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Time perception in children treated for a cerebellar medulloblastoma

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A B S T R A C T

The aim of the present study was to investigate temporal abilities in children treated by surgery for a malignant tumor in the cerebellum. Children with a diagnosed medulloblastoma and age-paired control children were given a temporal discrimination task (bisection task) and a temporal reproduction task with two duration ranges, one shorter than 1 s and the other longer than 4 s. The motor and cognitive capacities of these children were also assessed by a battery of age-adapted neuropsychological tests. The results did not show any significant difference in performance between the children with or without cerebellar lesions in the temporal discrimination task. It was only in the temporal reproduction task that the children with cerebellar lesions reproduced longer and more variable durations than the other children, but only for the short stimulus durations ($\leq$1 s). In addition, a hierarchical regression analysis revealed that the best predictor of variance in temporal performance was a significantly lower processing speed in children with cerebellar lesions in comparison to their controls. These results indicated that the major cause of deficits in temporal judgments in children with cerebellar lesions was due to their inability to reproduce accurately short temporal intervals in association with low processing speed, rather than to a specific deficit in the perception of time.

1. Introduction

One of the main causes of acquired cerebellar deficits in children is represented by posterior fossa tumors, medulloblastoma being the most frequent one. Medulloblastoma is a malignant brain tumor that originates in the cerebellum due to deficiencies in the dividing and differentiating processes of cerebellar stem cells into their normal cell types (von Hoff et al., 2010). Medulloblastoma is generally diagnosed before the age of 5 years (40%) or between 5 and 9 years (31%). Children with medulloblastoma are usually treated with excision of the tumor in the cerebellum followed by radiotherapy and/or chemotherapy. Quality of life of the survivors is significantly impaired, cognition in the healthy range

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being reported as impaired by the survivors and their family (Ribi, Landolt, Alber, Bolsthauszer, & Grotzer, 2005; Rutkowski et al., 2010). There is also an impairment of fine motor skills, as for adult patients with cerebellar damage (Ribi et al., 2005). Children with lesions of the cerebellum obtain low scores in the Purdue Pegboard test (PP) (Tiffin, 1948) used to assess manual dexterity (Callu et al., 2008; Grill et al., 2004; Puget et al., 2009). Recently, Puget et al. (2009) showed that the degree of dysfunction in coordination of fine movements measured by the PP test was directly correlated to the extent of injury to both dentate nuclei and inferior vermis, irrespective of other risk factors such as the age at diagnosis or the interval since radiotherapy. Motor deficits seem thus to be a major consequence of postoperative injury to the cerebellum in children as expected given the critical role of the cerebellum in motor control (Holmes, 1939).

Apart from motor deficits, children with medulloblastoma also exhibit poor performance in numerous cognitive tasks. After the excision of a cerebellar tumor, there is a decline in intellectual functions as revealed by low scores on different neuropsychological tests assessing working memory, processing speed, and attention/concentration (Callu, Viguier, et al., 2009; Lafay-Cousin, Bouffet, Hawkins Amid, Huang, & Mabbott, 2009; Puget et al., 2009; Ribi et al., 2005; Silverman et al., 1984). Among the different cognitive deficits, one may expect that children with medulloblastoma would also have difficulty within the perception of time, as the cerebellum is thought to be critically involved in time perception, at least in the sub-second range. Since the pioneering work of Braitenberg (1967), there is a debate as to the specific involvement of the cerebellum in time perception of human adults. Ivry and Keele (1989) observed that patients with cerebellar lesions were impaired in a timing task requiring the motor production of a regular rhythm (tapping task). This is consistent with the traditional view that the cerebellum is involved in the implementation and execution of motor responses, such as rhythmical activity during locomotion or speech. However, Ivry and Keele (1989) succeeded in extracting a temporal component (clock) from the motor component in the tapping behavior. Doing so, they showed that lesions in medial regions of the cerebellum impaired motor execution, whereas lesions in lateral regions of cerebellum impaired the timing process per se. In the same line, Malapani, Dubois, Rancurel, and Gibbon (1998) showed that patients with a focal mesial lesion that includes the vermis ($N = 5$) were not impaired in perceptive timing, whereas those with a lesion restricted to lateral parts of the cerebellum ($N = 3$) showed poor temporal judgment. Imaging studies using positron emission tomography (PET) (Jueptner et al., 1995) or functional magnetic resonance imagery (fMRI) (Smith, Taylor, Lidzba, & Rubia, 2003; Tracy, Faro, Mohamed, Pinsk, & Pinus, 2000) in healthy adults also provide results consistent with those found in patients with cerebellar damage. Activation of the medial parts of the cerebellum including the vermis was observed in different temporal and non-temporal tasks, but the cerebral hemispheres were specifically activated in the temporal task. Other studies using repetitive transcranial magnetic stimulation (rTMS) showed that stimulation of the lateral part of cerebellum also interfered with the encoding of time (Fierro et al., 2007; Koch et al., 2007; Lee et al., 2007). However, the localization of cerebellar structures involved in timing is not so clear. One study using a temporal reproduction task localized the neural substrates of time in the left lateral part of cerebellum (Koch et al., 2007), another using a temporal discrimination task in the right lateral (Fierro et al., 2007), and a third in both the medial and the lateral parts (right and left) of the cerebellum (Lee et al., 2007). Despite these conflicting results, according to these studies, the cerebellum appears to play an important role in timing beyond its simple role in motor control. Several authors therefore concluded that the cerebellum may be the locus of an internal clock (e.g., Keele & Ivry, 1990).

However, the function of cerebellum as internal clock is still debated. First, the activation of the cerebellum has not been systematically observed in imaging studies irrespective of the temporal tasks used (e.g., Macar et al., 2002; Maquet et al., 1996). For example, in an fMRI study, Rao, Mayer, and Harrington (2001) observed that the activation of the cerebellum, especially the vermis, happened just before or during the movement execution suggesting an involvement in processes other than explicit timing. In addition, there is a growing body of evidence suggesting that the cerebellum does not play a role in representation of all duration ranges, but only in the representation of sub-second durations (Ivry, Spencer, Zelaznik, & Diedrichsen, 2002; Penney & Vaitilingam, 2008; Wiener, Turkeltaub, & Coslette, 2010). Recent studies using rTMS showed that the cerebellum was required for accurate millisecond timing while it was not essential for longer interval timing (Fierro et al., 2007; Koch et al., 2007; Lee et al., 2007). This raises the question of why the cerebellum would be involved in the processing of durations in the milliseconds range and not those of several seconds, both being discriminable temporal values. Lewis and Miall (2003) argued that the cerebellum, as the sensory-motor areas (supplementary motor area, sensory-motor cortex) is specifically recruited in tasks involving only sub-seconds intervals defined by movement (e.g., rapid paced finger tapping). Harrington, Lee, Boyd, Rapcsak, and Knight (2004) go even further and cast doubt on the proposal that the cerebellum is the center of a time keeping mechanism that is common for all temporal tasks. Indeed, in their study on the consequence of cerebellar lesions, they did not observe any impaired temporal performance whatever the localization of the lesion and reduction in volume. Only a greater temporal variability occurred in some subjects that seemed related to other cognitive processes (namely a slowing down in processing speed), rather than to specific temporal processes. They thus concluded that it is not necessary to cast a hypothesis in terms of timing to account for the role of cerebellum in the timing of motor programs. The role of cerebellum would be thus in timing of action but not in the perception of time per se.

Until now, the majority of the studies on the cerebellum and timing have been conducted with adult subjects. Given the high prevalence of cerebellar insults in children and the interaction that timing processes may have with general cognitive development, it is critical to have a better understanding of the timing capabilities in children with cerebellar lesions. Only three studies have investigated time perception in children with cerebellar damage (Dennis et al., 2004; Hetherington, Dennis, & Spiegler, 2000; Mostofsky, Kunze, Cutting, Lederman, & Denckla, 2000). Mostofsky et al. (2000) and Dennis et al. (2004) have tested temporal discrimination tasks with children and adolescents with a degeneration of the cerebellar cortex