmful cold temperatures are perceived as pain with a motivation to take corrective action.

Consequently, lesions of the lamina I spinothalamocortical pathway terminating in dpIns can disinhibit a thermosensory network, including the PB, PAG and ACC.[4–6] Clearly, hemispheric imbalance also plays a role as CPSP rarely develops with bilateral thermosensory impairment.[5 11] The thermosensory disinhibition hypothesis proposes that lesions of the lamina I pathway can cause an imbalance in the bilateral integration of thermosensation in the brainstem by the PB and PAG and the development of CPSP.[6]

The parieto-insular vestibular cortex

Functional imaging during CVS demonstrates activation of the parietal and posterior insular cortices.[12 13] This area, the parieto-insular vestibular cortex (PIVC), is dominant in the hemisphere that is non-dominant for language.[14] Intriguingly, it has been reported that CPSP is twice as likely after non-dominant hemisphere strokes.[15] The major vestibular outflow from the thalamus to PIVC was obscure,[16] but was recently located in primates (AD Craig, personal communication, 2007) as lying in the posterolateral thalamus between VMpo and the magnocellular part of the medial geniculate body (see supplementary fig 2, available online). Craig found it to be about 4 mm posterior to the

Table 1 Pain ratings pre and post procedures

Subject	Condition	Pre	Post	Change	Radiology
A (0 days)	Left tepid	8.5	8.5	0	Lacunar infarct lateral nuclei right thalamus. Posterior pole of right thalamus spared. Also lacune right caudate (1.5 T)
	Left cold	8.5	5	−3.5	
	Ice pack	7	7	0	
	Right cold	8	5	−3	
B (1 day)	Left tepid[1]	8.5	7.5	1	AVM. Infarct involving entire right posterolateral thalamus and right PCA territory (3 T)
	Left cold[1]	8.5	8.5	0	
	Ice pack[2]	8.5	7	−1.5	
	Right cold[2]	7	5	−2	
C (1 day)	Right tepid[1]	6	4	−2	Lacunar infarct lateral nuclei right thalamus. Posterior pole of right thalamus spared. Hypertensive periventricular white matter changes and lacune right putamen (1.5 T)
	Left cold[1]	7.5	4	−3.5	
	Ice pack[2]	3	3	0	
	Right cold[2]	3	1	−2	
D (1 day)	Right tepid[1]	7.5	2.5	−5	Left posterior insula infarct with involvement of left parietal lobe and operculum (1.5 T)
	Right cold[1]	5.5	5	−0.5	
	Left cold[2]	6.5	5	−1.5	
	Left tepid[2]	7	6	−1	
E (0 days)	Right tepid	8	8	0	Haemorrhage right sub-insular white matter. Insula and thalamus both spared (1.5 T)
	Left cold	8	1	−7	
	Ice pack	1	1	0	
	Right cold	1	0	−1	
F (1 day)	Right tepid[1]	10	9	−1	SAH. Infarction left posterior insula and temporal pole. Tiny lacune left thalamus (region VMpo). Parietal operculum spared. (CT)
	Left cold[1]	9	5	−4	
	Ice pack[2]	10	10	0	
	Right cold[2]	10	8	−2	
G (20 days)	Right tepid[1]	7	6	−1	SAH. Right insula, frontal operculum and temporal pole infarcted. Parietal operculum spared (CT)
	Right cold[1]	6	3	−3	
	Ice pack[2]	4	4	0	
	Left cold[2]	4	2.5	−1.5	
H (1 and 6 days)	Left cold[1]	7	4	−3	Very large left internal carotid artery infarct. Complete infarction frontal lobe, except ACC. Involves ventrolateral thalamus, entire insula, internal capsule, caudate, putamen, parietal operculum and superior parietal lobe. Left medial thalamus and temporal operculum spared (CT)
	Left tepid[2]	7	7	0	
	Right cold[2]	7	3	−4	
	Ice pack[3]	4.5	4.5	0	
I (1 day)	Right tepid[1]	7.5	6	−1.5	Lacune right thalamus (1.5 T)
	Right cold[1]	7	4.5	−2.5	
	Ice pack[2]	5.5	5	−0.5	
	Left tepid[2]	5.5	4.5	−1	
	Left cold[2]	5.5	3	−2.5	

Number in parentheses indicates intersession interval and superscript indicates in which session the procedure was carried out. Imaging reported by RRL. We could not obtain a copy of patient I's scan. Imaging modality is in brackets.
ACC, anterior cingulate cortex; AVM, arteriovenous malformation; PCA, posterior cerebral artery; SAH, subarachnoid haemorrhage; VMpo, ventromedial nucleus.

part of VMpo that relays cool specific activity to the posterior insula.

METHODS

The institutional review board of the University of California, San Diego, granted ethics approval for the study. Nine patients with CPSP gave signed informed consent to participate and were run in two experimental sessions, separated by at least 1 day (except patients A and E who were seen in 1 day for logistical reasons). During each session, participants were administered one experimental cold water irrigation and one placebo intervention, either a body temperature irrigation or application of an ice pack to the pinna. Patients were blind to the experimental procedure. Before and after each procedure participants rated their pain on a numerical rating scale from 0, for no pain, to 10, for the worst imaginable.

Patients gave ratings every 10 min for 30 min after the procedure. If by then their pain level had not plateaued, we continued to measure it at 10 minute intervals until an hour after the procedure. Whatever level their pain plateaued at was taken as their post-procedure rating. They rated their overall pain level and the pain in their face, arm/hand and leg/foot (see appendix 1, available online).

RESULTS

Patient responses

The age range of the patients was 36–88 years, with three males and six females, and the duration post-stroke was 30–180 months (see supplementary table 1, available online). Seven of the patients were right-handed and two left-handed. All but one (patient H) had pain in their non-dominant side. Five of the strokes were ischaemic, one haemorrhagic, two subarachnoid haemorrhages (SAH) and one iatrogenic from embolisation of an arteriovenous malformation.

All participants described the cold CVS and ice pack control as unpleasant procedures. CVS produced vertigo and nystagmus in all. Clinically, the response to CVS split the population into three groups (table 1). The first group (patients A, E, G and H) had an excellent response; their pain was reduced immediately and stayed reduced for several days. The second group (patients

F, C and I) reported some reduction in their pain score but either this was not sustained (patients F and I) or the procedure was not tolerated (patient C). The third group (patients B and D) did not respond (see appendix 2, available online).

Patient A

Patient A was an 87-year-old right-handed man who had a right thalamic infarct in 1992 (fig 1A) centred on the right VMpo (supplementary fig 2, available online). The posterolateral thalamus, where the vestibular outflow lies, was spared. His baseline rating was 8 throughout. He responded to CVS, with greater relief in his face (0) and hand (1) than foot (7). The pain was replaced by numbness, similar to immediately post-stroke. He now describes 2 weeks of relief post-bilateral stimulations.

Patient B

Patient B was a 59-year-old right-handed woman who had a right posterior cerebral artery infarct in 1999. She described significant ongoing disequilibrium. She did not respond to CVS. Imaging (fig 1B) showed infarction of the posterolateral right thalamus with evident involvement of both the VMpo and the vestibular outflow.

Patient C

Patient C was a 78-year-old right-handed woman with a right thalamic infarct from 1993. Her pain fell following CVS and was replaced by numbness. However, she found CVS excruciating and has not continued.

Patient D

Patient D was a 36-year-old left-handed woman with a left posterior insula and parietal lobe infarct from 2004. She described ongoing disequilibrium and did not respond to CVS.

Patient E

Patient E was a 55-year-old right-handed woman who had a right sub-insular haemorrhage in 2002. After bilateral CVS she was pain free. Her pain was replaced by numbness. Although the pain in her foot returned after 24 h, the pain in her face (0.5 vs 2.5) and hand (2 vs 5) were reduced 3 weeks afterwards.

Patient F

Patient F was a 49-year-old left-handed man who had a left middle cerebral artery SAH in 2002. His pain did respond to CVS, with greater relief in his face and hand than foot, but rose again within a few hours.

Patient G

Patient A was a 49-year-old right-handed woman who had a right middle cerebral artery SAH in 2000. Her baseline was 7. She responded to CVS. This response was greater in her hand than foot. She has continued with CVS and reports a month of relief after bilateral stimulations.

Patient H

Patient H was a 69-year-old right-handed woman who in 1992 had a left internal carotid artery occlusion, rendering her hemiplegic and expressively aphasic. Her baseline was 7. She responded to CVS with greater relief in her face (2) and hand (3) than foot (5). It remained reduced for several weeks.

Patient I

Patient I was a 60-year-old right-handed man who had a right thalamic infarct in 2003. His pain only transiently responded to CVS.

Statistical analysis

An ANOVA analysis (appendix 3, available online) found a significant treatment effect of the cold CVS, with an average pain reduction of 2.58 points (SEM 0.52) for the experimental condition compared with 0.54 points (SEM 0.49) for the placebo conditions (supplementary fig 3, available online). There was no significant difference between the left and right stimulations.

DISCUSSION

Several aspects suggest that CVS alleviates CPSP by a distinct biological mechanism. These include: the duration of relief; differentially greater response in the face and hand compared with the foot, which corresponds with a map of these areas in the ACC[17]; that the pain is replaced by numbness; and the statistical analysis. It seems that patients with CPSP who gain relief from CVS are those in whom it is possible to activate the

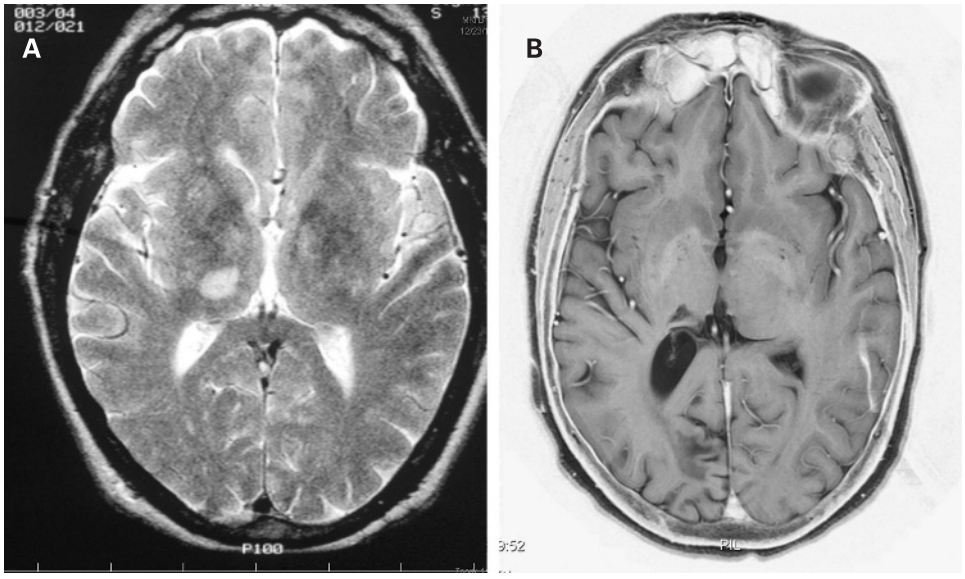

Figure 1 (A) 1.5 T MRI of patient A. Posterior pole of right thalamus spared by stroke. (B) 3 T MRI of patient B. Stroke involves the posterolateral pole of the right thalamus.

dominant PIVC, which is in the non-dominant hemisphere.[14] The two patients who failed to respond (patients B and D) gave a history of marked post-stroke disequilibrium. In fig 1B, the major vestibular output from the thalamus was infarcted. In patient D, the PIVC was destroyed. Notably, patient H responded to CVS despite destruction of her left PIVC. However, her non-dominant hemisphere and thus dominant PIVC was fully intact.

We propose two related (and not mutually exclusive) mechanisms by which the PIVC might relieve central pain. The first is by activating the adjacent thermosensory cortex in the dorsal posterior insula. This may occur directly even in the normal brain, or possibly deafferentation of the thermosensory cortex in dpIns causes cross activation with neighbouring areas of cortex (eg, the PIVC). Indeed, an analogous process is thought to underlie phantom limbs.[18]

However, two of the responders (patients G and F) were found to have significant damage to their right posterior insula, although in both cases the parietal operculum appeared to be spared and neither gave a history of disequilibrium. Our second proposal is that the PIVC is actually part of the interoceptive system. Indeed, both of these cortical areas lie in intimate anatomical proximity; receive, unlike the exteroceptive senses, relatively small diameter afferent nerve fibres[19]; and share the commonality of a fundamental sensory role in control of blood pressure.[20]

It is thought that dpIns acts via the PB and PAG to suppress the perception of thermal pain at the ACC and that these nuclei are important for the entire interoceptive cortex in its role of maintaining homeostasis.[5–7] Strong efferent projections back from the PIVC to the vestibular nuclei have been found in monkeys and in other mammals. Ongoing projections from these vestibular nuclei to the PB and PAG have been identified.[21–23] Therefore, if CPSP arises due to an imbalance, at the level of the brainstem, in the integration of thermosensory information from each hemisphere, then perhaps activation of the PIVC has the effect of rebalancing this integration.

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