

Functional Imaging of the Deep Cerebellar Nuclei: A Review

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Abstract The present mini-review focused on functional imaging of human deep cerebellar nuclei, mainly the dentate nucleus. Although these nuclei represent the unique output channel of the cerebellum, few data are available concerning their functional role. However, the dentate nucleus has been shown to participate in a widespread functional network including sensorimotor and associative cortices, striatum, hypothalamus, and thalamus, and plays a minor role in motor execution and a major role in sensorimotor coordination and learning, and cognition. The dentate nucleus appears to be predominantly involved in conjunction with the neocerebellum in executive and affective networks devoted, at least, to attention, working memory, procedural reasoning, and salience detection.

Keywords Deep cerebellar nuclei · Dentate nucleus · Neocerebellum · Functional imaging

Introduction

The deep cerebellar nuclei (DCN) (with the vestibular nucleus) constitute the unique source of cerebellar outputs. The fastigial (FN), globose/emboliform (GEN), and dentate nuclei (DN) receive inhibitory GABAergic projections from Purkinje cells of the vermis, paravermis, and lateral part of the cerebellar hemispheres, respectively, and sometimes send back fibers to the cerebellar cortex [1, 2]. These nuclei are also innervated by excitatory collaterals of mossy fibers

and climbing fibers derived from the bulbar olivary nuclei. The mossy-fiber influence on DCN firing appears to be weaker than the climbing-fiber influence. Despite the pivotal role of these nuclei, only very few results are available for functional imaging of the DCN, including PET scan and MRI techniques, and most of these data concern the DN. This lack of data is due to a number of reasons.

First, the human DCN mainly comprise the large, widespread, and easily identifiable DN which has a marked low-intensity signal on MRI T2*-weighted sequences and is clearly distinguished from the adjacent cortical structures. In contrast, FN and GEN are very thin and are both located very close to the gray matter of lobules VIII and IX, while these nuclei are situated on the medial aspect of the DN. Therefore, even with the help of an atlas, it is difficult to delineate the respective activation of the DCN.

Second, due to the low spatial resolution of functional images and the small size of FN and GEN, partial volume effects may have contributed to mislocation of nuclear activation.

Third, activation of these small nuclei may be too weak to be detected with a statistically significant threshold. This situation must be frequent since, as mentioned above, DCN are the sole cerebellar output channels. It is noteworthy that many studies dealing with the neocerebellum did not report any implication of DN either because they remained silent or because their activation remained undetectable. Moreover, DCN activation must be interpreted cautiously, as it has been demonstrated that activations recorded in BOLD-fMRI correspond to synaptic and dendritic processing rather than to spiking [3]. This also appears to be the case when labeled deoxyglucose (DG) is used in PET scan. In the cat, [¹⁴C]2-DG labeling corresponded to activated excitatory and inhibitory synapses [4]. DCN activation

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may therefore reflect a combination of inextricable macroscopic neuronal events, such as mossy, climbing or Purkinje inputs, and local dendritic postsynaptic processing, spiking, hyperpolarizing, or rebound spiking [5, 6], although this last possibility remains controversial *in vivo* [7]. Interestingly, rebound activation could be linked to synaptic plasticity. Consequently, DCN activation or the lack of DCN activation must be interpreted with caution, especially as plastic synaptic changes may occur in the cerebellum, especially during learning and may modify the synaptic weight and correlative neurovascular response at this level.

Fastigial and Globose/Emboliform Nuclei

Very few results are available for these nuclei that are mostly activated concomitantly with DN activation. FN was activated during *adiadochokinesis* in relation to task complexity or postural adjustment [8], thirst satiation [9], and with Vasalva maneuver [10], whereas GEN showed increased activity during sequential distal movements [11]. The three DCN are recruited in response to forced expiratory loading in congenital central hypoventilation syndrome [12] and perceived pain intensity [13]. FN and GEN are therefore at least involved in controlling voluntary and automatic movements.

Dentate Nucleus

This nucleus is predominantly recruited during complex motor, sensorimotor, and cognitive tasks (Table 1).

Motor Function Very weak DN activation is detected when simple digit movements are performed such as index finger-thumb opposition. When present, this activation accompanied self-initiated and externally triggered movements with a predominance for the latter [14]. However, DN is strongly activated during sequential movements of fingers and tongue [11], drawing/copying lines [15], coordinated eye/hand tracking movements [16, 17], and *adiadochokinesis* [8]. This activation is also observed when intentional eye movements such as optokinetic nystagmus and saccades are executed [18], and when no sensory feedback is present, as during pansensory neuropathy [19]. All these DN activations were ipsilateral to the movement and Dimitrova et al. [11] detected activation in the more ventro- and dorso-caudal parts of DN. Lutz et al. [20] demonstrated preferential activation of the DN when subjects paced their tapping with irregular stimuli rather than with regular stimuli. In contrast, Masuzawa et al. [21] reported DN activation during visual cue-synchronized and cue-delayed button depression. These data indicate a role of the dentate nucleus in attention to the stimuli needed to initiate and adjust the motor response, and in intentional motor

initiation. Decreased BOLD signal in DN was shown to parallel reduction in motor error during position- and velocity-dependent torque perturbation of arm movements [22]. DN is more strongly activated for low-rate movements than for high-rate movements [23]. DN activation therefore appears to be correlated with voluntary coordination of slow elementary movements or motor correction, with and without sensory control. In particular, DN activation increases with increasing length and complexity of finger movement sequences [24]. Hyperactivation of DN was also observed in patients with palatal myoclonus [25] and was due to bulbar olivary driving. Thus, DN ipsilateral to the movement is preferentially recruited during polymodal cue-guided and cue-timed, non-ballistic, complex motor activity requiring attentional and intentional executive control.

Motor Procedural Learning The DN and cerebellar cortex are also involved in motor or visuomotor skill learning, i.e., procedural motor memory. However, controversial results have been obtained concerning temporal variation of the DN activation profile. Most studies divided the learning process into (early) short-term and long-term phases. The most common pattern of DN and cerebello-cortical activity consisted of strong activation during the early phase, followed by a progressive reduction of activation during the last phase, in relation to practice improvement, while subjects performed 2D trajectorial movements [26], sequential finger movements [27–30], and visuomotor tasks [31–33]. On the contrary, Flament et al. [35] observed no reduction in DN activation during the whole visuomotor learning process and Doyon et al. [36] noted DN activity in the highly learned sequence condition. During a sensorimotor task, Nezafat et al. [37] demonstrated that, after an initial decrease, DCN activity increased with reduction in motor error while the cerebellar cortex activity decreased. Debaere et al. [38] also reported a learning-related increase in DN activation during complex cyclical bimanual movements. Interestingly, the switch from short-term to long-term learning was frequently followed by a subcortical switch from the cerebellar system to the striatal system [39], and from the cerebellar anterior lobe to the posterior lobe [40]. However, transitory activation of the posterior lobe (lobule VI) was also recorded at the early phase [31–33]. The posterior lobe recruitment has been attributed to timing of movement [14] or sensorimotor transformation [40]. It ensues that DN is involved in implicit and explicit skill learning, probably in relation to motor error detection and correction, sensory guidance of movements in the early phases, in conjunction with the cerebellar cortex, and in automation in the late phases, but the pattern of dentate activation appears highly task-, complexity-, and time-dependent. The reduction of DN activity could also be ascribed to decreased presynaptic activity of axons arising

Table 1 Complex motor, sensorimotor, and cognitive tasks

Reference	Imaging modality	Task	ND activation
Motor			
8	1.5 T-MRI	Unimanual and in-phase and antiphase bimanual prono-supination	R, B
11	1.5 T-MRI	Sequential finger movements, repetitive tongue and foot movements	R
14	1.5T-MRI	Different, self-initiated and externally triggered (at different rates) sequential movements performed with the left hand	B
15	PET	Sequence of finger movements, line drawing and line copying	R
16	2 T-MRI	Sensorimotor procedure: keeping a joystick trajectory as close as possible to a moving target two populations: a sleeping group and a sleep-deprived group	L
17	3 T-MRI	Visually guided tracking of a moving circle requiring varying degrees of eye–hand coordination	B
18	MRI	Horizontal optokinetic nystagmus and saccades	
19	PET	Auditory-paced finger movements with and without visual feedback	R
20	1.5 T-MRI	Right index finger tapping in synchrony with regular and irregular visual stimulus	R
21	3 T-MRI	Keypresses with synchronous and delayed visual feed-backs	
22	1.5 T-MRI	Arm movement during random position- or velocity-dependent torque perturbation	R
23	1.5 T-MRI	Force production of the right index finger	R
24	MRI	Right finger sequences of increasing length and complexity	R
Motor procedural learning			
26	PET	Writing (letters and) ideograms before and after practice	R
27	PET	Brisk sequential finger to thumb opposition	
28	PET	Learning of sequences of keypresses by trial and error	
29	PET	Learning of sequences of externally paced keypresses	B
30	3 T-MRI	Sequence of finger movements (eight pseudorandom moves) over a month training using the left hand	B
31	PET	Visuomotor sequence learning	R
32	3 T-MRI	Visual tracking of a moving target by varying the isometric force applied to a pressure plate held in the right hand	R
33	3 T-MRI	Sensorimotor task requiring variable isometric force development between the fingers and thumb of the right hand in predictable and continuous manner	R
34	PET	Writing ideograms	R
35	4 T-MRI	Superimposing a cursor onto a target while the relationship between movement of the joystick and cursor was reversed	R
36	1.5 T-MRI	Random and predictable sequences of finger movements	R
37	PET	Right arm movements in a random and learnable force field	R
38	MRI	Cyclical flexion-extension movements of both hands with a phase offset of 90°	B
41	3 T-MRI	Continuously maintaining the force level developed between right, middle finger and thumb to a target force level on a video screen or to remembered force level	R
Sensory			
42	PET	Tactile discrimination of rectangular parallelepipeda with the right hand	R
43	1.9 T-MRI	Passive and active tactile discrimination	B
44	MRI	Passive and active tactile discrimination	R
45	1.5 T-MRI	Tactile exploration of parallelepipeds with the right hand, and comparison of object pair	B
Cognition			
46	4 T-MRI	Procedural reasoning: moving pegs with the right hand on a pegboard using (1) simple rules (visually guided task) and (2) complex rules (insanity task)	1. R 2. B
47	1.5 T-MRI	1. Verbal working memory: number sequence learning 2. Planning task: virtual navigation through a labyrinth	1. B 2. R
48	1.5 T-MRI	Visual working memory	B
49	1.5 T-MRI	Verbal working memory	
50	1.5 T-MRI	Self-agency: self-generated voice versus passive speech listening	B
51	1.5 T-MRI	Semantic analysis: judgement about synonymy of presented words	L

R right, L left, B bilateral

from Purkinje cells, decreased activation of mossy fibers required to activate DN neurons, and transfer of commands from the DN to another neural system such as the sensorimotor striatum or cerebral cortex. It has been hypothesized that intense activation of the DN in the late phase of practice relied on the implicit learning when subjects did not know the embedded sequence being learned. Although DN activation was ipsilateral to the movements to be learned, Lehéricy et al. [30] reported bilateral cerebello-cortical activation and transient contralateral DN activation, suggesting time-dependent transfer of information within the cerebellar cortex and between the cerebellar cortex and the DN. During the learning process, the DN, initially in collaboration with neostriatal loops, appears to at least transiently participate in elaborating a motor representation, probably in relation to the skill, [39] which is subsequently under the dependence of sensorimotor striatal loops. DN activation observed during rehearsal of motor sequences could result from context-related adjustments of the mnemonic trace without ruling out a direct role of the dentate nucleus in this trace storage. Enhancement of functional correlations between DN and the superior temporal sulcus was observed during a visuomotor task and after sleeping showing learning- and sleeping-related and durable dentate functional reshaping and coupling [14].

Sensory Functions In addition to this role of the DN in motor performance and learning, this nucleus is also involved in tactile discrimination of object size [42] or relief [43]. It is noteworthy that passive sensory discrimination without finger movements significantly recruits DN [43, 44]. It has therefore been proposed that DN in conjunction with the lateral hemisphere of the cerebellum and the red nucleus plays a role in sensory acquisition rather than motor control. However, it could be argued that during active tactile discrimination, a tight and reciprocal coupling exists between: (1) finely coordinated, exploratory finger movements in order to actively reposition the tactile sensory surface of the fingers, (2) haptic inputs generated by these movements, and (3) sensory anticipations during the progressive elaboration of object mental representation. It is also noteworthy that DN is implicated in sensory motor transformations such as grip force control with visual feedbacks [40]. Principal component analysis of a fMRI study devoted to tactile object discrimination ascribed DN activation to perception of specific information and short-term memory processes, perceived dilemma of indistinguishable objects and to explicitly perceived discrimination [45]. DN activation may reflect complex motor coordination, sensory inputs as well as more cognitive functions such as attention, working memory, or executive control. Dietrich et al. [18] showed that dentate activity was

associated not only with ocular motor control but also with change in attention.

Cognitive Functions Kim et al. [46] found that the dentate nuclei were fourfold more intensely activated during attempts to solve a pegboard puzzle than during simple movements of the pegs. DN activation was found in the medial and dorsal parts of the nucleus ipsilateral to the moving arm and in the caudal part of the nucleus contralateral to the moving arm. This bilateral activation was partly ascribed to the visual guidance of arm movements. However, only the central region of DN was examined in this study. DN is also involved in planning tasks such as virtual navigation through a labyrinth [47] and in verbal working memory [47–49]. Küper et al. [47] recorded ventrocaudal activation of DN ipsilateral to the moving hand during both motor and cognitive tasks, and bilateral DN activation during cognitive tasks. Thus, dentate activity is strongly modulated by cognitive factors such as the attentional load, holding relevant information on-line and the procedural complexity of the task. DN constitutes a subcortical relay of a parietofrontal network devoted to dissociation between other/self in language, in other words to self-agency [50]. DN was also recruited during a semantic task consisting of identifying synonyms amongst a list of words [51]. The DN is assumed to be involved in a circuit comparing intended/expected and actual consequences of a mental act and evaluating their degree of discrepancy in all domains: perception, action, language, or cognition.

Furthermore, functional connectivity has allowed identification of cerebral areas functionally and anatomically related to the DN. Briefly, this method is based on temporal correlations between spontaneous, low-frequency (0.01–0.1 Hz) BOLD fluctuations between remote but functionally related brain areas at rest [52, 53]. Using a region-of-interest analysis, Allen et al. seeded the DN and found functional coherence between these nuclei and: (1) prefrontal, cingulate, insular, precentral, inferior parietal, and occipital cortices; (2) thalamus; (3) striatum; (4) hypothalamus; and (5) anterior and posterior cerebellum [54].

Habas et al. [55] explicitly investigated the role of the neocerebellum in several previously defined intrinsic connectivity networks (ICNs) involved in canonical cognitive functions such as memory, executive function, and salience detection. They applied independent component analysis to the resting-state data and used an unbiased template-matching procedure to identify the ICNs amongst the individual ICA maps: the executive control network, the salience network (dealing with interoceptive and emotional information), the default-mode network (dealing with episodic and semantic memories, stream of consciousness,

self-reflection), the motor network and group analysis. The DN was explicitly present in the sensorimotor and salience network. However, as the DN represents the sole neocerebellar output, it could be inferred that it also takes part in the executive control network and the default-mode network in relation to lobule VII (crus I and II) and lobule IX, respectively. These functional results are in line with human structural data based on tractography showing cerebellar projections from the dentate nucleus to prefrontal and posterior parietal cortices [56, 57]. More generally, these results strongly agree with and support the emerging concept of cerebellar contribution to higher function mainly based upon: (1) histological studies tracing in monkey afferents to the cerebellum from associative cortex [58] and to prefrontal cortex [59] and dentate efferents to prefrontal and parietal cortices [60]; (2) functional imaging studies showing activation of the cerebellar cortex during executive, visuo-spatial, linguistic, and emotional tasks [61]; and (3) clinical data showing cerebellar morphological abnormalities in psychiatric disorders [62] and the existence of a specific cerebellar cognitive and affective syndrome caused by focal cerebellar lesions in adults [63] and in children [64]. Therefore, the neocerebellar cortex and the dentate nuclei predominantly take part in cortico-neocerebellar loops involved in cognitive and emotional regulation. As aforementioned, whenever the cognitive condition was contrasted with the motor condition [43, 46], the strongest DN activation was observed during the cognitive task. Thus, DN in conjunction with the neocerebellum, especially lobule VII, appears to be preferentially recruited by higher executive functions.

Anatomofunctional Parcellation The ventrocaudal [47] and mediocentral [46] parts of DN are predominantly involved in cognitive functions whereas its dorsomedial part [46] is involved in motor function. These results are in keeping with histological data [60] showing in monkey projections from the dorsal, caudal, and ventral parts of DN to (pre-) motor, frontal eye field, and prefrontal (areas 9 and 46) cortices, respectively. However, overlaps between cognitive and motor domains exists in DN [47], especially in its caudal pole [11]. The rostral pole of DN has not been specifically investigated. It can be postulated that these overlapping domains may constitute an integrative interface between executive and motor inputs to DN and issued from mossy and climbing fibers and Purkinje cell axons. As aforementioned, whenever the experimental task included unilateral movements, activations were detected in DN ipsilateral to the moving arm/hand. In three studies, unimanual haptic discrimination [45], verbal working memory [47] and motor learning [29] tasks, however, yielded bilateral DN activation, possibly, in relation with

lateralized and specialized cognitive circuits such as left (verbal/syntactic) and right (visuo-spatial/holistic) executive control networks [55].

Conclusion

These findings raise several comments: (1) most of the functional imaging results about the cerebellar nuclei concern the dentate nucleus and showed that, as the neocerebellar cortex, this nucleus is preferentially involved in sensorimotor (exploratory movements), procedural memory such as motor skill acquisition, emotional and cognitive functions due to its interconnections with the sensorimotor and associative cortices; (2) only weak activation is observed during motor activity (complex and coordinated movements), with rather than without sensory feedback; (3) the strongest activation of the dentate nucleus occurs during cognitive tasks; (4) recruitment of deep cerebellar nuclei is underestimated by functional imaging techniques because of the low-spatial resolution (and low magnetic field for fMRI), partial volume and statistical thresholding; and (5) the physiological interpretation of macroscopic nuclear activation remains unclear as these nuclei receive multiple convergent inputs from extra- and intracerebellar sources.

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