Dehydration Enhances Pain-Evoked Activation in the Human Brain Compared with Rehydration

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BACKGROUND: Negative effects of dehydration on the human brain and cognitive function have been reported. In this study, we examined the effects of dehydration on pain thresholds and cortical activations in response to pain, compared with rehydration with an oral rehydration solution (ORS) by functional magnetic resonance imaging.

METHODS: Five healthy adult men were subjected to dehydration and rehydration on 2 different days. The condition on the first day was randomly assigned to each subject. They completed a 40-minute exercise protocol using a walking machine after 12 hours of fasting under both conditions. For rehydration, the subjects consumed up to 3000 mL ORS starting from the night before the test day. After exercise, a painful stimulus (cold pressor test) was applied to the subjects' medial forearm in a magnetic resonance imaging scanning gantry, and pain-evoked brain activation was analyzed.

RESULTS: On the rehydration day, each of the subjects consumed an average of 2040 mL (range; 1800–2500 mL) ORS. Physiological data revealed that subjects when dehydrated lost more weight from exercise than subjects when rehydrated had a larger heart rate increase, a higher tympanic temperature, and a higher urine osmolality. Subjective data revealed that the subjects reported significantly stronger thirst while dehydrated than while rehydrated with ORS, although the levels of hunger and anxiety and mood did not significantly differ between conditions. The cold pressor test robustly activated the pain-related neural network, notably the anterior cingulate cortex, insula, and thalamus. Such activations in the dehydrated subjects were greater than those in the rehydrated subjects in terms of peak and cluster, accompanied by a decrease in pain threshold ($P = 0.001$).

CONCLUSION: Our findings suggest that dehydration brings about increased brain activity related to painful stimuli together with enhanced thirst, whereas rehydration with ORS alleviates thirst and decreases brain activity related to painful stimuli. (Anesth Analg 2013;XXX:00–00)

Appropriate fluid intake is crucial to our vital functions. The negative effects of dehydration on not only physical[1] but also cognitive performance have been reported.[2,3] Using structural magnetic resonance imaging (MRI), Kempton et al.[4] have shown that dehydration through physical exercise or restricted fluid intake causes reversible brain changes that consist of reduced brain volume and associated increases in ventricular volume. However, these effects of dehydration on pain thresholds and cortical activation in response to the pain experience remain unclear.

Pain is a conscious experience easily influenced by emotion, mood, and cognitive setting such as expectation, placebo, hypervigilance, attention, and distraction.[5] Therefore, dehydration may affect the pain experience in humans. In previous studies, the effect of dehydration on human pain function, particularly on measures of brain function in humans, was not examined. Using functional MRI (fMRI), which allows indirect measurement of neural activity during event stimulus application, we specifically investigated the effects of dehydration on pain, compared with rehydration with an oral rehydration solution (ORS).

The aim of this study was to investigate the effects of dehydration on pain thresholds and cortical activation in response to evoked pain stimulus using fMRI and an executive function task (calculation test), compared with rehydration with ORS. At the central nervous system level, using fMRI, hemodynamic activity elicited by evoked pain stimulus in dehydrated subjects was compared with activity in rehydrated subjects given ORS. Blood-oxygen-level-dependent fMRI measures hemodynamic responses from changes in blood oxygenation, which are linked to changes in neural activity. To reproduce dehydration in healthy adult men in clear contrast to rehydration with ORS, the subjects performed 40 minutes of aerobic exercise in addition to 12-hour fasting without any oral rehydration. On a different day, subjects were rehydrated with ORS, although they performed an identical fasting and exercise routine. We hypothesized that pain experience, including pain thresholds and cortical activation, differs between dehydration and rehydration with ORS.

METHODS

Subjects

Five healthy, right-handed, neurologically normal men (mean age, 33.0 years; age range, 30–37 years), who provided

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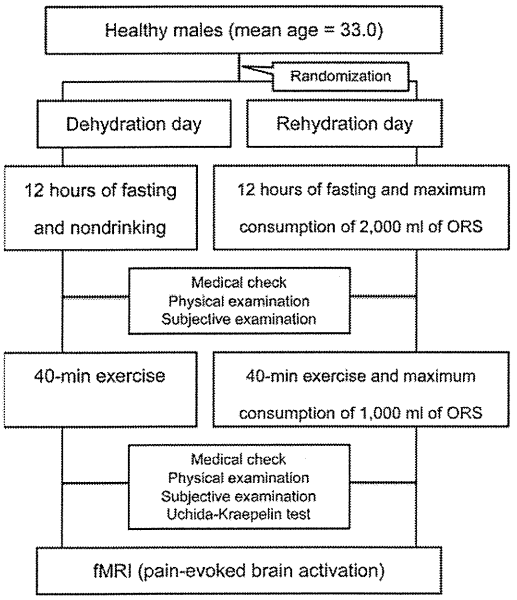

Figure 1. Schematic representation of the study design and conditions: dehydration and rehydration with ORS. ORS = oral rehydration solution; *f*MRI = functional magnetic resonance imaging.

their written informed consent, participated in this randomized, crossover, and repeated-measures design study (Fig. 1). This study was approved by the IRB of Gunma University Graduate School of Medicine, Maebashi, Japan and was conducted in accordance with institutional ethical provisions and the Declaration of Helsinki. The subjects were financially compensated for taking part in this study.

Conditions and Procedures

Participants were subjected to 2 separate hydration conditions on different days: dehydration day and rehydration day (Fig. 1). Each test day was held at intervals of >2 days to minimize the interaction between the conditions. Subjects underwent fMRI after exercise on either the dehydration or rehydration day. The subjects were instructed not to perform strenuous activity or consume alcohol. The condition on the first day was randomly assigned to each subject by tossing a coin.

On the dehydration day, subjects were instructed to refrain from eating and drinking for 12 hours before fMRI. On the rehydration day, subjects were instructed to fast for 12 hours similar to the dehydration condition, although they were instructed to consume up to 3000 mL (up to 2000 mL from the night before the test day until the time they started exercise and up to 1000 mL during exercise) ORS containing balanced amounts of glucose and electrolytes (OS-1®, [http://www.otsukakj.jp/en/profile/products/mf/os1.html], Otsuka Pharmaceutical Factory, Inc., Tokushima, Japan). Immediately before fMRI, they reported the total amount consumed since the night before.

Physiological Measures, Subjective State Measures, and Cognitive Test

Subjects gave their physiological and subjective state measures twice: before and after exercise (Fig. 1). On arrival at the laboratory, subjects first underwent a medical assessment, comprising initial assessment of clinical history, including details of any current or previous medical or surgical morbidity, medications taken, recent substance use, and allergies. All subjects were determined to be fit and healthy.

This was followed by general physical and physiological examinations including those of basic measures (nude body weight [accurate to 50 g, TANITA, Tokyo, Japan], arterial blood pressure, heart rate, and tympanic temperature). These examinations were also performed after exercise as a postexercise medical check. After exercise, the subjects provided a urine sample for determination of urine osmolality (mOsm/kg) (OM-6050, ARKRAY Inc., Kyoto Japan).

After physical and physiological examinations, to measure the subjective mood index of dehydration and rehydration with ORS, subjects rated the following 3 items on a 5-point scale questionnaire: thirst, hunger, and anxiety levels, rating them from 1 (not at all) to 5 (very). Similarly, the subjects rated their mood using the visual analog mood scale, which is a 100-mm horizontal line and simple, schematic faces representing mood states from 0 (worst imaginable health state) to 100 (best imaginable health state), first described by Aitken,[6] which has been shown to be a reliable and valid measure of mood in psychiatric populations.[7]

After exercise, subjects were given a 10-minute supine recovery period. Then, for a cool-down period of 50 minutes before fMRI, subjects underwent physiological and subjective measurements (30 minutes) and the Uchida-Kraepelin Performance test (20 minutes), which is a simple arithmetic test that measures task performance speed and task performance accuracy. In this test, subjects were instructed to add 2 single digits and answer only using single digits as fast as possible, and the results were evaluated from the number of calculations and error rate. We used the Uchida-Kraepelin Performance test (Nisseiken, Inc., Tokyo, Japan) to examine the effects of dehydration on executive cognitive functions.[8]

Exercise Protocol

Both conditions included identical 40-minute exercise in a training room in the laboratory. During the exercise, subjects wore light sports clothing (t-shirt, shorts, socks, and athletic shoes). The exercise protocol was identical for both conditions and was divided into two 20-minute sessions for a total of 40 minutes involving elliptical walking exercise on a total body elliptical walking machine, Reebok Body Trec Elliptical Trainer® (Reebok International Ltd., Canton, MA), in the "steady-climb" mode starting at level 3 (load level varied from 3 to 10), which was adjusted depending on individual physical pace. We gave subjects a 5-minute rest between the two 20-minute sessions. With elliptical trainers, the subjects stand on raised pedals and hold bars parallel to the machine, moving their arms forward and back while their legs move in an elliptical motion. The amount of exercise was determined using the estimated calories burned while exercising on the basis of elliptical walking machine algorithms using subject age, body weight, pace, and time. For the subjects' safety, 1 doctor or nurse was assigned to each subject during exercise, monitoring his health state constantly; the training room was also equipped with an automatic external defibrillator and a resuscitation kit.

Pain and Control Stimuli During fMRI Scanning

During fMRI scanning, 2 different pressure tests were used: the cold pressor test (CPT) for generating experimental pain and a test using a nonpainful pressure (as a control stimulus), perceived only as a light touch. CPT has been established as an easy, safe, and reliable method of pain induction using cold water that evokes cold pain.[9,10] Previously, we used a CPT by applying frozen ice packs (size, 9 × 9 cm, weight 37 g) on each subject's medial forearm to eliminate the need for large metal water baths in the MRI room and to avoid drenching the MRI gantry.[11] We applied the same packs as a control stimulus on each subject's medial forearm, but the packs were not frozen and were swathed in cotton tissue to approximate a light touch. We called this control stimulus "control" in this study. Each subject underwent a total of 20 blocks (CPT, 10 blocks; control, 10 blocks). The order of presentation of all stimulation blocks was randomized over the scanning time, preventing subjects from anticipating the event type, counterbalanced to be the same number between the CPT and control blocks.

Pain Threshold Measurements

In a CPT block, we measured a subject's pain threshold (defined as the time when the subject started to feel pain induced by an ice pack). In accordance with the experimental program, the experimenter applied an ice pack (frozen, CPT block; not frozen, control block) to a 15 × 5 cm^2 stimulation area marked on the subject's medial forearm, alternating between right and left arms in each block. In a CPT block, the subject pressed a button with his nonstimulated hand at the onset of pain; the time was recorded on the computer log as the pain threshold, which is the short-term pain threshold in CPT.[12] Twenty seconds after the start of CPT, the experimenter removed the ice pack. For each subject's safety, we limited the CPT time to 20 seconds regardless of whether the subject reported a pain threshold. fMRI scanning was started before the start of the CPT (10 scans used as the baseline) and lasted 21 seconds after the start of the CPT (7 scans). Between blocks, we provided a 2-minute interval to minimize the effect of the preceding stimulus, during which the subject's stimulated forearm was swaddled with a towel to minimize sensitization to the next stimulus.

Neuroimaging Assessments

MRI was performed using a 3.0-tesla Siemens MAGNETOM Trio scanner (MAGNETOM Trio A, Tim System; Siemens, Malvern, PA) at the Brain Activity Imaging Center (Kyoto, Japan). The acquired functional images consisted of 50 consecutive slices parallel to the anterior and posterior commissure planes, covering the whole brain. A T2*-weighted gradient-echo echo-planar imaging sequence was used with the following parameters: repetition time = 3000; echo time = 30 milliseconds; flip angle = 90°; matrix size = 64 × 64; voxel size = 3 × 3 × 3 mm^3. After acquisition of functional images, T1-weighted high-resolution anatomical images were obtained using a magnetization-prepared rapid acquisition gradient-echo sequence (repetition time = 2250 milliseconds ; echo time = 3.06 milliseconds; flip angle = 9°; field of view = 256 × 256 mm^2; voxel size = 1 × 1 × 1 mm^3).

Statistical Analyses

Physiological and Subjective Measurements

All subjects' physiological data including pain thresholds, subjective data (i.e., thirst, hunger, anxiety levels, and mood) and the results of the Uchida-Kraepelin performance test were compared between dehydration and rehydration using a 1-sample t test. A significance level of $P < 0.05$ was used.

fMRI Analyses

Image and statistical analyses were performed using the statistical parametric mapping package SPM8 (http://www.fil.ion.ucl.ac.uk/spm) implemented in MATLAB R2007a (Mathworks Inc., Natick, MA). Functional images in each run were realigned using the first scan as a reference to correct for head movements. Data from all 5 subjects required a small-motion correction (<2 mm). The obtained T1-weighted anatomical images were preprocessed by intensity inhomogeneity correction. The T1-weighted anatomical images were then coregistered to the first scan of the functional images. After this, the coregistered T1 anatomical images were normalized to a standard T1 template image, as defined by the Montreal Neurological Institute involving linear and nonlinear 3-dimensional transformations.[13,14] The parameters from this normalization process were then applied to each of the functional images. Finally, these spatial normalized functional images were resampled to a voxel size of 2 × 2 × 2 mm^3 and smoothed with an isotropic Gaussian kernel of 8 mm full width at half maximum to compensate for anatomic variability among subjects.

We used random effect analyses[15] to assess the statistical effects of stimulus type (CPT or control) under each condition (dehydration or rehydration with ORS). Data were first analyzed for each subject (a single-subject analysis) and then for the group. Random effect analysis considers the between-subject variability of the responses to allow for population inference. In SPM, random effect analysis can be implemented using a 2 -level summary statistics approach as follows. At the first level, individual brain responses under each condition are estimated using subject-specific statistical models, which include regressors of experimental effects (i.e., task-related neural activities) and additional nuisance variables (e.g., signal drift). These individual brain responses are then entered into a second-level analysis for a statistical test across the entire sample, thus allowing for population inference.

In our study, we specified the following model in the first-level analysis: the task-related (CPT or control) neural activity under each condition (dehydration or rehydration with ORS) was modeled with a boxcar function, which was convoluted with a canonical hemodynamic response function. Note that a canonical (or standard) hemodynamic response function is typical of an evoked blood-oxygen-level-dependent response to brief neural stimulation. The canonical hemodynamic response function used in SPM software shows a rising peak at approximately 6 seconds followed by an undershoot.[15] We used a high-pass filter to remove low-frequency signal drift. Serial autocorrelation, assuming a first-order autoregressive model, was also corrected.

In the second-level analysis, we used repeated-measures analysis of variance (ANOVA) using the full factorial design in SPM second-level statistics that tests each contrast against a pooled error term (with 16 degrees of freedom [df]), which can improve the normality of the statistics even with the use of few samples.[16] Note that the number of available df for an error term is 16 since there are 4 regressors for task conditions in our model with 4 df and hence leaving 16 df from 20 images (4 task conditions × 5 subjects). The subject-specific contrast images for dehydration and rehydration conditions were subjected to a 2 (stimulus type: CPT or control) × 2 (condition: dehydration or rehydration with ORS) ANOVA. Finally, we tested the following 4 contrasts of brain activities: (1) [CPT–control (dehydration)], CPT minus control stimulus during dehydration; (2) [CPT–control (rehydration)], CPT minus control stimulus during rehydration with ORS; (3) [control–CPT (dehydration)], control stimulus minus CPT during dehydration; 4) [control–CPT (rehydration)], control stimulus minus CPT during rehydration with ORS. Since we had no a priori predictions about the location of effects, we used a corrected threshold for multiple comparisons, which is commonly used in neuroimaging data analysis to search for significantly activated voxels across the whole brain on the basis of a random field theory.[17]

Significantly activated voxels were identified when they reached the extent threshold of $P < 0.05$ corrected for multiple comparisons, with a height threshold of $P < 0.001$ (uncorrected) across the whole brain. Brain activation is inherently a statistical image where each voxel contains 1 statistical value (i.e., t value) thresholded by some height and spatial extent thresholds that are specified by the experimenter. After thresholding, we can define significant topological features such as peak and cluster size. In Table 2, we present the cluster-level corrected P: the significant P-value for a cluster (quantified by the number of voxels) at a threshold of $P < 0.05$ after the correction of multiple comparisons, and t-values for a significant activation peak when they are above the threshold of $P < 0.001$.

Because of the small number of subjects, we also confirmed the consistency of effects across all subjects by conjunction analysis with a global null hypothesis[18,19] instead of the second-level random effect analysis to validate our approach. Results are shown in Figure 4.

RESULTS

Physiological Measures and Pain Threshold Measurement Results

On the rehydration day, subjects consumed an average of 2040 mL (range 1800–2500 ml) ORS. Table 1 shows a summary of physiological and subjective data for both conditions (dehydration and rehydration) including pain thresholds and Uchida-Kraepelin performance test results.

A 1-sample t test of physiological data revealed that physiological measurements showed statistically significant differences between the dehydrated and rehydrated subjects (Table 1). The pain threshold during dehydration was 13.4 ± 3.6 seconds (mean ± standard deviation: SD), and during rehydration was 16.2 ± 3.4 seconds (mean ± SD) (Fig. 2). During dehydration, a significant decrease in pain threshold was observed compared with that during rehydration with ORS.

Subjective State Measures and Cognitive Test Results

Subjective state measures and cognitive test results (the lower section of Table 1) revealed that subjects expressed a significantly stronger thirst while dehydrated than while rehydrated, although hunger and anxiety levels and mood did not significantly differ between conditions. An executive function task (Uchida-Kraepelin Performance test) performed after exercise revealed that dehydration is

Table 1. Physiological Measures, Subjective State Measures, and Executive Function Tests Results

Physiological measures	**Dehydration**	**Rehydration**	***t* test**
Nude body weight [pre-exercise] [kg]	72.46	72.49	$P = 0.138$
Body weight loss [postexercise] [kg]	−0.65	−0.30	$P = 0.010$*
Consumed calories during exercise [cal]	354.42	364.36	$P = 0.312$
Systolic/diastolic BP [pre-exercise] [mm Hg]	131.6/82.0	125.6/80.6	$P = 0.386/P = 0.760$
Systolic/diastolic BP [postexercise] [mm Hg]	115.2/79.8	116.4/76.4	$P = 0.803/P = 0.302$
Systolic BP change [post–pre-exercise] [mm Hg]	−16.4	−9.2	$P = 0.462$
Pulse rate [pre-exercise] [beats/min]	76.0 ± 18.8	79.4 ± 14.0	$P = 0.517$
Pulse rate [postexercise] [beats/min]	96.0 ± 10.6	93.6 ± 11.8	$P = 0.565$
Pulse rate change [post–pre-exercise] [beats/min]	+20.0	+14.2	$P = 0.034$*
Tympanic temperature [pre-exercise] [°C]	36.36	35.70	$P = 0.048$*
Tympanic temperature [postexercise] [°C]	36.80	36.04	$P = 0.011$*
Urine osmolality [mOsm/kg]	784.6	480.6	$P = 0.020$*
Subjective state measures	**Dehydration**	**Rehydration**	***t* test**
Thirsty [mean]	4.15	2.10	$P = 0.004$*
Hunger	2.80	2.20	$P = 0.07$
Anxiety	1.70	1.00	$P = 0.080$
Mood by VAMS	61.0	62.0	$P = 0.893$
Uchida-Kraepelin performance test results			
Task performance quantity	972.2 ± 92.9	1079.8 ± 93.4	$P = 0.007$*
Error rate	0.16 ± 0.08	0.19 ± 0.27	$P = 0.827$

On the rehydration day, each of the subjects consumed an average of 2040 mL (range 1800–2500 mL) ORS. Data are expressed as means.
SD = standard deviation; ORS = oral rehydration solution; BP = arterial blood pressure; VAMS = visual analog mood scale.
*$P < 0.05$ using 1-sample t test.

Table 2. Local Statistical Maxima in Activated Brain Regions in Each Contrast

Number of voxels	Cluster-level, corrected *P*	Brain region	Coordinate (mm) X	Y	Z	*t*-value
[CPT–Control (dehydration)]						
3350	0.000	Anterior cingulate cortex	2	32	36	10.84
			8	24	36	9.49
			−12	28	28	8.67
8631	0.000	(L) Insula	−34	14	−6	10.45
		(R) Insula	34	18	2	9.40
			30	14	−4	9.02
710	0.000	Cerebellum	−36	−58	−32	8.09
[CPT–Control (rehydration)]						
5407	0.000	(L) Insula	−24	18	8	9.13
			−26	10	8	7.56
		(R) Insula	34	20	2	8.31
811	0.000	Anterior cingulate cortex	2	32	36	8.43
			6	24	44	6.46
			−12	26	26	5.84
324	0.013	Cerebellum	−36	−58	−32	5.77
[Control–CPT (dehydration)]						
477	0.002	Ventromedial prefrontal cortex	8	34	−12	7.00
			5	25	−16	6.74
			14	30	−6	6.15
464	0.002	Posterior cingulate cortex	−10	−64	12	6.38
			−2	−64	22	5.91
			−5	−56	22	5.68
731	0.000	Amygdala	−28	−22	−22	5.85
			−28	−4	−28	5.74
			−26	−14	−20	5.16
[Control–CPT (rehydration)]						
1972	0.000	Ventromedial prefrontal cortex	8	34	−12	8.50
			−2	34	−8	8.14
			14	30	−6	7.84
1810	0.000	Posterior cingulate cortex	−4	−64	22	7.55
			−8	−58	38	7.22
			−10	−54	12	6.60
2309	0.000	(L) Amygdala	−26	−22	−22	6.89
			−42	18	−32	6.74
			−28	−38	−10	5.98
1062	0.000	Temporal lobe	60	−6	−20	7.56
			48	20	−32	7.41
			52	14	−26	7.29
327	0.012	Fusiform gyrus	30	−42	−14	5.18
			36	−42	−24	4.69
297	0.018	(R) Amygdala	28	−10	−16	5.08
			22	−20	−24	5.07
			30	−4	−22	4.60

Coordinates refer to local cluster maxima. A height threshold of $P < 0.001$ at the voxel level without correction and cluster $P < 0.05$ (corrected for multiple comparisons) were used.
(R) = right; (L) = left; CPT = cold pressor test.

associated with a significantly smaller amount of work than rehydration, although the error rate did not significantly differ between conditions.

Neuroimaging Results

From the 2 × 2 ANOVA results including brain images from CPT or control (2 × stimulus type) from dehydration and rehydration (2 × condition), [CPT–control] contrasts during both dehydration and rehydration conditions revealed a comprehensive representation of the pain network during CPT. Regions such as the anterior cingulate cortex (ACC), bilateral insula, thalamus, and cerebellum were activated. The overall activation during dehydration was greater than that during rehydration with ORS in terms of peak and cluster (Fig. 3, A and B and Table 2).

However, in the [control–CPT] contrasts under both conditions, there were significant clusters located in the ventromedial prefrontal cortex (VMPFC), posterior cingulate cortex, and amygdala. The overall activation during rehydration with ORS was greater than during dehydration in terms of peak and cluster (Fig. 3, C and D and Table 2). In Table 2, the activated brain regions in each contrast are listed with their numbers of voxels, cluster-level corrected *P*-values, coordinates, and *t*-values at the voxel level.

DISCUSSION

This study shows that dehydrated subjects exhibit increased pain-related brain activity in the ACC and insula during pain processing with decreased pain thresholds, compared with rehydrated subjects.

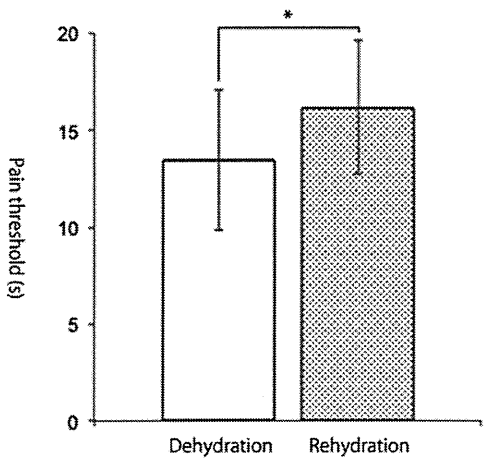

Figure 2. Pain threshold during dehydration and rehydration during cold pressor test. During dehydration, a significant decrease in pain threshold was observed compared with rehydration with ORS. Values represent means with SEM illustrated as vertical bars. *$P < 0.001$. ORS = oral rehydration solution.

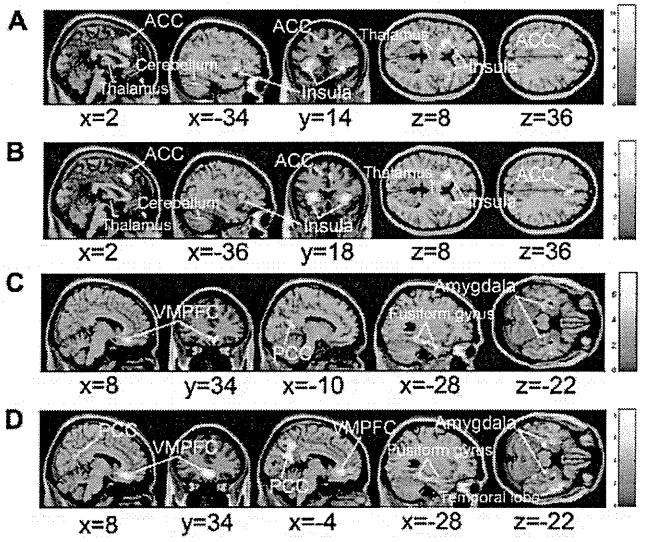

Figure 3. Brain activities in each contrast: (A) [CPT–control (dehydration)], (B) [CPT–control (rehydration)], (C) [control–CPT (dehydration)], and (D) [control–CPT (rehydration)]. The extent threshold of $P < 0.05$ corrected for multiple comparisons, with the height threshold of $P < 0.001$ (uncorrected) was used. The corresponding *t*-value is shown in the color scale on the right side for each contrast. CPT = cold pressor test; ACC = anterior cingulate cortex; PCC = posterior cingulate cortex; VMPFC = ventromedial prefrontal cortex

This study had the advantages of measuring supraspinal responses to painful stimuli and comparing the responses between dehydration and rehydration with ORS, as well as differences in pain threshold and thirst level. There was no previous study that used neuroimaging to investigate the effects of dehydration on pain perception. In 1 study, however, the effects of dehydration on brain function were examined by fMRI in healthy adolescents, demonstrating attenuated executive functions such as planning and visuospatial processing during dehydration.[20] In our executive function task (Uchida-Kraepelin performance test) after exercise, dehydration led to a significantly smaller amount of work than rehydration with ORS, although the error rate did not significantly differ between conditions (Table 1). In a previous study,[20] poor executive function task performance validated the notion that dehydration can lead to negative cognitive changes. Analogous findings of cognitive function impairment during dehydration have been reported.[21,22]

There are possible neural mechanisms by which dehydration affects pain experience negatively. This study shows clear differences in physiological data between dehydration and rehydration with ORS (Table 1). Subjects reported significantly strong thirst while dehydrated. Moreover, they did not report thirst while rehydrated, and there were no significant differences in other subjective measurements such as hunger, anxiety levels, and general mood. The only significant difference in subjective state measures between dehydration and rehydration with ORS was in thirst level (Table 1).

We, therefore, suggest that the key factor is the subjective feeling of "thirst," which leads to differences in pain-related brain activity between dehydration and rehydration with ORS (Fig. 3, A and B). Thirst is one of the most powerful sensations driving the need for moisture for survival.[23,24] Intriguingly, Egan et al.[25] using fMRI showed high activities in the ACC, insula, and cerebellum in thirsty human subjects. They showed that the ACC might be the region for consciousness of thirst, because when subjects were rehydrated with water, an immediate decrease in activity occurred in the ACC with the attenuation of thirst.[25]

When humans are dehydrated, it is not surprising that such a strong motivational sensation called thirst amplifies the pain-related cerebral activity, because pain is an unpleasant sensation. However, it is always subjective and associated with emotions.[26] A number of studies have suggested that negative conditions and emotion can lead to pain or pain exacerbation.[27,28] It seems likely that the ACC and insula are actually part of a multimodal network related to the detection of multiple salient sensory inputs.[29] Our finding of increased pain-related cerebral activity during dehydration might be exacerbated by thirst, which threatens our lives. There is evidence of such a causal relationship in which negative conditions and emotions can lead to pain or pain exacerbation.[30]

During rehydration with ORS, however, together with prolonged pain thresholds, our brain data on [control–CPT] contrasts demonstrate increased reward circuitry activity in regions such as the VMPFC and amygdala (Fig. 3, C and D), which are thought to be major dopaminergic targets and have been implicated in the reward network.[31] These denote significantly greater brain activation in response to light-touch stimulus (control stimulus) than in response to a pain stimulus (CPT). Generally, the brain's reward network activation is associated with pleasure, involving the VMPFC, amygdala, and ventral tegmental area, which respond to not only physical rewards such as food, drinks, drugs, and sexual activity but also social rewards such as having a good reputation[32] or fair treatment.[33]

As mentioned above, we suggest that dehydration generates strong thirst, leading to an unstable state and

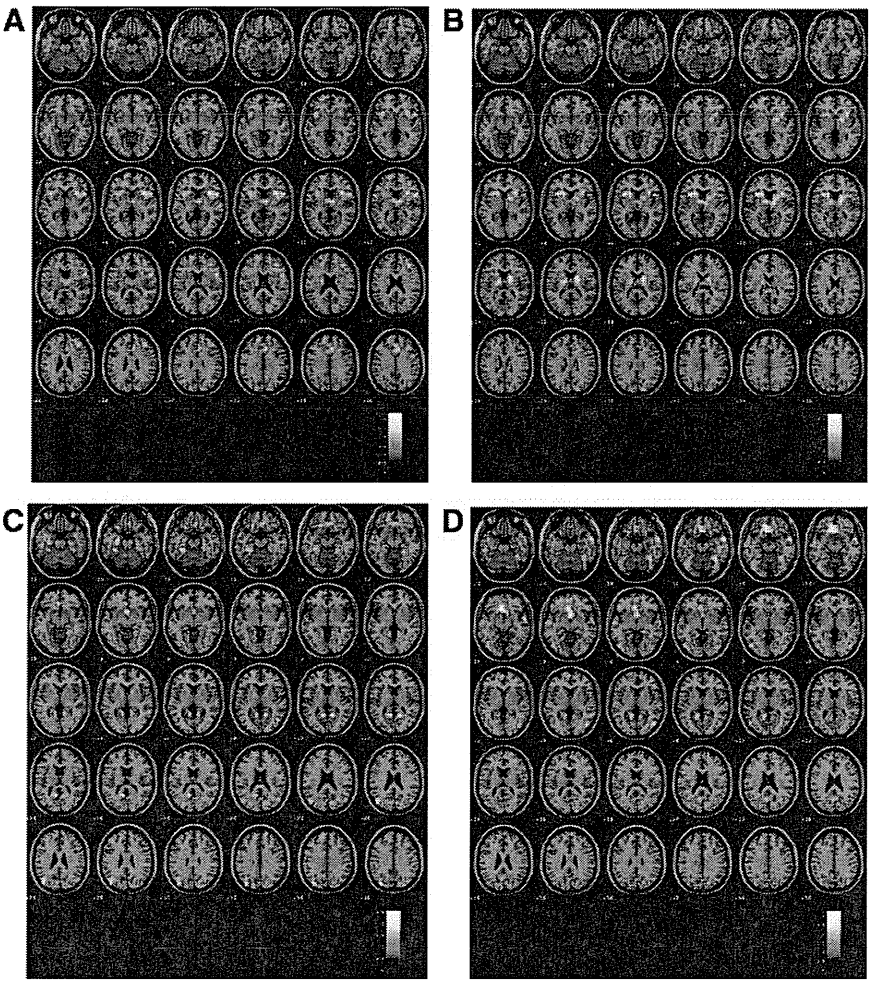

Figure 4. (A) [CPT–control (dehydration)], (B) [CPT–control (rehydration with ORS)], (C) [control–CPT (dehydration)], and (D) [control–CPT (rehydration with ORS)]. To assess the consistency of subject-specific neural activity evoked by CPT across our 5 subjects, we performed conjunction analysis with a global null hypothesis, which tests the combined null hypothesis for all subjects. The analysis was previously used for assessing the consistent effect between 1 or more subjects before the development of a random effect model. The results of the conjunction analysis show that there is a consistent effect among our 5 subjects. CPT = cold pressor test; ORS = oral rehydration solution.

sensitivity of subjects to painful stimuli, as represented by markedly high pain-related brain activity. Thus, the process of satisfying strong thirst must be pleasurable and rewarding (e.g., a cold beverage tastes better with a dry throat), as demonstrated by the increased reward circuitry brain activity in our rehydrated subjects. At the very least, thirst during dehydration might be a strong physical survival need; therefore, once subjects were rehydrated with ORS, the difference between the conditions with or without thirst may have affected the pain experience.

The mechanisms underlying the modulation of pain by emotion mainly involve the top-down pain modulatory system comprising the prefrontal cortex, amygdala, hypothalamus, and brainstem structures such as the periaqueductal grey and the descending projections to the spinal dorsal horn,[34,35] although we found no significant activation below the brainstem level or in the prefrontal region. However, Takahashi et al.[36] first demonstrated a correlative interplay between pain-related brain activation and reward network activation in their fMRI study. Hence, a feeling of thirst and its alleviation might have a considerable effect on pain experience by such a correlative interplay between dehydration (painful experience) and rehydration with ORS (reward), as mentioned above.

Limitations

First, the small number of subjects is a limitation of this study because statistical power depends on total sample size, and thus, it is desirable to have as many subjects as possible.[37] Therefore, more subjects are necessary for future studies. Second, the control group (rehydration with ORS in this study) did not include a real control group such as a group rehydrated with water without fasting or exercise, which would be a better control group. Third, a simple 5-point scale measurement method for anxiety level and mood using the visual analog mood scale might contribute to the absence of significant differences in anxiety level and mood between the conditions used in this study. Valid and specific tools for measuring anxiety (e.g., State-Trait Anxiety Inventory) may be ideal for future assessments. Last, the increased activity of the reward network shown during rehydration with ORS conditions is an intriguing observation in this study. However, it is difficult to speculate about the cause of this increased activity of the reward network and attenuated pain during rehydration with ORS. Difficulties in interpreting such interactions are also limitations of this study.

Conclusions

This study shows that dehydration increases brain activity related to painful stimuli with decreased pain threshold and

enhanced thirst in humans, whereas rehydration with ORS alleviates thirst and decreases this brain activity.

DISCLOSURES

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Attestation: Yuichi Ogino is the principal author and attests to the integrity of the original data and the analysis reported in this manuscript.
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Attestation: Takahiro Kakeda approved the final manuscript.
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Scientific Research

H-MR Spectroscopy of the Anterior Cingulated Cortex: Usefulness in the Prediction of Patients That Will Benefit from a Cognitive Behavioural Therapy in the Treatment of Chronic Pain

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ABSTRACT

Anterior cingulated cortex (ACC) is involved in "the state in which patients do not care much about pain despite its presence" which is a goal of psychosomatic treatment. To investigate the absolute concentration of N-acetylaspartate (NAA) in the anterior cingulated cortex (ACC) as predictors of patients that may benefit from cognitive behavioural therapy in the treatment of chronic pain. Proton magnetic resonance spectroscopy (^{1}H-MRS) was performed with a 1.5 T MR system on a voxel in the bilateral ACC in 85 chronic pain patients and 20 age-matched normal control subjects. Eighteen out of 24 (75.0%) patients whose NAA concentration decreased significantly in the ACC, respectively, compared to the mean NAA concentration of the normal control subjects, needed cognitive behavioural therapy. Our results suggest that decreased NAA concentration in the ACC is associated with the necessity of cognitive behavioural therapy. ^{1}H-MRS may serve as a useful non-invasive tool for evaluating chronic pain patients.

Keywords: Magnetic Resonance Spectroscopy; Chronic Pain; Anterior Cingulated Cortex; N-Acetylaspartate

1. Introduction

In recent years, studies using brain function imaging have gradually clarified the brain regions associated with pain leading to a more objective evaluation of pain [1]. The anterior cingulated cortex (ACC) have been demonstrated to be involved in cognitive-evaluative and affective-motivational aspects of pain in several functional neuroimaging studies including those using functional magnetic resonance imaging (fMRI) [1,2]. Studies using voxel-based morphometry (VBM) or fMRI in patients with chronic pain have shown atrophy of the ACC [3], and activation of ACC have been produced by virtual pain stimulation using a video [4]. Thus, functional changes in the ACC are considered to be closely involved in chronic pain [1-4].

It was reported that patients no longer showed psychological suffering despite the presence of pain after ACC resection as treatment for chronic pain [5]. Other studies have also shown a marked increase in blood flow in the ACC and pain relief during electrical stimulation of the cerebral cortex [6], ACC activation by the anticipation of pain [7], and activation of the ACC by placebo administration [8]. In patients with central pain, a functional decrease in the ACC is considered to be the cause of specific unpleasantness [9], and ACC activity was reported to be correlated with the degree of pain and unpleasantness [9]. A recent study using Proton magnetic resonance spectroscopy (^{1}H-MRS) showed suffering in neuropathic pain patients after spinal cord injury are associated with the level of N-acetylaspartate (NAA) in the ACC [10]. These findings also suggest that ACC is involved in "the state in which patients do not care much about pain despite its presence" which is a goal of psychosomatic treatment.

We measured neural activity in Brodmann Area 24 (BA24) in the ACC, using ^{1}H-MR spectroscopy (^{1}H-MRS) to evaluate the effect of chronic pain. MRS is a noninvasive method for the measurement of metabolites in the brain using an MRI system. N-acethyl-aspartate (NAA) obtained using ^{1}H-MRS is amino acid specific to and present only in neurons [11,12]. Furthermore, there is no age-related differences on the level of NAA in the ACC and PFC [11,12]. Therefore, it is clinically used as a noninvasive parameter of local neural function in the

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brain for the differential diagnosis of Alzheimer's disease [13] and post-traumatic stress disorder (PTSD) [14].

In this study, to investigate whether the absolute concentration of NAA in the ACC can be a valuable evaluation tool of chronic pain that may benefit from a cognitive behavioural therapy (CBT), we investigated the absolute concentration of NAA in the ACC bilaterally, of chronic pain patients and healthy comparison subjects by ^{1}H-MRS.

2. Materials and Methods

2.1. Subjects

The subjects consisted of 85 patients (41 males, 44 females, ages 17 - 83 years, 55.91 ± 15.02 years) with chronic pain (neuropathic pain, 20; complex regional pain syndrome: CRPS, 20; chronic low back pain, 20; whiplash syndrome, 9; other chronic pain, 16) who were referred to the pain management clinic of the Department of Anesthesiology of the Shiga University of Medical Science Hospital. The left side was affected in 24 patients, and the right side was affected in 27. The duration of pain was 4 - 396 months. Psychological approach, such as a cognitive behavioral approach by psychologist was determined by multidisciplinary conference with psychologist. These patients were compared with 20 age- and sex-matched healthy controls (11 males, 9 females, ages 17 - 79 years). They were screened with a questionnaire and an interview, and those with current or a history of mental disorder, neurological disease or head trauma were excluded.

This study was approved by the ethics committee of Shiga University of Medical Science Hospital and informed written consent for participation in this study was obtained from all patients and volunteers.

2.2. MR Imaging

^{1}H-MRS examinations were performed at 1.5 T (SIGNA MR System, General Electric, Milwaukee, WI, USA) using a standard circular polarized head coil. The voxels of interest were selected in the bilateral ACC region on sagittal and coronal T1-weighted images of the head (**Figure 1**). ^{1}H-MRS spectra were obtained using the simulated-echo method (STEAM) with chemical shift selective saturation (CHESS) pulse sequence with a repetition time (TR) of 2 sec, echo time (TE) of 30 msec and 96 acquisitions in the anterior cingulated cortex.

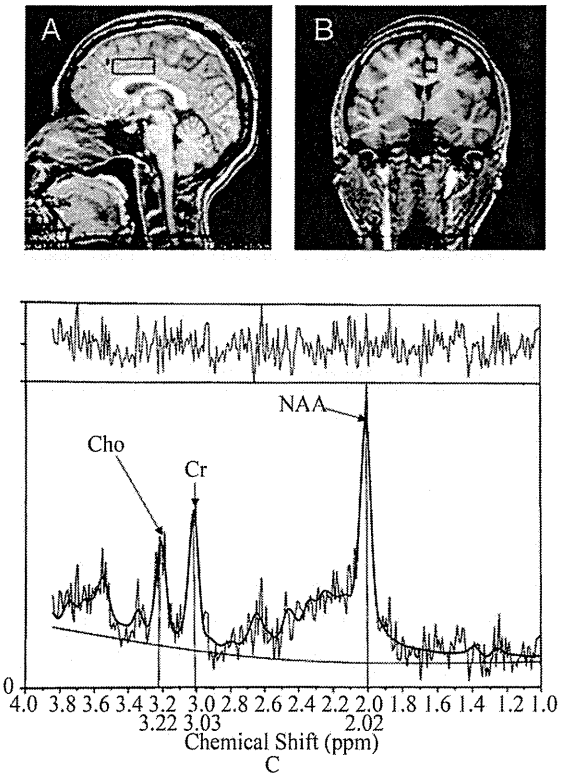

Figure 1. Axial and sagittal MRI scans showing the location of the spectroscopic voxel in the prefrontal cortex and anterior cingulate cortex. ^{1}H-MRS spectra from the anterior cingulated cortex of a chronic pain patient. ROIs in the ACC were selected on T1-weighted images. MR spectra obtained in each region were analyzed using the LC model. NAA, N-acetyl-aspartate; Cr, creatine and phosphocreatine; Cho, choline-containing compounds. Chemical shifts are indicated in parts per million (ppm).

Based on the peaks of spectra, the NAA concentrations were determined.

Spectral analysis was performed using linear combination model (LC model) software [15], which yields concentrations of NAA (**Figure 1**). Brain voxels of interest were chosen in gray matter of the ACC (BA 23) from the axial plane by a skilled neuroradiologist.

2.3. Evaluation Items and Statistical Analysis

The intensity of pain in the patients was evaluated using a Visual Analogue Scale (VAS). VAS levels of pain severity were rated as 0 - 100 mm (0 = no pain; 100 mm = maximal pain). The Hospital Anxiety Depression (HAD) test [16] was performed, and the severity of anxiety and depression associated with pain in the patients was evaluated.

In each region of interest, the NAA concentrations ipsilateral and contralateral to the affected limb were compared to determine whether there was a hemisphere predominance. The possible correlations between the NAA concentration in each region and the intensity of pain, duration of disease, or pain-associated affective-motivational changes were evaluated. We compared the absolute concentration of NAA in the ACC bilaterally, of chronic pain patients who needed CBT and those that did not require CBT. The NAA concentrations were also compared between the patients and control group.

The NAA concentrations are expressed as the mean ± standard deviation, and the two groups were statistically compared using Mann-Whitney's test. $P < 0.05$ was regarded as significant.

3. Results

The affected side and NAA concentration in each region (hemispherical predominance):

In the left side-affected patients (n = 24), there was no significant difference in the NAA concentration between the left and right ACC (right ACC; 5.55 ± 0.54, left ACC; 5.49 ± 0.42). In the right side-affected patients (n = 27), there was no significant difference in the NAA concentration between the left and right ACC (right ACC; 5.56 ± 0.44, left ACC; 5.55 ± 0.51). No significant difference ($P > 0.05$) was observed between NAA concentrations ipsilateral to the affected side and those contralateral to the affected either in the ACC in chronic pain patients.

In the healthy control subjects (N = 20), the mean left and right NAA concentration of the ACC was 6.12 ± 0.35, and the range was 5.77 to 6.47. There was no association between age and the mean NAA concentration on the left and right sides in the ACC in the control group.

Compared with the 20 healthy controls, the NAA concentration was significantly (mean ± 2SD) lower in the ACC in 22 of the 68 patients with chronic pain.

In the chronic pain patients (N = 85), the mean NAA concentration (5.70 ± 0.50) of the ACC was significantly lower in the patients than in the control group (6.12 ± 0.35) (**Figure 2**).

Twenty-four out of 85 chronic pain patients required a

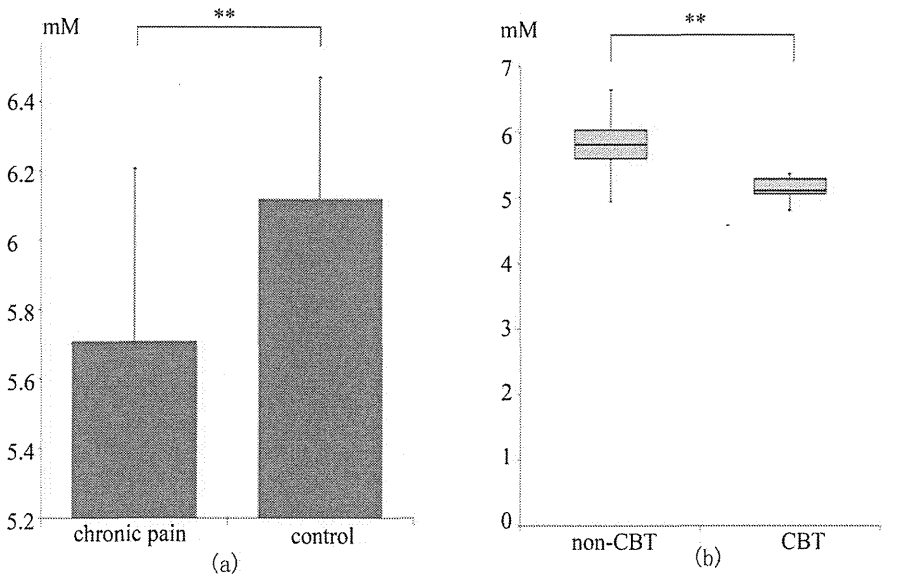

Figure 2. (a) Concentration of NAA in the ACC in chronic pain patients and control group; (b) The mean NAA concentration of the ACC in chronic pain patients who required a cognitive behavioural therapy performed by a psychologist and controls. In chronic pain patients (N = 85) the mean NAA concentration (5.70 ± 0.50) in the ACC was significantly lower in the patient than in the control group (6.12 ± 0.35) (a). The mean NAA concentration (5.16 ± 0.24) of the ACC in chronic pain patients who required CBT performed by psychiatrist (N = 24) was significantly lower than the NAA concentration (5.88 ± 0.44) in patients not needing CBT (N = 61).

cognitive behavioral approach performed by a psycologist. Eighteen of 24 (75.0%) patients that had a decrease in NAA concentration in the ACC required a cognitive behavioral approach performed by psychologist.

The mean NAA concentration (5.16 ± 0.24) of the ACC of chronic pain patients who required CBT performed by a psychologist (N = 24) was significantly lower than the NAA concentration (5.88 ± 0.44) in patients that did not need CBT (N = 61) (**Figure 2**).

There was no correlation between the intensity of pain, the pain duration and the NAA concentration in ACC. There was no significant difference in the NAA concentration of the ACC between the patient group with marked anxiety (n = 17; anxiety > 11) (ACC; 5.70 ± 0.43) in the HAD test and the patient group without anxiety (n = 68; anxiety < 10) (ACC; 5.79 ± 0.48). There was no significant difference in the NAA concentration between the patient group showing marked depression associated with pain (n = 27; depression > 11) (ACC; 5.68 ± 0.47) in the HAD test and the patient group without depression (n = 58; depression < 10) (ACC; 5.66 ± 0.48).

4. Discussion

^{1}H-MRS is a noninvasive method for the measurement of biological metabolites that are difficult to morphologically evaluate [11,13,17,18]. NAA is localized in neurons at high concentrations and therefore is correlated with the density of normal neurons [11,13,14]. In ACC, the NAA concentrations ipsilateral to the affected limb were similar to those contralateral to the affected limb, showing no hemispherical predominance. Further, Coghill *et al.* [19] reported bilateral activation of ACC following painful stimulation. Therefore, in this study, irrespective of the affected side, the mean NAA concentration on the left and right sides of ACC was used for evaluation.

Reductions of NAA in the ACC were reported to be specifically linked to the presence of chronic pain with spinal cord injury [17]. A study using ^{1}H-MRS in patients with diabetic neuropathy showed a decrease in the NAA concentration in the ACC in patients with marked pain [18]. Thus, the decrease in the NAA concentration suggests a decrease in the function of normal neurons in the ACC due to persistent unpleasantness associated with pain. In this study, the chronic pain patient group showed a significant decrease in the NAA concentration in ACC, compared to normal controls. Evaluation of ACC function may be a key to the successful treatment of chronic pain.

In the clinical setting, we often encounter patients with chronic pain showing depression and anxiety in which these affective changes further modify pain. However, the results of this study showed no significant difference in NAA concentration in the ACC in the patient group with marked anxiety and depression associated pain. There was no association between the intensity of pain, duration of pain, depression, anxiety and NAA concentration in ACC.

In this study, cognitive behavioural therapies were necessary in patients showing a decrease in the NAA concentration in the ACC. Our results using ^{1}H-MRS suggest that the decreased NAA concentration of the ACC may be related to the necessity for CBT.

After treatment using a CBT performed by psychologist, although the intensity of pain remained the same, "pain obsession" decreased which led to psychological relief. When patients do not care as much about the pain, management for chronic pain may be more successful.

Our results using ^{1}H-MRS suggest that the chronic pain patients who need CBT tend to have decreased neural activity in the ACC. Our results suggest that ^{1}H-MRS is a noninvasive method that does not burden patients and is also useful for selecting treatment methods, and can be a new evaluation method in patients with chronic pain.

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原著 Original Article

腰部脊柱管狭窄症に対する理学療法有効例の多面的評価を用いた検討

Effectiveness of Physical Therapy for Patients with Neurogenic Claudication Due to Lumbar Spinal Stenosis

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要 旨

外来腰部脊柱管狭窄症患者を対象に理学療法を行い，精神・心理面を含めた多面的評価を用いて，どのような症例が理学療法の効果が得られるかを検討した．治療後のチューリッヒ跛行質問票の満足度 cut-off 値により有効群22例，無効群12例に振り分けされ，無効群では治療前の仮面うつ自己評価法が有効群に比べ有意に高く，画像所見，疼痛，歩行能力に差はなかった．したがって，仮面うつの程度が低い症例では治療効果が得られやすかった．

Abstract

Study Design : Retrospective study.

Objective : To examine the efficacy of physical therapy using multimodal assessments and evaluate which patients with lumbar spinal stenosis (LSS) are responders.

Summary of Background Data : It has been reported that the preoperative depression status significantly affects the postoperative outcome in patients with LSS treated surgically. However, responders to physical therapy in patients with LSS are still unknown.

Methods : Patients presenting with symptoms of neurogenic claudication caused by LSS (confirmed by magnetic resonance imaging or computed tomography) were enrolled. Patients were treated with manual therapy, stretching and strengthening exercises, and body-weight-supported treadmill walking once a week for 6 weeks. Clinical outcomes were measured using the Zurich Claudication Questionnaire (ZCQ) ; a visual analog scale of low back pain, leg pain, and leg numbness ; the Japanese Orthopaedic Association Back Pain Evaluation Questionnaire ; the Pain Catastrophizing Scale ; the Pain Anxiety Symptoms Scale ; the Hospital Anxiety and Depression Scale ; the Self-Rating Questionnaire for Depression (SRQ-D) ; and a Biodex isokinetic dynamometer. According to Stucki's criteria for the satisfaction scores of ZCQ subscales, patients were divided into an effective group (Group I) and an ineffective group (Group II). The characteristics of patients with LSS who achieved satisfactory results with our physical therapy programs were clarified.

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Results：Groups I and II had 22 and 12 patients, respectively. There were no differences in the demographic data and MRI findings between the two groups. At the baseline, however, there was a significant difference in the SRQ-D (Group I , 7.1 points vs. Group II , 10.8 points).

Conclusions：Depressive symptoms interfere with the ability of patients to achieve an optimal physical therapy outcome. Our results suggest that assessments of depression are needed to improve the clinical outcomes of physical therapy for patients with LSS.

Key words：腰部脊柱管狭窄症(lumbar spinal stenosis)，理学療法(physical therapy)，うつ(depression)

緒　言

腰部脊柱管狭窄症(以下 LSS)患者は，身体的健康度だけでなく，精神的健康度も低下している．松平ら[8]は，LSS 患者の症状と抑うつおよび健康関連 QOL を調査した結果，抑うつ傾向は32%の患者にみられ，精神的健康度の下位尺度の低下を報告している．Sinikallio[13]らは，LSS の手術患者に対する術前，術後3か月の調査から，術前のうつ状態が術後の Oswestry Disability Index，Stucki 重症度，visual analog scale(VAS)と高い相関があることを示し，術前に各症例のうつ状態を評価することが重要と結論している．すなわち，LSS 患者に十分な治療効果が得られるためには治療前の多面的評価が必要である．

一方，LSS 患者に対する保存療法としてはリマプロストなどの薬物療法[7]や理学療法[4,5,9,10]の有用性を示した報告が散見されている．Whitman[15]ら無作為対照試験(RCT)では，特に徒手療法，筋力増強運動，体重免荷トレッドミル歩行を組み合わせた介入が，腰椎屈曲運動，通常トレッドミル歩行の介入に比べ，より効果的であることを示している．しかし，評価法は疼痛や歩行距離にとどまっていて，LSS 患者に対する理学療法の有効性を多面的に評価した研究は未だみられない．LSS 患者の理学療法の有効性を検証するためには多面的な評価を行うことが重要で，理学療法有効な症例を明確にすることが可能となる．本研究の目的は，理学療法の介入が治療成績を向上させるかどうか，理学療法有効例と無効例の間にどのような差があるかどうかを多面的評価法を用いて検討することにある．

対象と方法

2011年4月から2012年10月までの期間，歩行で下肢神経症状が出現し，前屈で症状が消失する神経性間欠跛行を呈し，MRI または CT にて LSS と診断された患者を対象に後ろ向き研究を行った．下記の理学療法を希望しない・できない患者，膀胱直腸障害を有する症例，外傷，骨粗鬆症，脊椎手術既往例，下肢機能に影響する他の疾患を有する患者，糖尿病，末梢動脈疾患，認知症，精神科受診既往例，神経ブロック療法併用例を除外した．理学療法は，週1回6週間の体幹・股関節周囲筋のストレッチ，腰痛体操，体重免荷トレッドミル歩行を実施し，ホームエクササイズは腰痛体操と歩行を指導した．評価は，腰痛，下肢痛，下肢しびれ VAS，チューリッヒ跛行質問票(ZCQ)，日本整形外科学会腰痛評価質問票(JOABPEQ)，痛みに対する破局的思考尺度(PCS)，痛みに対する不安症状尺度(PASS-20)，不安・抑うつ尺度(HADS)，仮面うつ自己評価表(SRQ-D)を用いた．LSS の重症度は MRI で評価し[11]，体幹と膝関節の筋力を Biodex にて測定した．

統計学的処理は，治療前後の比較には対応のある t 検定またはウィルコクソンの符号順位検定を用い，理学療法が治療成績を向上させるかを検討した．次に，治療後の ZCQ 満足度の cut-off 値2.5点[14]により有効群と無効群の2群に分け，治療前に有効群と無効群でどのような差があるかを Student's t 検定または Mann-Whitney の U 検定，名義尺度には Fisher の直接法を用い，比較検討した．また，両群それぞれの治療前後の比較も行った．統計処理は，SPSS version 20.0 J を用い，有意水準は5%未満とした．

表1　対象者の内訳

	Group I, II ($N=34$)	Group I ($n=22$)	Group II ($n=12$)	P^*
年齢(歳)	70.8±7.7	70.8±7.4	70.2±7.6	0.73
性別(男性：女性)	12：22	9：13	3：9	0.47†
Body mass index(kg/m^2)	22.3±3.4	21.8±3	23.3±4.3	0.23
発症期間(月)	17.1±20.6	14.1±19.2	23±22.8	0.54**
ホームエクササイズの順守	38.5±6.6	38.2±7.1	40.5±3	0.64**

平均値±標準偏差，*Student's t 検定，**Mann-Whitney の U 検定，†Fisher の直接法

結　果

34例(男性12例，女性22例，平均年齢70.8歳)が包括された(表1)．治療前後の比較では，ZCQ 身体機能(治療前，2.3；6週後，2.1点)と Biodex 腰伸展(治療前，129.5 Nm/kg；6週後，183.9 Nm/kg)，左右膝伸展(右膝伸展：治療前，116.9 Nm/kg，6週後，134.2 Nm/kg；左膝伸展：治療前，107.3 Nm/kg，6週後，121.8 Nm/kg)ピークトルク/体重比で有意な改善が認められた($p<0.05$)(表2)．

治療後の ZCQ 満足度により，有効群(Group I) 22例，無効群(Group II)12例に振り分けされた．2群間においては，治療前の SRQ-D(7.1 vs. 10.8点)に有意差があり，年齢，性別，発症期間，MRI 重症度，その他の治療前の評価項目に有意差は認められなかった($p<0.05$)(表2，3)．有効群では，ZCQ 身体機能(治療前，2.2；6週後，2.0点)，PCS(治療前，26.6；6週後，22.4点)，Biodex 腰伸展(治療前，128.1 Nm/kg；6週後，181.6 Nm/kg)，左右膝伸展(右膝伸展：治療前，118.3 Nm/kg，6週後，135.4 Nm/kg；左膝伸展：治療前，109.1 Nm/kg，6週後，122.9 Nm/kg)ピークトルク/体重比で有意な改善が認められた($p<0.05$)．

考　察

理学療法の介入によって，歩行能力と体幹，下肢筋力に有意な改善が認められた．ZCQ 満足度でみると，34例中22例(65%)が有効であった．Zucherman ら[16]は，ZCQ をアウトカムに用い，手術療法と理学療法を含めた保存療法の比較を RCT にて行った結果，6週後の満足度が得られた症例は，手術療法約75%，保存療法約45%であったと報告している．したがって，今回のストレッチ，腰痛体操，体重免荷トレッドミル歩行を含めた理学療法は非常に効果的であったと考える．一方，先行研究[4,5,9,10,15]では，歩行能力に加え，疼痛の改善も得られている．先行研究では，週2回6週間もしくは，入院患者を対象に週5回2～3週間と計10～12回の理学療法を行っているので，本研究の週1回6週間の介入では，治療回数が少なかった可能性が考えられる．

有効群と無効群の治療前における比較では，SRQ-D にのみ有意差があり，画像所見や疼痛，機能障害などの重症度に差は認められなかった．うつの治療への悪影響については様々な報告があり，Linton[6]は，腰痛と頚部痛の患者においてうつや不安などの心理的因子は，画像所見など臨床所見よりも治療成績に悪影響を及ぼすことを報告，Gallagher ら[3]は，うつと慢性疼痛があると単独の場合よりも治療困難，Bair ら[1]は，慢性疼痛患者のうつは，複数個所の痛み，痛みの強度，罹患期間，治療の低反応に関連すると報告している．また，LSS 手術患者でも術前のうつ状態が治療後の疼痛や ADL の改善に悪影響を及ぼすことが報告[13]されており，今回の結果により LSS 患者に対する理学療法においてもうつがあると治療効果が得られにくいと考えられる．

本研究ではうつの評価を2種類使用したところ，精神症状よりも身体症状が表面に出る仮面うつを評価する SRQ-D と身体症状の影響を受けない抑うつを評価する HADS のうち，SRQ-D にのみ有意差を認めた．さらに SRQ-D は無効群が10.8点と正常範囲を超えており，HADS 抑うつは

表2　各評価結果の比較

		Group I, II ($N=34$)	Group I ($n=22$)	Group II ($n=12$)	Group I vs. II ($P^{\dagger}$)
ZCQ	治療前	3.1±0.6	3±0.6	3.3±0.5	0.09
重症度	6週後	2.9±0.7	2.8±0.7	3.1±0.7	0.30
	P^{*}	0.07	0.26	0.13	
ZCQ	治療前	2.3±0.5	2.2±0.5	2.5±0.5	0.17
身体機能	6週後	2.1±0.6	2±0.5	2.4±0.6	0.04
	P^{*}	0.02	0.01	0.53	
VAS	治療前	41.8±24	41.4±22.5	42.5±27.4	0.90
腰痛	6週後	43.1±28.1	33.6±25.7	60.4±24.6	0.01
	P^{*}	0.81	0.15	0.09	
VAS	治療前	59.4±27.4	54.7±27.4	67.9±26.3	0.18
下肢痛	6週後	52.9±29	43.8±25.4	69.5±28.7	0.02††
	P^{*}	0.33**	0.12	0.64**	
VAS	治療前	60.2±26.1	57.2±25	65.8±28.3	0.36
しびれ	6週後	58.8±24.9	51.9±26.6	71.6±15.3	0.01
	P^{*}	0.53**	0.26	0.54	
JOABPEQ	治療前	54.4±26.4	61.4±25.8	43.8±24.8	0.10††
疼痛関連障害	6週後	64.8±29.7	75.9±28.6	48±23.7	
	P^{*}	0.10**	0.06**	0.79**	
JOABPEQ	治療前	73.6±19.7	76.4±17.3	69±23.3	0.32††
腰椎機能障害	6週後	76±17.9	80±15.3	69.7±20.6	
	P^{*}	0.33**	0.28**	0.87**	
JOABPEQ	治療前	46±27.3	49.9±26.1	40±29.1	0.25††
歩行機能障害	6週後	47.9±27.7	57.6±26.1	33.5±24.4	
	P^{*}	0.72**	0.22**	0.44**	
JOABPEQ	治療前	55.8±18.4	60.5±17.8	47.3±16.9	0.06††
社会生活障害	6週後	55.2±17.6	59.1±16.5	48±18	
	P^{*}	0.84**	0.76**	0.92**	
JOABPEQ	治療前	52.6±14.1	55.3±15.1	47.6±10.8	0.20††
心理的障害	6週後	53.4±14.1	55.9±13.9	48.8±14	
	P^{*}	0.77**	0.74**	0.82**	
PCS	治療前	27.9±10.6	26.6±10.6	30.3±10.7	0.13††
	6週後	25.5±11.3	22.4±10.3	31.2±11.3	0.03
	P^{*}	0.14	0.04	0.56**	
PASS-20	治療前	35±16.5	33.9±18.5	37±12.6	0.61
	6週後	34.5±15.9	32.5±18.2	38.1±10.2	0.34
	P^{*}	0.82	0.67	0.61	
HADS	治療前	4.5±3	4.2±2.8	4.9±3.4	0.48††
不安	6週後	4.6±3	4±2.5	5.7±3.7	0.25††
	P^{*}	0.74**	0.70**	0.41**	
HADS	治療前	4.9±2.7	4.9±2.6	4.8±3	0.97††
抑うつ	6週後	4.9±3.5	4.1±3.1	6.3±4	0.10
	P^{*}	0.93**	0.17**	0.11	
SRQ-D	治療前	8.4±4.3	7.1±4.3	10.8±3	0.01
	6週後	8.6±4.3	7±4.4	11.6±3.7	0.00
	P^{*}	0.76	0.79	0.15	
Biodex 60°/s	治療前	129.5±51.2	128.1±53.8	134.1±46.6	0.74
腰伸展(Nm/kg)	6週後	183.9±63.1	181.6±57.8	191.5±86.4	0.93
	P^{*}	0.00	0.00	0.19	
Biodex 60°/s	治療前	94.6±30.6	93.7±25.5	97.7±47.9	0.23
腰屈曲(Nm/kg)	6週後	100.6±36.5	97.9±29.9	109.8±57.2	0.92
	P^{*}	0.45	0.64	0.52	
Biodex 60°/s	治療前	116.9±52	118.3±52.8	112.2±55	0.27
右膝伸展(Nm/kg)	6週後	134.2±55.2	135.4±56.7	129.9±55.9	0.82
	P^{*}	0.01	0.01	0.43	
Biodex 60°/s	治療前	56±27.8	57.7±27.7	50.4±30.6	0.13
右膝屈曲(Nm/kg)	6週後	58.3±23.4	60.6±22	50.6±29	0.30
	P^{*}	0.62	0.58	0.99	
Biodex 60°/s	治療前	107.3±45.4	109.1±49.6	101.3±30.4	0.15
左膝伸展(Nm/kg)	6週後	121.8±43.8	122.9±47.1	117.9±34.5	0.52
	P^{*}	0.00	0.01	0.12	
Biodex 60°/s	治療前	53.6±28.9	56.4±29.6	44.3±27.3	0.10
左膝屈曲(Nm/kg)	6週後	61±26.3	63.4±26.4	52.6±26.9	0.35
	P^{*}	0.05	0.09	0.40	

平均値±標準偏差，†Student's t 検定，††Mann-Whitney の U 検定，*対応のある t 検定，**Wilcoxon の符号順位検定

表3　画像所見の比較

	Group I ($n=19$)			Group II ($n=12$)			P^*
	Minor	Moderate	Severe	Minor	Moderate	Severe	
L1-L2	19	0	0	12	0	0	0.51
L2-L3	15	4	0	11	1	0	0.90
L3-L4	12	6	1	7	5	0	0.80
L4-L5	11	5	3	5	2	5	0.49
L5-S1	19	0	0	12	0	0	0.49

*Mann-Whitney の U 検定

両群ともに正常範囲であった．したがって，抑うつがなくても仮面うつがあると治療効果が得られにくいと考えられる．仮面うつは，身体症状の訴えが主で精神症状が隠れている，また軽度のうつ状態と言われている．Simon ら[12]は，うつ患者の約半数が複数，または医学的に説明できない痛みすなわち身体症状を訴える，Cuijpers ら[2]は，軽度のうつでも機能障害に影響し，うつがない人に比べ，SF-36のすべての項目で有意に低下すると報告していることから，抑うつだけでなくうつ患者に多い身体症状や軽度のうつをとらえる仮面うつの評価も必要であると考える．

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ORIGINAL ARTICLE

Usefulness of QuickDASH in patients with cervical laminoplasty

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Abstract
Purpose Clumsiness and numbness of the upper extremity is one of the most common complaints of patients with cervical myelopathy. However, most previous evaluations after cervical laminoplasty have only been based on physicians' points of view. We used Quick Disabilities of the Arm, Shoulder, and Hand (QuickDASH) self-report questionnaire, which was designed to measure physical function and symptoms in people with upper-limb disorders to evaluate functional outcomes after laminoplasty.
Methods Ninety-four patients who underwent laminoplasty for cervical myelopathy and replied to the questionnaire were included in this study. The average age was 62 years, and mean follow-up period was 61 months. The Japanese Orthopedic Association (JOA) score, Neck Disability Index (NDI), Short-Form Health Questionnaire of 36 questions (physical component score, PCS), upper-extremity pain (Numerical Rating Scale), and QuickDASH (0–100, 0 being least severe) were used to evaluate surgical outcomes. Satisfaction with treatment was also investigated, and internal consistency and criterion-related validity were evaluated. The QuickDASH cutoff value for patient satisfaction was determined by receiver operating characteristic curve (ROC) analysis.
Results The mean total JOA scores were 10 before and 13 after surgery, and average postoperative QuickDASH score was 30. Cronbach α of the QuickDASH was 0.94. QuickDASH was significantly correlated with JOA score for upper-extremity motor and sensation, NDI, PCS, and pain. Cutoff value of the QuickDASH was 34.0 by ROC analysis. Significantly better QuickDASH scores were found for patients who were satisfied with treatment than for those who were not, whereas JOA score for upper-extremity motor function did not show a significant difference.
Discussion QuickDASH had significant correlations with disease-specific JOA scores and other generic outcome measures. Moreover, QuickDASH significantly reflected patients' satisfaction with treatment, whereas the JOA score for upper-extremity motor function did not.
Conclusion QuickDASH was useful in evaluating upper-extremity functional outcomes after cervical laminoplasty.

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Introduction

Patients with cervical compressive myelopathy usually have loss of dexterity and nonspecific weakness, numbness, and paresthesia of the upper extremities, as well as gait disturbances and urinary dysfunction [1]. These symptoms have an insidious course and gradually deteriorate. In cases of severe compression or progressive course, operative decompression is the accepted treatment for cervical myelopathy [2]. Cervical laminoplasty is a well-established procedure for the disease, and several studies on cervical laminoplasty report favorable results even after 10 years or more [3, 4]. However, most previous evaluations were determined from assessment methods based on physicians' points of view, such as the Japanese Orthopedic Association (JOA) score.

Dysfunction in the upper extremity is one of the main disabilities that could affect patients' activity of daily

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