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ERP, fMRI and Functional Connectivity Studies of Brain Response to Odor in Normal Aging and Alzheimer's Disease

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Introduction

More than 14 million Americans over 50 suffer from smell impairment (Murphy *et al.*, 2002). In a series of studies we have sought the underlying cortical substrates of olfactory loss with aging. We used psychophysical, neuropsychological, event related potentials (ERPs) and functional magnetic resonance imaging (fMRI) techniques to address the problem. Psychophysical investigations have revealed significant losses in olfactory threshold sensitivity, odor identification and odor memory. These impairments are significantly worse in patients with neurodegenerative diseases such as Alzheimer's disease (AD) (Murphy, 2002). The earliest lesions of AD are in the mesial temporal regions of the brain critical to olfactory processing, thus the potential exists for reflection of incipient disease in olfactory tasks. The investigation of olfactory function in aging and AD is of basic science interest and may contribute to the development of more sensitive diagnostic batteries for AD (Murphy, 2002).

ERPs provide real-time temporal information about the brain's response to odor stimulation. We have used this technique to investigate brain response over the lifespan in the normally aging brain (Murphy *et al.*, 2000) and in patients with neurodegenerative diseases such as Alzheimer's disease (Morgan and Murphy, 2002). The results suggest that the odor evoked response of the brain is significantly reduced in amplitude and delayed in its latency in normally aging persons and dramatically more delayed in Alzheimer's patients. These results confirm the importance of considering a central origin for the olfactory loss associated with aging and AD.

fMRI is a powerful tool for investigation of brain structure and of functional activation in specific regions of interest (ROIs). We have used fMRI to investigate the cortical substrate of olfactory impairment in the elderly. The fMRI data were analyzed with individual, group and ROI analyses. Results are described in Cerf-Ducastel and Murphy (2003), Ferdon and Murphy (2003) and Wiser *et al.* (2000). Older adults showed less activation in important olfactory ROIs: entorhinal cortex, amygdala, insula and piriform cortex. Cerebellar activation was lower in areas Crus I and II.

A number of approaches have been taken to achieve an understanding of integrated brain activity. Functional connectivity involves correlation between fMRI activity in two brain regions during performance of a task. The technique permits testing the hypothesis that interacting brain regions, rather than isolated regions of interest, are the cortical substrate for performance. We have approached functional connectivity with more than one analysis strategy. Calhoun-Haney *et al.* (2004) used the seed voxel method to examine correlations between individual voxels in hippocampus and in ROIs for olfactory processing during an olfactory task.

A number of investigators have conducted connectivity analysis on regional brain activation using correlational methods (Horwitz, 1989). Here we aimed to identify significant correlations in fMRI activation among ROIs for olfactory tasks and to test the hypothesis that the pattern of correlations among these regions is significantly impacted by aging. Activity was correlated separately for young adults, older adults and AD patients.

Methods

Participants were young adults, older adults who had been screened for dementia and patients with Alzheimer's disease.

FMRI was accomplished with a 1.5 T Siemens magnet, acquiring 32 sagittal EPI slices with a voxel size of $4 \times 4 \times 4$ mm and a T_R of 4 s. Functional data were superimposed on structural images acquired for anatomical verification using Mprage, 180 sagittal slices, 1 mm thick. FMRI activation was correlated with a perception profile to extract the data (Cerf-Ducastel and Murphy, 2003). Image analysis was conducted with AFNI. The correlation method was employed for functional connectivity analysis across ROIs.

Results and discussion

Activation in orbito-frontal cortex was highly correlated with activation in mesial temporal lobe in young adults. Young subjects also showed significantly correlated activity within mesial temporal lobe (Table 1). Older adults showed a breakdown of connectivity between orbito-frontal cortex and mesial temporal lobe (Table 1) and this was especially true in AD. Patients showed lower overall activation, particularly in mesial temporal lobe (Figure 1).

Results suggest that disconnection of olfactory areas from incoming information and higher processing areas is an important underlying cortical substrate of olfactory impairment in old age and is likely to be especially prominent in patients with AD. The consonant results from Calhoun-Haney et al., (2004) using a different method suggest the robustness of the findings.

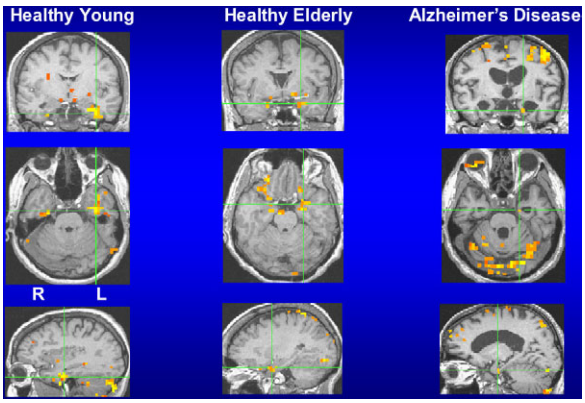

Figure 1 fMRI of mesial temporal lobe areas shows less activation in older than young adults and less activation in AD patients.

Table 1 Significant correlations of activation in frontal and mesial temporal regions of interest in young and older adults

	AC L	AC R	PC L	PC R	OFC L	OFC R	INS L	INS R	PHC L	PHC R	PIR L	PIR R	HIP L	HIP R
Young														
AC L	1													
AC R	**0.86**	1												
PC L	**0.98**	**0.74**	1											
PC R	**0.94**	**0.91**	**0.88**	1										
OFC L	ns	ns	ns	ns	1									
OFC R	ns	**0.71**	ns	ns	ns	1								
INS L	**0.70**	**0.92**	ns	**0.77**	ns	**0.82**	1							
INS R	ns	**0.90**	ns	**0.75**	ns	**0.90**	**0.98**	1						
PHC L	ns	ns	ns	ns	ns	ns	ns	ns	1					
PHC R	ns	ns	ns	ns	ns	**0.68**	ns	ns	ns	1				
PIR L	ns	**0.64**	ns	ns	ns	**0.88**	**0.65**	**0.73**	ns	**0.75**	1			
PIR R	ns	**0.86**	ns	**0.76**	ns	**0.96**	ns	**0.97**	ns	ns	**0.82**	1		
HIP L	ns	ns	**0.67**	ns	ns	ns	ns	ns	ns	ns	ns	ns	1	
HIP R	ns	ns	ns	ns	ns	**0.88**	ns	**0.68**	ns	**0.81**	**0.81**	**0.78**	ns	1

	OFC L	OFC R	AC L	AC R	PC L	PC R	INS L	INS R	HIP L	HIP R	PHC L	PHC R	PIR L	PIR R
Old														
OFC L	1													
OFC R	ns	1												
AC L	ns	ns	1											
AC R	ns	ns	**0.92**	1										
PC L	ns	ns	ns	ns	1									
PC R	ns	ns	**0.78**	**0.92**	ns	1								
INS L	ns	ns	ns	ns	ns	ns	1							
INS R	ns	ns	**0.68**	ns	ns	ns	**0.69**	1						
HIP L	ns	ns	ns	ns	ns	ns	ns	ns	1					
HIP R	ns	ns	ns	ns	ns	ns	ns	**0.73**	**0.76**	1				
PHC L	ns	ns	ns	ns	ns	ns	ns	**0.69**	**0.98**	**0.76**	1			
PHC R	ns	ns	ns	ns	ns	ns	**0.76**	ns	ns	ns	ns	1		
PIR L	ns	ns	ns	ns	ns	ns	ns	**0.73**	**0.76**	ns	**0.76**	ns	1	
PIR R	ns	**0.92**	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	1

OFC, orbitofrontal cortex; AC, anterior cingulate; PC, posterior cingulate; INS, insula; HIP, hippocampus; PHC, parahippocampal cortex; PIR, piriform cortex; L, left hemisphere; R, right hemisphere; ns, not significant.

Conclusions

The data suggest fronto-temporal disconnection and disruption in mesial temporal lobe connectivity in the aging brain. The functional connectivity analysis suggests that these disruptions may reflect large-scale age-related changes to olfactory network processing in addition to differences in processing in specific regions of interest.

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