

CASE STUDY

Improvement of hemispatial neglect with cold-water calorics: An electrophysiological test of the arousal hypothesis of neglect

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Abstract

Introducing ice-water into the left ear of right-brain-damaged patients attenuates unilateral neglect symptoms. By examining EEG changes over each hemisphere during this procedure, we were able to test a hypothesis concerning the mechanism of cold-water calorics and the attention–arousal hypothesis of hemispatial neglect. We present a case study of an 83-year-old woman with a massive right-hemisphere CVA exhibiting severe hemispatial neglect. Caloric stimulation produced a leftward eye deviation to central position, and a temporary partial remission of neglect symptoms. Significant changes in EEG activation indicated a central mechanism associated with the regularization of eye gaze. Caloric stimulation also produced a significant interaction between EEG frequency band and hemisphere, indicating that while both hemispheres increased in cortical activation, the right hemisphere increase was significantly greater. This supports the activation–arousal hypothesis of neglect over the mutual inhibition model. (*JINS*, 1997, 3, 394–402.)

Keywords: Hemispatial neglect, Caloric stimulation, EEG, Stroke

INTRODUCTION

Hemispatial neglect is a multimodal syndrome characterized by an inability to report, respond, or orient to information presented contralateral to the side of brain damage (Heilman, 1979), which can occur in the absence of sensory and motor deficits (Heilman et al., 1985). During the acute phase of neglect, many patients may also exhibit a partial or complete paralysis of contralateral gaze (Rubens, 1985). This directional gaze bias and corresponding head turning may contribute significantly to visual neglect. In turn, gaze bias and head turning may be related to vestibular disturbance. Although neglect improves in the first few months poststroke in the majority of patients, it may persist in as many as 20% (Columbo et al., 1976), and appears to be more

frequent and severe following right hemisphere damage (Heilman, 1979). The presence of neglect following stroke is considered a poor prognostic indicator for functional recovery (Jongbloed, 1986).

Caloric Test

The caloric test was first introduced by Bárány (1906) to demonstrate the integral role played by the vestibular end-organs in the regulation of eye and body position. Irrigating the external ear canal with iced water produces a vestibulo–ocular reflex with the slow phase of nystagmus towards the stimulated ear, with head turning and past-pointing in the same direction (Bárány, 1906; Precht, 1974; Baldenweck, 1982; Baloh & Honrubia, 1982). These movements of the head and neck, together known as laterotorsion, last longer and peak later than the nystagmus (Henriksson et al., 1962).

In terms of its action on the vestibular system, flooding the outer ear canal stimulates temperature fluctuations in

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the posterior labyrinth, particularly affecting the outer wall of the external canal. Temperature changes alter both the temperature and density of the endolymph, the fluid found within the external semicircular canal. The weight of the endolymph increases with cold water and decreases with warm water irrigation, determining the direction of endolymph circulation. Endolymph flow is in the same direction as the slow phase of nystagmus (Lorente de N6, 1936), and produces deviation of the cupula, the apex of the cochlea (Precht, 1974), which in turn stimulates the ampullae. Although it had been believed that the direction of cupula deflection was related to convection currents generated by the difference between body temperature and the temperature of the water (Precht, 1974), experiments conducted during the Spacelab 1 flight of November 1983 proved that the caloric reaction does not necessarily reflect thermal convection (von Baumgarten et al., 1984). Caloric stimulation in space produced nystagmus in the same direction as that experienced by humans on earth, yet thermoconvection does not occur in orbital weightlessness.

Since the thermoconvection theory cannot account for the caloric nystagmus observed on Spacelab, alternative hypotheses have been formulated. One theory postulates that caloric stimulation has a direct thermal effect on the hair cells, resulting in stimulation of the vestibular sensory epithelium. Another proposes that somatoafferent receptors located in the auditory canals and on the tympanic membrane communicate directly with vestibular nuclei (Stahle, 1987). Von Baumgarten et al. (1987) discussed the several systems that might be influenced by caloric stimulation, such as the sensory nerve endings that supply the walls of the external ear canal and are innervated by branches of cranial nerves V, VII, IX, and X (Jongkees, 1948). Alternatively, caloric stimulation could act on the afferent neuronal vestibular system by altering the generator potential of sensory cells, the synaptic transmission between sensory cells and afferent nerves, or the excitatory conduction along the vestibular portion of cranial nerve VIII. Investigations of these hypotheses through the partial or total blockage of the sensory nerve supplying the external ear canal have, however, thus far yielded negative results (von Baumgarten, 1987).

The most viable explanation postulates changes in perilymph and endolymph density, and volume associated with temperature fluctuations. Hydrostatic pressure within the constrictive bony canal would increase with warm and decrease with cold stimulation, influencing both the position and tension of the cupula. Preliminary support was found for this hypothesis when increased perilymphatic and endolymphatic pressure in the horizontal semicircular canal was shown to produce nystagmus towards the stimulated side, identical to that produced by ipsilateral caloric stimulation with warm water (von Baumgarten, 1987). When hydrostatic pressure is reduced, the direction of nystagmus is reversed, mimicking the effects of cold caloric stimulation. If water temperature is constant, the nystagmus following irrigation of one ear is in the opposite direction of that observed with irrigation of the other ear (Lorente de N6, 1936).

Caloric Stimulation in Neglect Patients

Silberpfennig (1941) reported transient remission of visual neglect with vestibular activation, but his observation was not confirmed for many years (Marshall & Maynard, 1983). Rubens (1985) used iced-water calorics to see if visual neglect could be attributed solely to gaze bias and head turning. Reasoning that the contralesional eye deviation and past-pointing associated with vestibular activation might minimize behavioral evidence of visual neglect, he tested a series of patients on visual tasks requiring exploration of extrapersonal space. He attributed the transient remission of neglect, thereby produced to caloric-stimulation-induced gaze deviation. Cappa et al. (1987), however, showed that post-stimulation performance, conducted with eyes closed, still demonstrated a temporary remission of neglect, and argued that improvement of neglect cannot be solely ascribed only to better visualization resulting from reduced gaze deviation.

In addition to studies of spatial exploration, the effects of caloric stimulation on neglect-related sensory deficits have also been examined. Tactile hemianesthesia, which can be associated with hemispatial neglect, and anosognosia for left hemiplegia, have both shown temporary improvement following caloric stimulation (Cappa, 1987; Vallar & Perani, 1987; Vallar et al., 1990). Vallar et al. (1993) also found that unilateral somatosensory deficits could be temporarily reduced with cold-water stimulation, but only for patients with right-hemisphere damage, almost all of whom had some neglect symptoms, and left-hemisphere-damaged patients who showed signs of (right-sided) hemispatial neglect. Thus, cold-water calorics seems to be related to some attentional parameters. Mental representations, measured by descriptions of landmarks from memory using a variety of specified vantage points (Bisiach, 1978), have also shown improvement with vestibular activation (Bisiach et al., 1991). Bisiach et al. (1991) investigated the effects of caloric stimulation on somatoparaphrenic delusion, or denial of ownership of a contralesional limb (Gerstmann, 1942). Prior to stimulation, their patient insisted that her left upper limb actually belonged to her mother, but for a brief period after cold-water stimulation, she recognized the arm as her own.

Activation of the peripheral vestibular system in one ear with warm water, and inhibition of the peripheral vestibular system in the other ear with iced water, produce similar eye movement responses (Leigh & Zee, 1983; Cappa et al., 1987; Rubens, 1985). The greater effectiveness of cold stimulation, however, has been attributed to the steeper gradient in the difference between body temperature and the water temperature, which can be tolerated safely when using cold water.

There is some discussion as to whether caloric vestibular stimulation acts at a cortical, as opposed to subcortical, level. While not ruling out additional subcortical activation centers, there are now clear data indicating a change in cortical activation. Friberg et al. (1985) tested 10 patients with relatively normal resting cortical activation levels, and showed that warm-water stimulation in an ear increased regional cerebral blood flow (rCBF) in the contralateral superior, pos-

terior temporal cortex. This occurred for both left and right hemispheres (for right- and left-ear stimulation, respectively), although they did not measure rCBF in the ipsilateral hemisphere, and therefore we cannot know the degree of ipsilateral activation. Their rCBF technique only registers tissue 20 to 25 mm below the brain surface, thus reflecting cortical activity. The warm-water stimulation induced a nystagmus towards the stimulated side.

Similarly, Bottini et al. (1994) showed with PET that in normals, cold-water stimulation activates cortical and some subcortical regions (temporoparietal cortex, insula, putamen, and anterior cingulate cortex) virtually only contralaterally. This is compatible with Friberg et al.'s (1985) data. Both studies reflect activation rising above a resting pattern that is normal; such a limitation to changing only contralateral cortical activation may not apply to patients with cortical activation levels radically different from normals as in most stroke cases. These results are somewhat in disagreement with Mennemeier et al.'s (1995) brief report of increased bilateral cortical and subcortical activation in a normal individual (measured by SPECT) with cold caloric stimulation, and bilateral subcortical activation in a patient.

Arousal, Attention, and Orientation Bias in Neglect

The orientation bias exhibited in neglect can be conceived of as either an increased attention to the right side of space or a decreased attention to the left side of space. In normals, increased attention to the right side of space has been demonstrated by increasing the activation of the left hemisphere through verbal mediation (Kinsbourne, 1970, 1972; Segalowitz & Plantery, 1985) and to the left side of space through spatial or musical mediation (Kinsbourne, 1972, 1974a; Segalowitz & Plantery, 1985). Kinsbourne (1970) suggests that the two hemispheres compete with each other for control over brainstem output mechanisms, and in neglect, decreased inhibition of the left hemisphere by a damaged right hemisphere results in increased attention to the right side of space, exacerbated by verbal communication with the examiner. He further suggests that spontaneous recovery from neglect symptoms would come from a resolution of the imbalance between the hemispheres. Thus, for attention to be directed centrally, hemispheric activation must be in balance (Sherrington, 1906; Crosby, 1950; Kinsbourne, 1975). An imbalance in this mechanism, allowing one hemisphere to become more activated than the other, would bias attention in the contralateral direction (Bakan & Shotland, 1969; Kinsbourne, 1972, 1973, 1974b; Heilman & Watson, 1977).

Another approach developed by Heilman and his colleagues (Heilman, 1979; Heilman et al., 1985) and Mesulam (1982) suggests that the right hemisphere is dominant for attention. This attention–arousal hypothesis conceptualizes neglect as a unilateral defect in attention–arousal induced by disruption of a corticolimbic–reticular loop, or more simply, a defect in the orienting response. They pro-

posed that lesions responsible for neglect induce a unilateral hypoarousal, with an ensuing ipsilateral orienting bias, and an impaired ability to shift attention in the contralesional direction. Because of the right-hemisphere dominance for attention, unilateral inattention is more likely to result from right-hemisphere damage than from left. This would be equally so if, for some reason, right-hemisphere damage were more likely to lower cortical arousal than left-hemisphere damage.

While the two models have many predictions in common, they do diverge in one way: A mutual-inhibition model implies a release from inhibition of the left hemisphere, that is, lowered activation in the right-lesioned hemisphere and increased activation in the left hemisphere, while the hypoarousal model predicts simply lower activation in the right hemisphere. If neglect is ameliorated, as for example with caloric stimulation, according to the inhibitory model this should be associated with a rise in the activation level of the right hemisphere and a lowering in the left, whereas according to the hypoarousal model, reduction in neglect with caloric stimulation should be associated with a rise in right-hemisphere activation with no reduction on the left. We tested this set of predictions by examining electroencephalogram (EEG) changes over each hemisphere with the administration of caloric stimulation in a single case study.

Electrophysiological Measures of Arousal

The fast, low-voltage EEG activity associated with alert wakefulness is considered an “activation pattern,” reflecting intense firing of cortical neurons. Decreasing alertness level is associated with reduced beta, increased delta, theta, and alpha. Drowsiness is also represented by increased slowing across frequencies (Kooi et al., 1964). One of the first indications of drowsiness and relaxation is mild slowing accompanied by increased alpha amplitude (Warburton, 1979; Erwin et al., 1984) and recent data from three studies suggest that later increases in drowsiness during sleep onset are accompanied by increases in theta (Alloway, 1995; Lamarche, 1995; Murphy, 1995). In the majority of the population, drowsiness may involve either irregular posterior theta and delta intermixed with reduced amplitude posterior alpha, or more rhythmic centrofrontal delta and theta with increased posterior alpha (Davies, 1965; Morrell, 1966).

Unilateral lesions affect hemispheric activation in several different ways, but generally regional slowing and/or attenuation appear over the site of damage (Fuhrmann, 1953; Carreras et al., 1966) and may be accompanied by abnormalities over the nondamaged side (Chatrian, 1964; Reeves & Hagamen, 1971).

Purpose of the Present Study

In this case study, we sought to determine the electrophysiological correlates of gaze change associated with neglect symptom remission following vestibular stimulation. Accord-

ing to the attention–arousal theory, improved bilateral attention resulting from cold-water calorics would be associated with an overall increase in arousal in the right hemisphere, with no reduction in the left. Increased poststimulation arousal would be demonstrated by a general reduction in EEG slowing. According to the mutual inhibition model, reduction in neglect with cold-water calorics should result in reduced left-hemisphere activation and increased right-hemisphere activation.

METHOD

Case Report

An 83-year-old right-handed woman, was in good health and living independently until she suddenly collapsed in her home. On admission she exhibited rightward eye and head deviation, left hemiplegia, left homonymous hemianopia, and left hemianesthesia. The patient was drowsy and, for the first 2 days, anosognosic for her stroke. A CT scan performed 3 days poststroke confirmed a massive MCA infarct involving frontal, parietal, and temporal regions of the right hemisphere, extending into the deep white matter and basal ganglia (see Figure 1). A SPECT scan revealed hypoperfusion in these areas.

Design and Procedure

Behavioral neglect

The presence of behavioral neglect was determined at the bedside 12 days poststroke by the Sunnybrook Neglect Battery (Black et al., 1990), a bedside measure that consists of drawings, line bisection, and line and figure cancellation tasks. Scores on this test range from 0 to 100 with those under 6 representing *minimal neglect*, those falling between 6 and 40 indicating *mild to moderate neglect*, and those over 40 representing *severe neglect*. Using her unaffected right hand, the patient attempted these tasks on paper held directly in front of her at the midline. A maximum score of 100 confirmed the patient was suffering from severe visuoconstructive neglect.

At 18 days poststroke, behavioral neglect was again evaluated on line bisection and line cancellation tasks both prior to and immediately following caloric stimulation.

Caloric stimulation

During the procedure, the patient's left external ear canal was irrigated with 20 ml of iced water over approximately 1 min. The patient remained in the supine position with her head elevated at 30°, to allow optimal stimulation of the horizontal semicircular canal (Guedry, 1974; Kornhuber, 1974).

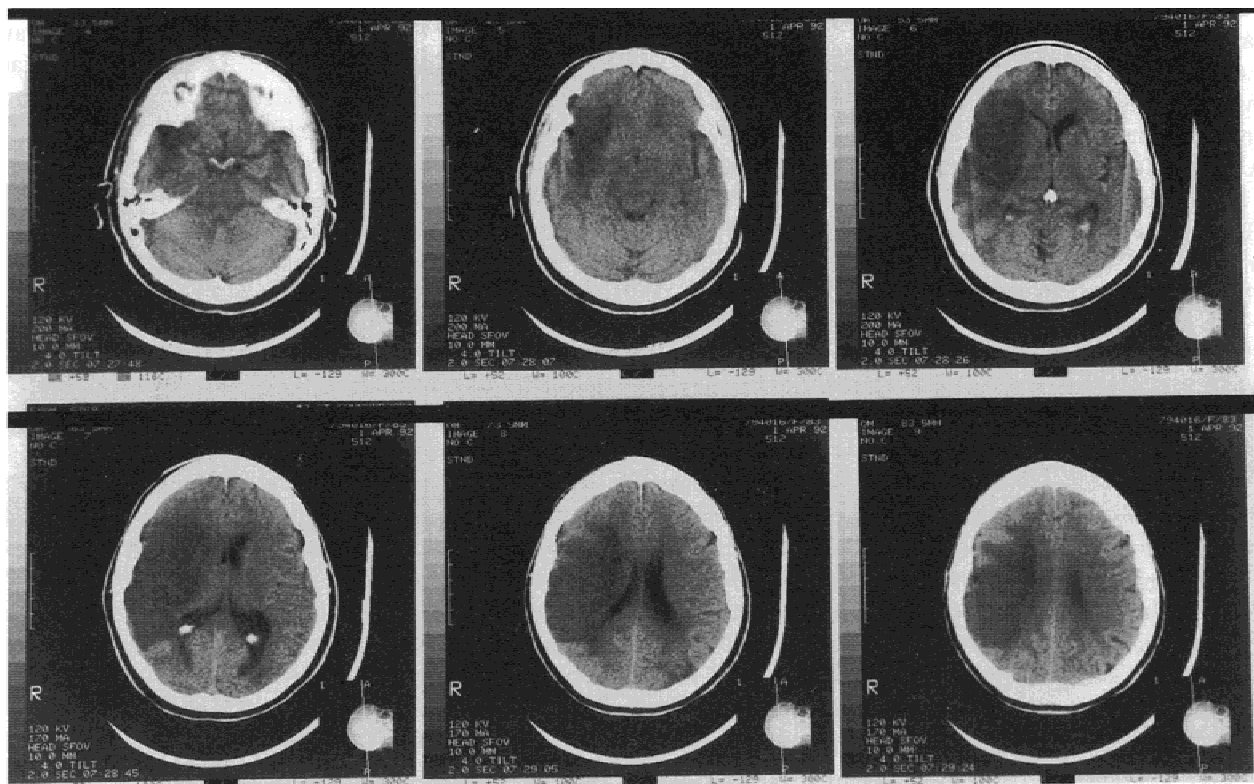


Fig. 1. The patient's CT scan 3 days after onset showed a large right middle cerebral artery infarction involving the frontal, temporal, and parietal lobes.

She did not report any discomfort, vertigo, or sense of displacement, symptoms commonly reported by normals undergoing such treatment (Collins, 1965; Tokita, 1965; Jongkees, 1974). The vertigo associated with caloric stimulation has been attributed to disturbances of the vestibular end-organs (Kornhuber, 1974).

Simple auditory choice vigilance task

A simple vigilance task required the patient to press a micro-switch button inserted into a squash ball that was held in her right hand with her thumb. The patient pressed the button in response to a binaurally presented high tone (2000-Hz, 60-db SPL square wave for 165 ms), and withheld pressing when a 1500-Hz tone sounded. There were 40 response tones randomized within a series of 160 nonresponse tones. Reaction times and the number of missed targets were automatically recorded. The response intertrial interval (ITI) was 1.5 s, while the ITI for nonresponse trials was 1.25 s.

EEG recording and scoring

EEG was recorded from the scalp using the 19-active-electrode montage of the International 10–20 system of electrode placement (Jasper, 1958), referenced to linked ears, with a midforehead ground. Following scalp preparation, using an alcohol rub and electrolyte cream to minimize resistance, Grass gold cup electrodes were affixed with electrode paste. Ocular movement was monitored by two electrodes, one placed on the outer canthus of each eye. Impedance was maintained below 5 k Ω . EEG was sampled at 409.6 Hz with a gain of 20,000 and was collected during the vigilance task, with the patient required to keep her eyes open and fixated.

A fast fourier transform algorithm was used to determine the relative power in the delta (1.0–3.4 Hz), theta (4.0–7.4 Hz), alpha (8.0–11.8 Hz), and beta (15.4–29.8 Hz) bands. Spindle activity (12.4–14.8 Hz) was occasionally seen and so this band was avoided.

RESULTS

Behavioral Measures

In two successive prestimulation attempts, the patient bisected two 20-cm lines at the extreme right end, a percent deviation from the midline of 51.5%. On the line cancellation task, which consisted of 30 lines scattered on a 3.35 \times 4.33 cm page, the patient marked only 5 lines, all located on the far right side of the page.

Caloric stimulation produced a leftward eye deviation with an immediate horizontal rightward beating nystagmus, and a temporary improvement of neglect symptoms. Poststimulation performance on the line bisection demonstrated a percent deviation of 9.0%. On the cancellation task, the patient marked 6 lines, 2 of which were midline, the others on

the right. Extrapersonal neglect returned to baseline levels 10 min poststimulation.

To compare behavioral vigilance between conditions, responses to tones were divided into anticipatory (reaction times less than 200 ms; too early to have been actual responses to the stimulus), regular (reaction times between 200 and 1000 ms, considered to be a truer reflection of central tendency and optimal information processing time), and slow (reaction times greater than 1000 ms). Chi-square analysis revealed a significant distribution change in reaction time [$\chi^2(2) = 6.23, p < .05$], with anticipatory responses decreasing from 10 to 5, regular responses increasing from 22 to 27, and slow responses decreasing from 7 to 1 with stimulation. If we group anticipatory and slow responses together, then the contrast is stronger [$\chi^2(1) = 13.2, p < .001$]. The number of missed targets increased from 1 to 7 in the poststimulation condition. There was a poststimulation decrease in mean reaction time [$M = 600.5$ ms, $SD = 400.8$, vs. $M = 581.5$ ms, $SD = 287.6$; $t(70) = 0.22$, n.s.], and a reduction in reaction time variability [$F_{\max}(38,32) = 1.94, p < .05$].

Electrophysiological Measures

Due to extensive artifactual contamination, a power spectrum analysis was conducted only on the latter 75% of the movement-free 2.5-s epochs during the pre- and poststimulation conditions (80 and 75 epochs, respectively). Lower arousal should be reflected in a higher ratio of slow wave to fast wave on an epoch-to-epoch basis. An analysis including all frequency bands requires standardization to avoid slow wave frequencies accounting for most of the variance. The analysis compares the lateralized, posterior electrode sites T3, T4, P3, P4, T5, and T6. (There were several significant interactions with site, which indicate that the effects of interest are stronger at some sites than at others; since they do not relate to our research hypothesis, we will not detail them here.)

There was a significant overall change in power [$F(1,255) = 5.23, p < .05$], indicating an overall drop with caloric stimulation. This was due to the drop in the three lower frequency bands compared to the rise in beta. This Condition \times Frequency interaction was significant [$F(3,765) = 18.21, p < .001$], with the greatest change in theta and beta bands (see Figure 2). Delta, theta, and alpha, however, were consistent with each other in terms of *versus* poststimulation changes. There was also a Condition \times Frequency \times Hemisphere interaction [$F(6,1530) = 7.35, p < .001$; see Figure 3], indicating a difference between the two hemispheres. While caloric stimulation increased fast wave and reduced slow-wave activity in both hemispheres, this effect was greater in the right. It is interesting to note that the slower frequency bands that were sensitive to the caloric stimulation differed across the hemispheres: The left hemisphere sites showed sensitivity to theta and alpha, whereas the right hemisphere was sensitive to delta and theta, and both were sensitive to beta increases

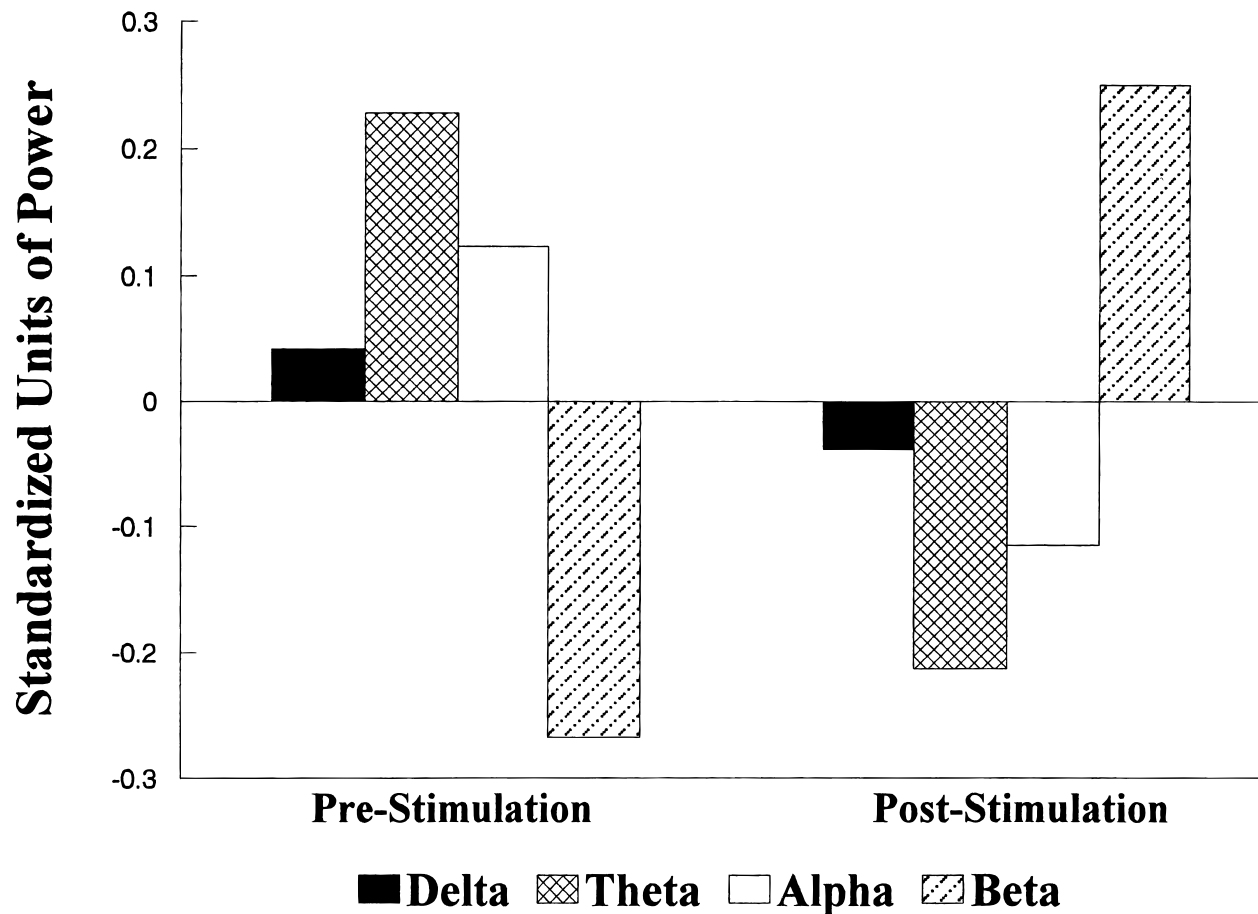


Fig. 2. The Condition \times Frequency interaction of standardized relative EEG power (μV^2) over the six electrode sites, indicating a drop in delta, theta, and alpha bands and rise in beta following administration of cold-water calorics [$F(3,765) = 18.21, p < .001$]. The frequency bands have been standardized (z -scored) to reduce the preponderance of delta and alpha so that we could detect the sensitivity of each to the experimental manipulation.

with the stimulation. The frequency bands, therefore, that appear equally sensitive at sites over both hemisphere are theta and beta. Redoing the analyses with only these two bands produced the same results.

DISCUSSION

These data confirm previous research demonstrating transitory partial remission of neglect symptoms following vestibular stimulation (Rubens, 1985; Cappa et al., 1987; Valler et al., 1993). Whereas her baseline neglect score was at maximum, after vestibular stimulation some of the neglect symptoms were reduced, especially, for example, her line bisection error, which was attenuated by over 80%. Her performance on the vigilance task also became regularized in terms of more stable response times.

These data also provide the first evidence of the electrophysiological concomitants of the reduction in neglect impairment. The pervasive shift from slow to faster frequencies indicates that cold-water calorics produces more than a pe-

ripheral effect limited to shift in gaze and head turning, this conclusion being consistent with the rCBF results of Friberg et al. (1985) and PET results of Bottini et al. (1994). Central activation of the cortex increases generally, indicating raised arousal level with presumed increases in attentional capacity (Kahneman, 1973). Improved control in the patient's responses during the vigilance task verifies this interpretation and is consistent with the results of Segalowitz et al. (1997), who report that the degree of variability in response time among brain-injured subjects is related to the amplitude of ERP components reflecting their ability to allocate attention. In our patient, however, the increase in missed responses raises the possibility that while response control improved, overall ability to sustain focus on what is otherwise a boring task did not see dramatic improvement.

The significant difference in hemispheric effects, in addition to the general increase in arousal, supports the attention–arousal hypothesis over the mutual-inhibition model. The latter predicts that an alleviation of the right-hemisphere hypoarousal would occur in the context of decreased left-hemisphere arousal level because of mutual

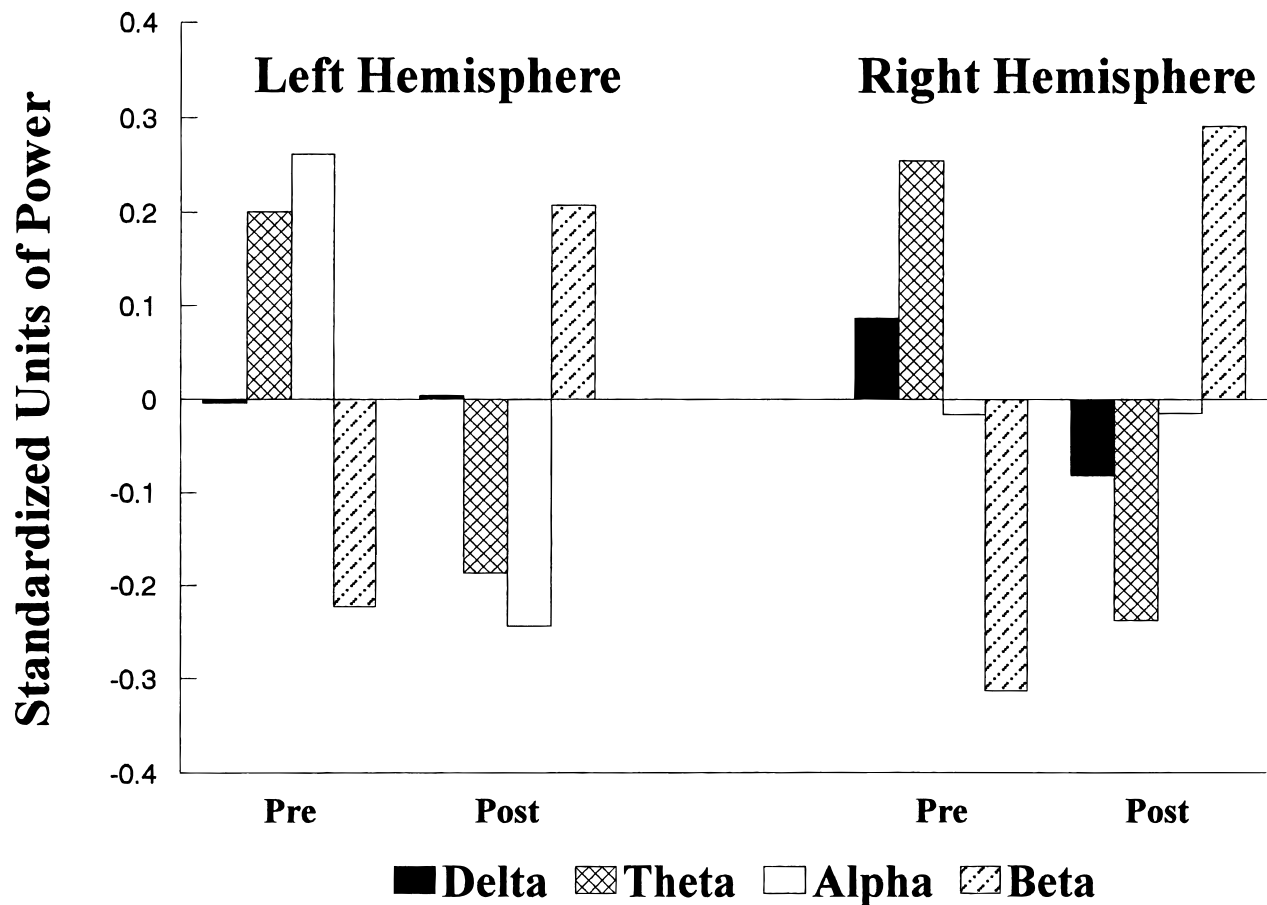


Fig. 3. The Condition \times Frequency \times Hemisphere interaction of standardized relative EEG power (μV^2) indicating that the Condition \times Frequency effect is stronger in the right hemisphere [$F(6,1530) = 7.35, p < .001$]. The slow frequencies sensitive to caloric stimulation are different across the two hemispheres.

inhibition between the hemispheres. The former suggests that relief from right-hemisphere hypoarousal can occur even with increased left-hemisphere activation, although for a balancing of attentional hemisphere, the increase in the right hemisphere would have to be greater than that in the left hemisphere. This is what we found. If we consider the alterations in the relative changes in theta and beta EEG bands to represent the linear shifts in activation, then the right hemisphere increase is about 1.3 times greater than that in the left hemisphere (1.27 for theta and 1.4 for beta). However, the left-hemisphere EEG activation did increase after cold-water stimulation, which is somewhat different from Bottini et al.'s (1994) PET data, which showed increased activation almost only in the hemisphere contralateral to the stimulated ear. However, Bottini et al.'s data concern changes in normal adult subjects whose overall arousal level would not be as reduced as in our patient at the start of the study. This suggests that the studies on changes in cortical activation resulting from caloric stimulation may produce different results in a brain with a normal resting activation level compared with a brain with a reduced level. This may account for the seeming contradictory effects of warm water vestibular stimulation in the Friberg et al. (1985) study, which

showed results similar to cold water application, *versus* the von Baumgarten et al. (1987) study, which showed the opposite.

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