RESTING STATE FUNCTIONAL CONNECTIVITY IN OLFACTORY NETWORK IN DE NOVO PARKINSON'S DISEASE

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INTRODUCTION

It is now widely accepted that early non-motor signs indicate preclinical stages of Parkinson's disease (PD) before the onset of motor symptoms. It is now largely accepted that an important non motor symptom at early stages of PD is olfactory impairment (Ansari and Johnson, 1975). Olfactory dysfunction is a salient non-motor feature of Parkinson's disease, occurring in at least 90% of PD patients. It often manifests years before the development of parkinsonian motor symptoms, such as tremor, bradykinesia, rigidity, or gait impairment [1]. Previous fMRI studies showed altered neuronal activity in the amygdaloid complex and hippocampal formation during olfactory stimulation [2]. Voxel-based morphometry has been proven to correlate clinical features with structural gray matter changes in PD, such as executive and visuospatial impairment and depression. To date, olfactory dysfunction as an early symptom of PD has not yet been investigated with respect to structural changes in the brain.

MATERIALS AND METHODS

Study Population: We studied 10 de novo drug-naïve PD patients (6 males and 4 females, mean age: 58.4±4.2 years) and 10 age-matched normal controls (NC) (4 females and 6 males, mean age: 57.1±3.1 years). UPDRS motor subscore III: median 26. Disease duration: 2.1±1.3 years. H&Y stage: 1.5. MMSE score>27. No anti-parkinsonian or antidepressive treatment.

Olfactory Testing: Olfactory function was studied by using the Sniffin' Sticks Test (fig. 1). This is based on pen-like odour dispensing devices and includes sub-tests for olfactory threshold, discrimination and identification of odours. The sum of these three sub-tests shows the TDI (T=threshold, D=discrimination, I=identification) score allows a classification of olfactory function as normosmia (TDI=48–31), hyposmia (TDI=30–16) or anosmia (TDI≤15).

MRI Data acquisition: Functional data preprocessing included the correction for slice scan timing acquisition, the 3D rigid body motion correction and the application of a temporal high-pass filter with cut-off set to three cycles per time course. Structural and functional data were co-registered and spatially normalized to the Talairach standard space. To account for possible blood oxygen level–dependent effects due to cardiac pulsation and respiratory cycle [3], physiological noise correction was performed on each functional scan. Caudate was defined as ROI, to study olfactory-dependent RS functional networks in PD patients. The time series for data in each ROI were averaged, and Pearson's correlation coefficient maps were created for each individual subject. To study the correlation between the functional connectivity, a multiple regression analysis between the functional connectivity and TDI scores in two groups (PD and NC) was performed. Age, gender and disease duration were inserted as covariates in the regression analysis. The statistical maps were corrected for multiple comparisons to a significance level of $p<0.05$.

RESULTS

PD patients were hyposmic as indicated by mean scores of 20.2±2.1. NC were normosmic (mean score: 37.3±1.7) ($P< 0.05$). MRI examination did not show structural abnormalities, also in olfactory areas. The PD patients showed increased positive striato-cortical connectivity in the left frontal areas and decreased connectivity in the right occipital area (Talaraich Coordinates: L precentral gyrus -38 -12 +58; R middle occipital gyrus +48 -78 +8) (fig. 2).

DISCUSSION

This study showed that the patterns of RS functional connectivity differ according to olfactory performance in de novo and drug-naïve PD patients and NC. RSN analysis with the caudate seed in this study showed that PD patients had increased cortical functional connectivity mainly in the occipital and frontal areas compared to NC. It is known that the caudate nucleus is also functionally connected to large parts of the prefrontal cortex, as well as the parietal, temporal and cerebellar cortices, and plays a role in the discrimination of odor quality. These data suggest that RS functional connectivity should be closely correlated with the level of olfactory performance in de novo PD patients.
These findings should be interpreted very cautiously. Although this study included important cortical and subcortical seeds, these could not represent complete functional connectivity analysis. Therefore, a further study using other cortical and subcortical seeds or other imaging analytic tools, such as independent component analysis, a larger sample size, a longitudinal evaluation and OERPS examination, are needed to better understand functional networks. However, these data might shed light olfactory impairment as predictive outcome marker in de novo PD patients.

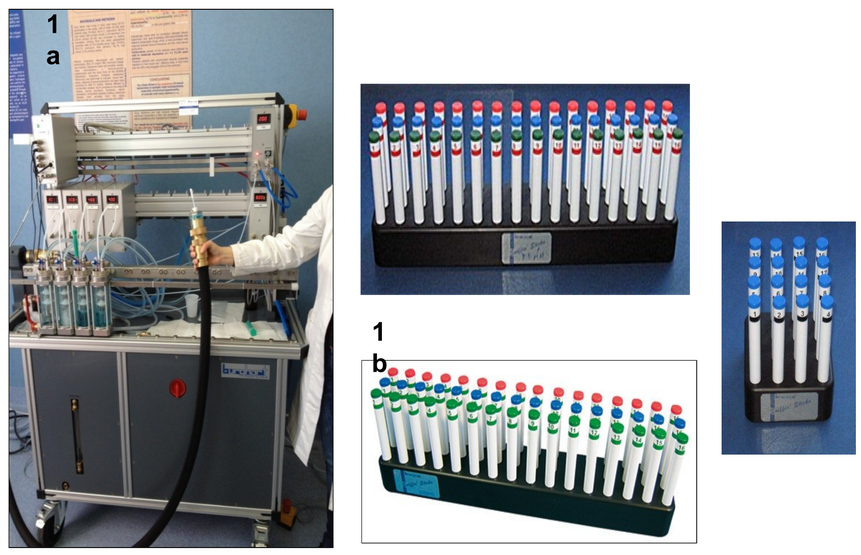

Figure 1. "Sniffin' Sticks": Olfactory performance were assessed by the combined testing of odor identification, odor discrimination and olfactory threshold.

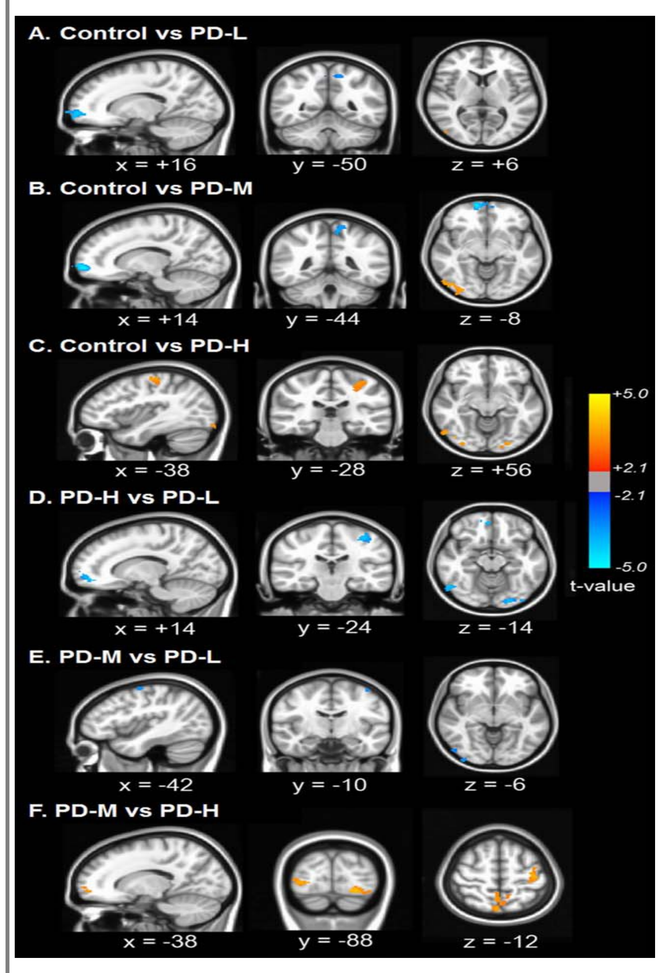

Figure 2. PD patients showed increased positive striato-cortical connectivity in the left frontal areas and decreased connectivity in the right occipital area.

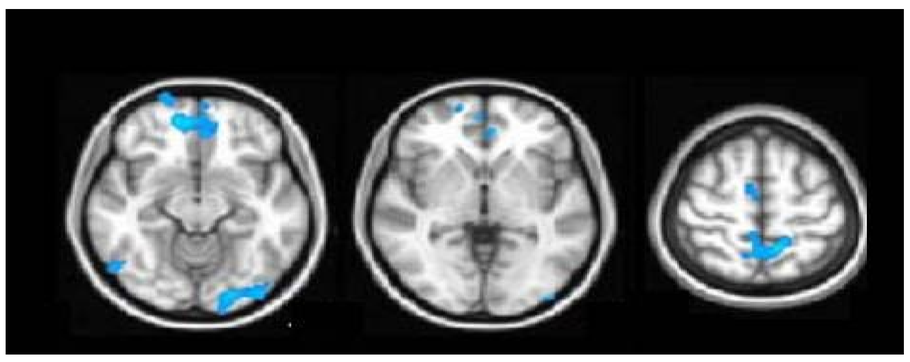

Figure 3. The cortical functional connectivity with the caudate was negatively correlated with the TDI scores in the bilateral frontal areas, left occipital area and precuneus.

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