Neuropsychologia 46 (2008) 1679–1687

NEUROPSYCHOLOGIA

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Altered deactivation in individuals with genetic risk for Alzheimer's disease

J. Persson [a,*], J. Lind [b], A. Larsson [c], M. Ingvar [b], K. Sleegers [d,e], C. Van Broeckhoven [d,e], R. Adolfsson [f], L.-G. Nilsson [a], L. Nyberg [g]

[a] *Department of Psychology, Stockholm University, S-106 91 Stockholm, Sweden*
[b] *MR Research Center, Karolinska Hospital, S-171 76 Stockholm, Sweden*
[c] *Department of Radiation Sciences-Radiation Physics, Umeå University, S-901 87 Umeå, Sweden*
[d] *Neurodegenerative Brain Diseases Group, Department of Molecular Genetics, Flanders Interuniversity Institute for Biotechnology, Antwerpen, Belgium*
[e] *University of Antwerp, Antwerpen, Belgium*
[f] *Clinical Sciences and Psychiatry, Umeå University, Sweden*
[g] *Department of Radiation Sciences (Diagnostic Radiology) and Integrative Medical Biology (Physiology Section), Umeå University, S-901 87 Sweden*

Received 30 April 2007; received in revised form 24 January 2008; accepted 30 January 2008
Available online 14 February 2008

Abstract

Regions that show task-induced deactivations may be part of a default-mode network related to processes that are more engaged during passive than active task conditions. Alteration of task-induced deactivations with age and dementia is indicated by atypical engagement of default-mode network regions. Genetic studies show a relation between the apolipoprotein E4 (*APOE*4) allele and the common form of Alzheimer's disease (AD), and altered functional brain activation has been observed in non-demented *APOE*4 carriers compared to non-carriers. Here we investigate the hypothesis of altered default-mode network brain responses in individuals with genetic risk for AD. Functional MRI was used to assess task-induced deactivation in 60 subjects of which 30 carried at least one copy of the *APOE*4 allele, and 30 non-carriers. Subjects were scanned while performing a semantic categorization task shown to promote episodic memory encoding. The results show patterns of deactivation consistent with the default-mode network. We also found reduced deactivation in non-demented *APOE*4 carriers compared to non-carriers, suggesting alterations in the default-mode network in the absence of dementia. These results implicate possibilities for investigating altered properties of task-induced deactivations in individuals with genetic risk for AD, and may prove useful for pre-clinical identification of individuals susceptible to memory problems and AD.

Keywords: Deactivation; Aging; *APOE*; Genetic; AD; Alzheimer's disease; fMRI; Compensation; Memory encoding

Task-induced deactivations in neuroimaging studies can be characterized as decreases in the measured brain response during an experimental condition compared to a low-level rest baseline or a control condition. Such deactivations (task < baseline) may reflect active processes engaged during the resting state. Deactivations have consistently been found in a set of brain regions including the medial frontal, medial and lateral parietal, and posterior cingulate cortex (e.g. Binder et al., 1999; Mazoyer et al., 2001). The consistency of deactivation in these regions across tasks suggests that they are independent of task characteristics and study material. One hypothesis is that regions that show deactivations are part of a "default-mode network" related to processes that are more engaged during passive- than active-task conditions (Raichle et al., 2001). According to the default-mode hypothesis, passive baseline is a state of structured processes that are interrupted when individuals engage in experimental tasks, resulting in relative deactivation when experimental conditions are compared with baseline conditions.

Recently, several studies have focused on to what extent task-related deactivation differs between young adults, healthy older adults, and patients with Alzheimer's disease (AD) (Grady, Springer, Hongwanishkul, McIntosh, & Winocur, 2006; Lustig et al., 2003; Persson, Lustig, Nelson, & Reuter-Lorenz, 2007; Rombouts, Barkhof, Goekoop, Stam, & Scheltens, 2005). For example, functional deactivation patterns in the medial PFC and PCC differ between patients with AD, healthy older adults, and young adults using a semantic classification task (Lustig et al., 2003). Lustig et al. (2003) found that deactivation in the medial PFC was reduced for both patients with AD and healthy older adults compared to young adults. Another intriguing finding was

* Corresponding author. Tel.: +46 8 163871; fax: +46 8 159342.
E-mail address: jonas.persson@psychology.su.se (J. Persson).

0028-3932/$ – see front matter
doi:10.1016/j.neuropsychologia.2008.01.026

found in the PCC, in which young adults showed deactivation, while older adults without dementia showed a marginal increase in activation. Individuals with AD had positive activations that were greater than for older subjects without dementia. This suggests age-related changes in deactivation, and that these changes get more severe with the progression of dementia.

Genetic studies have identified a relation between the apolipoprotein E-4 (*APOE*4) allele and the common form of AD (Strittmatter et al., 1993). Measures of resting state glucose metabolism using FDG-PET have found altered patterns of brain activity in *APOE*4 carriers compared to non-carriers (Reiman et al., 1996; Small et al., 2000). Typically, the characteristic changes observed in AD (reduced parietal, temporal, and posterior cingulate metabolism) appear in a less pronounced form in carriers of non-demented *APOE*4 carriers. More recently, neuroimaging studies have investigated task-related brain activation patterns in non-demented *APOE*4 carriers (Bookheimer et al., 2000; Lind et al., 2006b; Smith et al., 1999). A common finding is that increased risk for AD is associated with reduced activation in temporal, parietal and posterior cingulate regions (e.g. Lind et al., 2006b; Smith et al., 1999). In relation to the default-mode network, it is important to note that many of the regions that show reduced resting state metabolism in *APOE*4 carriers and patients with AD are regions that show deactivation in young adults.

One possibility is that altered PCC activity in AD reflects disrupted connectivity with medial temporal lobe (MTL) structures that are the earliest and most affected sites for AD pathology (Braak & Braak, 1994). Also, human and animal lesion studies show that damage to MTL regions result in reduced PCC resting metabolism similar to what is observed in AD (Aupee et al., 2001; Meguro et al., 1999; Reed et al., 1999). The analysis of deactivations may be critical to the understanding of the neural dynamics and network activity that underlie efficient and optimal brain function. This may prove to be especially important for characterizing global alterations in neural functioning that accompany normal and abnormal aging.

In the present study, we investigate the hypothesis that the default-mode network is abnormal in subjects with increased genetic risk for AD. We used fMRI to assess task-induced deactivations in 60 subjects of which 30 carried at least one copy of the *APOE* ε4 allele, and 30 non-carriers. Subjects were scanned while performing a semantic (abstract/concrete) categorization task shown to promote episodic memory encoding (e.g. Kapur et al., 1994). Of main concern was whether task-induced deactivation in frontal and parietal regions would differ as a function of genetic risk. Here we investigated differences in deactivation between carriers and non-carriers of the *APOE*4, as well as dose-related differences between carriers of either one or two alleles (*APOE*44 and *APOE*34), and non-carriers (*APOE*33), respectively.

1. Methods

1.1. Participants

Sixty cognitively intact persons between the ages 49 and 79 years participated in the present study. They were all recruited from *The Betula prospective cohort study: Memory, health, and aging* (Nilsson et al., 1997, 2004). Thirty subjects were carriers of at least one copy of the *APOE*4: 10 were homozygous (44) and 20 were heterozygous (34). The remaining thirty subjects carried two copies of *APOE*3 and were considered as controls. The same participants were included in prior studies, and the results have been reported elsewhere (Lind et al., 2006a, 2006b, 2006c; Persson et al., 2006a, 2006b). To examine a possible dose–effect, three subgroups consisting of 10 subjects each were composed: *APOE*44, *APOE*34 and *APOE*33. Participants were closely matched according to sex, age and years of education (see Table 1 for group characteristics). All subjects were non-demented and scored at or above the standard cut-off point of 25 on the mini-mental state examination (MMSE) (Folstein, Folstein, & McHugh, 1975). They were all right-handed, native Swedish speakers, and had no reported neurological problems that might cause dementia. Vision was normal or corrected to near normal using scanner compatible glasses or contact lenses. Subjects were paid for participation and informed consent was obtained in accordance with the guidelines of the Swedish Council for Research in the Humanities and Social Sciences.

Approximately 2 years after the reported MRI testing, 55 of the original 60 subjects were re-tested on a wide range of cognitive tasks as a part of the longitudinal Betula project and they still showed no signs of dementia. In addition, we compared the *APOE*4 carriers' explicit memory performance (based on three tests—face recognition, verbal recall, and recall of actions, for detailed description of the tests, see Nilsson et al., 1997) with normative data available from the Betula database. Twenty-eight of the 30 *APOE*4 carriers performed within 1 S.D. of the mean of their age group; two subjects scored below 1 S.D., but performed within 1 S.D. at the follow-up test (see above) 2 years after MRI testing. Together, these results provide evidence that all participants were cognitively intact.

1.2. APOE genotyping

A PCR was performed using 200 ng of genomic DNA as template in a 25-ml reaction mixture containing 20 pmol of PCR primers *APOE*-A (5′-TCC-AAG-GAG-CTG-CAG-GCG-GCG-CA-3′) and *APOE*-B (5′-ACA-

Table 1
Group characteristics

	APOE ε4 (*n* = 30)	*APOE* ε3/3 (*n* = 30)	*APOE* ε4/4 (*n* = 10)	*APOE* ε3/4 (*n* = 10)	*APOE* ε3/3 (*n* = 10)
Female/male	19/11	18/12	9/1	7/3	8/2
Age	65.6 (7.9)	66.6 (8.9)	63.1 (8.6)	65.6 (8.2)	64 (11.1)
Range	49–74	50–79	49–74	51–74	50–79
Education (years)	10.8 (3.6)	10.2 (3.2)	11.7 (3.1)	10.7 (4.0)	11.8 (3.1)
Range	6–17	6–16	8–16	6–17	9–16
MMSE	28.6 (1.3)	28.2 (1.3)	28.6 (1.2)	28.8 (1.2)	28 (1.2)
Range	25–30	26–30	27–30	26–30	26–29
SRB	24 (3.2)	21.6 (4.4)	22.8 (3.1)	24.7 (3.6)	22.2 (4.1)
Range	16–29	11–29	16–26	17–28	18–28

Note: Means and standard deviations (in parenthesis). MMSE = mini mental state examination (maximum = 30). SRB = word comprehension (maximum = 30).