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Altered experimental pain perception after cerebellar infarction

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ABSTRACT

Animal studies have suggested that the cerebellum, in addition to its motor functions, also has a role in pain processing and modulation, possibly because of its extensive connections with the prefrontal cortex and with brainstem regions involved in descending pain control. Consistently, human imaging studies have shown cerebellar activation in response to painful stimulation. However, it is presently not clear whether cerebellar lesions affect pain perception in humans. In the present study, we used experimental pain testing to compare acute pain perception and endogenous pain inhibition in 30 patients 1 to 11 years after cerebellar infarction and in 30 sex- and age-matched healthy control subjects. Compared to controls, patients exhibited a significantly increased pain perception in response to acute heat stimuli (44°C–48°C, average pain intensity rating for patients 3.4 ± 2.8 and for controls 1.5 ± 1.7 [on a numeric rating scale of 0–10], $P < .01$) and to repeated 256 mN pinprick stimuli (1.3 ± 1.9 vs 0.6 ± 1.0 [0–10], $P < .05$). Heat hyperalgesia in patients was more pronounced on the body side ipsilateral to the infarction. In addition, patients showed reduced offset analgesia (change in pain intensity rating: 0.0% ± 15.8% vs −16.9% ± 36.3%, $P < .05$) and reduced placebo analgesia (change in pain intensity rating: −1.0 ± 1.1 vs −1.8 ± 1.3 [0–10], $P < .05$) compared to controls. In contrast, heat and pressure pain thresholds were not significantly different between groups. These results show that, after cerebellar infarction, patients perceive heat and repeated mechanical stimuli as more painful than do healthy control subjects and have deficient activation of endogenous pain inhibitory mechanisms (offset and placebo analgesia). This suggests that the cerebellum has a previously underestimated role in human pain perception and modulation.

1. Introduction

The cerebellum is classically considered to be a brain region involved in motor control. However, in recent years, the cerebellum has also been linked to nonmotor functions such as cognitive processing [43] and associative learning [49]. In addition, evidence has accumulated that the cerebellum also has a role in pain processing [33,42]. Animal experiments have shown that nociceptive input from primary afferent Aδ- and C-fibers reaches the cerebellar cortex via the pontine nuclei and mossy fibers on 1 hand and via the postsynaptic dorsal column pathway, the inferior olive and the climbing fibers on the other hand [15,16,21,51]. Cerebellar activation is regularly seen in response to experimental nociceptive stimulation in human functional imaging studies. A meta-analysis shows that the cerebellar regions most frequently activated during pain stimuli are vermal lobules IV and V and bilateral hemispheric lobules VI, with ipsilateral activation somewhat more prominent than contralateral activation [33]. A correlation of ipsilateral hemispheric lobules III and VI activation with pain intensity has been reported [24]. It has also been proposed that emotional and sensorimotor responses to pain are represented in different cerebrocerebellar networks [32]. In addition, the cerebellum is well positioned for modulating nociceptive processing. It has afferent and efferent connections with a wealth of cortical regions, including the dorsolateral prefrontal cortex (DLPFC) [26,31], which has an important role in endogenous pain modulation [50,54]. It is also anatomically and functionally connected to the periaqueductal gray (PAG) [8,12,29,48] and several caudal brainstem regions [48], which are at the origin of pain modulatory pathways descending to the spinal cord [17]. Indeed, animal experiments have shown that nociceptive responses are affected by electrical or chemical stimulation of the cerebellum [10,39,40,45]. This includes nociceptive

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responses of spinal neurons, suggesting that the cerebellum may target descending pain-modulatory pathways [23,39,41].

Despite this wealth of animal and imaging data, the effect of cerebellar disease on human nociception has not been tested directly. In the present study, we used standardized experimental pain testing to compare acute pain perception and modulation of pain perception during placebo analgesia and offset analgesia in 30 patients after cerebellar infarction and 30 healthy control subjects matched for age and sex.

2. Methods

2.1. Subjects

The study was conducted in accordance with the Declaration of Helsinki and approved by the local ethics committee at the University of Munich. All participants were required to meet the following criteria: age greater than 18 years; sufficient knowledge of the German language; no major neurological, psychiatric, or medical conditions (apart from cerebellar infarction in the patient group); no chronic pain disorders; no chronic intake of painkillers; and not pregnant or breast-feeding. In addition, intake of painkillers was not allowed 24 hours before testing. If subjects had an acute pain condition, the experimental session was rescheduled. Subjects were eligible for the patient group if they had a history of uni- or bilateral infarction limited to the cerebellum. Patients with additional infarction of other brain regions were excluded.

Thirty patients with a history of infarction limited to the cerebellum that had been treated at the Department of Neurology of the University of Munich between 2001 and 2011 were recruited by sending invitations for study participation by mail (a total of 79 patients [mostly pre-selected for not presenting any of the exclusion criteria] were contacted; 30 were included, 15 declined to participate, 2 were hospitalized at the time of invitation, 2 were excluded because of chronic pain, 1 had polyneuropathy, and the remaining patients did not respond to the invitation). The presence of cerebellar infarction and the absence of infarction in other brain regions were verified either by inspecting the cranial computed tomography (CT) or magnetic resonance (MR) images or based on the documented radiologist's report on the MR or CT images obtained at the time of diagnosis in those cases in which the images were no longer available at the time of the study. A total of 30 control subjects were recruited by advertisements on the university campus (49 subjects were interested in participation, 1 was excluded because of polyneuropathy, and 30 were selected to match the patient group for age and sex). Subjects were paid € 40 for participation in the study.

Characteristics of the study population are provided in Table 1

2.2. Overview of experimental procedure

The study consisted of 2 sessions (1.5–2 hours each), separated by a maximum of 3 weeks.

In the first session, after obtaining written informed consent, subjects completed a set of questionnaires, consisting of the Hospital Anxiety and Depression Scale (HADS) [53] and the Pain Catastrophizing Scale (PCS) [47]. Next, the Mini-Mental State Examination (MMSE) [20] was administered, and cerebellar ataxia was assessed using the Scale for the Assessment and Rating of Ataxia (SARA) [44]. Skin temperature was measured at the dominant volar forearm. Next, experimental pain tests were performed in the following order: heat pain rating, pinprick intensity rating and windup ratio, and offset analgesia.

In the second session, reaction time was measured. Again, skin temperature was measured at the dominant volar forearm. Next, experimental pain tests were performed in the following order: heat pain and pressure pain thresholds, and placebo analgesia. Care was taken not to apply heat stimuli twice to the same skin area because of the known rapid habituation to heat stimuli. Therefore, not only the standard area (volar forearm) but also alternative areas (dorsal forearm, upper arm) were used for testing. Both body sides were assessed in all tests except offset and placebo analgesia. For these 2 tests, the body side ipsilateral to cerebellar infarction was used in patients (side of the larger infarction for bilateral infarctions) and body side was randomized for control subjects.

2.3. Reaction time

Reaction time was measured using a custom-made software running under Matlab version 7.4 (MathWorks, Natick, MA) using the Psychophysics Toolbox Version 3. Subjects were seated in front of a computer and instructed to press the space bar as quickly as possible when a white cross (size 5×5 cm, line width 1 cm) appeared on the otherwise black monitor. The white cross was presented for 0.5 seconds a total of 31 times, with an interstimulus interval randomized between 2 and 4 seconds. The time between the start of the cross presentation and the key press was recorded and the mean response time to the last 30 responses was taken as the reaction time.

2.4. Experimental pain tests

The experimental pain testing program was chosen to cover different modalities (heat, pressure, pinprick) and measures (pain thresholds, pain intensity rating of suprathreshold stimuli, windup ratio, endogenous pain modulation). With the exception of the measures of endogenous pain modulation, all experiments were

Table 1
Overview of the study population.

Characteristic	Controls	Patients	Statistics
N	30	30	
Age (y)	66.0 ± 11.4 (37–86)	65.5 ± 10.8 (46–82)	$T_{58} = 0.2$, $P = .87$
Sex	11 Female, 19 male	9 Female, 21 male	$\chi^2_1 = 0.3$, $P = .58$
MMSE (0–30)	29.4 ± 1.1 (25–30)	29.2 ± 0.9 (27–30)	$T_{58} = 0.6$, $P = .52$
HADS-Anxiety (0–21)	3.6 ± 2.3 (0–8)	4.9 ± 3.4 (0–11)	$T_{58} = 1.8$, $P = .08$
HADS-Depression (0–21)	**2.1 ± 2.0 (0–7)**	**3.5 ± 3.3 (0–12)**	$\mathbf{T_{58} = 2.1, P < .05}$
PCS (0–52)	8.7 ± 9.2 (0–31)	12.2 ± 10.0 (0–36)	$T_{58} = 1.4$, $P = .16$
SARA (0–40)	**0.2 ± 0.6 (0–2)**	**1.6 ± 1.7 (0–6)**	$\mathbf{T_{58} = 4.2, P < .001}$
Skin temperature (°C)	**33.4 ± 0.9 (31.0–35.0)**	**32.9 ± 0.8 (31.0–34.5)**	$\mathbf{T_{58} = 2.3, P < 0.05}$
Reaction time (s)	289 ± 40 (233–406)	310 ± 53 (207–417)	$T_{58} = 1.8$, $P = .08$

Values are mean ± standard deviation, with ranges given in parentheses.
HADS = Hospital Anxiety and Depression Scale; MMSE = Mini-Mental State Examination; PCS = Pain Catastrophizing Scale; SARA = Scale for the Assessment and Rating of Ataxia.
Results of unpaired *t* tests or of χ^2-tests are given. Significant differences are indicated by boldface type.

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