Functional brain imaging as a looking-glass into the degraded brain: reviewing evidence from Alzheimer disease in relation to normal aging

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Abstract

Research on the real-time relationship between brain activity and mental performance is intense. However, relatively few studies have been devoted to patients with different diseases or lesions. Such studies may cast light on certain aspects of brain activity, such as plasticity. This review summarizes studies on Alzheimer’s disease (AD) patients where the techniques to map brain activity in relation to mental performance have been utilized. Research findings suggest, that there is a spectrum of changes in AD patients that is distinct from that seen in healthy aging. These changes include: (i) loss of activated regions, (ii) reduced activation possibly due to brain degeneration typical of AD, (iii) the emergence of newly activated regions in order to compensate for minor brain deterioration (e.g., an enlargement of activated regions sometimes manifested as an increased bilaterality or a hemispheric shift of activation, and dedifferentiation), (iv) decreased level of activation, and (v) no change at all, which may occur in easy tasks or tasks that do not involve regions exposed to brain atrophy. In conclusion, the pattern of activation in AD depends on interactions between the clinical stage of patients, and the pattern of brain degeneration, as well as the task difficulty and specific networks necessary for solving the task.

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1. Introduction

This review is focused on research findings in Alzheimer’s disease (AD) using various functional techniques to describe patterns of brain activity that are parallel to the performance of specific cognitive tasks. Although only AD is reviewed, both the patterns of performance and activation may vary, due to the degree of disease. This point may be crucial, because AD is a progressive degenerative disease with a continuous course that starts in healthy aging where only minor changes in the brain and performance of cognitive tasks are seen compared to healthy young individuals. After many years, the course of AD finally develops into a terminal stage when the brain is heavily affected by the disease process. The fact that AD has a long duration has to be taken into account by stating the disease stage when talking about the disorder. Therefore, this review begins with a brief presentation of the stage-related erosion of the brain and cognitive deterioration that occur during the disease course of AD.

AD is characterized by progressive cognitive, affective, and behavioral changes, which will be described as a disease course in three stages. The starting point of AD is an impairment of episodic memory that occurs during the preclinical period of the disease, when it is not possible to set a diagnosis. During this period, some elderly individuals, otherwise regarded as normally aged, may be influenced by incipient AD resulting in symptoms and minor cognitive difficulties that are mainly associated with episodic memory (Almkvist et al., 1998). At some point during the disease process, changes in the brain have become serious enough to make possible a diagnosis of AD according to clinical manuals (American Psychiatric Association, 1994). At this early clinical stage the deficit of episodic memory is more serious. In addition, there are clear abnormalities in several cognitive domains such as executive functions, attention, semantic memory, and visuospatial ability. Despite the fact that there are pronounced multifactorial changes in cognition, certain other aspects of cognition may be relatively spared. Sensory and motor performance, immediate and implicit memory, as well as procedural skills and memory are all examples of those abilities that are relatively preserved in the early part of AD. This stage is often noted in the literature as very mild or mild degree of dementia. Finally, the third stage of AD is reached, during which patients are recognized as demented to a moderate or severe extent. At this stage, the cognitive and behavioral deficits are so pronounced that an independent living is impossible for the patient. The whole disease process may last many years, often for at least one decade. This causes serious problems for defining the stage of the patient and level of performance.

The cause of the cognitive changes in AD is a continuous degeneration of the central nervous system, which follows a certain course (Braak & Braak, 1995; Price, Davis, Morris, & White, 1991). The neuropathology of AD is characterized by the number of senile plaques (SP) and neurofibrillary tangles (NFT) in various brain regions, which has been used for definite diagnosis (Khatchaturian, 1985). Based on the number and distribution of NFTs, it has been possible to model the pathology of the disease process into three stages, termed the transentorhinal, limbic, and isocortical (Arriagada, Marzloff, & Hyman, 1992; Braak & Braak, 1995). The tran-
sentorhinal is identified as the preclinical stage of AD and is demarcated by mild changes in the hippocampus and transentorhinal region, whereas no changes are observed in the isocortex itself. Interestingly, many elderly individuals recognized as normal have neuropathological changes that are typical for this first stage of AD (Arrigada et al., 1992; Ball, 1977). The limbic stage is mentioned as the first clinical stage and is defined by the appearance of NFT neuropathology in the isocortex, in addition to a marked number of NFTs in the medial temporal lobe. At the same time, there are no findings of neuropathology in the sensory or motor regions of the brain. In the last stage of fully developed AD, the isocortex is severely affected by NFTs, but there is still comparatively little neuropathology in the sensory or motor regions of the brain. This three-stage model summarizes the neuropathological distribution seen during time course of AD.

It is well-known from previous research that elderly individuals may be impaired in episodic memory. Parallel to the cognitive changes seen in elderly individuals, the brain may also show subtle degeneration in normal aging as demonstrated in studies of neuropathology (Ball, 1977) as well as by structural brain imaging (Pfefferbaum et al., 1994; Smith, 1996). The changes of brain morphology seen in normal aging are characterized by selective cell loss in posterior association areas, as well as in medial temporal regions (Ball, 1977). These changes are similar to those that appear in very early preclinical stages of AD, when the disease can not be diagnosed according to standard diagnostic manuals. These features suggest that there are similarities both in cognitive functioning and brain conditions in at least some non-demented elderly individuals, and in preclinical AD. Because of this, knowledge obtained on elderly individuals is relevant for AD. Because normal aging is associated with subtle brain changes that are similar in type but not extent to those found in AD, normal aging may be viewed as a very first stage of AD, that is followed by the continuous deterioration, across preclinical stages of AD into the full-blown clinical manifestations of AD.

2. Methods

To study brain activation in conjunction with mental performance, a number of techniques are available including positron emission tomography (PET) with $H_2^15O$ as a tracer of blood flow or glucose as a tracer of energy metabolism, functional magnetic resonance imaging (fMRI), regional cerebral blood flow (rCBF) using single photon emission computed tomography (SPECT) with HMPAO or $^{133}$Xenon as tracers of blood flow, magnetic encephalography (MEG), as well as electrophysiological techniques as exemplified by event-related potentials (ERP). The present review covers studies using all these types of functional imaging techniques, although they differ markedly in temporal and spatial resolution. Temporal resolution is most favorable with ERP and MEG (time resolution in ms), whereas spatial resolution is best obtained with fMRI (approximately a few mm$^3$). The time and spatial resolution for PET is poor (approximately 40 s, and 0.5 cm$^3$, respectively) for most current equipments.
3. Empirical findings in aging and AD patients

Section 4 summarizes empirical findings organized in cognitive domains and processes within domains. Each domain is introduced by presenting findings from studies of aging (if any) which serve as the point of reference for findings in AD. The present review is based on a MEDLINE search of functional studies in AD and in healthy aging.

3.1. Perception

In visual perception, there is abundant research to support the view that there is an occipito–temporal stream (ventral system) subserving object identification, and an occipito–parietal stream (dorsal system) that is responsible for perceiving spatial relations between objects.

3.1.1. Perception in aging

Grady et al. (1993, 1996) reported results from experiments on a face-matching task (indicated by pressing a button for which of two faces was the same as the target picture) and a location matching task (indicated by pressing a button for which of two squares contained an inner smaller square in the same position as the target square), both tasks performed as forced-choice and match-to-sample. For both experimental tasks, the control task was similar to the location task except for location information. The subjects were elderly 65 ± 9 yr, and did not include those that might be compromised by health problems influencing the brain. The response consisted of pressing a button, right or left, depending on whether the correct item was to the right or the left side of the stimulus array. In the face matching task, there was a selective activation of the ventral occipito–temporal region bilaterally (fusiform gyrus), whereas the location matching task activated superior parietal cortex bilaterally. This was in accordance with the expectation of finding activation of the ventral and dorsal systems for visual perception. Interestingly, the size of the activated regions was much larger in elderly individuals than in young subjects, although the level of performance was similar. The finding that larger areas were activated in elderly individuals was interpreted as a compensatory effort to maintain the efficacy of performance.

A MEG study of auditory evoked potentials during tone pips presented to the left ear revealed that healthy aged persons had delayed signal processing, as measured by latencies of P50 and N100 compared to young subjects in the ipsilateral auditory cortex (Pekkonen et al., 1995).

3.1.2. Perception in AD

Grady et al. (1993) used a face-matching task (see above) was used in a study of very mild to moderately demented AD patients ranging in MMSE scores between 14–28, compared to age-matched controls (Grady et al., 1993). Results showed a significant activation of the lateral and medial occipital and occipito–temporal cortex bilaterally during face-matching in AD patients. This effect was similar to that
found in healthy elderly subjects. The interaction between subject groups (AD vs controls) and task (face-matching vs control task) was significant in two regions that showed greater activation in the AD group, namely the occipital pole and a frontal region (eye fields). In both these regions, the activation was greater in the right, compared to the left hemisphere. These differences between groups occurred despite a similar performance level, accuracy of response or reaction time. The correlations between task performance and brain activation were not statistically significant for any region or group of subjects, although clearly positive in many cases.

A study of the mental rotation task compared to resting state in AD by Deutsch and Halsey (1990) using rCBF with $^{133}$Xenon as a tracer of blood flow demonstrated a bilateral symmetrical activation and a significant correlation between performance and right hemisphere activation in AD patients. In contrast, controls activated only the right hemisphere. Interestingly, there was a reduced activation of the right hemisphere in both very competent and poor subjects.

A MEG study of auditory evoked potentials during tone pips presented to the left ear revealed that AD patients had impaired auditory processing as shown by prolonged P50 and N100 latencies in the ipsilateral but not contralateral auditory cortex and as compared to health aged persons (Pekkonen et al., 1996).

To summarize, the pattern of brain activation in the face-matching task seems to be similar in elderly individuals and AD patients who vary in their degree of global cognitive deterioration from mild to moderate. The selective activation of some regions within the AD groups may be interpreted as a compensatory measure to maintain performance when there is a reduced ability to process visual stimuli. MEG studies have demonstrated that both AD and aging may be characterized by a delayed processing of auditory stimuli.

### 3.2. Attention

Attention is commonly subdivided into three types, namely selective, divided and sustained attention. Most studies have investigated selective attention, in which the typical findings are an activation of the prefrontal, midfrontal, and posterior parietal cortices in addition to the anterior cingulate and thalamus (Frackowiak, Friston, Frith, Dolan, & Mazziotta, 1997).

#### 3.2.1. Attention in aging

Using PET, Johannsen et al. (1997) studied sustained and divided attention. The subject was instructed to detect change in frequency in one or both of two sensory stimulations, a visual red–black checkerboard oscillating at 7 Hz and a vibrotactile stimulus applied to the right-hand fingers at 110 Hz. The same stimulation was presented during experimental and control sessions, the only difference being the instruction to detect frequency changes during experimental session, although this did not occur. After the experimental sessions, the subjects were asked whether a change had occurred or not. The subjects tested were in the age range of 51–73 yr. The health status was investigated by means of physical examination and structural imaging of the brain with MR. Two main areas were significantly activated for both
tasks, namely the right middle frontal gyrus (BA 46) and the right inferior parietal lobe (BA 40). There were no marked differences due to the type of stimulation. The findings were interpreted as confirming the hypotheses that the right posterior parietal area is a center of a cortical network subserving both divided and sustained attention as well as selective attention.

3.2.2. Attention in AD

In a subsequent study (Johannsen, Jakobsen, Bruhn, & Gjedde, 1999), normal elderly persons and age-matched AD patients were investigated using the same two tasks of detection of change in one stimulus (sustained attention) or two stimuli (divided attention). The AD patients varied between mild to moderate and in a few cases severe, as assessed by the Mini-Mental Examination score (10–24). When all attentional tasks were aggregated, the results showed a significant activation in the right middle frontal gyrus (BAs 46, 10), inferior parietal lobe (BA 40) and right medial frontal gyrus (BA 6) for the normal elderly. The AD patients showed a significant deactivation in the medial frontal regions (BA 11), left orbital (B 11), right lingula (BA 17), and posterior cingulate cortex (BA 23); whereas no region was significantly activated.

In sustained attention, significant activation occurred in the right inferior parietal lobe (BA 40), and the right middle temporal lobe (BA 20), whereas deactivation occurred in the right cerebellum and left parahippocampal gyrus (BAs 28, 35) for the controls. For AD patients, a significant activation was observed in the left anterior cingulate gyrus (BA 24), and deactivation in the right and left medial frontal gyri (BA 19), right posterior cingulate (BAs 23, 31) and left superior frontal gyrus (BA 10), as well as cerebellum.

In divided attention, the control subjects activated the right middle (BA 46) and inferior (BA 45) frontal gyri, whereas no deactivation were found. In AD patients, the right medial frontal gyrus (BA 32) was activated, but no deactivations were found.

An ongoing study of ours on attention has been designed to combine the measurement of blood flow and nicotinic receptor activity in relation to mental performance (Almkvist et al., in preparation). In this study, attention was operationally defined using the Rapid Visual Information Processing task. This is a task of sustained attention, which in comparison to rest shows an activated inferior frontal gyri bilaterally, parietal cortex and fusiform gyrus, and right superior frontal gyrus in healthy young subjects (Coull, Frith, Frackowiak, & Grasby, 1996). Preliminary results demonstrated that mildly demented untreated AD patients (MMSE between 21–29) demonstrated a significant activation of the anterior cingulate cortex, thalamus, and cerebellum comparing task performance with resting state. After treatment with cholinesterase inhibitors during 12 weeks, an increase in activation was observed in bilateral parietal regions as measured by blood flow. If the finding holds true, that parietal regions may be reactivated, then this study would indicate that drug treatment may support a restoration of networks that are utilized in normal subjects, but there are probably distressed or partly destroyed by the disease process in untreated AD patients.
ERP-studies of attention in AD patients using an auditory oddball paradigm have yielded conflicting results (Green & Levey, 1999; Boutros, Torello, Burns, & Wu, 1995). Green and Levey (1999) observed that subjects at an increased risk of developing AD showed a prolonged latency of the P3 component at the central parietal derivation, as compared to low-risk individuals. There were no group differences at other derivations or in amplitude. A similar study (Boutros et al., 1995) showed that there was an increased amplitude in subjects at an increased at risk to develop AD, but no group differences in latency.

In summary, group comparisons demonstrated that the pattern of activation for AD patients resembled that of the healthy aged individuals during sustained attention, which primarily involved increased activation of the anterior cingulate cortex. Also the pattern of activation for AD cases differed from healthy aging during divided attention. According to Johannsen et al. (1999), the main difference between AD patients and controls in divided attention was a lack of activation in AD patients. This may have been due to a number of factors including, misunderstanding of task demands, differential responses of anxiety during the experiment, the use of different strategies to perform the task, impaired task performances, destroyed neural tissue, or most probably a combination of the last two points. In addition, ERP-studies have provided evidence for a possible negative influence in parietal areas in AD during sustained attention.

3.3. Priming

Priming refers to the facilitation effect that prior exposure may have on memory performance. For example, the exposure of the word “PROBLEM” increases the probability above chance to come up with that specific word when asked to complete the word fragment PRO—. This kind of implicit memory performance relies to a large extent on brain regions that are related to the modality of stimulus presentation.

3.3.1. Priming in aging

In a PET study (Bäckman, Almkvist, Andersson, Nordberg, Winblad, Reineck, & Längström, 1996), young as well as healthy elderly individuals demonstrate a decreased blood flow on PET in the right occipital cortex (BA 19) in association with priming. The experimental condition comprised of studying a list of words followed by word-stem completion with visual presentation of stimuli. In the baseline condition, there was word-stem completion only.

There is also converging evidence from studies using event-related potentials that young and healthy elderly individuals perform similarly in word repetition priming (press a button in response to target word vs no response to non-target words). Furthermore, young and healthy elderly individuals demonstrate similar brain activity during priming (Friedman, Hamberger, Stern, & Marder, 1992).
3.3.2. Priming in AD

In contrast to decreased activity seen in healthy elderly individuals, very mildly demented AD patients (mean age: 60 ± 7, MMSE: 26 ± 7) have shown an increased activity in the same regions during priming (Bäckman, Almkvist, Nyberg, & Andersson, 2000). In this study, priming was evaluated by word stem completion comparing condition preceded vs. not preceded by a study list of target words. Thus, a poorer priming performance is associated with an increased activity in AD. This may be interpreted as a compensatory action by the nervous system, when the neuronal substrate has begun to lose its operational capacity.

By using event-related potentials to observe brain activity in relation to word repetition priming with semantic (animal target words) and orthographic (target words in uppercase letters) orienting tasks (Friedman et al., 1992), it has been shown that mild AD patients display the same general trends of ERP-activity as do old controls. However, ERP activities were not as marked in the mild AD patients, which may be due to an impaired performance, compared to controls. The spatial distribution of the ERP-effect was most pronounced at frontal derivations and was generally larger in the right hemisphere. Furthermore, the ERP-effect was more marked in word repetition priming with semantic than with orthographic orienting tasks. There was a lack of significant correlations between ERP-activity and dementia severity.

Recent research on semantic word repetition priming with a lexical decision task (words vs non-words) in AD patients vs age-matched controls showed no evidence of a priming effect either in behavioral data or in ERP-activity at long time lags. In contrast, clear priming was seen at short time lags (Schnyer, Allen, Kaszniak, & Forster, 1999). These data suggest that short- and long-term priming effects may have a different origin, whereby a perceptually based and automatic priming is related to central parietal region and, and a non-perceptually based priming with some degree of awareness is related to frontotemporal augmentation of the ERP-activity.

To summarize, previous research has shown that AD patients demonstrate a reduced performance in many priming tasks as compared to healthy elderly subjects. It has also been shown that brain activity is changed in AD, as evidenced by reduced ERP-activity and increased blood flow. This may indicate a compensatory action taken by the brain to balance the reduced ability to perform the task.

3.4. Working memory

Working memory is divided into two parts according to recent research. One component is devoted to processing of temporary information, mentioned as slave-systems (e.g., a phonological loop or visuospatial scratch-pad depending on the internal information representation). The other attentional component organizes the specific slave systems (see e.g., Frackowiak et al., 1997). A number of left hemisphere regions are occupied for verbal material, for instance Broca’s and Wernicke’s areas, as well as inferior parietal and other regions. Right hemisphere regions are activated for visuospatial material, and the specific regions activated appear to depend on the task, or operations on visual or spatial information.
3.4.1. Working memory in AD

Working memory has been studied in healthy aging and AD by Becker et al. (1996a,b). This research group used an experimental paradigm, in which the task to repeat three words orally after being presented to material was compared to the rest. This paradigm, therefore, tested auditory processing, working memory, and speech output. The small differences in performance seen between groups did not reach statistical significance, and the regions activated during this subspan task were equivalent for AD patients and controls, although the field of activity was greater in AD patients. The regions activated in both groups included the precentral gyrus (BA 6), superior and middle temporal gyrus (BAs 22, 21), postcentral gyrus (BA 40), temporal cortex (BA 42), and Broca’s area (BA 44), which was suggested to represent phonological processing and temporary storage. In contrast, some regions showed deactivation in both groups, namely the anterior and posterior cingulate cortex, and precuneus. No disease-related effects were found for the pattern of brain activation seen during these working memory tasks.

3.5. Semantic memory

Semantic memory concerns a network of associations and concepts of basic knowledge about the world that appear to be comparatively preserved in old age, but which are impaired in AD. The reason for this loss of knowledge can most probably be accounted for by positing a breakdown of the semantic network rather than an increased difficulty to access the knowledge searched for. Functional imaging on young adults and lesion studies have yielded a left hemisphere involvement in semantic memory tasks, particularly an involvement of inferior frontal and temporo–parietal regions.

3.5.1. Semantic memory in AD

A fMRI study on mildly demented AD patients with a mean age of 79 yr and healthy controls with a mean age of 71 yr, used two semantic processing tasks (comparison of correct vs. incorrect category–exemplar and category–function word pairs) and one phonological decision task (comparison of whether pseudo-words were similar or not). All tasks were presented auditorily and required squeezing a bulb when correct pairs appeared (Saykin et al., 1999). In both semantic tasks, there was a consistent activation of the inferior frontal lobes both in controls and AD patients, although the areas of activation were larger in AD patients. These findings were corroborated by statistically significant correlations between mental performance and signal strength in the frontal regions for both groups. Furthermore, there was evidence of more remote areas activated by the AD group, suggesting other mechanisms of reallocation of brain resources. As expected, the temporo–parietal region was significantly activated in controls but not in AD patients during category–exemplar decisions. This finding may be due to the typical bilateral morphological temporo–parietal reduction of the brain seen in early AD.

Subjects at high risk for developing AD (estimated 40%; n = 14), as assessed by apolipoprotein genotyping and the existence of a first degree relative with AD, were
compared with subjects at low risk for developing AD (estimated 9%; \( n = 12 \)) in covert object naming (initiated by a line drawing of a common object) and covert letter fluency (initiated by a letter on the screen) by fMRI (Smith et al., 1999). In the baseline task, the subject was asked to monitor the continuous change in gray of a square presented. All subjects were about 50 yr of age, well educated, and healthy according to a screening procedure. They all performed well in a number of neuropsychological tests. The high risk group was thought to represent preclinical AD. Results showed that both groups activated similar regions, such as for naming the occipital lobe (BA 19), precuneus (BA 7), inferior temporal region (BA 37), inferior frontal lobe (BAs 45, 47), and for letter fluency the bilateral occipital lobe (BAs 18, 19), inferior temporal lobe (BA 37), inferior frontal lobe (BAs 44, 45), and left premotor cortex (BA 6). Although the two groups performed similarly in naming and letter fluency at clinical examination, the high risk group showed a significantly reduced activation in a couple of regions, these being for naming and letter fluency in the inferior temporal lobe (BAs 19, 37) and for naming only the precuneus (BA 7). Although, the results of this study are seductive, they should be interpreted with caution due to the relatively small difference between groups in terms of risk to develop AD.

Two ERP-based studies of semantic memory using the N400 potential have been reported (Castaneda, Ostrosky-Solis, Perez, Bobes, & Rangel, 1997; Ostrosky-Solis, Castaneda, Perez, Castillo, & Bobes, 1998). One study investigated a decision task of congruency (congruent vs. non-congruent pairs of pictures of objects and animals) in AD patients (MMSE: 14–22), 59–89 yr old, compared to controls, 54–82 yr old (Castaneda et al., 1997). Results showed a poorer performance in AD patients in conjunction with a main effect of group on ERP-activity as well as a more posterior and right hemispheric maximum for elderly controls. The topographic distribution was more diffusely located in AD patients. These results were interpreted as providing evidence for deficient associative connections within the semantic network in AD.

Another ERP-based study investigated the congruency between sequentially presented pairs of pictures (match vs. mismatch of pairs of objects) in AD patients (MMSE: 14–22) and elderly control subjects (Ostrosky-Solis et al., 1998). Results showed that AD patients were impaired in task performance as compared to controls, and had a reduced amplitude of the N400 potential, which marked in incongruent trials. The scalp distribution was different between controls and AD patients. The largest effect was seen in the right central parietal area for elderly controls, whereas no significant amplitude gradient was seen in the AD group. Also, the peak latency differed between groups; the amplitude peak being more delayed in the AD patients, as compared to controls. The difference between groups was clear in response to incongruent trials, but was less so in congruent trials. This finding can be related to a hypothesis that the N400 potential represents spread of activation in the semantic network, which may be less efficient in AD patients, as compared to healthy aged individuals.

In summary, various tasks requiring semantic processing (decision, naming, and fluency) appear to involve frontal as well as posterior areas, such as the inferior...
temporal lobe in addition to areas involving stimulus and response processing. The degree of activity in the temporal areas may be less in AD patients than controls probably due to degradation of the semantic network. ERP-studies have shown that there is a delayed response and a more wide-spread pattern of activation during semantic decision tasks in AD compared to aging.

3.6. Episodic memory

There has been much research on postmortem examination of brain structures, focal brain lesions, and brain measurement in vivo using structural imaging techniques, as well as resting state brain metabolism, showing that medial temporal structures, particularly the hippocampus, are crucial for episodic memory. There have been many studies in young adults using functional imaging of episodic memory. However, relatively few functional imaging studies have investigated elderly person’s encoding and retrieval operations (Bäckman et al., 1997; Cabeza et al., 1997; Grady et al., 1994; Madden et al., 1999; Mark & Rugg, 1998), or episodic memory in AD (Bäckman et al., 1999; Becker et al., 1996a,b; Cardebat et al., 1998; Duara et al., 1992; Herbster et al., 1996; Kessler, Herholz, Grond, & Heiss, 1991; Miller, De Leon, & Ferris, 1987; Small, Perera, DeLaPaz, Mayeux, & Stern, 1999; Tendolkar et al., 1999).

3.6.1. Encoding in aging

Encoding of word pairs was studied in healthy well educated elderly subjects (67–75 yr of age) by a group of Toronto (Cabeza et al., 1997). Encoding (reading the first word silently and the second aloud during instruction to memorize) was compared to the average of encoding and two retrieval tasks (see below under retrieval in aging). Results showed an age-related decrease of activation in left prefrontal regions and bilateral occipito–temporal regions. This was interpreted as reflecting encoding operations proper and object perception, respectively. An age-related increase of activation was observed in bilateral insular regions, which may have reflected functional compensation.

Grady, McIntosh, Rajah, Beig, and Craik (1999) studied encoding during three types of instruction to encode words and pictures (to make judgements on semantic features living/non-living, and physical features of size, or intentional learning instructions) in healthy elderly individuals (age range: 58–73 yr). An analysis of brain activation in combined experimental conditions using partial least square technique showed that old subjects utilized the same network as young subjects, but to a lesser degree of activation. The first pattern of brain activation concerned material-specific encoding and included bilateral, prefrontal, premotor, temporo–parietal, and cingulate regions during word encoding. These activations were more pronounced for the left hemisphere. For picture encoding, the network included bilateral ventral and dorsal extrastriate regions, were more pronounced for the right hemisphere. For picture encoding, medial temporal regions were included, but not for elderly subjects.
A second pattern of brain activation concerned strategy-specific encoding. Again the elderly utilized the same network as young subjects, but the degree of activation was lower. The network included anterior prefrontal regions, cingulate, hippocampus, and thalamus during semantic encoding. No group difference in brain activation could be found, when deep and shallow encoding was compared. Deep processing relied on left prefrontal and bilateral medial temporal regions. Finally, it was noted that the age-related findings were more marked for words than for pictures.

In summary, encoding operations in healthy elderly individuals appear to involve the same regions as are found in healthy young subjects, although the degree of activation is lower. Parallel to this finding of brain activation, behavioral results show poorer performance in old as compared to young adults of comparable health status. Hypothetically the pattern of brain activation reflects both operations on the material as demonstrated by the involvement of frontal regions, as well as mental representation of the material, as demonstrated by involvement of posterior regions.

3.6.2. Encoding in AD

Four studies have been published on encoding in AD (Cardebat et al., 1998; Duara et al., 1992; Madden et al., 1999; Small et al., 1999).

Duara et al. (1992) investigated very mild to severe AD (MMSE: 9–30) during reading of prose for 30 min with the instruction to memorize the material. Patients were studied using PET with 18F-fluorodeoxyglucose as a tracer of brain glucose metabolism. This procedure showed a significant increase during task performance, compared to resting state, in brain metabolism for both groups in all 16 regions measured (right and left cortex of prefrontal, premotor, orbito–frontal, inferior parietal, superior and medial temporal, medial and lateral occipital). This increase was greatest in occipital regions. There were no diagnostic group by task interactions or task by region interactions. There was no statistically significant relationship between the extent of brain activation and degree of dementia. The study concluded by stating that hypometabolic brain regions in AD, for instance the temporo–parietal regions, were still viable.

A SPECT study using 133Xenon as a tracer of blood flow (Cardebat et al., 1998) in AD patients (MMSE 6–26) and healthy controls during encoding (auditory presentation of words and instruction to memorize) vs. the control condition of passive listening to words showed no significant difference between memorizing and listening in AD patients. This lack of significant difference may be owing to the relatively poor performance during encoding seen in the AD patients examined. However, the AD patients showed a pattern of brain activation in listening to words vs. rest that was similar to the pattern that was found in healthy elderly control subjects. Activation was seen in the left posterior inferior frontal regions, and to a lesser extent in several left-sided regions (cerebellum, thalamus, lenticular, anterior middle frontal, superior middle temporal, and superior frontal). This finding was interpreted as an activation pattern associated with verbal processing, for example repetition and rehearsal of presented information.

Madden et al. (1999) studied encoding (living/non-living judgements of words) compared to baseline (uppercase/lowercase judgments of words) in healthy older
adults between 62 and 79 yr of age. During encoding significant rCBF increased activation occurred in the left occipito–temporal (BA 19) and bilateral prefrontal (BAs 10, 45) regions, thalamus and left parahippocampal gyrus (BA 37). Decreased activation occurred in the left anterior cingulate (BA 24) and right parietal lobe (BA 40). A significant correlation was observed between reaction time during encoding and activation in the left parahippocampal gyrus (BA 37) and right middle frontal gyrus (BA 10). Older persons demonstrated recruitment of activation in more cortical regions, as compared to young adults. The age-related effect during encoding involved increased activation in the thalamus and decreased activation in the left anterior cingulate and inferior parietal lobe.

In a study by Small et al. (1999), an fMRI protocol was developed to perform regional analysis of only the hippocampal formation. AD patients with mild dementia (CDR = 1) had to decide whether black-and-white photographs represented a male or a female with button press as the response. The baseline condition included looking at a fixation point. Results revealed two distinct patterns. One pattern involved all hippocampal regions studied, including the entorhinal cortex, and hippocampus proper together with dentate gyrus and CA subfields, as well as subiculum. Non-demented patients with isolated memory impairment who were considered as preclinical AD only showed activation subiculum.

In summary, these studies have shown that at least bilateral frontal areas and the hippocampus are significantly activated during various encoding operations in AD. In addition, a number of other areas may be activated in support of encoding processing. These appear to vary due to other task demands of the study.

3.6.3. Retrieval in aging

Grady and co-workers (1995, 1996), studied recognition memory of faces (subjects had to indicate which of two faces was presented previously) in healthy elderly individuals in relation to a sensorimotor control task used in experiments on perception. Performance was poorer in elderly as compared to young subjects. The elderly individuals demonstrated an increase activity in the right inferior prefrontal area, right superior parietal cortex, and bilateral ventral occipital cortex.

Cabeza et al. (1997) investigated recall (say the second word aloud in response to a word pair shown previously, or say pass), and recognition of words (if you think that the second word of a word pair was correct, say it aloud, otherwise say pass). Partial least square analysis showed age-related decrease in right prefrontal and right parietal regions, suggesting that elderly individuals show impaired retrieval operations. Age-related increases were seen in the left prefrontal cortex during recall and in cuneus/precuneus during recongnition. The hemisphere encoding retrieval asymmetry, that is usually observed in young individuals, was not seen in the elderly.

Studies by Bäckman and co-workers (1997, 1999) of healthy elderly individuals have reported bilateral activation of the dorsolateral prefrontal cortex (BAs 10, 46), anterior cingulate BA 32), perirhinal cortex (BA 36), left precuneus, right cerebellum, left parietal cortex, during cued recall of words presented visually (cues were word stems of target words) after previous study of a target word in relation to the control task using word stem completion. However, some regions showed no activation in
the elderly, as compared to significant activation in young adults (left cerebellum and the Wernicke region, BA 22). In contrast, the bilateral medial–temporal region (BA 36) was significantly activated only in the elderly group. These changes probably reflect both atrophy and compensation in AD patients.

Madden et al. (1999) studied retrieval after encoding (living/non-living judgments of words) as compared to baseline (uppercase/lowercase judgments of words) in healthy older adults between 62 and 79 yr of age. During retrieval the rCBF increased significantly in the bilateral prefrontal regions (BAs 8, 10, 11), inferior parietal lobe (BA 40), left inferior temporal cortex (BA 21) and left cerebellum. Decreased activation occurred in the bilateral inferior parietal lobe (BA 40) and several regions of the occipital and temporal lobes. The old adults also exhibited retrieval-related activation in the inferior parietal lobe bilaterally (BA 40), left inferior temporal cortex (BA 21), and the cerebellum. The data indicated two types of age-related effect, namely an increased degree of activation, as well as a more pronounced bilaterality. Both of these may be the result of functional compensation.

An electrophysiological study using ERP during recognition of words as old or new (rate of success about 90%) revealed that the task performance was similar in elderly individuals (age range: 62–79) and young subjects, and also that the ERP-activity was equivalent across groups in terms of magnitude and scalp topography (Mark and Rugg, 1998). Two patterns were found; one was left parietal possibly reflecting hippocampal activity in retrieval operations and the other was right frontal reflecting operations on products of retrieval. However, the older group was more delayed by about 100 ms in onset of relevant ERP-activity at some electrode sites, except for the right frontal site. It was suggested that the data supported the idea that recognition, at least when successful, is relatively unaffected by advancing age.

A couple of common findings seen in those studies published on retrieval in aging, is that the that dorsolateral prefrontal cortex of both hemispheres appears to be involved in retrieval operations, recognition, as well as recall. In addition, hippocampal regions, and the precuneus and cerebellum may also be involved. Furthermore, some of these regions may be related to the level of retrieval success. However, it is still an open question as to which regions are most important and to what extent this relation holds. Finally, an increased bilaterality has been observed in aging vs. young adults.

3.6.4. Retrieval in AD

The first functional imaging study on memory in AD patients using PET with $^{11}$C-2-dexoy-D-glucose was reported by Miller et al. (1987). The AD patients ranging from mild to severe dementia had to press a button when they recognized a previously presented word. The inter-stimulus interval ranged from 0 to 8 min. When the task performance (almost at chance level) was compared to rest, it was found that the AD patients showed a relative shift in metabolic activity from the left to the right temporal lobe. No group by task interactions were found in any other regions. Because of task difficulty, the interpretation of the significant effect of a shift in metabolic activity in the temporal regions was uncertain.
Kessler et al. (1991) studied regional cerebral glucose metabolism in mild to moderately demented (MMSE: 1.69 ± 5.7) AD patients and age-matched controls using PET with 2(18)F-fluoro-deoxy-D-glucose as tracer during conditions of rest and continuous recognition. The task included both presentation of visual stimuli and oral response (yes/no, whether the stimulus was presented previously or not; lags varied between 2 and 24). During task performance, the global metabolic rate increased in both groups but was significantly less in AD patients. The greatest change in metabolic rate occurred in the visual cortex and in temporo–parietal association areas. There was no significant correlation between task performance and metabolic rate. However, a significant correlation was found between metabolic rate in areas sensitive to AD neuropathology (e.g., the temporo–parietal cortex) and degree of dementia. This effect was more pronounced during task performance. The correlation was not significant for other areas (e.g., sensori-motor cortex). There was no shift in the hemispheric metabolic rate, when the task was compared to rest (cf. Miller et al., 1987). From these results, it was concluded that the metabolic rate during task performance reflected the reserve capacity of the brain to respond to mental demands.

A study by Becker et al. (1996a,b) investigated brain activation during repetition of eight words compared to three words (both encoding and retrieval were included) in AD patients (MMSE: 21.7 ± 3.4) and age-matched healthy controls. AD patients showed significant activation of the bilateral dorsolateral prefrontal cortex (BAs 8, 9, 10), left supramarginal (BA 40) and angular gyri (BA 39), and finally precuneus (BA 31). Deactivation was found in the superior temporal gyrus (BA 42). These results indicate that AD patients have a greater activation in regions normally involved in memory, as well as the activation of regions not activated by normal elderly subjects.

Herbster et al. (1996) performed a principle component analysis on previously reported retrieval data (repetition of one, three, or eight words) (Becker et al., 1996a,b). Unexpectedly, it was found that the patterns for AD patients and healthy controls were to a large extent similar. This finding suggested that the network used by AD patients is similar to that used by healthy controls.

Bäckman et al. (1999) studied very mildly demented (MMSE >24) AD patients, between 55 and 67 yr of age during cued recall of words (word stem cues) compared to baseline (word stem completion). An AD-related increase of brain activation was found in the left orbital prefrontal cortex and left cerebellum, in addition to an increased activation in a number of regions that were common both for AD and healthy elderly persons (see above; Bäckman et al., 1997). The AD-related increases in the left prefrontal region and left cerebellum were interpreted as efforts to compensate for retrieval problems and as an error-driven adaptive system for cognitive failures in general. Some regions were significantly activated by healthy elderly individuals only (left parietal cortex and left hippocampal formation). This finding was interpreted as reflecting a failure in semantic processing and unsuccessful retrieval in AD patients.

Tendolkar et al. (1999) studied ERP-activity in mild to moderately demented (MMSE: 19.4 ± 2.3) patients with AD in connection to two types of memory processes as assessed by means of: (i) judgment as to whether a certain stimulus has been
presented previously or not (familiarity); and (ii) for words judged as old the color of that word was to be named (context). The performance of AD patients was poor for context but less so for familiarity. It was markedly poorer than for age-matched controls. ERP-activity in familiarity judgments showed a main significant effect of group that was more pronounced at frontal scalp sites to short latency range and at posterior scalp sites to long latency range. Despite hippocampal atrophy and a disproportional reduction of the temporo–parietal ERP-effect, the AD patients were able to make judgments of familiarity.

The main empirical finding of retrieval studies in AD patients is that of an AD-related increase of activation in the prefrontal regions and cerebellum, that may indicate compensatory actions taken by the patients. At the same time, some areas are not activated in AD patients, although these areas are normally activated in elderly, probably reflecting loss of brain tissue and mental resources.

4. Discussion

4.1. Potential problems in functional studies of degraded brains

In the present review, it is assumed that AD represents a unitary disease category. It also assumed that the disease represents a continuous progression of brain degeneration during the clinical part of the process. Finally, it is assumed that the starting point of the disease process can be defined by the typical features that are found in normal aging. At this point, there are signs of some brain degeneration that could be conceptualized as one end point of the disease. Therefore, the whole spectrum from normal aging to AD has to be considered when looking at the typical feature of AD. When departing from this view, it has to be admitted that the continuous change occurring from healthy aging to early AD is at present unknown. There is strong need to perform studies comparing normal aging with non-demented patients showing only minor cognitive symptoms are performed, so as to elucidate the continuum from normal aging, across mild memory impairment to AD.

Although AD is thought to represent a unitary disease in terms of neuropathological characteristics and development, there are reports describing the disorder in terms of two or three subtypes (for example, predominant left- or right-hemispheric degeneration). There is, therefore, a risk that findings in functional neuroimaging studies are not valid for AD as a whole, but rather for the specific sample of AD patients in a particular study. Typical research studies of functional neuroimaging in AD do not specify the individual characteristics of patients. Rather, they state briefly that the sample was diagnosed according to standard manuals of clinical diagnosis, such as the DSM-IV (American Psychiatric Association, 1994) or other criteria. Therefore, there may be some room for inter-individual variation in cognition within the sample studied, resulting in a parallel variation in the pattern of brain activation. For the future, it is to be recommended that individuals should not only be diagnosed properly, but also matched with respect to individual cognitive features that may be relevant for the study.
There is evidence indicating that the preclinical manifestations of AD appear at least 5–10 yr prior to the clinical diagnosis of the disorder. Therefore, it has been argued that unidentified preclinical cases of AD may contaminate conclusions from studies that focus on so called “normal aging”. The inclusion of persons with preclinical AD may give an underestimation of the true mean for elderly individuals (Sliwinski, Lipton, Buschke, and Stewart, 1996). Similarly, it may result in invalid characterization of activated regions in functional studies investigating those cognitive functions that are sensitive to aging. Furthermore, it may be argued that studies of aging may be a reference point for studying AD, or the very point of departure for the disease process in AD, when the performance of the cognitive task is impaired compared to healthy subjects.

The atrophic process in AD also poses a methodological dilemma for functional imaging studies. The AD brain undergoes progressive atrophy which varies in amount across the disease process as well as between different brain regions. These changes need to be taken into consideration when analyzing brain activation data. The observation that certain regions are activated in healthy elderly may not in AD may be due to the process of atrophy in AD. This issue has been investigated by determining the correlation between degree of atrophy with brain activation during category decision in AD patients and healthy controls (Johnson et al., 2000). In healthy controls, the activation of language regions was independent of brain volume. In contrast, for AD patients the activation showed a significant positive correlation with degree of atrophy in the left inferior frontal gyrus. This supports the idea that atrophy results in compensation by increased activation in certain regions. Moreover, the association between metabolism and performance may be selective as demonstrated by positive correlations in disease-related brain regions and lack of significant correlations in other non-AD-related regions (Kessler et al., 1991).

Brain activation in relation to degree of AD atrophy has been discussed above as an issue of how the brain compensates for lacking resources due to issue degeneration. A related issue in that of how the brain allocates resources when the task difficulty is varied by increasing the demands. Again, a number of questions may be asked; such as are the same areas activated to a higher degree when the demands increase, or are new areas involved, and if so, according to which principle? These questions may be possible to investigate experimentally (see, Grady et al., 1993).

In functional studies comparing persons with and without brain degeneration, it may be important to consider the potential problem of poor performance in the degenerated group, as compared to intact performance in the control group. It is possible that the difference in performance level between groups will have a far-reaching impact on the level and pattern of activation. There have been no studies whereby task difficulty was varied in order to make the groups perform at an equal level of success. However, efforts have been made in some studies to have the AD and control groups perform on a similar level by means of choosing simple tasks (cf. Small et al., 1999), and by matching groups (cf. Smith et al., 1999). However, in the majority of studies no such measures were taken. This means that interpretation of results may be hard to make without ambiguity. Alternatively, the performance level may be investigated in relation to the degree of activation using regression models, as
exemplified by a number of studies (Cabeza et al., 1997; Cardebat et al., 1998; Grady et al., 1993; Madden et al., 1999; Saykin et al., 1999). Many researchers have stated that this issue deserves to be investigated more comprehensively in the future.

Although strong measures are usually taken to control for strategic variation in the execution of a specific study task, the risk of strategy variation cannot be ruled out. This is important, especially when comparing AD patients to healthy elderly individuals, since not only the brain conditions, but possibly also the strategies used may differ. Thus, differences in the pattern of activation may vary both depending on brain degeneration and the possible variation of strategy that is used for task performance.

The power of statistical analysis is also a major drawback in functional imaging studies. A lack of activation in certain areas does not imply that this region is not involved in the execution of the task. Consideration of type II errors is especially warranted in functional imaging studies (Petersson, Nichols, Poline, and Holmes, 1999).

When discussing the typical features of AD brain activity, it is necessary to comment on the specificity of these empirical findings. It may be argued that reported findings are general for brain disease rather than being specific for AD. So far, there are no studies that have compared AD with other dementia disorders of with other groups of brain lesioned patients. A final conclusion on the specificity of reported findings awaits data from such studies. Until then, it is reasonable to assume that reported findings are valid for the specific pattern and degree of brain pathology characteristic of AD. It is also worth noting that the pattern of brain pathology is rather selective in AD, at least early in the disease course.

Finally, a note should be made regarding the techniques used for brain imaging. The various techniques used for functional imaging do have some impetus on the results obtained, mainly due to the characteristics of temporal and spatial resolution. Certain methods are disadvantaged by their pool spatial resolution, particularly ERP, but also SPECT, whereas other techniques such as PET are associated with comparatively poor temporal resolution. Consideration need to be taken into account when comparing results obtained using different techniques.

4.2. AD in relation to aging

The review has demonstrated that there are both similarities and differences in the pattern and level of activation between AD patients and normal elderly individuals. As discussed below, these may be described in terms of five principles. The differences may be due to group-related variation in degree of brain atrophy, performance level, available mental resources with regard to knowledge and mental operations, compensatory efforts, and strategy utilization. Further more, secondary reactions to task demand anxiety (cf. Duara et al., 1992) and stress (cf. Kessler et al., 1991) may differ between groups and thereby confound the results. For a comprehensive discussion of empirical findings of activation studies in AD vs. aging, the reader is referred to Raz (2000).
4.3. Principle effects of brain degeneration in functional studies

The fact that AD patients are subjected to brain degeneration may result in changes in terms of regions or degree of activation. These may include: (a) loss of activated regions, or (b) diminished activation. Handling these changes may be a require compensation for loss of brain function or utilization of the possible plasticity of the central nervous system. To compensate for the deranged brain, three options are possible including: (c) using regions not usually involved in a certain task, or (d) regions usually involved in a certain task may be activated to a higher degree. Alternatively, it could be the case (e) that there are no AD-related changes at all.

The first alternative of an AD-related loss of activated regions has been observed in a number of studies including loss of activation in temporo–parietal regions with semantic memory (Saykin et al., 1999), left parietal cortex and left hippocampal region during retrieval (Bäckman et al., 1999), and loss of temporo–parietal ERP-effect in retrieval (Tendolkar et al., 1999). These losses are compatible with brain degeneration in early AD (Braak and Braak, 1995; Pfefferbaum et al., 1994).

The second alternative of a reduced degree of activation in AD compared to healthy aging was reported in an ERP-study of priming (Friedman et al., 1992), in semantic memory for possible preclinical AD (Smith et al., 1999), an ERP-study of semantic memory (Ostrosky-Solis et al., 1998), and in continuous recognition (Kessler et al., 1991). Hypothetically, these findings represent non-episodic memory tasks, which rely on non-medial temporal lobe structures in order to be executed properly.

The third alternative that new regions are activated may occur in various ways, as exemplified by increased bilaterality in mental rotation (Deutsch and Halsey, 1990), semantic memory (Saykin et al., 1999), a more diffuse distribution of ERP-activity in semantic memory (Castaneda et al., 1997), a hemispheric shift from the left to right hemisphere in recognition of words (Miller et al., 1987), and retrieval (Bäckman et al., 1999). This type of compensation may reflect substitution of vulnerable regions by regions preserved during the course of AD. Furthermore, there may be a hierarchy of substitution, whereby there is a first step that occurs with only minor brain derangement during mild dementia for which it is possible to compensate. The second step occurs with more devastating changes of brain capacity during moderate to severe dementia with loss of brain function (Rapoport, 1999).

Evidence for a fourth alternative of increased activation has been presented during facematching (Grady et al., 1993), and priming (Bäckman et al., 2000). These changes may indicate compensation in tasks that are possible to solve in early AD without losing performance efficacy.

The fifth alternative that AD and healthy aging activate equivalent regions has been found in several studies including; sustained attention (Johannsen et al., 1999), working memory (Becker et al., 1996a,b), semantic memory (Saykin et al., 1999), encoding (Duara et al., 1992; Cardebat et al., 1998), and word repetition (Becker et al., 1996a,b; Herbster et al., 1996). This type of pattern appears to be compatible
with the execution of tasks by means of regions spared in preclinical or early clinical AD (cf. Braak and Braak, 1995).

With respect to healthy aging as compared to young controls, the principle differences are similar to the principles found for AD compared to healthy aging. Loss of regions (A-type) was reported in retrieval (Grady et al., 1994; Mark and Rugg, 1998; Bäckman et al., 1996). Decreased activation (B-type) was found during encoding (Cabeza et al., 1997; Grady et al., 1999). C-type is exemplified by the observation that similar regions were activated, but the size of regions were enlarged during perception (Grady et al., 1994). and by more pronounced bilateral involvement during recognition (Madden et al., 1999), and bilateral medial temporal regions (Bäckman et al., 1996). Increased activation (D-type) was observed in encoding (Cabeza et al., 1997), and retrieval (Cabeza et al., 1997; Madden et al., 1999). The E-type pattern, of no difference, has been demonstrated in priming (Bäckman et al., 1996; Friedman et al., 1992).

Finally, the interesting finding of activation of the cerebellum has been shown as a common observation in functional imaging studies of elderly individuals as well as AD patients. If this type of activation is true, then it opens up the possibility of a wealth of further studies and theories about the functional role of cerebellum during normal aging and brain disease.

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