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Neurobiology of Aging 29 (2008) 397–407

NEUROBIOLOGY OF AGING

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Fronto-striatal deficit in Parkinson's disease during semantic event sequencing

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Received 14 June 2006; received in revised form 15 October 2006; accepted 27 October 2006
Available online 8 December 2006

Abstract

Studies of Parkinson's disease (PD) suggest that cognitive deficits accompany the classically recognized motor symptoms, and that these cognitive deficits may result from damage to frontal–basal ganglia circuits. PD patients are impaired on ordering events and action components into coherent sequences. In this study, we examined early-stage, nondemented, medicated PD subjects and matched control subjects during a semantic event sequencing task using functional MRI (fMRI). The task required subjects to examine four pictures of meaningful events, determine the correct temporal relationship between each picture, and re-order the pictures into a coherent sequence. There were two main findings. First, we found abnormal activation within the prefrontal cortex (PFC) and the "default" network in the PD group. Distinct areas of the PFC showed both hypoactivation and hyperactivation, whereas the "default" network showed reduced levels of resting activation in PD. Secondly, we observed left caudate hyperactivation in the PD group. The findings are discussed in relationship to how more activation may be compensatory, but does not necessarily mean efficient and correlated brain function.

Keywords: Dopamine; Basal ganglia; Dorsolateral prefrontal cortex; Executive functions; fMRI

1. Introduction

Parkinson's disease (PD) is an aging-related neurodegenerative disorder characterized by the classical motor symptoms of bradykinesia, rigidity, tremor, postural instability, and gait disturbances. A growing body of neuropsychological and neuroimaging evidence suggests that patients with PD also have diverse cognitive problems affecting spatial, memory, and executive abilities, even at relatively early stages of the disease (Amick et al., 2006; Cronin-Golomb and Amick, 2001; Dubois and Pillon, 1997). Behavioral research on PD has demonstrated deficits in strategic control, attention shifting, planning, working memory, and perceptuomotor temporal sequencing. Yet, most neuroimaging studies focus on motor symptoms and few on cognitive problems, and so relatively little is known about the brain basis of high-level cognitive dysfunction in PD (Carbon and Marie, 2003). The present functional magnetic resonance imaging (fMRI) study sought to examine the functional integrity of frontal–basal ganglia circuits in early-stage, nondemented, medicated PD participants during a semantic event sequencing task, an executive function that is known to be impaired in PD and is central to many high-level activities of daily living, such as following a recipe to prepare a meal or organizing a daily schedule.

Neuropsychological findings suggest that damage to the fronto-striatal system in PD results in problems with sequencing meaningful events. PD patients have been shown to be impaired on picture arrangement tests in which scrambled picture sets must be re-ordered to tell a story (Beatty and Monson, 1990; Cooper et al., 1991; Sullivan et al., 1989)

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doi:10.1016/j.neurobiolaging.2006.10.025

and on related tasks entailing ordering and organizing script information that is presented as action sequence components in a scrambled order (Godbout and Doyon, 2000; Zalla et al., 1998).

We designed a semantic event sequencing task that is an fMRI variant (Tinaz et al., 2006) of the Picture Arrangement subtest of the Wechsler Adult Intelligence Scale-III (WAIS-III) (Wechsler, 1997). Similarly, our picture sequencing task required subjects to examine four pictures of meaningful events, determine the correct temporal relationship, and, finally, re-order the pictures into a coherent sequence (Groth-Marnat, 1999; Lezak, 1995). In a previous fMRI study using this sequencing task with young healthy subjects, we demonstrated that this task engages a distributed network of occipitotemporal, parietal, frontal and basal ganglia regions (Tinaz et al., 2006). More important, we found that the crucial components of this network for accomplishing semantic event sequencing are the dorsolateral prefrontal cortex (DLPFC) and the globus pallidus internal part (GPi), especially in the left hemisphere.

The goal in the present study was to examine the functional integrity of these frontal–basal ganglia circuits in patients with PD. We predicted that PD patients would show abnormal brain activity relative to a matched control group, specifically in the prefrontal cortex and the basal ganglia.

2. Methods

2.1. Subjects

Thirteen volunteers with idiopathic PD (mean age: 57.6 ± 6.8 years (range: 46–67), mean education: 16.1 ± 2.4 years (range: 14–21), 3 males) and 13 matched healthy control volunteers (mean age: 57 ± 8.6 years (range: 42–70), mean education: 16.4 ± 1.9 years (range: 13–19), 3 males) (Table 1) participated with informed consent and approval of Massachusetts General Hospital and Boston University. Diagnoses were made by staff neurologists in the outpatient clinic of the Parkinson's Disease Center in the Department of Neurology, Boston Medical Center. The PD and control participants were recruited through the Vision & Cognition Laboratory in the Department of Psychology at Boston University. Some of the control participants were also recruited through the Harvard Cooperative Program on Aging.

Exclusion criteria for all participants included neurological disease or medical disorders that impair central nervous system function, head trauma with more than a few minutes loss of consciousness or other complications, learning disability, psychiatric conditions, including schizophrenia, bipolar disorder, personality disorder, but not anxiety and depression because these conditions are often comorbid with PD, history of substance (drug, alcohol) dependence, or intravenous drug use, history of electro-shock treatment, English as non-native language, and specific MRI safety considerations.

Table 1
Demographic data

	Control ($n = 13$)	PD ($n = 13$)
Age (years)	57 ± 2.4	57.6 ± 1.9
Education (years)	16.4 ± 0.5	16.1 ± 0.7
Onset side	N/A	7 LPD, 6 RPD
Disease duration (years)	N/A	5.5 ± 0.5
Hoehn and Yahr stage	N/A	2.15 ± 0.09
UPDRS score	N/A	34.15 ± 2.7
UPDRS motor score	N/A	22.4 ± 2
MMSE	29.3 ± 0.5 ($n = 10$)	29.6 ± 0.2 ($n = 11$)
DRS	143.2 ± 0.2 ($n = 9$)	143.5 ± 0.15 ($n = 12$)
ANART	122.5 ± 1.7	121.6 ± 1.1
Digit symbol*	74.5 ± 4.2	62.3 ± 3 ($n = 12$)
Symbol search	32.4 ± 1.6	29.3 ± 1.7 ($n = 12$)
Trails A (s)†	29.2 ± 2.3	37.3 ± 3.1 ($n = 12$)
Trails B (s)	61.4 ± 3.7	82.3 ± 10.5 ($n = 12$)
BDI-II^	2.2 ± 1.2	8.5 ± 2
STAI-S	27.9 ± 2.5	31.2 ± 1.7 ($n = 12$)
STAI-T	31.2 ± 2.9	34 ± 3.1 ($n = 12$)

Demographic data (mean ± S.E.M.) for Parkinson's disease (PD) and control subjects ($N = 13$, unless noted otherwise). UPDRS: Unified Parkinson's Disease Rating Scale, MMSE: Mini Mental State Examination, DRS: Dementia Rating Scale, ANART: American National Adult Reading Test, BDI: Beck Depression Inventory, STAI: Spielberger State and Trait Anxiety Inventory, S: State, T: Trait. All PD subjects and 10 control subjects had at least one dementia measure (either MMSE or DRS). Ten PD and 9 control subjects had both MMSE and DRS measures.

* $p = 0.029$.
† $p = 0.045$.
^ $p = 0.019$.

All PD patients had unilateral symptom onset (left-onset in 7, and right-onset in 6 PD participants) and asymmetrical disease course. The average duration of disease was 5.5 ± 1.9 years. All patients were responsive to either levodopa-carbidopa or dopamine receptor agonists. Eleven patients were on a combination of up to 4 medications including levodopa-carbidopa, dopamine receptor agonists (pramipexole, ropinirole, pergolide), catechol-*O*-methyl-transferase (COMT) inhibitors (entacapone, tolcapone), monoamine oxidase B (MAO-B) inhibitors (selegiline), amantadine, and anticholinergics (trihexyphenidyl), and 2 were on dopamine receptor agonists only. Seven patients were on antidepressants, three on antianxiety medications as needed, and four were taking wakefulness-promoting drugs (modafinil). Only one patient was on anticholinergic medication. Three patients who were on anxiolytics on an as needed basis did not take their medications on the scanning day and the day before scanning.

Scanning started within 2 ± 1.5 h after the first dose of dopaminergic medication for the day. Before scanning, patients underwent a neurological assessment while on dopaminergic medication, including Hoehn and Yahr (1967) staging and the Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn and Elton, 1987). The mean UPDRS score was 34.1 ± 9.8 points, including the mentation, behavior, mood and activities of daily living components rated by interview, motor examination, and therapy-related complications (e.g., dyskinesia, dystonia, clinical fluctuations,