CHAPTER 9

Timing in the Cerebellum and Cerebellar Disorders

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1 Introduction

Over the past century, the function of the cerebellum was largely assumed to be that of movement coordination. This assumption, along with its geographic segregation from the cortex, led the cerebellum to be overlooked in many early neuroimaging studies. Yet the cerebellum contains roughly 10% of the brain’s mass (Hutchinson et al., 2003; Swanson, 1995). Perhaps more striking, the cerebellum contains 65–75% of the total neurons of the brain (Herculano-Houzel, 2010). In other words, for every one cortical neuron there are three to four cerebellar neurons. Moreover, neurons of the cerebellum are uniquely arranged into arrays of neural loops. These loops repeat millions of times throughout the cerebellum, and are arranged into lobules. Those lobules are, in turn, composed of folia, structures reminiscent of the fractalian structure of a tree or cauliflower (Voogd and Glickstein, 1998). Thus, the cerebellum is architecturally unique and capable of performing a redundant computation. It has been proposed that the computation performed by the cerebellum is that of timing (Braitenberg, 1983; see review in Spencer and Ivry, 2013).

2 Timing in Cerebellar Ataxia

In humans, focal cerebellar damage is rare. While a hemorrhagic stroke to the cerebellum is particularly rare, ischemic stroke, the more common cerebellar stroke, nonetheless accounts for only 1–7% of all strokes (Bogousslavsky, Van Melle, and Regli, 1988; Macdonell, Kalnins, and Donnan, 1987; Vemmos et al., 2000). Other focal cerebellar lesions, due to tumors and tumor resection, are also uncommon particularly in adults.

Cerebellar atrophy that typically results in widespread cerebellar damage can arise in a number of ways. Genetic degenerative diseases, primarily spinocerebellar ataxia (SCA), that affect the cerebellum are heterogeneous. SCA is a

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group of autosomal dominant neurodegenerative disorders, many of which result in cerebellar degeneration. Prevalence estimates of SCA vary from .3 to 3 per 100,000 (van de Warrenburg et al., 2002). Moreover, of the approximately 30 different SCA subtypes (Schols et al., 2004), only a handful have a primarily cerebellar focus (e.g., SCA 6, 8, 15/16; Durr, 2010; Marelli et al., 2011). Of the degenerative cerebellar disorders, sporadic idiopathic cerebellar atrophy may have the greatest prevalence, estimated to have a prevalence rate of 8.4 per 100,000 (Muzaimi et al., 2004). Sporadic cases of cerebellar agenesis have also been reported (e.g., Glickstein, 1994; Macchi and Bentivoglio, 1977; Nowak, Timmann, and Hermsdorfer, 2007; Velioglu, Kuzeyli, and Ozmenoglu, 1998). Surprisingly, in many of these cases, motor performance is largely normal, suggesting possible compensatory mechanisms (for a review see: Glickstein, 1994; Macchi and Bentivoglio, 1977).

Seminal neurologists, Joseph Babinski and Gordon Holmes, are both credited for the earliest reports of the deficits associated with cerebellar damage in humans (Holmes, 1939, 1917; Trouillas et al., 1997). Babinski and Holmes described core symptoms associated with damage to the cerebellum – such as slurred speech, unsteady gait, and incoordination – and collectively referred to these as ‘cerebellar syndrome’. Holmes, studying survivors of gunshot wounds to the back of the head in World War I, came to use the term ‘ataxic’ to specifically describe the movements of individuals with cerebellar syndrome. Ataxia remains the commonly used term to describe the movements associated with cerebellar disorders. Ataxia is broadly characterized by postural deficits, impairments in upper and lower limb movements, speech impairments, and oculomotor dysfunction (Trouillas et al., 1997). However, the array of symptomatology varies according to localization and extent of damage (Dichgans and Diener, 1984).

There is evidence that the montage of symptoms associated with cerebellar ataxia is due to impaired timing. Most prominently, atactic movements are uncoordinated. It has been suggested that the lack of coordination between muscles is due to increased time and temporal variability of muscle initiation for individual sub-movements (Day et al., 1998). Upper and lower limb ataxia is also marked by intention tremor, dysmetria, and dysdiadochokinesis on a clinical exam. Unlike the resting tremor that visibly marks Parkinson’s disease, intention tremor is not observed at rest; rather, it is most obvious at the endpoints of visually-guided movements. Intention tremor contributes to dysmetria. Dysmetria is the tendency to overshoot or undershoot a target such as the physician’s finger. This, too, may be the result of impaired timing, in this case there is a breakdown in the timing between agonist and antagonist muscle contractions composing the movement (Flament and Hore, 1986). Impaired