Available online at www.sciencedirect.com
SCIENCE DIRECT®
Brain and Cognition 58 (2005) 49–61
Brain and Cognition
www.elsevier.com/locate/b&c

Variable foreperiod deficits in Parkinson's disease: Dissociation across reflexive and voluntary behaviors

Anita J. Jurkowski[a,*], Elizabeth Stepp[b], Steven A. Hackley[b]

[a] *Duke University Center for the Study of Aging and Human Development, Brain Imaging and Analysis Center, Box 3918, Duke University Medical Center, Durham, NC 27710, USA*
[b] *University of Missouri-Columbia, USA*

Received 16 September 2004
Available online 18 November 2004

Abstract

The effect of a visual warning signal (1.0–6.5 s random foreperiod, FP) on the latency of voluntary (hand-grip) and reflexive (startle-eyeblink) reactions was investigated in Parkinson's disease (PD) patients and in young and aged control subjects. Equivalent FP effects on blink were observed across groups. By contrast, FP effects diverged for voluntary responses across groups with no effect of foreperiod duration for PD patients. The convergence of these results with findings from animal research suggests that interval-timing processes associated with higher level voluntary behaviors are dependent upon intact dopaminergic pathways, while those associated with lower level reflexive behaviors are spared in PD.

Keywords: Variable foreperiod; Interval-timing; Parkinson's disease; Startle-eyeblink; Startle reflex; Basal ganglia; Dopamine

1. Introduction

In both reflexive eyeblink studies and voluntary reaction time tasks, a warning signal presented prior to an imperative stimulus shortens the response time for both young and aged adults, including those with Parkinson's disease (*reflex*: Durrington, 1998; *voluntary*: Jahanshahi, Brown, & Marsden, 1992). This warning effect is apparent for voluntary behaviors with both simple reaction time tasks (predefined response) and choice reaction time tasks (response selected from among various alternatives). Although the effect of presenting a warning stimulus prior to an imperative stimulus has been thoroughly investigated in each of these populations, the effect of varying the temporal interval between warning stimulus and imperative stimulus (foreperiod) across trials has not been directly assessed in aged or Parkinsonian adults.

When the foreperiod is varied from trial to trial, young adults demonstrate faster reaction times with longer as compared to shorter foreperiods. The generally accepted explanation for this variable foreperiod effect is that certainty regarding when the imperative stimulus will arrive increases as the foreperiod lengthens (Niemi & Naatanen, 1981). In other words, as the temporal interval after presentation of the warning stimulus lengthens, the conditional probability of the longest foreperiod increases toward 100%. This increase in certainty regarding time of arrival of the imperative stimulus is manifested in reduced reaction time, presumably due to increased preparedness.

Even though the variable foreperiod effect has not been directly assessed in aged and Parkinsonian populations, relevant data can be gleaned from six studies designed to investigate other variables affecting reaction time. Of these six studies, two reported significant

* Corresponding author. Fax: +1 919 681 7033.
E-mail address: jurkowski@biac.duke.edu (A.J. Jurkowski).

0278-2626/$ - see front matter © 2004 Elsevier Inc. All rights reserved.
doi:10.1016/j.bandc.2004.09.008

speeding of reaction time at longer relative to shorter foreperiods in PD patients (Jahanshahi, Brown, & Marsden, 1993; Rafal, Posner, Walker, & Friedrich, 1984), and the other four demonstrated trends in that direction (Bloxham, Dick, & Moore, 1987; Bloxham, Mindel, & Frith, 1984; Jahanshahi et al., 1992; Jordan, Sagar, & Cooper, 1992).

A number of animal studies have investigated the role of dopamine in foreperiod dependent speeding of reaction time (Brown & Robbins, 1991; Carli, Jones, & Robbins, 1989; MacDonald & Meck, 2004). Using an established animal model of PD, both experiments demonstrated that unilateral striatal dopamine depletion by 6-hydroxydopamine (6-OHDA) in rats abolished the speeding of voluntary reactions contralateral to the lesion in a variable foreperiod task. In the Brown and Robbins study, equivalent reaction times were observed across all foreperiods for responses contralateral to the lesion, while the normal linear decrease in reaction time as a function of foreperiod duration was observed for responses ipsilateral to the lesion. These results suggest that the dopaminergic system in the basal ganglia may mediate the use of the temporal information available in a variable foreperiod design, at least within the temporal range investigated (600–1500 ms). Other researchers have suggested that dopamine activity is essential for the optimal functioning of mesocortical circuits involved in attention, working memory, and the perception of time intervals (for review, see Lustig, Matell, & Meck, 2004; Meck & Benson, 2002; Posner & Rothbart, 1998; Robbins et al., 1994).

On the surface it appears that the results of the human studies are in direct contradiction to the animal studies. Whether this discrepancy is due to stimulus, design, or task differences, or to an inherent dissimilarity between the rat model and idiopathic PD in humans is unclear. The finding of a normal variable foreperiod effect in humans with PD is also surprising in light of evidence from the field of interval timing. Convergence across various techniques, including lesion analysis (Harrington, Haaland, & Knight, 1998), positron emission tomography (PET, Jueptner et al., 1995; Maquet et al., 1996), functional magnetic resonance imaging (fMRI, Hinton & Meck, 2004; Rao et al., 1997), and neuropharmacology (Meck, 1996), has implicated dopaminergic circuits within the frontal cortex, the basal ganglia, and striatofrontal-feedback circuits in temporal processing tasks. On the assumption that temporal judgment plays a vital role in the variable foreperiod effect, it would be surprising if PD does not alter this phenomenon.

Another line of research that encourages the re-examination of the variable foreperiod effect in PD concerns warning effects in schizophrenic patients. It is generally agreed that many schizophrenic symptoms are due to enhanced dopamine sensitivity. Patients with this disorder demonstrate an exaggerated variable foreperiod effect (Zahn, Rosenthal, & Shakow, 1963). It would follow that if excess midbrain/diencephalic dopamine activity can increase reaction time (RT) differences across warning interval conditions, then deficiencies in dopamine levels could cause a reduction in this effect (i.e., in normal aging and PD). The present experiment was designed to assess this possibility.

It is known that midbrain dopamine levels decrease with normal aging (van Dyck et al., 2002). Therefore, a comparison of young adults' to aged adults' reaction times was made in our study to assess the effect of moderate loss of dopamine. Medication-withdrawn, moderately impaired PD patients were included to investigate the effect of loss of midbrain dopamine beyond that which can be accounted for by general aging. The results of such comparisons could generalize the findings of Robbins and colleagues (Brown & Robbins, 1991; Carli et al., 1989) from laboratory animals to humans with PD.

Based on the results of Brown and Robbins (1991), it would be expected that the variable foreperiod effect might be deficient in some manner in the aged adult group compared to the young adult group, and that the variable foreperiod effect would be reduced or eliminated in the non-medicated PD group. This prediction is also consistent with the human data in that medicated PD patients appear to demonstrate a stronger foreperiod effect than non-medicated patients (Jordan et al., 1992; Rafal et al. (1984)).

In normal individuals similar warning effects occur for reflexive behaviors as well as voluntary behaviors. The facilitation of reflex latency by a warning stimulus is a reliable and widely studied effect in the startle-eyeblink literature (Graham, 1975; Putnam & Vanman, 1999). This effect is not only evident with startle-eyeblink reflexes, but also with postural reflexes (McChesney, Sveistrup, & Woolacott, 1996). In the startle-reflex literature this reduction in time to the blink onset is referred to as long-interval prepulse facilitation of blink latency; in the field of learning and memory, it is referred to as conditioned facilitation of unconditioned response latency.

Previous studies (Low, Larson, Burke, & Hackley, 1996; Sollers & Hackley, 1997; Zeigler, Graham, & Hackley, 2001) have demonstrated the feasibility of simultaneously recording reflexive and voluntary reactions to the same stimulus.[1] Most relevant to the present

[1] The results of Sollers and Hackley (1997) suggest that simultaneously recording a reflex during a voluntary reaction time task does not seriously distort measurement of voluntary reaction time. Conversely, Zeigler et al. (2001) demonstrated that having the subject perform a voluntary reaction time task during an eyeblink reflex study does not significantly interfere with the reflexive response. It is apparent that a large degree of independence exists between these two behavioral systems.