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Neuroimaging evidence implicating cerebellum in support of sensory/cognitive processes associated with thirst

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Recent studies implicate the cerebellum, long considered strictly a motor control structure, in cognitive, sensory, and affective phenomenon. The cerebellum, a phylogenetically ancient structure, has reciprocal ancient connections to the hypothalamus, a structure important in vegetative functions. The present study investigated whether the cerebellum was involved in vegetative functions and the primal emotions engendered by them. Using positron emission tomography, we examined the effects on the cerebellum of the rise of plasma sodium concentration and the emergence of thirst in 10 healthy adults. The correlation of regional cerebral blood flow with subjects' ratings of thirst showed major activation in the vermal central lobule. During the development of thirst, the anterior and posterior quadrangular lobule, lingula, and the vermis were activated. At maximum thirst and then during irrigation of the mouth with water to alleviate dryness, the cerebellum was less activated. However, 3 min after drinking to satiation, the anterior quadrangular lobule and posterior cerebellum were highly activated. The increased cerebellar activity was not related to motor behavior as this did not occur. Instead, responses in ancient cerebellar regions (vermis, fastigial nucleus, archicerebellum) may be more directly related to vegetative and affective aspects of thirst experiences, whereas activity in neocerebellar (posterior) regions may be related to sensory and cognitive aspects. Moreover, the cerebellum is apparently not involved in the computation of thirst per se but rather is activated during changes in thirst/satiation state when the brain is "vigilant" and is monitoring its sensory systems. Some neocerebellar activity may also reflect an intentionality for gratification by drinking inherent in the consciousness of thirst.

Approximately 70% of the neurons in the human brain are densely packed into the nearly crystalline microstructure of the cerebellum. The cerebellum receives input from possibly all sensory systems and projects to many cerebral cortical areas. It has a separate embryonic origin (the rhombencephalon) from that of the other brain subdivisions (prosencephalon and mesencephalon). It has recently been observed that the cerebellum in both pongid and hylobatid apes is on average 45% larger than in monkeys. So, all primate brains are not similarly organized, suggesting that there may have been a decoupling of the development of cerebellum from other segments of the brain due to natural selection (1).

This new view of the evolution of the cerebellum takes on added interest in the light of emergent data indicating that the cerebellum has a different function in brain activity than previously attributed to it (2–5). Neuroimaging and neurological studies have implicated the cerebellum in a variety of sensory and cognitive tasks, as well as in certain motor (or sensory-motor) tasks. In particular, these data suggest cerebellar involvement in the generation of words according to a semantic rule, timing of events, solving perceptual and spatial reasoning problems, mental rotation, visual information processing, cutaneous

and tactile discrimination, kinesthetic sensation, and working memory, among other processes (6–12). It has been proposed that the lateral cerebellum may be activated during several motor, perceptual, and cognitive processes specifically because of the requirement to monitor and adjust the acquisition of sensory data (2, 13). Furthermore, there are reports suggesting the involvement of posterior vermal cerebellum in affect (14, 15).

The findings implicating the cerebellum in sensory processing and emotional states make it of great interest to examine whether the cerebellum has a role in basic vegetative functions and the primal emotions thus generated, particularly given the cerebellum's ancient phylogenetic origin. Anatomical studies show that there are substantial anterograde and retrograde connections in humans between the hypothalamic nuclei and all four cerebellar nuclei (and cerebellar cortex), as well as with thalamic neural groups (16). There is also evidence of reciprocal connections between the hypothalamus and the cerebellar cortex in nonmammalian invertebrate species, suggesting these are phylogenetically old connections (17, 18). Such data imply that regions of the cerebellum may be involved in genetically programmed vegetative functions that are subserved by the hypothalamic neural organization. In this context, it was of particular interest to examine the effects on the cerebellum of the rapid rise of plasma sodium concentration and the contemporaneous emergence of thirst.

In a positron emission tomography (PET) experiment reported earlier, thirst was generated by rapid intravenous infusion of 0.51 M NaCl in normal hydrated male volunteers. Major brain regions activated with maximum thirst included the anterior and posterior cingulate gyri, parahippocampus, insula, and the thalamus (19). It was also reported that areas of the anterior cingulate [Brodmann areas (BAs) 24 and 32] were correlated with the change of plasma sodium concentration ([Na]) (20). The present paper examines cerebellar areas in the context of this experimental paradigm, which involved genesis and satiation of thirst. Recent PET experiments during hunger and satiation of hunger (21) have also noted cerebellar activations.

Methods

As described in detail in earlier publications (19, 20), thirst was produced in 10 male volunteers (24–36 years old) by an attested method of rapid intravenous infusion of hypertonic 0.51 M NaCl. After control PET scans, scans were made during increasing

Abbreviations: PET, positron emission tomography; BA, Brodmann area; [Na], sodium concentration.

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plasma [Na] when 50 and 100% of the NaCl infusion had been given, and when thirst had reached an apogee at a mean of 43 min after the end of the intravenous infusion. Thereupon, the subjects washed out their mouths with water without swallowing, thereby removing the “dry mouth” component, though thirst sensation remained. After scanning during this condition, when the mouth was wet but thirst persisting, they were permitted to drink water to fully satiate thirst and were scanned sequentially at 3, 14, 45, and 60 min after the act of satiation.

Each condition was contrasted with the first preinfusion nonthirsty scan. The PET data were registered onto the anatomical magnetic resonance images acquired from each subject. Each of the six primary comparisons achieved significance ($P < 0.001$) by a histogram-based, nonregional omnibus statistic. The significance of the activations and deactivations were tested with voxel-based Z statistic analyses. A correlation analysis was also performed in which regional cerebral blood flow was correlated against the subjects' reported thirst scores (using $Z > 3.1$, $P < 0.001$). Cerebellar foci were labeled in consensus anatomical terms as well as in Schmahmann's anatomical nomenclature (22), which is based on Larsell's earlier system (23). The Schmahmann labels are included in parentheses for each cerebellar focus reported in the present paper.

Results

Plasma [Na] increased by an average of 4 mmol/liter at the end of the 0.51 M NaCl infusion (0.2 ml/kg/min for 25 or 50 min), and the increased concentration persisted over the remainder of the experiment (for further detail, see refs. 19 and 20). The subjects evaluated their thirst on the basis of 10 being equivalent to the worst thirst the subject had ever experienced and 0 being no sensation of thirst. The thirst score at baseline of 0.2 ± 0.2 (mean \pm SEM) increased during the intravenous infusion to 1.40 ± 0.56 at 50% infusion and to 2.30 ± 0.64 at 100% infusion, and reached an apogee of 5.25 ± 0.90 at 43 ± 2.5 min after the infusion finished. The thirst score decreased to 3.55 ± 0.64 but still remained highly significantly elevated after irrigating the mouth with water, and then fell to near baseline (0.85 ± 0.43) within 3 min of drinking water to satiation.

Activity Correlated with Plasma Sodium Concentration. No cerebellar activity was positively or negatively correlated with changes in plasma [Na]. In the cerebral cortex, as reported in our prior papers (19, 20), the areas most strongly correlated with the change in plasma [Na] were in the left anterior and midcingulate gyri (BA 24 and BA 32) and bilaterally in the middle temporal gyri. The most strongly correlated subcortical area was in the periaqueductal gray, with noteworthy activations in the ventral pons and in the brainstem in the region of the medullary reticular formation.

Cerebellar Activation Correlated with Thirst Score. However, cortical and cerebellar regions were strongly correlated with changes in the thirst score. The single cerebellar focus (Fig. 1), which was in the vermal region of the right central lobule (III) of the anterior hemisphere (0, -58, -2; cluster size = 576 mm), was the third largest brain area having a significant correlation with thirst score. In the cerebral cortex, as reported in our prior publications, the principal regions correlated with the thirst score were in the posterior cingulate area (BAs 29 and 26) bilaterally (0, -44, 8), extending across the midline from $x = +6$ to $x = -6$. No significant negative correlations with the thirst score were observed in cerebellar regions.

Subtraction Analyses During Rapid Infusion of Hypertonic NaCl (0.51 M). There were considerable cerebellar activations (see Table 1) during the infusion of hypertonic NaCl and the development of moderate thirst. At both 50 and 100% of the infused

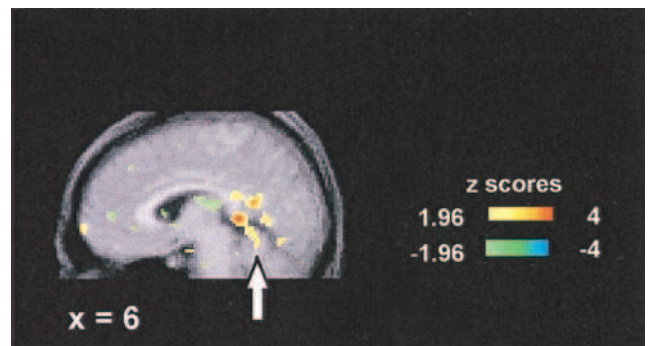


Fig. 1. The correlation of changes in regional cerebral blood flow and the change-of-thirst score derived from 99 PET scans from 10 subjects during the experimental sequence. The sagittal section is at $x = 6$ mm and shows activations (red-yellow) and deactivations (blue-green). The color coding of Z scores is shown. The activation in right central lobule (III) of the anterior cerebellum is evident (arrow).

load, cerebellar activations accounted for 13% of the total extent of brain activation (by comparison to the baseline scan, $Z > 3.00$). When 50% of the infusion was given (Fig. 2a), cerebellar activations were observed in two foci in the right anterior quadrangular lobule (V) and in foci in the right tuber of vermis (VIIIAt), left lingula (I, II), and the left posterior quadrangular lobule (VI). Outside the cerebellum, there were strong activations in the right thalamus (ventral posterior lateral nucleus), the left posterior cingulate (BAs 29 and 31), bilaterally in the fusiform gyri (BA 36), and bilaterally in the occipital cortex (BA 18, lingual and cuneus gyri). Cortical activations for the scans taken at 50 and 100% of infused NaCl were not reported in our previous two papers, and the major cortical activations noted above are consistent with the regions previously reported for maximum thirst (19, 20). At 100% infusion (Fig. 2b), cerebellar foci were detected in the right anterior quadrangular lobule (V), the left posterior quadrangular lobule (VI), tonsil of the right posterior hemisphere (IX), the lingula of left anterior hemisphere (I, II), and in the pyramis of the right posterior vermis (VIIIb). Outside the cerebellum, there were strong activations in the right pulvinar, bilaterally in the cingulate (BA 24), right ventral pons, left midbrain, and in the right parahippocampal gyrus.

Subtraction Analysis of Maximum Thirst. Cerebellar activity was also present at the point of maximum thirst. This activation, all in the posterior hemisphere, was in the left vermal uvula (X), in the right superior semilunar lobule (Crus I), and in the right quadrangular lobule (VI).

Wetting the Mouth During Maximum Thirst. Little cerebellar activity was detected shortly after the subjects had wet their mouth during maximum thirst. This activity, which was all in the right hemisphere, was concentrated in two foci, one each in the anterior (V) and posterior quadrangular lobule (VI).

Satiation of Thirst. The cerebellum was again strongly activated 3 min after drinking to satiation, when the thirst score had returned to baseline. Cerebellar activations accounted for 18% of the total extent of detected brain activation, more than in any other functional area (Fig. 2c). Indeed, the most intense activations detected in the brain was in the left anterior quadrangular lobule (VI) (-18, -57, -10; cluster size = 480 mm; $Z = 4.26$). Other left hemisphere cerebellar activations were present in the gracile lobule (VIb), fastigial nucleus, and the biventer posterior lobule (VIIIa). Right hemisphere cerebellar activity was focused in the biventer lobule (VIIIa) and the tonsil in the

Table 1. Local maxima in cerebellar regions demonstrating significant regional cerebral blood flow increases relative to rest ($P < 0.001$)

Lobule or region*	Hemisphere	Talairach coordinates†			Extent, mm ³	Z score
		x	y	z		
50% infusion [Na]						
Quadrangular (VI)	L Posterior	-12	-56	-14	432	3.60
Quadrangular (V)	R Anterior	20	-58	-22	528	3.52
Tuber (Vermis) (VIIAt)	R Posterior	2	-82	-32	384	3.40
Quadrangular (V)	R Anterior	18	-40	-20	160	3.26
Lingula (I,II)	L Anterior	-4	-40	-8	176	3.01
100% infusion [Na]						
Lingula (I,II)	L Anterior	-2	-42	-8	520	3.95
Quadrangular (VI)	L Posterior	-14	-58	-16	312	3.56
Tonsil (IX)	R Posterior	30	-40	-40	288	3.06
Quadrangular (V)	R Anterior	36	-50	-28	136	3.04
Pyramus (Vermis) (VIIIb)	R Posterior	3	-88	-28	288	3.04
Maximum thirst						
Uvula (Vermis) (X)	L Posterior	-2	-72	-36	304	3.80
Superior Semilunar (Crus I)	R Posterior	16	-60	-22	296	3.23
Quadrangular (VI)	R Posterior	18	-78	-22	296	3.17
Wet mouth						
Quadrangular (V)	R Anterior	8	-51	-33	264	3.19
Quadrangular (VI)	R Posterior	36	-58	-22	160	3.10
3 min after satiation						
Quadrangular (V)	L Anterior	-18	-57	-10	480	4.26
Biventer (VIIIa)	L Posterior	-30	-51	-33	336	3.65
Biventer (VIIIa)	R Posterior	16	-80	-38	104	3.24
Fastigial nucleus	L Anterior	-8	-46	-20	312	3.19
Gracile (VIIB)	L Posterior	-8	-66	-24	184	3.19
Tonsil (IX)	R Posterior	20	-60	-24	256	3.19
14 min after satiation						
Quadrangular (V)	R Anterior	10	-52	-6	328	3.27
Tonsil (IX)	L Posterior	-10	-54	-24	304	3.11
Biventer (VIIIb)	L Posterior	-40	-48	-44	240	3.11

R, right; L, left.

*In parenthesis is the equivalent anatomical label of Schmahmann *et al.* (22) [based on Larsell (23)].

†Brain atlas coordinates are in millimeters along left–right (x), anterior–posterior (y), and superior–inferior (z) axes.

posterior hemisphere (IX). This extensive cerebellar activation had subsided by 14 min after drinking to satiation. At this point, cerebellar activity accounted for 9% of the total extent of detected brain activation, with a focus each in the right anterior quadrangular lobule (V) ($Z = 3.27$), the tonsil in left posterior hemisphere (IX), and the left biventer lobule in the posterior hemisphere (VIIIb).

Deactivations. There were only a few deactivations in the cerebellum during the development and satiation of thirst, with the exception of the period of maximum thirst. At 50% of infusion, a small extent of the cerebellum was deactivated, with a focus each in the right anterior quadrangular lobule (V) ($Z = -3.71$), right fastigial nucleus ($Z = -3.37$), and the left anterior nodule (X) ($Z = -3.88$). At 100% of infusion, there were also a modest number of deactivations, with observed foci in the left gracile lobule (VIIB) ($Z = -3.59$), right tonsil (IX) ($Z = -3.02$), and the right fastigial nucleus ($Z = -3.45$). At maximum thirst, however, there were considerable deactivations. Foci were present in the left anterior quadrangular lobule (V) ($Z = -3.15$), the left flocculus ($Z = -3.21$), right central lobule (III) ($Z = -3.38$), and the right posterior quadrangular lobule (VI) ($Z = -3.32$). Cerebellar deactivations were present when the subjects wet their mouths during maximum thirst, with left hemisphere foci in the inferior semilunar lobule (Crus II) ($Z = -3.01$), the lingula (I, II) ($Z = -3.23$), and the flocculus (X) ($Z = -3.23$),

and right hemisphere foci in the anterior quadrangular lobule (V) ($Z = -3.09$) and the tonsil (IX) ($Z = -2.98$). Three minutes after drinking to satiation, only a few cerebellar deactivations were observed, with foci in the right anterior (V) and posterior quadrangular lobule (VI) ($Z = -3.55$, $Z = -3.00$), left anterior quadrangular lobule (V) ($Z = -3.35$), and the left central lobule (III) ($Z = -3.24$). Finally, 10 min after drinking to satiation, once more only a small extent of the cerebellum was deactivated. Foci were detected in the right anterior quadrangular lobule (V) ($Z = -3.45$), right inferior semilunar lobule (Crus II) ($Z = -3.23$), right central lobule (III) ($Z = -3.16$), and the left biventer lobule (VIIIb) ($Z = -3.02$).

Discussion

Considerable evidence has been reported here for the involvement of specific regions of the cerebellum in reacting to changes associated with the development and satiation of thirst. A large vermal region of anterior central lobule (III) was highly correlated with measures of subjective thirst. In addition, at the stages of 50 and 100% infusion of hypertonic sodium chloride producing moderate thirst, areas of the anterior and posterior quadrangular lobule (V, VI), lingula (I, II), and the vermis (VIIAt, VIIIb) were activated. Later, at the point of maximum thirst and then during irrigation of the mouth (without drinking), cerebellar regions were somewhat less activated. However, 3 min after drinking to satiation, the anterior quadrangular lobule (V) and

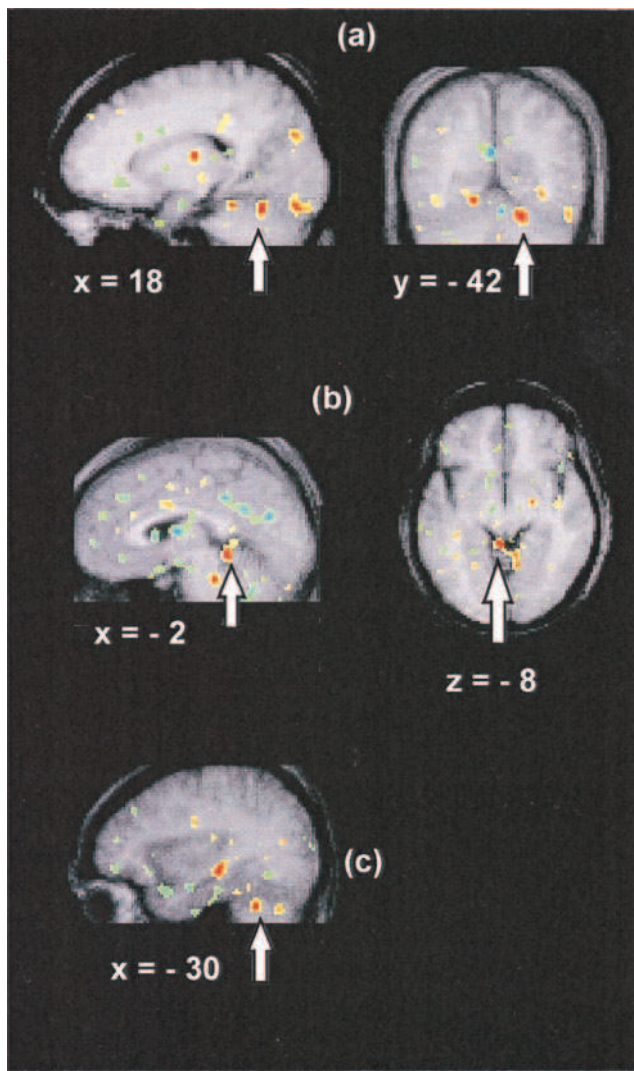


Fig. 2. PET activations displayed on the average MR brain image of the 10 subjects in which the initial resting nonthirsty state is compared with three conditions of thirst. *a* shows activation (arrow) in anterior quadrangular lobule (V) (coronal section $y = -42$ and sagittal section $x = 18$) when 50% of the hypertonic NaCl had been infused. *b* shows activation (arrow) in left lingula (I, II) (sagittal section $x = -2$ and axial section $z = -8$) when 100% of hypertonic NaCl had been infused. *c* shows activation (arrow) in the left posterior biventer (VIII B) (sagittal section $x = -30$) 3 min after drinking to satiation.

various posterior cerebellar areas (VI, VIIB, VIIIA, IX) were once more activated, before subsiding 10 min later. It is noteworthy that a recent PET study on hunger (21) observed responses in the lingula and quadrangular lobule, structures also active in response to thirst.

In summary, the focal activations in the cerebellum were fairly dispersed, occurring bilaterally and in several different lobules of the anterior and posterior hemispheres. However, we speculate that activations in the older cerebellar regions (vermis, fastigial nucleus, and archicerebellum) are more directly related to vegetative and affective aspects of the experience of thirst, whereas activity in neocerebellar regions (lateral hemispheres) are more related to the sensory and cognitive aspects of thirst and thirst satiation. This interpretation is consistent with recent analyses of cerebellar function on the basis of nonhuman and human neurophysiology, anatomy, neurology, and neuroimaging (2, 24).

We also note that strong cerebellar activity is present early in the development of moderate thirst and is especially strong for a short period after drinking to satiation. This pattern suggests that cerebellar responses increase with salient changes from nonthirst to thirst and, in turn, from thirst to thirst satiation.

It is important to observe that there was no overt motor activity occurring during the scan period. Indeed, there was no detected activity in motor areas of the cerebral cortex. The latter fact is also consistent with an absence of covert or preparatory motor activity (25). Thus, the present cerebellar responses do not appear to be related to the processing of motor information but rather to processing of another kind. This interpretation is consistent with the recent neuroimaging and neurological data described above implicating the cerebellum in sensation, cognition, affect, and hunger, as dissociated from motor behavior (2–12, 21).

Our data published earlier (19, 20) showed that the distributed pattern of activations and deactivations that occurred with maximum thirst was strongest in phylogenetically ancient areas of the cortex (anterior and posterior cingulate, insula, and parahippocampus) along with the thalamus, amygdala, and the midbrain. In conjunction with the present cerebellar data, in which activations are often observed in older regions of the cerebellum, our findings confirm that thirst, which is a vegetative function associated with primal emotion, is subserved by a distributed pattern of activations, with functional changes occurring primarily in phylogenetically ancient brain areas. These observations are thus consistent with the proposal that consciousness may have emerged phylogenetically with interceptor-initiated brain events, rather than distance receptor-initiated events (20).

Although our imaging data have revealed strong systematic cerebellar activation consequent to the development and satiation of thirst, we are hesitant to assign specific responsibility to the cerebellum for primary processing related to thirst. Increased cerebellar activity was not directly correlated with the increases in plasma [Na]. Neither dysfunction nor congenital absence of the cerebellum appears to compromise innate ingestive behaviors, including thirst (26). Moreover, imaging data in particular has increasingly implicated the cerebellum in a progressively wider variety of (nonmotor) tasks. Instead of assuming that the cerebellum has many different functions, it is more plausible, in view of the uniform microstructure of cerebellar tissue, to assume that the cerebellum has a narrow range of computations that can be applied generally to various kinds of neural information permitted by the anatomical connections (2, 26). If so, then the cerebellum is likely to be involved in an indirect way in the behavioral response to thirst.

One recent hypothesis of cerebellar function, which our laboratory has been exploring, is that the cerebellum performs a general support function for the nervous system as a whole (2, 3, 13): monitoring and adjusting the acquisition of sensory data. We have been examining cerebellar involvement in tactile and auditory processing and have accumulated evidence in both cases that the cerebellum may play a central role in regulating the sensory data on which computation in the somatosensory and auditory systems depends (2, 13, 27). Considered in this context, it is possible that the increased cerebellar activity observed here is related to the vigilant state of the nervous system in collecting pertinent sensory data under conditions of change in thirst status (i.e., thirst stress and satiation). The fact that cerebellar activations persist after thirst satiation is consistent with the proposal that the cerebellum is not involved in the calculation of thirst per se but instead is more reactive during periods when the brain is “vigilant” and is closely monitoring its sensory receptors. This interpretation is also consistent with recent imaging studies involving tactile sensory discrimination with the fingers (28). Further research is necessary to evaluate this account of cere-

bellar involvement in thirst. For example, research has not clearly elucidated either the sensory input to the cerebellar regions that respond during thirst or where those regions project to (e.g., thalamic, hypothalamic, or midbrain nuclei).

An alternative view is that the cerebellum is intrinsically involved in thirst because thirst is inexorably associated with the intention to drink, an intention closely related to expectations or plans for action, which in turn are associated with implicit or preparatory motor activity. This kind of hypothesis may be best exemplified with Ito's prominent motor cerebellar theory (29, 30). In this theory, the cerebellum is viewed as an error-driven, adaptive control mechanism that includes a model-building capacity. The theory has recently been broadened to include analogous functions in the (feedforward) control of concepts and ideas. In addition, this theory proposes that cerebellar microcomplexes (its structural and functional units), which are assumed to control compound movements adaptively in a changing environment, might also contrive adaptiveness in innate behavior that otherwise is stereotyped. The cerebellar microcomplexes are thought to form an internal model representing the dynamic properties of the musculoskeletal system that is controlled by the motor cortex. Analogous to this, cognitive operations may involve the prefrontal cortex acting on ideas and concepts encoded in the parietal and temporal cortices, under regulatory influences from the limbic system, cerebellum, and the basal ganglia. In this context, cerebellar involvement in thirst may be related to the intention to drink, inextricably interwoven in the subjective state of thirst, together with a conscious state oriented toward satiation of a desire.

A more direct cerebellar involvement in thirst is perhaps suggested by research on the involvement of the cerebellum in visceral activities. One line of study has produced a variety of reports of visceral responses in human and nonhuman species to cerebellar stimulation or lesion. In light of the reciprocal con-

nectivity between the cerebellum and hypothalamus, these findings have led to suggestions that the cerebellum is proactively involved in regulating a wide range of visceral functions and that, in turn, the hypothalamus may directly modulate cerebellar nuclei or cortical neurons (16). Furthermore, it has been shown that many aggressive monkeys become docile after midline cerebellar lesions (31). A related hypothesis is suggested by other findings from nonhuman stimulation or lesion studies. These data suggest that the cerebellar fastigial nucleus is involved in widespread autonomic, metabolic, and behavioral control, independent of motor control (32). Without eliciting any motor behavior in awake unanesthetized animals, electrical stimulation of the fastigial nucleus elevates arterial pressure, releases vasoactive hormones, and modulates systemic circulation, regional cerebral blood flow, and glucose metabolism, as well as eliciting consummatory behavioral and other autonomic events. This pattern of results is consistent with the possibility that the cerebellum receives information from many elements of the primary autonomic areas, including the amygdala, hypothalamus, periaqueductal gray, and parabrachial and solitary nuclei. This transmitted information would appear to include not only feedback signals from viscera relayed via primary visceral afferents, but also information about how visceral inputs are integrated at higher centers into autonomic and associated behaviors. In conclusion, although our results clearly affirm the involvement of the cerebellum in thirst, much further research is necessary to clarify the exact nature and function of that involvement.

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