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Brain metabolism in the cerebellum and visual cortex correlates with neuropsychological testing in patients with Alzheimer's disease

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Summary

This study was designed to measure glucose metabolic deficits in areas not typically recognized as abnormal on ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) scans in patients with Alzheimer's disease (AD), and to correlate such findings with subtle neuropsychological impairment. FDG-PET scans on 38 AD patients with no clinical evidence of visual, spatial or motor deficits were acquired on the PET HEAD scanner 40 min following the intravenous administration of 115 μCi·kg^{-1} of FDG. All FDG-PET scans were analysed blindly using a region of interest (ROI) template with regions for the primary visual cortex (PVC), secondary visual cortex (SVC) and cerebellum. Counts from the ROIs of these regions were normalized to whole brain activity and the results were compared with psychometric and neuropsychological measures. A number of significant correlations were found between these structures and various neuropsychological measures ($P < 0.05$). Specifically, there were significant correlations between clock drawing and the cerebellum activity; memory and activity in the PVC, SVC and cerebellum; social score and activity in the PVC and left cerebellum; judgement and activity in the right SVC and right PVC; and the overall Mini-Mental State Examination and activity in the PVC, SVC and cerebellum. The results of this study suggest that metabolism in areas not typically recognized as abnormal on FDG-PET scans in AD, such as the PVC, SVC and cerebellum, is correlated with deficits in neuropsychological function. This may have important clinical and pathophysiological implications in the study of AD and other illnesses of dementia. (© 2003 Lippincott Williams & Wilkins)

Keywords: alzheimers' disease, PET, neuropsychological.

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that usually presents with memory loss, followed by decreases in high-order cognitive skills, such as language, attention and planning. Functional brain imaging studies performed on AD patients using ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) usually identify significant reductions in the regional cerebral metabolic rate for glucose (CMRGlc) in the temporal and parietal lobes, and less frequently also in the frontal lobe [1–6]. The cerebellum, primary visual cortex (PVC) and secondary visual cortex (SVC) are usually considered to be relatively undisturbed by AD. Nevertheless, neuropathological findings and neuroimaging studies suggest the participation of these regions in the progression of the disease.

Cerebellar involvement in AD

Although the understanding of the diverse functions of the cerebellum has gradually increased, it is still

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primarily regarded as a centre of motor function. However, recent studies have shown that the cerebellum also subserves cognitive functions, such as the modification of linguistic, cognitive and affective behaviour [7, 8]. It seems likely that the cerebellum modulates rather than generates cognition [9, 10]. Using magnetic resonance imaging (MRI), Allin *et al*. [11] examined children born very pre-term, i.e. before 33 weeks of gestation. They found significant associations between cerebellar volume and several cognitive test scores, particularly the Wechsler Intelligence Scale for Children. Furthermore, the cerebellum might also be involved in social behaviour. A functional magnetic resonance imaging (fMRI) study performed by Critchley *et al*. [12] on patients suffering from autism or Asperger syndrome demonstrated reduced cerebral blood flow in the left cerebellum during the unconscious processing of emotional facial expressions. Utilizing fMRI, Bischoff-Grethe *et al*. [13] showed that areas of the lateral cerebellar cortex are involved during response reassignment or the coordination of rapid shifts of attention.

Neuropathological studies have revealed that the cerebellar cortex exhibits a characteristic and severe involvement in AD. Although classical staining techniques reveal amyloid plaques in the cerebellum of AD patients only sporadically [14], these plaques can be demonstrated in most cases if specific silver staining or immunocytochemical techniques are applied [15–18]. It has been demonstrated further that these plaques are frequently associated with dystrophic neurites [19, 20], and that microglia may play a fundamental role in their pathogenesis [21].

Although cerebellar glucose metabolism is often used to normalize regional metabolic data in AD, changes can be found there as well. A functional neuroimaging study performed by Ishii *et al*. [22] demonstrated not only a reduction in temporal and parietal glucose metabolism, but also a significantly lower cerebellar glucose metabolism in patients suffering from severe AD when compared with controls. Therefore, they suggested that the normalization of the regional glucose metabolism to cerebellar values might result in the inappropriate evaluation of cortical activity.

Visual cortex findings in AD

Although the visual cortex is commonly considered to be relatively unaffected by AD, there is a subgroup of patients who present with prominent visual symptoms [23, 24]. Functional brain imaging studies reported that the prominent visual symptoms are probably caused by cortical malfunction in the occipital and parietal lobes. Kiyosawa *et al*. [25] found hypometabolism in the visual association cortex and inferior parietal cortex in AD patients with visual symptoms when compared with AD patients without visual symptoms, whilst Pietrini *et al*. [26] demonstrated metabolic deficits in the parietal and occipital cortices, including the PVC, in AD patients with visual complaints. In another study, Mielke *et al*. [27] found a decrease in the regional CMRGlc in the PVC and SVC in AD patients with visual disturbances.

Although most studies regard this group as a disease entity different from classic AD, Rizzo *et al*. [28] suggested that they may 'represent the extreme end of a continuum of involvement in visual cortical areas, with most AD patients showing less but still significant visual dysfunction'. Furthermore, Cronin-Golomb *et al*. [29] investigated the relation between vision (examining colour discrimination, stereoacuity, contrast sensitivity and backward pattern masking) and cognition (examining object recognition) in AD. They found that visual dysfunction is 'not only a significant predictor of cognitive dysfunction in AD', but may also have 'a strong functional impact on performance in specific cognitive domains'. Thus, the involvement of visual cortical areas may be present in most AD patients and might add to the typical cognitive decline.

The involvement of visual cortical areas in non-motor tasks has been found in many studies. In a study performed on two monkeys [30], it was demonstrated that an early visual area, such as the PVC, may be more than a feature-detecting area, and may be involved in complex functions such as memory.

Pathological studies of the visual cortices in AD patients have demonstrated a number of changes. Examining the visual cortex, Leuba and Kraftsik [31] found decreased neuronal density, increased glial density, senile plaques (SP) and neurofibrillary tangles (NFT). In order to explain the predominantly inferior visual field defects seen in AD, Armstrong [32] examined both the cuneal and lingual gyri of area V1 in AD, and found a significantly greater density of NFT and SP in the cuneal gyrus in 39% of subjects. In an earlier study of 18 AD patients, Armstrong demonstrated that the density of SP and NFT was slightly greater in Brodmann's area 18 (B18) than in B17 in cases of earlier onset and shorter duration [33].

Purpose of this study

Although neither the cerebellum nor the visual cortex are areas usually associated with AD, the findings described above indicate that dysfunction in these structures may contribute to the cognitive changes experienced by AD victims. The aim of this retrospective study was to determine whether semiquantitative metabolic measures in regions not typically considered to be abnormal on FDG-PET scans in patients with AD, such as the

cerebellum, PVC and SVC, actually are associated with subtle cognitive and behavioural changes as determined on neuropsychological testing.

Methods

Subjects

In this study, approved by the University of Pennsylvania's Institutional Review Board, we retrospectively studied PET scans from 38 patients, aged 56–87 years, with a clinical diagnosis of AD based on the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) Work Group criteria [34]. These patients all suffered from progressive cognitive decline. Patients were included in the study if the results of their medical history, physical examination and laboratory studies were not indicative of an underlying disease process that could have caused or maintained the dementia. As we studied areas of the brain that were supposedly not involved in the pathogenesis of AD in these patients, it was confirmed that the subjects did not initially complain of deficits associated with the areas of interest.

PET imaging

Patients were scanned approximately 1 h after the intravenous administration of 115 μCi·kg^{-1} of FDG for 40 min on the HEAD PENN PET scanner. The scanner has a field of view of 25.6 cm, data are reconstructed using a three-dimensional reconstruction algorithm into an image matrix of 128^3, and the maximal spatial resolution at full width at half-maximum (FWHM) is approximately 4 mm. The patients were injected in a dimly lit room with their eyes open and their ears unoccluded. Ambient room noise was kept to a minimum. Patients had their head placed in a specially designed head holder to minimize movement during the study. In addition to the parameters described above, the images were acquired according to previously described methods and reconstructed using a Weiner filter with Chang first-order attenuation correction in axial, coronal and sagittal planes [35].

Image analysis

PET studies were analysed blindly on a Sun Microsytems workstation using the PETVIEW program. All images were re-sliced and re-aligned according to the anterior-posterior commissure line so that they could be analysed in the same orientation using a standard atlas overlay of regions of interest (ROIs) which has been validated previously [36]. The template's ROIs could then be manually adjusted in order to fit the brain of each individual subject. The specific ROIs from the template that were evaluated in this study were the PVC, SVC and cerebellum. Each ROI was normalized to whole brain activity. Whole brain counts were determined by the weighted mean average of the regional values for all available slices.

Neuropsychological examination

All patients underwent neuropsychological examination using the Mini-Mental State Examination (MMSE) with possible scores of zero (severely demented) to 30 (normal) [37] and the Dementia Severity Rating Scale (DSRS). The DSRS has been described previously and is a functional measurement incorporating both cognitive impairment and activities of daily living [38]. For the DSRS, zero is normal and the higher the score, the worse the cognitive impairment. An experienced neuropsychologist, who was blind to any of the PET imaging results, performed the testing.

Data analysis

For further analysis, we used both the overall MMSE score and the DSRS scores in memory, judgement, social skills and orientation in time and space. To demonstrate the relation between both social skills and orientation in time and the ROIs mentioned above, Spearman correlations were calculated. Linear regressions were calculated to demonstrate the relation between the ROIs and scores in memory, judgement, orientation in place and overall MMSE. Furthermore, descriptive statistics were determined for all measures. All calculations were performed using Graphpad Prism Version 3.02 for Windows. As the number of regions analysed was very small, we did not account for multiple comparisons; however, most of the results presented would also hold in such a case.

Results

A number of significant correlations were found between the metabolism in the cerebellum and visual cortex in AD and various neuropsychological measures. Specifically, there were significant correlations between clock drawing and right cerebellar activity ($R = 0.40$, $P = 0.02$). The correlation between clock drawing and left cerebellar activity was not as significant ($R = 0.34$, $P = 0.05$). There was a significant correlation between the scores on memory testing and activity in the PVC, right cerebellum and left cerebellum (see Table 1). There was also a

Table 1. Correlation between metabolism in the primary visual cortex areas and results from neuropsychological tests of memory, Mini-Mental State Examination (MMSE) and social function.

	Memory		*MMSE*		*Social*	
Structure	*R*	*P*	*R*	*P*	*R*	*P*
Primary visual cortex						
Left posterior	0.23	0.16	0.49	0.001	0.29	0.07
Left anterior	0.3	0.06	0.27	0.09	0.27	NS
Right posterior	0.4	0.01	0.57	<0.001	0.4	0.01
Right anterior	0.34	0.03	0.54	<0.001	0.4	0.01
Secondary visual cortex						
Left	0.39	0.01	0.15	NS	0.25	NS
Right	0.4	0.01	0.19	NS	0.24	0.03
Cerebellum						
Left	0.42	0.006	0.39	0.01	0.43	0.01
Right	0.38	0.01	0.29	0.06	0.36	0.02

significant correlation between the scores on memory testing and activity in the left and right SVC ($R = 0.39$ and $R = 0.40$, respectively, $P = 0.01$). The social score correlated significantly with activity in the PVC, right SVC and right and left cerebellum (see Table 1). Judgement correlated significantly with activity in the right SVC ($R = 0.36$, $P = 0.03$) and the right posterior PVC ($R = 0.34$, $P = 0.03$). Finally, the overall MMSE correlated significantly with activity in the PVC and left cerebellum. The correlation of the MMSE with the right cerebellum was not as significant ($R = 0.29$, $P = 0.06$).

Discussion

AD typically presents as a progressive cognitive decline that can begin in patients from the age of 50 years. This dementia is also associated with the histological appearance of amyloid plaques and NFT. From an imaging standpoint, FDG-PET has been widely used for the study and diagnosis of AD. Initial FDG-PET studies have shown that there is a 20–30% decrease in whole brain CMRGlc values in patients with AD when compared with healthy age-matched controls [39]. Other studies have shown that patients with AD have decreased whole brain glucose metabolism, with the bilateral parietal and temporal lobes particularly affected [40, 41]. Thus, the 'typical' pattern of AD on FDG-PET studies is temporoparietal hypometabolism. In fact, in a study of 26 patients with cognitive dysfunction, bilateral parietal hypometabolism was successful in predicting AD as much as 13 months prior to the clinical diagnosis of AD by NINCDS-ADRDA criteria [42]. However, it should be noted that, although the bilateral parietal pattern is highly predictive of AD, it is not pathognomonic for AD and can be seen in patients with other neurological disorders [43]. Furthermore, it is not possible to distinguish AD patients from non-Alzheimer's dementia patients based on the quantitative measurement of absolute whole brain metabolism [44].

In patients with AD of varying severity, the magnitude and extent of hypometabolism have been shown to correlate with the severity of the dementia symptoms [45]. There are no significant metabolic changes or only minor decreases in the parietal lobes in patients with early AD. Moderately affected patients show significantly decreased metabolism in the bilateral parietal lobes and the superior temporal regions. In patients with severe AD, the same regions are affected, but the hypometabolism is much more pronounced. Longitudinal studies have shown that cerebral glucose metabolism decreases more rapidly over time in patients with AD than in age-matched control subjects [46]. There is also a more severe decrement in parietal lobe metabolism compared to frontal lobe metabolism over time.

Other areas, such as the sensorimotor and visual cortices, subcortical nuclei, brain stem and cerebellum, have relatively preserved glucose metabolism in patients with AD, except where there is a specific clinical deficit. In AD patients with visual complaints, the PVC and SVC have been found to show metabolic dysfunction [26, 27]. The finding in other studies that dysfunction in the visual cortices may be related to cognitive deficits is pertinent, and may be useful in the assessment of AD patients over time [29]. The role of the cerebellum in the modulation of cognition [9, 10] is also significant to the assessment of AD patients. The cerebellum, not thought to be abnormal on FDG-PET scans in patients with AD, exhibits changes on both neuropathological examination [15–21] and functional imaging of AD patients [22]. In many cases,

dysfunction in these areas may be present and may contribute to cognitive decline, but is not readily apparent in the daily function of patients.

In this study, it was particularly important that the patients did not specify clinical symptoms directly related to the visual cortex or cerebellum. These areas were supposedly not involved in the pathophysiology of AD in these patients and should not have been abnormal on FDG-PET scans. This study not only demonstrated metabolic changes in these areas, but also found that such changes were associated with dysfunction when subjects were extensively studied by neuropsychological testing. Studies correlating cerebral glucose metabolism to MMSE scores and other neuropsychological tests have consistently shown a relationship between these measures in patients with AD [47, 48]. This association is particularly true when parietal and temporal lobe metabolic rates are compared with neuropsychological deficits. Thus, PET imaging with a focus not only on the areas typically involved in AD, but on other brain structures as well, can provide important clinical information in patients with AD, and may also have a role in the evaluation of the extent and progression of cognitive dysfunction.

Conclusions

The results of this study suggest that metabolism in areas not typically recognized as abnormal on FDG-PET scans in patients with AD, such as the PVC, SVC and cerebellum, is correlated with deficits in neuropsychological function in AD patients. This observation may have important clinical and pathophysiological implications in the study of AD and other illnesses of dementia.

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