Functional activation imaging in aging and dementia

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Abstract

With life expectancy increasing continuously, the effects of neurodegeneration on brain function are a topic of ever increasing importance. Thus there is a need for tools and models that probe both the functional consequences of neurodegenerative processes and compensatory mechanisms that might occur. As neurodegenerative burden and compensatory mechanisms may change over time, these tools will ideally be applied multiple times over the lifespan. Specifically, in order to elucidate whether brain-activation patterns in Alzheimer’s disease (AD) and in healthy aging follow general rules in the context of degeneration and compensation, it is necessary to compare functional brain-activation patterns during different stages of neurodegeneration. This article integrates the findings of functional activation studies at different stages of neurodegeneration: in healthy aging, in subjects at high risk of developing dementia, in subjects with mild cognitive impairment (MCI), and in patients suffering from AD. We review existing theoretical models that aim to explain the underlying mechanisms of functional activation changes in aging and dementia, and we propose an integrative account, which allows for different neural response patterns depending on the amount of neuronal damage and the recruitment of compensatory pathways.

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1. Introduction

Alzheimer’s disease (AD) is the most common cause of dementia. The age-related exponential increase of the incidence of AD (Jorm and Jolley, 1998) gives evidence for a close relation between AD and aging. The course of AD is characterised...
by a unique progression of clinical (e.g. Almkvist and Winblad, 1999) and neuropathological (Braak and Braak, 1991) features that separates AD from “normal aging”. Furthermore, some evidence suggests that brain regions differ in their vulnerability to age-related and to AD-related degenerative processes (Raz et al., 2004; Small et al., 2004). However, although the spatial distribution, extent, time of onset and velocity of progression of neurodegeneration differ in aging and dementia, both lead to progressive synaptic dysfunction and synaptic loss (Adams, 1987). It has thus been hypothesized that even normal aging may result in dementia when a threshold of synaptic loss has been reached, provided that the lifespan is long enough (Terry and Katzman, 2001).

Synaptic integrity and function are closely related to cognitive, motor and sensory performance (e.g. Luebke and Rosene, 2003). Synaptic function is furthermore the basis of measures of brain activation as revealed by regional metabolic, blood flow or BOLD-signal changes (Logothetis et al., 2001). Since the predominant impairment of temporo-parietal regional glucose metabolism (rCMRglu) and blood flow (rCBF) during the resting state has been established as an early and reliable diagnostic marker in AD (e.g. Frackowiak et al., 1981; Duara et al., 1986; Silverman et al., 2001), this review will focus on the recent advances made by functional activation studies (Almkvist, 2000), which investigate the response of the brain to external stimulation or cognitive tasks. This approach may provide deeper insights into the impact of neural degeneration on the function of the cortico-subcortical networks of perception and cognition.

The neuronal activity that is needed to perform a task usually depends on the task demands and increases with parametric changes in task difficulty. In the context of aging and dementia, however, the subjective task demand is additionally influenced by the amount of damage to the brain structures that are involved in task processing. With increasing regional damage, compensatory mechanisms such as the recruitment of additional areas will be required to perform the task. The interaction between task difficulty, different levels of synaptic damage and task performance is thus not only complex but also very dynamic as aging- and dementia-related degenerative processes increase over time. These complex relations have so far not been investigated systematically. Ideally, a combined longitudinal study would be needed, tracking subjects from early adulthood to old age and during different stages in the course of dementia (including mild cognitive impairment). Additionally a parametric task design should be applied to test for interactions between different levels of neuronal damage and different levels of task demand. However, this approach is cumbersome and lengthy, and it has not been applied so far. As a substitute, we will try to derive some general insight about the interactions between neurodegeneration and brain activation by reviewing existing cross-sectional studies that compared demented patients with non-demented subjects or old with young participants. Some of these studies also investigated healthy subjects at high genetic risk of developing AD and subjects with mild cognitive impairment. The latter groups are both considered to reveal a neuropathological burden that has not reached the threshold of clinically manifest AD. A subgroup of those affected is supposed to represent preclinical stages of AD. We discuss the heterogeneous functional imaging findings on healthy aging, dementia, and at-risk populations in the light of existing models of cognitive reserve capacity and functional compensation. Finally, we propose an integrated account that relates functional activation changes in aging and dementia to the level of neurodegeneration, task demand, and task performance.

2. Review of functional activation studies

2.1. Functional activation studies in healthy aging

A number of functional activation studies have compared brain activation patterns during sensory, motor and cognitive processing between young and older healthy adults. While the results seem to be rather heterogeneous at first, they converge on several points:

– Studies that required the subjects to perform very simple motor tasks or used passive sensory stimulation revealed decreased activation of the involved
sensory or motor cortical regions in older subjects compared with younger adults (Cerf-Ducastel and Murphy, 2003; Suzuki et al., 2001; Ross et al., 1997; Yousem et al., 1999; Hesselmann et al., 2001; D’Esposito et al., 1999).

- Even when simple motor tasks were used, additional attentional or cognitive effort led to marked increases of activation across motor, premotor and other cortical regions in older compared with younger subjects (Mattay et al., 2002).

- In visual perceptual studies older subjects showed decreased activation in the occipital but increased activation in prefrontal cortex (Grady et al., 1994; Madden et al., 1997). Grady and Craik (2000) also demonstrated that older subjects, when compared with young adults, recruited different cortical and subcortical regions (hippocampus, thalamus) during a face-recognition task and that their performance correlated with this compensatory activation.

- The so called “HAROLD” phenomenon (hemispheric asymmetry reduction in old adults [Cabeza, 2001]): While young adults show a hemispheric encoding/retrieval asymmetry (HERA) (Tulving et al., 1994) with higher left prefrontal activation during episodic encoding and higher right prefrontal activation during retrieval, this asymmetry is decreased in older adults (Cabeza et al., 1997; Bäckman et al., 1997; Madden et al., 1999). The reduced lateralization of prefrontal cortex activity in older participants was shown to aid performance of a verbal working memory task, possibly indicating compensatory recruitment of the non-dominant hemisphere (Reuter-Lorenz et al., 2000).

- In a study of regional metabolic activity with fluorodeoxyglucose-PET (FDG-PET), Hazlett et al. (1998) found a decrease of frontal task-related activation during a verbal memory task with increasing age. Interestingly, a re-analysis of the same sample based on a division into good and bad performers revealed that young good performers had strong frontal activation, while old good performers had strong occipital activation.

2.2. Functional activation studies in subjects at genetic risk to develop AD

ApoE 4 has been identified as a susceptibility gene that significantly increases the rate of clinical manifestation of familial late-onset and sporadic AD and decreases the mean age of onset (see Strittmatter and Roses, 1995). Although not all carriers of ApoE ε4 develop AD, it has been shown that middle-aged and even young adults with ApoE ε4 exhibit abnormal brain metabolism that is in part similar to regional resting state metabolic decreases found in AD (Reiman et al., 1996, 2004). When compared with “low-risk” subjects, cognitively intact subjects who have an increased genetic risk of developing AD have shown deviant functional activation patterns depending on the particular cognitive task. No activation differences between high- and low-risk subjects were found during an auditory attention task (Burggren et al., 2002). In contrast, high-risk subjects revealed a significantly higher amount and extent of hippocampal, prefrontal and parietal cortex activation during a verbal learning task when compared with low-risk subjects (Bookheimer et al., 2000). Finally, in semantic and verbal fluency tasks, high-risk subjects showed decreased activation in temporal (Smith et al., 1999) and increased activation in parietal cortex (Smith et al., 2002).

2.3. Functional activation studies in patients with mild cognitive impairment

Mild cognitive impairment (MCI) is characterised by subjective memory complaints, impaired performance on memory tests, normal general cognitive function, and absence of additional criteria for dementia (Petersen et al., 1999). The annual conversion rate from MCI to AD is estimated at 10%–15% (e.g., Artero et al., 2003). However, some proportion of MCI subjects do not seem to develop AD at all. In the course of AD, memory and learning deficits are usually amongst the very first symptoms to occur. The development of cognitive deficits is assumed to be related to the specific progression of neurofibrillary accumulation that starts in entorhinal cortex and spreads to the hippocampus and other limbic structures that are critically involved in memory processing (Braak and Braak, 1991). On the basis of its phenom-
enology and natural history, MCI can thus be regarded as a preclinical stage of AD in those patients who actually develop AD during the subsequent years. In all other cases that do not end in dementia, the isolated memory dysfunction in MCI might not be related to AD-specific pathology and thus may represent a separate entity.

In a very intriguing study by Small et al. (1999), senior subjects with and without memory complaints and AD patients participated in a visual memory encoding task. While AD patients showed strongly reduced task-related activation across all investigated regions of the hippocampal formation, participants with isolated memory complaints showed reductions either in the subiculum or in the entorhinal cortex. The authors of this study suggested that the subgroup that revealed underactivation in the entorhinal cortex (EC) might represent preclinical AD because of the early involvement of this area in AD pathology. Similarly, the hippocampal formation was found to be less active in MCI subjects and AD patients during memory encoding when compared with age-matched healthy senior subjects (Machulda et al., 2003).

2.4. Functional activation studies in patients with manifest AD

Memory is one of the first cognitive systems to be affected in AD. In memory tasks that engage visual and verbal encoding, AD patients consistently reveal marked activation deficits in the hippocampal formation and in frontal and temporal neocortex (Small et al., 1999; Kato et al., 2001; Rombouts et al., 2000; Schröder et al., 2001; Sperling et al., 2003; Machulda et al., 2003). Hippocampal activation deficits in AD patients have also been found during olfactory memory tasks (Buchsbaum et al., 1991).

When the task-related activity was measured during retrieval from memory, AD patients showed whole brain activation deficits (Kessler et al., 1991) or reduced activation in hippocampus and parietal cortex (Bäckman et al., 1999). Bäckman et al.
(1999) additionally found increased activation in left prefrontal cortex in AD patients. Grady et al. (2003) demonstrated extended activation in bilateral prefrontal and temporoparietal areas in AD patients during episodic retrieval as opposed to only left prefrontal and temporal areas activated by control subjects.

In short-term memory studies, the results are somewhat more complex. AD patients and controls demonstrated similar activation patterns when a verbal working memory task was not difficult (3-word repetition); however, at a more difficult level (8-word repetition), AD patients showed higher activation in prefrontal and inferior parietal cortex (Becker et al., 1996). In contrast, when a visual working memory task (face recognition) was used, prefrontal activation was not higher in AD patients than in controls. Instead, AD patients revealed higher activation in left medial temporal regions, comprising hippocampus and amygdala. Grady et al. (2001).

In visual perceptual tasks the results depend greatly on the tasks used. During passive visual stimulation, AD patients revealed activation deficits in middle temporal and occipital cortex (Mentis et al., 1996). In a face-matching task, Grady et al. (1993) found higher activation in frontal areas (frontal eye field) and occipital pole in AD patients. Functional activation related to angle discrimination was significantly decreased in parietal cortex but increased in occipitotemporal cortex in AD patients compared with healthy controls (Prvulovic et al., 2002; Fig. 1).

3. Impact of performance and task difficulty on functional activation

The impact of task performance and task difficulty on functional activation studies in healthy young participants indicates a complex relationship between performance in a cognitive task and task-related functional brain activation. During memory encoding, higher activation in the medial temporal lobe and frontal areas strongly correlated with the rate of successful retrieval (Wagner et al., 1998; Brewer et al., 1998; Kirchhoff et al., 2000), indicating that successful processing is reflected by higher activation than unsuccessful task processing. However, higher activity may also indicate a longer time spent on the task. For example, subjects who needed longer to respond to items presented during a visual working memory task revealed higher activation in parietal cortex than those who had lower response latencies (Honey et al., 2000). A similar relationship between reaction times and functional activation was also found in visuospatial tasks (Ng et al., 2001). When discrimination of visual features was difficult in visual perceptual tasks, healthy young subjects showed additional activation in prefrontal cortex (PFC, especially in the right hemisphere) during visual perceptual and memory tasks, even when their accuracy was compromised at higher difficulty levels (Grady et al., 1996; Barch et al., 1997; Sunaert et al., 2000). Right PFC has been associated with supervisory and attentional functions (Paus et al., 1997; Elliott et al., 1999), and its activation increases in parametric tasks have been suggested to reflect task difficulty (Sunaert et al., 2000).

Task-related activation across multiple association and sensory cortical areas can also be modulated by attention. For example, stimulus-related activation in striate and extrastriate visual areas is enhanced when attention is focused on the corresponding areas in the visual field (Tootell et al., 1998). While the attentional enhancement of brain activation in some cases seems to follow an “all or nothing” rule, a linear correlation has been found between attentional load and task-related functional activation in many brain regions (Culham et al., 2001). As a general rule in healthy young volunteers, areas subserving a cognitive task show increased or extended activation, and/or additional areas are recruited with increasing task difficulty (Grasby et al., 1994; Carpenter et al., 1999; Sunaert et al., 2000; Vannini et al., 2004).

How do the findings in healthy senior subjects and patients compare with regard to the activation–performance relationship? Morcom et al. (2003) compared the subsequent memory effect (i.e., increased functional activation during successful memory encoding compared with unsuccessful encoding) between healthy young and older subjects. They found that bilateral prefrontal activation was associated with successful encoding in the senior subjects as opposed to only left hemispheric prefrontal activation in the young group. Moreover, only the young subjects showed activation increases in left temporal cortex that correlated with successful encoding.
In a remarkable study of MCI patients, Dickerson et al. (2004) measured functional activation patterns during episodic memory encoding. They demonstrated that the extent of activation in the medial temporal lobe correlated with better memory performance. Additionally, they found that activation was most extended in patients with the worst clinical state at the time of the measurement and in those who showed the fastest cognitive decline during follow-up. This finding may result from higher task demand in the more impaired subjects who, in turn, revealed additional compensatory recruitment of adjacent neuronal tissue in order to maintain task performance. Similarly, healthy subjects at high risk to develop AD (Bookheimer et al., 2000; Smith et al., 2002) and even AD patients (Woodard et al., 1998) showed a higher extent of functional activation than healthy controls when they maintained good task performance.

In most functional activation studies that compared AD patients with age-matched healthy controls, lower task performance in AD patients was accompanied by significant activation deficits (Rombouts et al., 2000; Schröder et al., 2001; Kato et al., 2001; Sperling et al., 2003). In a study that compared healthy young and older participants, a subgroup of older subjects with reduced task performance revealed activation deficits during memory encoding in medial temporal lobe (MTL) when compared with young subjects, even when only the successful trials were considered (Dasehaar et al., 2003). The authors of this study related this finding to MTL dysfunction in memory-impaired older subjects. In the specific cases where functional activation during rehearsal (Woodard et al., 1998) or retrieval from memory (Bäckman et al., 1999) was measured, AD patients showed extended task-related activation despite normal or impaired performance. During a working memory task (including encoding and retrieval), Grady et al. (2001) found that task-related functional activation in the right PFC correlated with better performance in healthy old subjects as well as AD patients, while activation increases in the amygdala were correlated with better performance only in AD patients.

In sum, under normal conditions, when brain function is not altered by neurodegeneration or aging, increased or extended functional activation might indicate that the underlying neuronal processing is a) successful (e.g., in memory encoding), b) enhanced by attention (e.g., in visual perceptual tasks) or c) more time-consuming and more difficult (perceptual discrimination tasks and memory tasks with increasing load). These rules may also account for altered functional activation responses in patients with declining brain function (i.e., aging, at-risk state and manifest dementia) where task difficulty is influenced not only by parametric manipulations of the task but (most importantly) also by the level of neurodegeneration. The progression of neurodegeneration can either lead to elevated or extended activation (accompanying unaffected or mildly impaired performance) or to activation deficits (often with severely impaired performance) and thus explain the apparently conflicting findings of hyperactivation and hypoactivation in old age or cognitive impairment due to dementia.

4. Models and hypotheses for the interpretation of functional activation effects in aging and dementia

4.1. Review of existing models

Even after the consideration of confounding factors such as task difficulty, altered baseline activation and task performance, it remains difficult to understand why dementia patients sometimes show more task-related activation than healthy controls and sometimes less, in the same cortical regions. Several models have been proposed in order to integrate some of the basic mechanisms that link the damage to cortical systems to their functional activation patterns. Logan et al. (2002) proposed “under-recruitment” and “non-selective recruitment” as possible mechanisms that may play a role in the observed changes of activation patterns during memory-related cognitive processes in healthy aging. This model summarizes the inability of the aging brain sufficiently to engage specific cortical regions during cognitive performance. In order to compensate for this failure, additional areas that had originally not been designated for the specific task are recruited and become activated. This model would explain task-related activation of additional areas in older than in younger subjects. Yet, this model can also be applied to functional activation studies of preclinical or already demented patients. Fig. 1 documents that AD patients fail to activate the
parietal cortex to the same extent as controls during visuospatial processing (Prvulovic et al., 2002). Instead, they recruit an area less specific for visuospatial computation (the fusiform gyrus). However, the parietal cortex is unspecifically overactivated in at-risk patients during a verbal fluency task (Smith et al., 2002).

Some functional activation studies of AD (Grady et al., 2003) and healthy aging (Hazlett et al., 1998) also revealed very distinct cortical activation patterns, which correlated with performance benefits. It can thus be assumed that, faced with the impaired access to specific task-subseriving areas, the damaged brain can under certain circumstances engage alternative pathways in order to maintain successful task performance. These observations can be interpreted with a view to the theory of “degenerate systems”, which is based on the ability of different structures to subserve the same function. This theory has been discussed with reference to several biological systems, cognitive networks being a particularly prominent example (Tononi et al., 1999; Price and Friston, 2002). When different neuronal systems are sufficient to perform a cognitive task each on their own, the damage to only one or a subset of those systems will have no adverse effect on task performance but lead to important differences in the brain-activation pattern. This would explain why in functional activation studies not all healthy individuals activate the exact same brain regions during the same task, and why patients with lesions within areas that are usually activated during a cognitive task often have preserved performance. Task performance will only be impaired when a necessary neuronal system has been damaged that cannot be compensated by any other system or when the complete set of degenerate systems is affected. This model is complementary to that of Logan et al. (2002) in that it introduces the distinction between neuronal systems that are sufficient and those that are necessary for a particular cognitive task. For example, a lesion to either the left or the right anterior temporal lobe (which are assumed to be separate systems, both of which are sufficient for semantic processing) does not impair the performance in semantic tasks, while lesions to both left and right anterior temporal cortex do (Mummery et al., 2000; Price and Friston, 2002). Activation in brain regions that are usually not activated by the investigated cognitive task might thus indicate a degenerate system with one sufficient part being damaged and other parts being activated instead, especially if the unexpected activation correlates with performance. This concept works very well for circumscribed brain lesions (e.g., focal temporal atrophy in semantic dementia). Yet, when neural damage is more global, as in AD, it is more likely that all subsystems of a degenerate system will be impaired, leading to global activation deficits or non-specific (“aberrant”) activation patterns across the brain, which no longer support normal performance.

While these models of compensatory activation and degeneracy explain the recruitment of different areas in patients and controls, additional theoretical assumptions are required to explain why in different studies with AD patients, the same brain areas are sometimes overactivated and sometimes underactivated. Rapoport and Grady (1993) introduced the model of a sigmoidal relation between regional cerebral blood flow (rCBF) (y-axis) and a function of task difficulty and individual task performance (x-axis). In this model, several degrees of neuronal damage are implemented, which alter the shape of the brain response curve. In early stages of the disease, pathological damage shifts only the rising phase of the sigmoidal brain response curve to the right. This reflects the finding that AD patients show reduced rCBF during rest or during control tasks with very low processing demand. Consequently, the task-related increase of rCBF during highly demanding tasks would often be higher in early AD than in controls. In their model, early AD patients ultimately reach the same absolute amount of task-related rCBF as controls. With increasing neuronal damage, the maximum activation capacity of the brain decreases, and AD patients reach a lower maximum rCBF in activated states than controls. However, the model by Rapoport and Grady (1993) concentrates on the response behaviour of a cortical region without further consideration of its embedding in a network.

4.2. Integrative model for the interpretation of functional activation in aging and dementia

The previously described models explicitly considered distributed specific (degenerate systems, Price and Friston, 2002) or unspecific coactivation (Logan et al., 2002), but they did not account for the multiple
response patterns within the specifically affected area (Rapoport and Grady, 1993). Hence, it may be useful to combine some elements of all three approaches into an integrated model (Fig. 2). Our model attempts to clarify the heterogeneous findings of functional activation studies (both PET and fMRI) in AD and aging, and to overcome the restrictions of the former models. It addresses the different response patterns of cortical regions to increasing task demand. Additionally it considers various possible ways of interaction between brain regions in relation to brain damage and compensatory mechanisms. This model was designed to explain activation patterns in experiments with a measurable behavioural response (reaction time, accuracy), whereas experiments that merely involve passive stimulation or resting state measurements do not fall within its scope.

The central element of the model (Fig. 2) is a cortical region (processing unit: PU) that is part of a cortical circuitry required for successful processing of the task at hand. The functional activation in the PU at any given time point is dictated by the number of subunits within the PU (e.g. single neurons or populations) recruited at this time point. Increasing task difficulty will lead to increased total activation of the PU until the task difficulty exceeds the maximal

![Diagram](image-url)

Fig. 2. An integrated model of possible relations between damage to a processing unit, the dynamics of its activation response in relation to task difficulty, and the integrated network engaged during the processing of a cognitive task (see text). For purposes of simplification, possible feedback loops are not considered. PU = processing unit; MOD = modulation unit; AUX = auxiliary unit. The relation between task performance and task difficulty is also integrated (red lines).
processing capacity (=total number of functioning subunits) of the PU. Consequently, the amount of available functional subunits at a certain level of task demand can be termed “functional reserve capacity”. The reserve capacity, or buffer, partly determines how much additional task difficulty can be mastered without loss of task performance or, in cases of neurodegeneration, how much damage to the subunits and their connections can be sustained. In terms of metabolic parameters, the processing in the PU will lead to higher local glucose consumption as well as to increased local blood flow and to an increased amount of oxygenated haemoglobin (BOLD signal change) in the vascular bed. All these changes lead to “activation” that can be measured with PET, SPECT or fMRI. The system furthermore comprises an INPUT module, a cortical region that provides information that is essential for the PU to process the task, and a unit (MOD) that can modulate the activity of the PU. Modulatory effects can consist in a direct enhancement of processing efficiency in the PU or of the amount or the quality of the input signal into the PU (e.g., attentional modulation). For instance, Woodard et al. (1998) showed additional activation of parietal attention-related regions in AD patients during a memory task compared with age-matched controls, suggesting that in these patients successful task performance was supported by increased attentional effort. Prefrontal cortex (PFC) activation is related to attentional load and can enhance the performance of different cognitive tasks. Conversely, the failure of attentional enhancement due to deficient PFC activation or to disrupted connections between the PFC and other parts of the neural network involved in memory encoding can lead to impaired processing. The observation of Grady et al. (2001) that AD patients revealed a significantly impaired functional connectivity between frontal and temporal areas during a visual working memory task is a case in point.

However, if task processing cannot be sufficiently conducted by the PU, other brain areas that initially are not directly related to PU and that are more or less specific for the processing of the task may become involved (auxiliary pathway: AUX) in order to partly or completely compensate for the insufficient output from the PU. This effect has indeed been shown in functional imaging studies, with additional cortical regions being activated in AD (Prvulovic et al., 2002; Grady et al., 2001). The use of auxiliary pathways may reflect a different processing strategy. Moreover, the proposed model of auxiliary pathways conforms to the finding that aged and demented patients lose hemispheric asymmetry during encoding and retrieval, (Backman et al., 1997; Madden et al., 1999; Reuter-Lorenz et al., 2000). In terms of the degeneracy concept, the auxiliary pathway would represent a separate system that is capable of sufficiently processing the task. In terms of Logan’s compensation model (Logan et al., 2002), the auxiliary pathway is less specific for a particular cognitive task than the PU and can thus only partly compensate for performance deficits.

The amount of activation in the PU itself is determined by the relation between its processing efficiency (the integrity of processing within single subunits of the PU and the integrity of communication between subunits within the PU), its processing capacity (the number of subunits), the task difficulty, the task performance of the subject, and the quality of the input signals. Processing efficiency impacts the slope of functional activation, while processing capacity limits the maximum of functional activation that can be reached in the PU. These five factors together determine the work load of the PU in a specific task. Depending on the combination of these factors, two main scenarios can occur:

1. Decreased processing efficiency in combination with almost preserved processing capacity and input will lead to a compensatory recruitment of an increased number of subunits within the PU to compensate for the diminished processing efficiency (dashed functional activation curve in the PU, Fig. 2). The resulting work load is higher than normal and leads to increased total activation in the PU (e.g., Bookheimer et al., 2000). Because an impairment of processing capacity and the consequent higher work load automatically lead to a reduced “reserve capacity” in the PU, the limits of the processing capacity of the PU will be reached earlier with increasing task difficulty and thus lead to earlier decompensation of task-performance (dashed red line in Fig. 2). Findings from studies investigating the effects of practice on functional brain activation support this view (for review, see
Linden, 2003). In most perceptual and cognitive paradigms, practice leads to decreased activation, indicating more efficient and thus less effortful processing (e.g., Haier et al., 1992; Schiltz et al., 2001).

2. A greater amount of damage in the PU with a significant decrease of processing capacity or disruptions of the input channel(s) to the PU (Morrison et al., 1991) will lead to diminished activation in the PU (dotted black functional activation curve, Fig. 2) (e.g. Small et al., 1999; Smith et al., 1999; Schröder et al., 2001). In this scenario, only a small part of the PU can be recruited for task processing. While in very simple tasks performance might be preserved, even slight increases of task difficulty will lead to a fast decrease of task performance (dotted red line in Fig. 2). The importance of preserved input channels has been shown by McCon nell et al. (2003), who demonstrated that direct electromagnetic stimulation of the motor cortex leads to similar activation in old and young subjects, whereas motor activity resulting from voluntary finger tapping is decreased in old subjects (Hesselmann et al., 2001). Impaired functional connectivity might be an indicator of disrupted input channels and has been demonstrated between frontal and temporal brain regions in AD patients (Grady et al., 2001).

5. Discussion

Our integrative model applies to the functional activation studies of both healthy aging and dementia and its precursors. Proposed models are being discussed for other neuropsychiatric disorders with a neurodegenerative component, particularly schizophrenia (Manoach, 2003). Progressive impairment of synaptic transmission (e.g., by synapse loss) has been proposed to be a crucial factor in both age-related and dementia-related cognitive decline, with synaptic decay being much more accelerated in dementia than in normal aging (Terry and Katzman, 2001). The results of the functional activation studies reviewed in this article show that damage to cortical systems – independently of its cause – may lead to changes of functional activation, which seem to follow similar rules in aging and dementia. Reduction of the processing efficiency in a specific region can induce different compensation mechanisms within and/or outside the concerned region. These mechanisms include the recruitment of a higher number of neurons (or neuronal populations) (increasing peak activation and/or spatial extent) and the coactivation of specific or less specific remote areas, which can either directly take over a part of the processing burden (auxiliary pathway) or facilitate the task processing in the affected region. To what extent these compensatory mechanisms will come into play seems ultimately to depend on the specific combination of several biological and study-related factors, including the task difficulty, the functional specialisation of a damaged brain area, its natural contribution to the cognitive task, the amount of damage, the quality of the input, and the recruitment of potential alternative processing pathways. Cholineacetyltransferase (CHAT) activity has been found to be up-regulated in some parts of the brain in patients with MCI (DeKosky et al., 2002). This finding has been interpreted as a compensatory mechanism in preclinical AD stages. Compensatory processes of this type might account for the steeper slope of functional activation in slightly damaged processing units in the brain.

The observation that even in normal aging brain areas are underactivated in some conditions (e.g. Logan et al., 2002) seems, at first glance, not to conform to the proposed model. According to our model, these slight impairments of processing efficiency should lead to compensatory overactivation rather than underactivation of the PU. However, assuming that even slight damage to grey and particularly white matter leads to impaired coordination of the processing network, functional activation will not be distributed in the most efficient way, and the most specialized area for a certain task might not become fully engaged. This would result in underactivation of PU and overactivation of less specific areas. However, these effects might potentially also be caused by methodological issues that will be discussed in more detail.

5.1. Neurovascular coupling

An important question that is not answered by our (or any of the previous) models is whether the cou-
pling between the measured parameters (blood flow, BOLD-signal change, glucose consumption) and actual neuronal activity is preserved in the degenerative brain. For a valid comparison of functional imaging results of young, older and demented subjects, we will ultimately have to show that vascular and metabolic parameters correctly reflect neuronal activity in all these groups. There is some evidence that the coupling between neural activity and hemodynamic response may be altered by age, cerebrovascular processes, drug intake and neurodegenerative diseases, and all of these factors might account for activation deficits in elderly people and dementia patients (Ross et al., 1997; D’Esposito et al., 1999; for review, see D’Esposito et al., 2003). For example, age-related changes of the microvasculature may alter the responsiveness of cerebral arterioles to metabolic changes (vascular reactivity) or to neuronal activity (decoupling). Elderly participants have indeed shown reduced resting state cerebral blood flow (Bentourkia et al., 2000), impaired vascular reactivity to hypercapnia (Ito et al., 2002) and reduced BOLD-signal change during sensory or simple motor tasks (see above, Section 2). Furthermore, chronic cerebral ischemia can lead to secondary poststenotic vasodilatation, which will reduce the difference in rCBF between resting and activated states and thus decrease the amount of functional activation changes (Derdyn et al., 1999). The intake of non-steroidal anti-inflammatory drugs (NSAIDs), which is prevalent in the elderly, reduces the production and the release of eicosanoids from astrocytes, which in turn may significantly reduce vasodilatation and reactive increases in rCBF (Zonta et al., 2003). Finally, glutamate and acetylcholine have been found to increase CBF in different brain regions and pathological changes in these neurotransmitter systems (e.g., the loss of cholinergic neurons in AD) may additionally impair the neurovascular response (Vaucher and Hamel, 1995; Zonta et al., 2003) in degenerative brain diseases. It is thus extremely difficult to attribute activation differences between young and old subjects or between healthy subjects and patients with degenerative brain diseases to an altered neurovascular response or to altered neuronal activity.

Some measures have been proposed to control for the influence of (potentially) different hemodynamic response functions between groups in functional activation studies. These include the performance of simple sensorimotor tasks in addition to cognitive tasks or the analysis of group-by-task interactions rather than main group differences (D’Esposito et al., 2003). However, even when activation differences (e.g., in primary motor cortex) might be related to changes in neurovascular coupling, this might not necessarily apply to other brain regions (e.g., in association areas), at least not to the same degree. Even the calculation of activation differences between different cognitive tasks or between different difficulty levels of a parametric task does not completely control for different hemodynamic response functions (HRF) in different populations because such HRF differences could have a non-linear relation to neuronal activation in different tasks. Thus, although very important, such measures are unfortunately not magic bullets that can completely solve the problem of different HRF response functions in different populations. It is therefore advisable to control for vascular risk factors (hypertension, diabetes) and already present (cerebro-)vascular changes (e.g. arteriosclerosis, cortical infarctions, white matter lesions) and to exclude such subjects from functional activation studies on healthy aging or AD (D’Esposito et al., 2003).

Nonetheless, even if neurovascular decoupling might be a confound in healthy elderly participants and dementia patients, it cannot explain the widespread occurrence of task-related overactivations in these groups. Although many elements of the dynamics of cortical activation are not fully understood, the functional activation studies of the aging brain conducted so far permitted the in vivo observation of the physiological effects of the brain’s efforts to counteract its progressive destruction.

5.2. The question of the “baseline”

In the functional imaging literature, brain activation is determined as the change of the level of activity (rCBF, BOLD-signal, metabolic changes) during a task from a baseline condition. The baseline is commonly assumed to represent a “null” level of brain activity during rest or during a control task that is not hypothesized to change activity parameters in specific brain areas. Thus, the amount of task-induced activation in the brain is inevitably related to the baseline level. However, recent findings and
debates have indicated that this approach must be considered with caution (Stark and Squire, 2001), perhaps even more so in functional activation studies of dementia.

In healthy participants, functional networks of sensory and motor areas, as well as frontal and parietal areas, are detectable during the resting condition (Van de Ven et al., 2004). The contribution of brain areas to these networks might change with different pathological states (e.g., Malaspina et al., 2004), thereby potentially contributing to the observed differences in activation patterns across groups during task performance.

Some brain areas show high intrinsic activation during the rest condition, in comparison to other brain areas, and become deactivated during various cognitive tasks. These include the medial parietal cortex (precuneus and posterior cingulate), the medial frontal cortex, and the bilateral inferior parietal cortex (see Shulman et al., 1997). These areas have been suggested to constitute a “default mode” network that is more active during rest (i.e., not performing any task) and that becomes deactivated with increasing cognitive task demand (Raichle et al., 2001). The physiological role of this network has not yet been resolved, but it has been associated with “inner thinking” and monitoring of both mental and environmental processes (Raichle et al., 2001; McKiernan et al., 2003). In AD patients, this “default mode” network has been found to be less active during rest when compared with healthy age-matched controls (Minoshima et al., 1997; Johnson et al., 1998; Greicius et al., 2004). Furthermore, in an active semantic task, healthy AD patients showed less task-related deactivation in the posterior cingulate cortex when compared with age-matched control subjects and healthy young controls (Lustig et al., 2003). This finding may be explained by impaired suppression of competing processes during cognitive processing, by a decreased baseline activity, or both. When comparing task-related functional activation between AD subjects, healthy senior and young subjects, the potential contribution of differential baseline activity to the functional activation differences should be considered, especially in brain regions of the “default mode” network.

Several other methodological issues might account for potentially artifactual functional activation differences between control and patient groups. Not controlling for these factors in the experimental design or analysis may lead to systematic errors when comparing the signals of the patient group with controls. Fortunately, some of these factors can be explicitly considered and quantified.

5.3. Performance measurements

Without the adequate measurement of response accuracy and latency in cognitive tasks, it is difficult to know whether an activation difference between patients and controls is caused by worse performance or non-compliance in the patients. Thus, performance measurements are necessary in order to attribute functional activation differences to the disease, to differences in performance, or to lack of cooperation. The use of event-related fMRI allows investigators to measure functional activation separately for task items that have been processed accurately and for those that have not. This approach can greatly help to distinguish between functional activation differences that are due to physiological dysfunction, performance deficits, or both.

5.4. Atrophy correction

Especially when using functional imaging techniques with lower spatial resolution (PET, SPET), the measured activation signals have been found to be confounded by atrophy (partial volume effect) (Bokde et al., 2001). Because atrophy is generally higher in AD than in normal aging, this is a systematic effect that can lead to artificially low activation signals in AD. It is therefore useful to control for the impact of local atrophy on brain activation differences especially in brain regions with high atrophy (Dickerson et al., 2004; Prvulovic et al., 2002).

5.5. Eye-movements

As abnormal eye movement patterns have been described in AD patients (Schewe et al., 1999), the consideration of eye movements as a confounding factor may be beneficial for the interpretation of the differences of activation patterns between patients and controls. However, the control for eye movements is
not yet a standard procedure because it requires systems that are not only expensive but also make the imaging procedure more complex and time-consuming. Other potential confounds that should be considered in functional imaging studies with AD patients include dementia severity, head movements and acetylcholinesterase inhibitor status.

5.6. Conclusion

In sum, the differences of brain functional activation patterns between healthy young and senior subjects and patients with degenerative brain diseases can in great part be explained by a combination of physiological mechanisms within single functional units and by large-scale mechanisms within networks of multiple units. These mechanisms comprise the activation of alternative processing pathways and that of supportive modulatory systems. In normal conditions, these mechanisms aid successful adaptation to task demands. In functionally impaired brains, these same processes are engaged to maintain task performance as well, but only compensate for the reduced processing capacity up to a certain level. The measured functional activation patterns finally result from a complex interplay between task difficulty and task performance, effort, amount of damage to functional processing units, their necessity for the processing of a particular task, and the integrity of connections within large-scale networks. One of the great methodological challenges for the coming years will be to resolve the pathophysiology of neurovascular coupling and its impact on the results of functional activation studies in aging and dementia. Further developments such as improved imaging technologies (e.g., higher spatial resolution by using MR scanners with higher magnetic fields) and more sophisticated statistical approaches (e.g., analysis of functional connectivity, Van de Ven et al., 2004) may in the future help to unravel the interaction between the processes of degeneration and functional activation in the human brain.

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Task demand modulations of visuospatial processing measured with functional magnetic resonance imaging. NeuroImage 21, 58–68.


