CHAPTER 8

Timing in Neurogenerative Disorders of the Basal Ganglia

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1 Introduction

Time is an integral facet of behavior that structures our perceptions, experiences, and memories. Although there is no clinical disorder that is specifically characterized by timing disturbances, some are known to alter certain interrelated cognitive functions, such as planning. A host of neurological and psychiatric diseases that affect basal ganglia, cerebellar, and cerebral cortex functioning affect timing within the scale of tenths of milliseconds on up to seconds or even minutes. As such, there has been a lively debate over the neural sources of temporal processing deficits in various disease processes. Presently, there is substantial support for the centrality of the striatum and dopamine neurotransmission in explicit timing (Balci et al., 2012; Hohn et al., 2011; Lake and Meck, 2012; Meck, 2006a,b; Rammsayer, 1993). This chapter discusses timing disturbances in two disorders of the basal ganglia in which dopaminergic functioning is decreased, namely Parkinson’s disease (PD) and prodromal Huntington disease (HD). There is a growing interest in these disorders since temporal processing deficits contribute to the breakdown in the spatiotemporal organization of movement in PD (Vercruysse et al., 2012) and timing ability is a marker of proximity to a diagnosis of manifest HD (Harrington et al., 2012; Rowe et al., 2010). This chapter places an emphasis on functional imaging investigations of timing disturbances in PD and prodromal HD, as this has received little attention in the literature to date. To set the stage for our discussion, we first review two influential timing models that underscore the crucial roles of key component processes and neurophysiological mechanisms. The framework provided by these models, together with advancements in neuroanatomical connectivity, has guided research into the

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neurocognitive mechanisms of timing and its breakdown. We then give an overview of timing disturbances in PD and the effects of dopamine therapy, followed by research into prodromal phases of HD. This section is not intended to provide a thorough treatment of this topic as there are several excellent, recent reviews of temporal processing disturbances in PD (Allman and Meck, 2012; Koch, Oliveri, and Caltagirone, 2009). We then discuss emerging functional imaging research, which is beginning to reveal brain circuits that govern timing deficits in these disorders. Lastly, we consider the clinical relevance of temporal processing dysfunction in these diseases and future avenues for research.

2 Models of Timing

We lead with a brief description of two influential models that have driven research in neurologically intact adults and in clinical disorders of temporal processing. The information processing model has provided a strong framework for studying component processes of interval timing, which can have distinct effects on timing accuracy and variability. In contrast, a leading neurophysiological model delineates the physiological and neuroanatomical properties of timing networks, thereby fostering an understanding of the functional significance of abnormalities in corticostriatal networks that underlie timing disturbances.

2.1 Information Processing Model

Over the last two decades there has been an explosion of research into the neuroanatomical underpinnings of interval timing in disorders of the basal ganglia. Initially, a driving force behind much of this work was scalar expectancy theory (SET; Gibbon, 1977; Gibbon, Church, and Meck, 1984), which defined sources of timing variability that were derived from clock, memory, and decision processes (Figure 8.1A). Empirical findings in pharmacological and lesion studies in animals further suggested that the clock process depended on dopamine neurotransmission and the striatum (Buhusi and Meck, 2002; Maricq and Church, 1983; Meck, 1996). In SET, timing is implemented via a pacemaker mechanism, which represents time through the accumulation of pulses. Pulses are turned on and off by a mode switch and then passed onto an accumulator to be counted. Perceived duration is intimately related to the interplay between the pacemaker and the level of attention given to the passage of time. Attention affects the mode switch, which controls the flexible starting and stopping of pulses from the pacemaker, thereby enabling