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Orbital and ventromedial prefrontal cortex functioning in Parkinson's disease: Neuropsychological evidence

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ABSTRACT

A recent paper (Zald & Andreotti, 2010) reviewed neuropsychological tasks that assess the function of the orbital and ventromedial portions of the prefrontal cortex (OMPFC). Neuropathological studies have shown that the function of the OMPFC should be preserved in the early stages of Parkinson's disease (PD) but becomes affected in the advanced stages of PD. This pattern has also been suggested by studies that have shown that dopaminergic drugs impair the performance of early PD patients in OMPFC tasks that involve reinforcement learning but enhance the performance of advanced PD patients. Based on these empirical findings, we reviewed the neuropsychological evidence of OMPFC functions in PD patients to test two hypotheses regarding the following: (1) OMPFC functions at different stages of PD; (2) different effects of dopaminergic drugs on OMPFC functions based on PD stage and task demand. We focused our review only on the neuropsychological tasks that were specific and sensitive to the functions of the OMPFC and that were adopted at different stages of PD, such as reversal learning tasks, the Iowa Gambling Task and the affective Theory of Mind task. We found robust empirical evidence that in early PD, OMPFC functions are preserved and dopaminergic drugs result in a detrimental effect when the task involves reinforcement learning. Further studies are needed to verify the status of OMPFC functions in non-demented, advanced PD and to describe the longitudinal course of OMPFC functions in this clinical population.

1. Introduction

A recent paper (Zald & Andreotti, 2010) reviewed the neuropsychological tasks that permit assessment of cognitive functions of the orbital prefrontal cortex (OFC) and of the ventromedial prefrontal cortex (VMPFC). The following cognitive domains were reviewed: (1) the ability to change prepotent or previously acquired stimulus–reinforcer associations; (2) olfactory processing; (3) social processing; (4) autobiographical memory; and (5) emotional characteristics of personality. Different tasks were analyzed within each functional domain, which demonstrated that different tasks are supported by varying levels of neuropsychological evidence with regards to their sensitivity and specificity to damages to the OFC and VMPFC.

Parkinson's disease (PD) is a progressive neurodegenerative disorder diagnosed based on characteristic motor disturbances (bradykinesia, resting tremor, rigidity and postural instability), asymmetrical motor onset and good response to levodopa (Litvan et al., 2003). As a synucleinopathy, PD is linked to the pathogenic fibrillization of the unstructured soluble protein, α-synuclein. It is also characterized by the formation of Lewy bodies in nigral regions, limbic and brainstem nuclei and neocortical regions (Kalaitzakis & Pearce, 2009), although neurofibrillary tangles and plaques are also commonly present in these areas (Braak et al., 2003). The resulting neuronal degeneration directly affects catecholaminergic (i.e., dopamine and norepinephrine) and cholinergic (acetylcholine) neurotransmission (Bohnen et al., 2006; Brooks & Piccini, 2006; Calabresi, Picconi, Parnetti, & Di Filippo, 2006).

Cognitive impairments are frequently reported in patients with PD, beginning in the untreated early clinical stages (Aarsland et al., 2010). They principally involve executive functions, based on the Dorsolateral Prefrontal Cortex (DLPFC) (for review, see Cools, 2006; Koerts, Leenders, & Brouwer, 2009, or Poletti, Emre, & Bonuccelli, 2011). Cognitive impairment in early PD is related to the progressive loss of dopaminergic neurons in the substantia nigra,

Abbreviations: GPi, internal segment of globus pallidus; SNr, substantia nigra pars reticulata; VP, ventral pallidum; MD, medialis dorsalis; MDpc, medialis dorsalis pars parvocellularis; MDmc, medialis dorsalis pars magnocellularis; VAmc, ventralis anterior pars magnocellularis; VApc, ventralis anterior pars parvocellularis; VLo, ventralis lateralis pars oralis; VLm, ventralis lateralis pars medialis; cl, caudolateral; ldm, lateral dorsalmedial; mdm, medial dorsomedial; pm, posteromedial; rd, rostrodorsal; rl, rostrolateral; rm, rostromedial.

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which is an essential component of the basal ganglia circuitry (Kehagia, Barker, & Robbins, 2010). On the other hand, dementia is a common feature in the advanced stages of PD and is related to the cortical diffusion of Lewy bodies (Emre et al., 2007; Kalaitzakis & Pearce, 2009). While the impairment of DLPFC functions is a well-established feature of PD patients, the status of OFC and VMPFC functions in this clinical population has been investigated less thoroughly.

This paper aims at providing an up-to-date review of current neuropsychological evidence about functions related to the OFC and VMPFC in patients with PD. Here, we first present the anatomy of the OFC and VMPFC in healthy subjects and in PD patients (in Section 2), as well as show models of the interaction between dopamine depletion (PD stage) and the dopaminergic replacement therapy (in Section 3). Secondly, we formulate working hypotheses on the functioning of the OFC and VMPFC and on the effect of dopaminergic therapies on these functions in PD (in Section 4). Then, we present a critical literature review (in Section 5), and we present empirical findings on OMPFC functions in PD (in Sections 6 and 7). Finally, in Section 8 we discuss the results of the literature review to test working hypotheses on OMPFC functions in PD and suggest future research directions.

2. Anatomy of the OFC and the VMPFC

The OFC and VMPFC include the medial portions of Brodmann's areas 9, 10, 11, and 12, areas 13 and 25 and the inferior portion of area 47 (Damasio, 1996). The OFC comprises the ventral surface of the PFC, while the VMPFC comprises the inferior portion of the medial wall of the frontal lobe. Although there are cyto-architectural and connectional differences between the OFC and the VMPFC (Carmichael & Price, 1996; Price, 2006), pathologies that affect the PFC usually damage both of these areas. In fact, in studies describing patients with OFC damages, VMPFC damages are also often present and vice versa. For this reason, while electrophysiological methods in monkeys may detect differences of activation in these areas (e.g., Bouret & Richmond, 2010), neuropsychological studies in brain-damaged patients failed to find clear functional differences between these areas and to disentangle their relative contributions in isolation. Therefore, the term OMPFC could be adopted to refer to the combination of the OFC and VMPFC (Zald & Andreotti, 2010). For the purpose of this review, we would like to emphasize that the OMPFC is connected to limbic structures, such as the amygdala and the hypothalamus. The DLPFC, on the other hand, is an important source of cortico-striatal inputs to the nucleus accumbens, which reciprocally modulates the activity of the midbrain dopaminergic neurons and is itself an important node in the circuit that processes reinforcement (Damasio, 1996; Price, 2006; Rolls, 2004).

2.1. The OMPFC in Parkinson's disease

Four frontostriatal loops are involved in the motor, cognitive, affective and motivational aspects of behavior (Fig. 1) (Alexander, Delong, & Strick, 1986; Middleton & Strick, 2001; Yeterian & Pandya, 1991) as follows: the "dorsolateral" loop includes the Dorsolateral Prefrontal Cortex (DLPFC), the striatum (dorsolateral caudate nucleus and dorsolateral putamen), the globus pallidus (dorsomedial) and the thalamus; the "orbital" loop includes the orbitofrontal cortex (OFC), the striatum (ventromedial caudate nucleus and ventral putamen), the globus pallidus (dorsomedial) and the thalamus; the "anterior cingulate" loop includes the anterior cingulate cortex (ACC), the striatum (ventromedial caudate nucleus and ventral putamen), the nucleus accumbens, the olfactory tubercle, the globus pallidus (rostromedial) and the thalamus; and the "motor" loop includes the supplementary motor area, the putamen, the globus pallidus (ventrolateral) and the thalamus. Additionally, within each circuit, two loops connect the striatum with the PFC: a direct excitatory loop and an indirect inhibitory loop (Alexander, Crutcher, & DeLong, 1990).

With regards to the neuropathological staging of PD, we refer to Braak et al. (2003). In PD patients, the progressive striatal dopamine depletion has different effects on the functioning of the frontostriatal loops. In early PD (Braak stages 3 and 4), the dopamine depletion is greatest in the ventrolateral tier of the substantia nigra pars compacta, which projects primarily to the dorsal striatum (i.e., the dorsolateral putamen and the dorsal parts of the caudate nucleus), an area involved in the dorsolateral loop. The ventral striatum and the related orbital loop, however, are mostly preserved (Kish, Shannak, & Hornykiewicz, 1988), as Lewy bodies do not impair the PFC in these stages of PD (Braak et al., 2003). With the progression of PD, dopamine depletion at the striatal level also impairs the functioning of the orbital loop. Moreover, in these stages of illness, the PFC is directly damaged by the cortical diffusion of Lewy bodies (Braak et al., 2003; Scatton, Rouquier, Javoy-Agid, & Agid, 1982). Thereafter, in advanced PD (Braak stages 5 and 6), OMPFC functions can be impaired by two mechanisms: (1) indirectly, by the reduced striatal dopaminergic stimulation and (2) directly, by the cortical diffusion of Lewy bodies.

3. The interaction between dopamine depletion and dopaminergic therapy in PD

Levodopa and dopamine agonists represent the gold-standard therapy for treating the motor symptoms of PD patients (Bonuccelli & Pavese, 2006; Poewe, Antonini, Zijlmans, Burkhard, & Vingerhoets, 2010). How does the dopaminergic therapy interact with the progressive striatal dopamine depletion? Different models on this topic have been proposed. The inverted U-shape curve model (Cools, 2006) proposed that, in early PD patients, the withdrawal of dopaminergic medication has a detrimental effect on cognitive functions associated with the dorsolateral loop, and a beneficial effect on the cognitive functions associated with the orbital loop. As levodopa mainly elevates dopamine levels in the striatum (Hornykiewicz, 1974), these differential effects are likely due to opposing effects of levodopa in the dorsal and the ventral striatum, which are connected to different cortical areas via segregated frontostriatal loops (Alexander et al., 1986). This double dissociation is evident when directly comparing patients "on" and "off" dopaminergic medication and represents an empirical confirmation of the "dopamine overdose hypothesis" (Gotham, Brown, & Marsden, 1986; Gotham, Brown, & Marsden, 1988). This hypothesis states that the administration of dopaminergic medication to early PD patients may replete dopamine-depleted circuits (including the dorsal striatum), thus improving performances in tasks related to the dorsolateral loop while "overdosing" relatively intact circuits (including the orbital loop).

In the neurocomputational model of frontostriatal circuitry in PD proposed by Frank and colleagues (2004), the basal ganglia modulate the selection of actions under consideration in the PFC. Two main projection pathways from the striatum travel up to the cortex through the thalamus via different basal ganglia output structures. The subthalamic nucleus provides a self-adaptive, dynamic control signal that temporarily prevents the execution of any response, depending on decision conflict (Frank, 2006). The direct frontostriatal "orbital" pathway is excitatory and the indirect frontostriatal "orbital" pathway is inhibitory. Transient changes in dopamine levels that occur during positive and negative feedback loops have opposite effects on the D1 and D2 (dopamine) receptors, which are relatively segregated in the direct and indirect pathways, respectively (Hernandez-Lopez et al., 2000). Dopamine