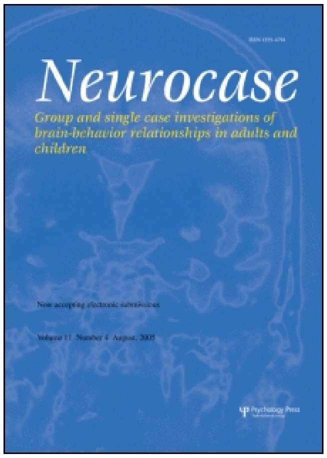

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Vilayanur S. Ramachandran [a]; Paul D. McGeoch [a]; Lisa Williams [a]; Gerard Arcilla [a]
[a] Center for Brain and Cognition, University of California San Diego, La Jolla, CA, USA

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Rapid Relief of Thalamic Pain Syndrome Induced by Vestibular Caloric Stimulation

VILAYANUR S. RAMACHANDRAN, PAUL D. McGEOCH, LISA WILLIAMS and GERARD ARCILLA

Center for Brain and Cognition, University of California San Diego, La Jolla, CA, USA

Central post-stroke pain syndrome develops in a minority of patients following a stroke. The most usual causative lesion involves the lateral thalamus. The classic presentation is of severe, unrelenting pain that involves the entire contralateral half of the body. It is largely refractory to current treatments. We found that in two patients with this condition their pain was substantially improved by vestibular caloric stimulation, whereas placebo procedures had no effect. We proposed that this is because vestibular stimulation activates the posterior insula, which in turn inhibits the generation of pain in the anterior cingulate.

Keywords: Dejerine–Roussy syndrome, thalamic pain, central pain, post-stroke pain, vestibular stimulation, insula, anterior cingulate, thalamus, stroke

Introduction

Chronic thalamic pain (Dejerine–Roussy) syndrome (Donaghy, 2001) is characterized by intense allodynia and dysaesthesia that develops in the contralateral limbs, body and face soon after a stroke. The pain is relentless and the slightest touch or pressure, sometimes even a puff of air, can trigger excruciating pain. Analgesic and anti-epileptic medication can provide slight relief but the disorder is generally considered permanent and incurable.

We (Ramachandran & Hirstein, 1998; Ramachandran & Rogers-Ramachandran, 2000), and others (Flor et al., 1995; McCabe, Haigh, Halligan, & Blake, 2003), have shown that other types of chronic pain, such as phantom pain and the pain of RSD (complex regional pain type 1), result mainly from central reorganisation of thalamic and cortical pathways in response to deafferentation.

It was suggested (Ramachandran, 1995) that the left hemisphere tends to "smooth over" discrepancies in sensory input to confer stability on behaviour, whereas the right hemisphere alerts one to discrepancies – allowing reorientation. Speculating farther on these possibilities Harris (1999) suggested that pain may be, fundamentally, the organism's response to a discrepancy – a departure from the status quo. Thalamic pain might represent a pathological amplification of the thalamic/posterior insular response to pain signaled by discrepant sensory input. Given the substantial vestibular input to the insula we postulated that thalamic pain might be relieved by vestibular caloric stimulation. In this paper we tested this.

Methods

We recruited two patients with Dejerine–Roussy syndrome post stroke, in order to test this conjecture. The study was approved by the UCSD institutional review board. The diagnosis was confirmed based on each patient's history, neurological examination and imaging findings.

Informed consent was obtained, in writing, from both patients. They were told that we were investigating a number of procedures that may or may not reduce their pain. The nature of the caloric irrigation procedure was explained to them, although they were simply told that we would be using water of different temperatures. They were blind to the fact that we only anticipated any potential effect from the ice-cold water.

In both patients all the procedures were carried out with the patient supine with their heads at 30 degrees. All of the irrigation procedures were conducted using about 30 ml of water and over, at least, a 30-s period. They were asked to rate the intensity of their pain using a visual analogue scale before and after each procedure. This scale goes from 0, for no pain, to 10, for the worst pain imaginable. These ratings

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Address correspondence to Dr Paul McGeoch, Center for Brain and Cognition, UCSD, La Jolla, CA 92093, USA. Tel: +1 858 822 0606. E-mail: pmcgeoch@psy.ucsd.edu

were all carried out whilst the patient was in the position that they found their pain was most uncomfortable: standing for FY and supine for CC.

In the experimental condition, the patients' ear canals were irrigated with ice-cold (4°C) water. As a control to the procedure itself they also underwent a sham irrigation of an ear canal with body temperature water. This consisted of an identical administration procedure to the experimental condition but without the associated neural effects. In order to attempt to control for the unpleasant and potentially distracting effect of the ice-cold water they both had crushed ice packs applied to their heads. These ice packs were applied until the patients complained of discomfort, indicating the effectiveness of this distraction. The order of administration of the different procedures was counterbalanced across the sessions. During all procedures patients were asked whether they experienced vertigo, how the painful side of their body felt throughout the stimulation, and their eyes were checked for nystagmus.

Results

The first patient (FY) was a right-handed 87-year-old male. In 1992 he developed sudden onset numbness and weakness of the left side. The weakness resolved over the subsequent few days, however, after about 2 months the left-sided numbness was slowly replaced by dysaesthesia and allodynia. This worsened and reached its zenith over the course of the next year. It has remained constant since. Imaging (MRI) revealed lacunar strokes in the right thalamus and internal capsule.

When we initially saw him in 2006 he complained of unrelenting, severe pain affecting the entire left side of his body. This was despite his current medication regime of methadone, oxycodone, oxazepam and naproxen. He reported that he had previously tried phenytoin, gabapentin, sodium valproate and amitriptyline, all to no avail. He also commented that in 1996 he had undergone an epidural injection of local anaesthetic. This had not altered his pain at all; producing neither immediate nor long-term relief.

On examination he was mentally alert and, other than allodynia on the left side of his face, his cranial nerves were unremarkable. His tone, power and reflexes were equal and normal but sensory testing showed increased sensitivity to light touch and pin-prick on the entire left side. Both plantars were flexor.

Using the visual-analogue chart he rated his constant left sided pain as 8.5 out of 10. As a placebo control for the caloric procedure, we first performed a sham irrigation of the left ear canal with water at body temperature. The patient reported that his pain was unchanged and still at 8.5. We then waited 10 min and irrigated the left ear canal with ice-cold water. The onset of nystagmus was observed 30 s after the irrigation began. He reported, with surprise, that his pain was falling; half an hour later he rated his pain as 5.

His pain then gradually rose in intensity again over the next 30 min. In order to control for the unpleasant and potentially distracting effect of the ice-cold water, an ice pack was applied to his left pinna for over a minute. He was told that this procedure had lowered pain in other patients. It was applied until he complained of pain in his left ear and of feeling dizzy. However, his pain level was unchanged by this control procedure and he rated it as a 7 both before and after.

Indeed, 15 min after the ice pack his pain increased to a rating of 8 out of 10. We then performed an ice-cold caloric stimulation of the right ear. Again nystagmus was seen. Immediately after this stimulation the patient reported that his pain level had fallen from 8 to 5.5. He stayed with us for another 30 min and at that time he rated his pain level as 5.

Eleven days later the patient returned to our facility. Surprisingly, he reported that his pain was still reduced and overall was around a 6. However, he commented that the reduction was not uniform. The left side of his face and most of his left arm was virtually free of pain. In the arm there was some "numbness" but no pain. There was some reduction of pain in his left leg, but not to the same extent.

He again underwent ice-cold water irrigation of both ears. After irrigation of the right ear his pain rating fell from 6.5 to 4.5, and then rose back to baseline again over the next hour.

Irrigation of the left ear with ice-cold water caused his pain rating to fall from 6 to 5. It was after this irrigation that he went home.

He contacted us the next morning to report that his pain rating had fallen overnight to a 3 and he felt the best he had in "over a decade." Four weeks after the first visit he reported that his pain was still substantially reduced. He now has no pain (0) in his face and he rated the pain in his left arm as 1. The least reduction has been in his left leg, where he rates the pain as a 7. Notably, he is keen to continue to attend for farther stimulations.

Our second patient (CC) was a right-handed 69-year-old female. In 1992 she awoke after a left carotid endarterectomy with a right hemiplegia and an expressive (Broca's) aphasia. In the weeks following the stroke she developed severe right-sided allodynia and dysaesthesia suggestive of thalamic pain. This worsened over several months and then plateaued at a constant and severe intensity. Her pain had proved largely refractory to medication.

On neurological examination her mental status was surprisingly normal, perhaps from functional restitution and recovery over the 14 years. Despite her expressive aphasia, her "yes" or "no" answers and nonverbal signaling in response to questions suggested that that she was lucid, intelligent and oriented. She had a mild right facial weakness, a profound, spastic hemiplegia of her right arm and leg and an extensor right plantar. Neurological examination was normal on the left side, save for reduced pinprick sensation in the C6/7 dermatomes corresponding to a known left cervical disc prolapse. Imaging, including a recent head CT, showed an old infarct in the territory of the left middle cerebral artery – including the insula and posteroinferior frontal lobe – and also in the left ventromedial and lateral thalamus.

We again asked this patient to rate her pain on the visual-analogue scale. Her rating was 7 before caloric irrigation. This was true on repeated questioning. Her pain was considerably amplified by light touch. We then performed a left ice-cold water caloric irrigation over a 30-s period until nystagmus appeared. The pain rating dropped to 2 on her face, 3 on her right arm and 5 on her right leg. Her pain remained low even when touched, whereas normally she would have screamed from the pain. Even after 7 h the pain was still less than normal, though it had started to increase again.

The next day, as a placebo control for the procedure, we performed a sham, body temperature water irrigation in her left ear. Pain before irrigation was 4 on her face, 6 on her arm (presumably residual from previous day's irrigation) and 8 on her leg. Her pain ratings remained unchanged post procedure. After 25 min a right-sided ice-cold water caloric was performed. Her pain dropped from the ratings above to 0 (face), 3 (arm) and 5 (leg).

When we returned to see the patient 5 days later the pain was still reduced compared to pretreatment and she rated it overall as 4.5. Her general demeanor was much improved. At this stage as an additional placebo, to control for the distracting effect of the ice-cold water, we placed a crushed ice pack on her forehead for 40 s after telling her it would reduce her pain. The patient indicated that this was an unpleasant experience. It had no effect on her pain rating.

Remarkably, when contacted 7 weeks after treatment, this patient reported that her pain was still reduced. She no longer had allodynia in her face or right arm and rated the pain in these areas as 3. Again she reported that the pain in her leg was not as greatly relieved and rated this area as 4.5. Her daughter reported that her mother's pain was the lowest it had been "for years." She also volunteered that her mother had started asking visitors to "touch or stroke" her right arm to demonstrate that this no longer hurt.

Discussion

Our findings on these two patients strongly support the idea that vestibular caloric stimulation can profoundly modulate thalamic pain and may pave the way for novel therapeutic options. Like pain itself, the vestibular system is a phylogenetically primitive orienting response and, perhaps, it is not altogether surprising that they should interact and be represented at least partially in close anatomic proximity. (Brandt & Dietrich, 1999; Ostrowsky et al., 2002) Whether you are a fish in the Devonian seas or an arboreal primate, it might be best to "gate" otherwise disabling chronic pain with the vestibular stimulation that would inevitably occur as you make sudden movements dodging a predator.

Might these dramatic responses to the caloric procedure have been a placebo effect? This is unlikely for four reasons. First, the pain reduction has outlasted the cold caloric irrigation by several weeks in both patients. Claiming that such a sustained reduction is from distraction due to an unpleasant procedure is untenable. Second, in neither patient did the placebo tepid water procedure, nor the distracting ice pack application have any initial effect.

Third, neither patient had previously shown any response – immediate or sustained – to epidural injections of local anaesthetic. These had been carried out in futile attempts to alleviate their thalamic pain. Indeed patient CC had undergone a cervical epidural injection only a week before we saw her. One would imagine that if these patients were susceptible to placebo then this invasive procedure would have caused some reduction in their pain. Fourth, if the reduction in their pain were due to a placebo effect, it would be highly unlikely that both patients would independently report a differential reduction in pain between their face, arm and leg.

It is known that the posterior insula receives both vestibular (Brandt & Dietrich, 1999) and pain (Ostrowsky et al., 2002) signals. It has also been previously demonstrated (Naito et al., 2003; Suzuki et al., 2001) that cold caloric irrigation activates, amongst other areas, the contralateral insular cortex. It has been proposed that central post-stroke pain arises due to disruption of the normal integration of cold and pain receptor signals passing through the thalamus to the posterior insula (cold) and anterior cingulate (pain), see Craig (2000). If so, the vestibular inhibition of thalamic pain may be mediated by the vestibular cortex in the posterior insula, acting to inhibit the sensation of pain arising from the anterior cingulate. Presumably, the differential reduction in pain in the face and arm compared to the leg, experienced by both patients, reflects the underlying topography of the insula. Indeed it has been shown (Brooks, Zambreanu, Godinez, Craig, & Tracey, 2005), using functional imaging that the posterior insula is somatotopically organised for pain, with the face area rostral to the hand area, which is, in turn, rostral to the foot area.

Given thalamic pain is notoriously resistant to treatment, the caloric procedure offers a new therapeutic approach to this form of chronic neuropathic pain. Indeed, we believe this is this first instance, in the history of neurology, that a chronic condition generally considered refractory to treatment, has been successfully treated by a simple, non-invasive procedure. It would be interesting to see whether there are laterality effects and whether repeated irrigation can produce permanent and more complete remission.

Addendum

This finding, though exciting, will need to be replicated on more patients; preferably in a double blind manner. It is likely that the effectiveness of the procedure will depend on such things as exact location and duration of the lesion. In particular, if the vestibular connections between the thalamus and insula are also damaged then the procedure is unlikely to work. It has not escaped our notice that central pain due to other causes (e.g., fibromyalgia, Wallenberg's syndrome or spinal chord injury) may well be relieved by vestibular stimulation.

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