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Dopaminergic medication alters auditory distractor processing in Parkinson's disease

Dejan Georgiev [a,b,*], Marjan Jahanshahi [b,1], Jurij Dreo [a,2], Anja Čuš [a,3], Zvezdan Pirtošek [a,4], Grega Repovš [c,5]

[a] Department of Neurology, University Medical Centre, Zaloška cesta 2, 1000 Ljubljana, Slovenia
[b] Sobell Department of Motor Neuroscience and Movement Disorders, Institute of Neurology, University College London, 33 Queen Square, London WC1N 3BG, United Kingdom
[c] Department of Psychology, Faculty of Arts, Aškerčeva 2, 1000 Ljubljana, Slovenia

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ABSTRACT

Parkinson's disease (PD) patients show signs of cognitive impairment, such as executive dysfunction, working memory problems and attentional disturbances, even in the early stages of the disease. Though motor symptoms of the disease are often successfully addressed by dopaminergic medication, it still remains unclear, how dopaminergic therapy affects cognitive function. The main objective of this study was to assess the effect of dopaminergic medication on visual and auditory attentional processing. 14 PD patients and 13 matched healthy controls performed a three-stimulus auditory and visual oddball task while their EEG was recorded. The patients performed the task twice, once on- and once off-medication. While the results showed no significant differences between PD patients and controls, they did reveal a significant increase in P3 amplitude on- vs. off-medication specific to processing of auditory distractors and no other stimuli. These results indicate significant effect of dopaminergic therapy on processing of distracting auditory stimuli. With a lack of between group differences the effect could reflect either 1) improved recruitment of attentional resources to auditory distractors; 2) reduced ability for cognitive inhibition of auditory distractors; 3) increased response to distractor stimuli resulting in impaired cognitive performance; or 4) hindered ability to discriminate between auditory distractors and targets. Further studies are needed to differentiate between these possibilities.

1. Introduction

Parkinson's disease (PD) is a chronic, neurodegenerative disease characterized by loss of dopamine-producing cells in the Substantia Nigra pars compacta (SNpc) (Thenganatt & Jankovic, 2014). In addition to the motor symptoms (resting tremor, bradykinesia, rigidity, and in later stages, impaired postural reflexes), PD patients also show cognitive deficits even in the early stage of the disease (Dirnberger & Jahanshahi, 2013; Ryterska, Jahanshahi, & Osmana, 2013). Commonly reported cognitive difficulties in early stage PD patients are executive dysfunction (e.g. difficulties in planning, set-shifting, conflict resolution, and reduced ability to perform tasks concurrently) (Dirnberger & Jahanshahi, 2013), deficits in working memory (WM) (Lee, Cowan, Vogel, Fernando, & Hackley, 2010), visuospatial function, and conditional associative learning (Kehagia, Barker, & Robbins, 2010). In addition to these, attentional difficulties are also very common in PD. Selective attention deficits (Zhou et al., 2012), problems with involuntary attention (Solis-Vivanco et al., 2011), attention set-shifting and flexibility deficits and disturbance of auditory attention (Bronnick, Nordby, Larsen, & Aarsland, 2010) have all been reported in PD patients. Therefore, a range of cognitive deficits, including attentional deficits, are common in early stage PD and have been directly related to the basic neuropathological changes in PD — decreased production of dopamine in SNpc, that leads to decreased concentration of dopamine in the striatum and consequently disturbed neuronal activity, primarily in the frontostriatal circuits including the associative circuit between the caudate and the dorsolateral prefrontal cortex (DLPFC) (Cools, 2006; Gotham, Brown, & Marsden, 1988).

Even though dopaminergic medication undoubtedly improves the motor symptoms of the disease, the effect of dopaminergic medication

Abbreviations: BDI, Back Depression Inventory; CON, healthy controls; ICD, Impulse Control Disorder; MMN, mismatch negativity; MNV, mean normalized value; MoCA, Montreal Cognitive Assessment; PD OFF, PD patients off medication; PD ON, PD patients on medication; PD, Parkinson's disease; RON, reorientation of attention; WM, working memory.

* Corresponding author at: Department of Neurology, University Medical Centre, Zaloška cesta 2, 1000 Ljubljana, Slovenia. Tel.: +44 7429 088 621.
E-mail addresses: dgeorgiev@ucl.ac.uk, dejan.georgiev@kclj.si (D. Georgiev), m.jahanshahi@ucl.ac.uk (M. Jahanshahi), jurij.dreo@gmail.com (J. Dreo), anja.cus@gmail.com (A. Čuš), zvezdan.pirtosek@kclj.si (Z. Pirtošek), grega.repovs@psy.ff.uni-lj.si (G. Repovš).
[1] Tel.: +44 20 7837 3611.
[2] Tel.: +386 40 510 956.
[3] Tel.: +386 40 759 100.
[4] Tel.: +386 31 303 387.
[5] Tel.: +386 41 356 512.

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on cognition is diverse and often unpredictable. Namely, dopaminergic medication may either alleviate or deteriorate cognitive function, or have no effect on cognitive function (Briand, Hening, Poizner, & Sereno, 2001; Bronnick et al., 2010; Cools, 2006, 2011; Cools, Barker, Sahakian, & Robbins, 2001; Gauntlett-Gilbert, Roberts, & Brown, 1999; Gotham et al., 1988; Kiesel, Miller, Jolicoeur, & Brisson, 2008; Sawada et al., 2012; Solis-Vivanco et al., 2011; Tachibana, Toda, & Sugita, 1992; Tinaz, Courtney, & Stern, 2011; Tombaugh, 2004; Tsuchiya, Yamaguchi, & Kobayashi, 2000). It has been postulated that these contrasting effects of dopaminergic medication stem from an imbalance of dopamine in distinct regions of the striatum (Gotham et al., 1988).

Research in healthy subjects (Cools & D'Esposito, 2011) has indicated that cognitive function depends on the optimal level of dopamine, which can be disrupted either by lack of or an overabundance of dopamine, resulting in an inverted-U-shape dependence of cognitive performance on dopamine level. In the early stages of PD the dopamine depletion is restricted to the dorsal striatum, leaving the ventral striatum relatively spared (Gotham et al., 1988; Kish, Shannak, & Hornykiewicz, 1988). This leads to a specific pattern of cognitive dysfunction dependent on specific neuronal circuits needed for the execution of the cognitive task tested. Relatedly, when dopaminergic medication is adjusted to ameliorate the depleted levels of dopamine in the dorsal striatum, it may overdose the ventral striatum, resulting in improvement of those symptoms and functions that depend on the dorsal, and deterioration of those that depend on the ventral striatum (Gotham et al., 1988). In summary, due to the way the dopaminergic system is affected in different parts of the striatum in early PD, the effect of dopaminergic medication on cognition in PD patients is complex and depends on many factors, such as the specific nature of the task, the engaged neuronal circuit, and the stage of the disease (Cools, 2006; Gotham et al., 1988).

Attention is one of the central concepts in neuropsychology and underlines most cognitive processes (Bocquillon et al., 2012). The involvement of the basal ganglia and dopamine in attention is complex (Bocquillon et al., 2012; Knight, Grabowecky, & Scabini, 1995). PD, characterized by dopamine depleted basal ganglia circuits, is a good model for studying the relation of attention to dopamine. In the study of human cognition a P3 cognitive event related potential (ERP) is probably the most used neural correlate of attention. Elicited when processing low-probability (rare) target stimuli (Polich, 2007), it has been shown to significantly correlate with attentional processes (Bledowski, Prvulovic, Goebel, Zanella, & Linden, 2004). The P3 has been robustly identified when actively or passively paying attention to rare target stimuli in a single (target only), double (rare target intermixed with frequent standard stimuli), or three (rare target intermixed with frequent standard and rare distractor stimuli) stimulus paradigms, in the auditory, visual, or somatosensory modality (Lugo et al., 2014; Polich, 2007; Wronka, Kaiser, & Coenen, 2008).

Interestingly, rare non-target, distractor stimuli also elicit a P3 response, which however, differs from the response to the target stimulus in its latency, amplitude and spatial distribution. The P3 response elicited by target stimuli (P3b) is characterized by a parietal maximum and a longer latency, compared to the P3 response elicited by distractor stimuli (P3a), which is more frontally distributed, has a shorter latency, and somewhat larger amplitude (Daffner, Mesulam, Holcomb, et al., 2000; Daffner, Mesulam, Scinto, et al., 2000). P3a is assumed to reflect attentional reorientation and subsequent reallocation of attention to salient but irrelevant stimuli, and can be regarded as a marker of response inhibition processes in response to irrelevant stimuli. In contrast, P3b is thought to reflect components of attentional, WM, or event categorization processes that lead to decision making (Bledowski et al., 2004). Both P3a and P3b are traditionally described by their amplitude and latency; the former is considered to reflect the selective attention resources devoted to processing of the stimuli, whereas the latter is assumed to index the time necessary for controlled information processing (Kok, 2001).

Empirical data from lesion and fMRI studies suggest different generators of P3a and P3b. For example, lesions of the prefrontal cortex decrease the response to distracting novel, but not to target stimuli in the three stimulus oddball paradigms (Knight, 1984; Wascher, Hoffmann, Sanger, & Grosjean, 2009). Similarly, patients with hippocampal damage can show a reduced response to distracting novel stimuli (Knight, 1996). In contrast, discrete lesions of the temporoparietal junction can result in reduced amplitude of both, P3a and P3b (Knight, Scabini, Woods, & Clayworth, 1989; Nieuwenhuis, Aston-Jones, & Cohen, 2005). It seems that the orienting response to rare (target or distractor) stimuli, which reflects the immediate response to any change in the environment, activates frontal regions first; this signal is then transmitted towards the temporoparietal regions of the brain, possibly reflecting memory related processes (Polich, 2007). Indeed, imaging data show that both target and distractor stimuli activate the ventrolateral frontoparietal network, indicating a common mechanism for detection of rare events engaging bottom-up attentional processes (Bledowski et al., 2004). Presence of distractor stimuli further activates the dorsolateral frontoparietal network. This network is believed to be engaged in attentional switch from the target/standard discrimination and consequent attention allocation to the salient, rare distractor stimulus (Bledowski et al., 2004). In summary, it seems that different neural mechanisms, possibly regulated by different neurotransmitter systems, are involved in processing of distractor and target stimuli. Indeed, according to the dual-transmitter hypothesis (Polich, 2007; Polich & Criado, 2006), frontally related P3a is likely mediated by dopaminergic activity, whereas P3b, which is related to parietotemporal brain regions, is probably mediated by noradrenaline activity. Furthermore, dopaminergic projections to the cortex are most abundant in frontal areas (Goldman-Rakic, 1998), whereas noradrenergic projections from locus coeruleus, are more diffusely distributed across the cortex, including the posterior and parietotemporal parts of the brain (Berridge & Waterhouse, 2003; Nieuwenhuis et al., 2005). Therefore, it could be expected that different medications have different effects on P3a and P3b, depending on the mechanism of action. Specifically, dopaminergic medication should affect P3a rather than P3b, as the modulation of P3a seems to be more heavily dependent on the dopaminergic system.

There are several lines of clinical evidence suggestive of the importance dopamine plays in the generation of the P3a/b response. For example, patients with restless leg syndrome, a condition marked by decreased dopaminergic state, show larger reduction of P3a compared to P3b amplitude (Choi, Ko, Lee, Jung, & Kim, 2012). A study by Takeshita and Ogura (1994) demonstrated that administration of a dopaminergic antagonist results in a differential effect depending on the baseline P3b amplitude: subjects with low P3b amplitude at baseline exhibited an increase of the amplitude after sulpiride (dopamine antagonist) administration; whereas conversely, subjects with high P3b at baseline exhibited an amplitude decrease after sulpiride administration.

Despite important differences in the processes underlying P3a and P3b evoked potentials and their assumed dependence on dopamine, many of the studies of PD focused exclusively on the P3b potential evoked by the standard two-stimulus oddball paradigm. Some of these studies (Elwan et al., 1996; Graham, Yiannikas, Gordon, Coyle, & Morris, 1990; Green et al., 1996; Karayanidis, Andrews, Ward, & Michie, 1995) found no differences between PD patients and healthy controls, whereas others reported reduced P3b amplitude (Koberskaia, Zenkov, and Iakhno (2003)), or prolonged P3b latency (Stanzione et al. (1998)) in PD patients compared to healthy controls. Additionally, Bodis-Wollner et al. (1995) have found that the P3b latencies in both auditory and visual oddball tasks significantly but differentially correlate with scores on cognitive tests. Specifically, P3b latency in the auditory oddball negatively correlated with basic visual perception, whereas P3b latency in the visual oddball task negatively correlated with tests of abstract reasoning.

Of the studies that did differentiate between P3a and P3b, Tsuchiya et al. (2000) reported somewhat smaller P3b amplitudes in PD patients