Alzheimer' Disease as a Disconnection Syndrome?

Delbeuck, Xavier; Van der Linden, Martial; Collette, F.

How to cite

DELBEUCK, Xavier, VAN DER LINDEN, Martial, COLLETTE, F. Alzheimer" Disease as a Disconnection Syndrome? In: Neuropsychology Review, 2003, vol. 13, n° 2, p. 79–92. doi: 10.1023/A:1023832305702

This publication URL: https://archive-ouverte.unige.ch//unige:120972
Publication DOI: 10.1023/A:1023832305702

Neuropsychology Review, Vol. 13, No. 2, June 2003 (© 2003)

Alzheimer's Disease as a Disconnection Syndrome?

X. Delbeuck,[1,3] M. Van der Linden,[1,2] and F. Collette[2]

This paper reviews the growing amount of evidence supporting the hypothesis that Alzheimer's disease includes a disconnection syndrome. This evidence came mainly from neuropathological, electrophysiological, and neuroimaging studies. Moreover, a few recent neuropsychological studies have also explored the effects of a disconnection between cerebral areas on cognitive functioning. Finally, and more generally, the contribution of this interpretation to the understanding of Alzheimer's disease cognitive deficits is considered.

KEY WORDS: Alzheimer's disease; disconnection; neuropsychology.

BACKGROUND

From Broca's initial research work in the 1860s, the functioning of the brain has been described in terms of functional separation. This view recognizes that different processes are mainly represented in different anatomical areas. In its extreme version, it considers the brain as a set of modules, processing the information more or less independently from each other. However, some authors challenged this strict modular and localisationist view (for a review see Finger, 1994). For example, Jackson (1874/1958) considered that a specific mental ability is not produced by one distinct group of localized brain cells but rather arises from a hierarchic organization, respectively from low to high, the spinal or brain stem, the motor or sensory, and the "frontal" level. According to Jackson, cognitive functioning is better conceptualized in terms of numerous interactions and influences among different brain areas rather than in terms of a strict modular perspective. From this perspective, cognitive deficits following brain damage can be attributed not only to a specific cerebral dysfunction but also to disconnection processes between different cerebral areas. Other authors such as Wernicke (1874/1977) and Lichtheim (1885) also used disconnection to explain certain neuropsychological deficits. After a long eclipse, this perspective re-emerged in the literature during the second half of the last century. This revival of the disconnection theory is directly attributable to Geschwind (1965), who was inspired by the work on split-brain patients done by Sperry (1961).

More recent models of brain functioning have also integrated the notion of functional connectivity, namely the influence that one neuronal system exerts over another (Friston, 1999). For example, Mesulam (1998) described a model of brain organization in which information is processed in a hierarchic fashion, through five functional areas, from the most specialized sensorial areas to the least differentiated limbic structures. While sensori-motor areas may be seen as related to aspects of the outside world, limbic areas are more concerned with the inner world (emotion regulation, motivation, memory and homeostasis). Between these two extremes, there are three areas of association cortices (unimodal, heteromodal and paralimbic) which create a link between the inner and the outer, external world. Mesulam (1998) argues that consciousness and cognition arise from this five-stage transfer.

Functional connectivity and its disturbance may also be represented and computed using artificial models (i.e., theoretical representation of processes for simulation of the cognitive functioning). For example, the Multiple Constraint Organization (MCO; see Peled, 1999) describes a system comprising numerous reciprocally

[1]Cognitive Psychopathology Unit, University of Geneva, Geneva, Switzerland.
[2]Neuropsychology Department, University of Liège, Liège, Belgium.
[3]To whom correspondence should be addressed at Unité de Psychopathologie Cognitive (Cognitive Psychopathology Unit), Faculté de Psychologie et des Sciences de l'Education, UNI MAIL 40, boulevard du Pont-d'Arve, CH-1205 Genève, Switzerland. E-mail: Xavier.Delbeuck@pse.unige.ch

1040-7308/03/0600-0079 © 2003 Plenum Publishing Corporation

interconnected units. Applying MCO to Mesulam's (1998) hierarchic model, Peled (1999) has proposed an interpretation of schizophrenic symptoms characterized as a MCO breakdown. According to Peled, MCO breakdowns would explain symptoms such as disorganization, reality distortion, or even delusions. Such a disconnection interpretation of schizophrenia has been defended by others (for a review see Friston, 1999) and supported by some findings (e.g., Frith et al., 1995).

Interestingly, a disconnection interpretation has also been advanced to explain part of Alzheimer's disease (AD) symptomatology (see for example Morris, 1996; Morrison et al., 1986). More specifically, AD pathology would not be the consequence of a pathophysiology in one or more neuronal systems but rather a disturbance of the brain's effective connectivity suggesting abnormal interactions between neuronal systems. In this paper, we will examine three lines of evidence pointing towards AD as a disconnection syndrome. First, we will briefly review neuropathological data. Indeed, the distribution of pathological changes in AD patients' brains does not appear in a random or widespread uniform fashion but is rather selective and restricted to some brain areas or even to some laminae within those areas. Second, we will report the electrophysiological and neuroimaging data concurring with the disconnection hypothesis. Finally, we will present the scarce neuropsychological data available on the topic and discuss the potential consequences that a disconnection problem would have on AD patients' cognitive performance.

NEUROPATHOLOGICAL DATA

Two principal neuropathological markers have been found in the brains of AD patients: neurofibrillary tangles (NFT) and neuritic plaques (NP). These markers (and especially NFT) are particularly present in brain areas that give rise to long corticocortical tracts linking cerebral areas (e.g., Damasio et al., 1990; Gòmez-Isla and Hyman, 1997; Pearson et al., 1985; Van Hoesen, 1990). Indeed, neuropathological data in AD (e.g., Pearson et al., 1985) reveal that NFT predominate in the associative cortices (in the temporal, parietal and frontal lobes), and especially in the large pyramidal neurons located in layers III and V of these areas. These pyramidal neurons permit corticocortical connections between and within the cerebral hemispheres. In their review of the literature, De Lacoste and White (1993) conclude that the distribution of neuritic plaques (NP) also appears organized and seems to affect the ends of corticocortical connections. Considering this distribution of AD neuropathological markers, the hypothesis has emerged that NFT would be observed in the body of cells giving rise to corticocortical tracts while NP would be seen at the end of these tracts and in their collateral branches. Consequently, AD might be partly a neocortical disconnection syndrome, i.e., characterized by the loss of afferent and efferent connections of cortical areas associated with the death of pyramidal neurons (Morrison et al., 1986).

Furthermore, some authors (e.g., Arriagada et al., 1992) proposed a hierarchic vulnerability of architectonic areas in AD. A consistent pattern emerges from neuropathological data showing that the most severely NFT affected areas would be the entorhinal cortex, the area CA1/subiculum of the hippocampus and amygdala, followed by less vulnerable association cortices and finally the primary sensory areas which would be less affected by NFT. This pattern of hierarchic vulnerability suggests that AD spreads in a stepwise fashion along the corticocortical connections. Moreover, the subcortical areas which are affected in AD are those which strongly interact with the cortex, such as the locus coeruleus, the raphe complex, and the Meynert's nucleus basalis (see Van Hoesen, 1990).

In a different perspective, changes in the heteromodal cortex of AD brain would suggest a disconnection disturbance. Indeed, these areas receive convergent input from unimodal areas of more than one sensorial modality (see Mesulam, 1998). Consequently, a disruption of these cortices would lead to a segregation of the different modalities and would produce a disconnection of the different systems. For example, Gòmez-Isla et al. (1997) reported neuronal loss in AD patients' superior temporal sulcus (50% loss compared to control participants). This neuronal loss parallels the chronological evolution of dementia and correlates significantly with the NFT formation. In nondemented participants, superior temporal sulcus neurons are stable across the sixth to ninth decades of life. Similarly, Buldyrev et al. (2000) showed disruptions of the microcolumnar ensembles in the neuronal architecture of the superior temporal sulcus region in AD patients. These microcolumnar ensembles are a cytoarchitectural characteristic detected by Buldyrev et al. in the higher order association cortex. Consequently, these data suggest disruptions of the heteromodal cortex in AD patients.

Considering all these neuropathological data, a disconnection might be a potentially valid interpretation of AD pathogenesis. In-depth examination of AD patients' hippocampal formation reinforces this disconnection view, by suggesting an isolation of the hippocampal formation (Damasio et al., 1990; Van Hoesen, 1990, 1997). The isolation of the hippocampal formation is documented by the presence of NFT in the entorhinal cortex, especially present in layers II and IV (even in mild

AD cases, Gòmez-Isla et al., 1996; see also for a review Damasio et al., 1990; Van Hoesen, 1990, 1997). Layer II of the entorhinal cortex gives rise to the perforant pathway, which links the entorhinal cortex with hippocampal structures. Therefore, the presence of these NFT will produce a "deafferentation" of the hippocampal system. Another AD affected structure is the subiculum, which gives rise to efferent links from the hippocampus to the cerebral cortex and to subcortical structures. The changes observed in the subiculum and layer IV of the entorhinal cortex (origin of projections from the hippocampus to the cerebral cortex) cause a disturbance of the projections from the hippocampus to the rest of the brain, producing a "deefferentation" of the hippocampal system.

The NP distribution in the hippocampal formation is also illustrative since NP are present at the termination of the pathways (for a review see De Lacoste and White, 1993). For example, there is a considerable amount of NP in the CA1 pyramidal cell layer and in the molecular layer of the CA1-subiculum area, areas receiving output from the hippocampal circuit. Similarly, the density of NP is greater in the molecular area of the dentate gyri, which is believed to be the end of part of the perforant pathway.

In summary, the neuropathological data show a disruption of most of the efferent and afferent linkages between the hippocampal formation and the rest of the brain, suggesting that AD might be considered as a disconnection syndrome. Progression of the disease may also support this conclusion since areas affected at the onset of the disease are the "associative areas" that integrate information, such as the heteromodal cortex, before sensory or motor areas. On the whole, these data highlight that the degeneration in AD is not global (see also Uylings and de Brabander, 2002) but rather specific to areas related to corticocortical connections.

ELECTROPHYSIOLOGICAL AND NEUROIMAGING DATA

Results from electroencephalography (EEG), positon emission tomography (PET) or even magnetic resonance imaging (MRI) studies have also documented the disconnection hypothesis in AD. These studies particularly suggest disconnection both between anterior and posterior areas of the brain and between the cerebral hemispheres. Using the electroencephalographic coherence paradigm, some studies (Leuchter et al., 1992; see also Besthorn et al., 1994; Le Roc'h et al., 1993; Locatelli et al., 1998; Wada et al., 1998a) have explored the integrity of structural connections between cerebral areas in AD. Coherence is a quantitative measure that determines the degree of functional connection between two or more cerebral areas. It is expressed by the synchrony, or coupling, of two electrodes in a given frequency band. In AD patients compared to control participants, for example, Leuchter et al. (1992) found a systematic decrease of coherence between areas linked by corticocortical tracts crossing the Rolandic fissure (e.g., the superior longitudinal fasciculus). In contrast, multi-infarct dementia (MID) is characterized by a significant decrease of coherency between areas located on the same side of the Rolandic fissure relative to the control participants group.

Magnetoencephalography (MEG), a non-invasive technique that enables the magnetic fields generated by electrical activity in the brain to be measured, has confirmed the presence of a loss in coherence in AD (Berendse et al., 2000). A general decrease of MEG coherence values was observed in AD patients relative to controls within all the frequencies analyzed but the relative coherence loss was greatest for the long distance fronto-parietal coherence measures.

In a more recent study, Golob et al. (2001) have used electrophysiological responses to specific sensory inputs (evoked potentials) to test the disconnection hypothesis in AD. More specifically, they measured evoked potentials between responses to pairs of sensory stimuli having the same modality (visual-visual or auditory-auditory; intramodal situation) and responses to pairs of stimuli of two different modalities (visual-auditory or auditory-visual; crossmodal situation). Considering the segregation of auditory and visual pathways, the physiological response to these crossmodal situations would characterize interactions between visual and auditory cortical regions. Previous studies have shown a refractory effect in these intra- and crossmodal situations (Davis et al., 1966, 1972). The refractory effect is the reduced amplitude and latency of electrophysiological components observed for a stimulus when another stimulus has been presented before. Young ($n = 12$) and elderly ($n = 12$) healthy groups were included in the Golob et al. (2001) study as well as groups of AD ($n = 11$) and mild cognitive impairment ($n = 10$) subjects. The mild cognitive impairment (MCI) group included elderly subjects reporting subjective memory complaints and having a score 1.5 standard deviations below the age-associated norms for memory but a normal performance in other cognitive domains (Petersen et al., 1999). These participants are considered as a group presenting vulnerability for the development of AD. Golob et al. (2001) recorded the electrophysiological response of these four groups (young, elderly, MCI and AD) in two conditions. In the intramodal conditions, a pair of visual (flash of light) or auditory (tones) stimuli is presented and the

electrophysiological response to the second stimuli of the pair is compared to the response for the first stimulus. In the crossmodal situations, a visual stimulus preceded an auditory stimulus and vice versa, and thus the response to a stimulus is studied in reaction to the presentation of a previous stimuli from a different modality. Results showed that refractory effects are observed in all the groups for the auditory as well as visual intramodal situation. Concerning the crossmodal conditions, no refractory effect was observed in any group when a visual stimulus was presented after an auditory stimulus (auditory-visual condition). However, when an auditory stimulus followed the presentation of a visual stimulus (visual-auditory condition), Golob et al. observed a refractory effect in all the groups except AD patients. Indeed, a reduced amplitude of at least one auditory component (P50, N100, and P200) was present in the young, elderly and MCI groups. Moreover, graded changes were observed in this visual-auditory condition between the groups. All the three auditory components analyzed were attenuated in the young healthy group, while only two components were modified in the elderly group. Of these two components modified in the elderly group, the amplitude of only one component was significantly reduced in the MCI group and no change was observed in the AD group. In conclusion, an intramodal refractory effect was present in all the groups but results in the crossmodal condition suggest functional differences between the groups. Assuming that crossmodal refractory effects are accomplished via a corticiocortical pathway, these data would reflect the presence of a cortical connectivity disturbance between the visual and auditory cortices in AD while the synaptic interactions within the auditory (or visual) pathway and cortex seemed preserved. Consequently, Golob et al. (2001) intrepreted the absence of crossmodal refractory effect in AD as suggesting a cortical disconnection syndrome in this pathology. However, the neural mechanisms for refractory effects in humans are still unknown and thus these results should be interpreted with caution.

Furthermore, Rose et al. (2000) evaluated the white matter integrity of mild to moderate AD patients ($n = 11$) using the magnetic resonance diffusion tensor imaging technique, which examines water diffusion in different tissues and the organization of white matter tracts. Compared to healthy controls, AD patients showed a significant decrease of associative white matter fibers such as the splenium of the corpus callosum, the superior longitudinal fasciculus (linking fronto-occipito-temporal areas), and the cingulum (the tract going through the cingular and parahippocampal circumvolutions).

Additional evidence for a disconnection process in AD consisted of measuring the distribution of regional cerebral blood flow at rest using the PET technique. In this manner, Horwitz et al. (1987) calculated correlation coefficients between values of regional cerebral metabolic rate for glucose consumption (rCMRglc) to estimate the functional association between cerebral areas. They determined rCMRglc in 28 pairs of bilateral (right-left hemisphere areas) and 3 midline regions of interest (ROI). Lower rCMRglc values in 22 of the 59 ROI were reported in the AD group (mild to moderate AD patients) as compared to controls, especially in the frontal, temporal, and parietal associative areas. For each group (patients and controls), the rCMRglc measurements were used in separate correlation matrices through the evaluation of partial correlations between every 59 pairs of ROI. In these correlation matrices, the brain regions were divided into frontal, parietal, temporal, occipital, and non-cortical sets. Statistical analyses evaluated the difference between correlation matrices in AD patients and controls. Within this brain matrix, Horwitz et al. observed a reduced number of frontal-parietal correlations in AD patients than in controls, in the resting state. This reduction in AD patients compared to the controls was more pronounced than the reduction observed between healthy elderly and young participants in Horwitz et al.'s (1986) study. Moreover, Horwitz et al. (1987) also showed a disorganized functional activity between the two hemispheres in the early stages of AD suggested by a loss of partial correlations between homologous right-left ROI.

Azari et al. (1992) extended and confirmed the results obtained by Horwitz et al. (1987). Indeed, they also evidenced weaker functional neocortical interactions (less positive correlations) in mild to moderate AD patients, especially between frontal association and both parietal association and paralimbic areas. Like Horwitz et al. (1987), they noticed a loss of positive correlations between the hemispheres, suggesting a breakdown of the interhemispheric functional association.

In addition, PET activation studies have also been analyzed in terms of functional connectivity. In a recent study, Grady et al. (2001) explored mild AD patients ($n = 11$) engaged in a memory task for unfamiliar faces using H_2O^{15}. Compared to controls, AD patients showed marked differences in brain activation patterns during the memory task. For example, in AD patients, an increased involvement of the amygdala compared to controls was noted. Changes in functional connectivity have also been identified in AD patients. Indeed, diminished functional interactions of the right prefrontal cortex with the right hippocampus and visual cortices were observed, which suggests an anterior-posterior disconnection. According to Grady et al., these results would imply that the memory breakdown observed in early AD relies, at least partly, on

a reduction of the integrated activity within a large distributed network.

In support of the disconnection hypothesis, it is also interesting to consider the interhemispheric relations in AD. In the studies described above, data in favor of an interhemispheric disconnection have been cited. For example, Rose et al. (2000) found a decrease of associative white matter fibers in the corpus callosum splenium of AD patients, and the PET studies by Horwitz et al. (1987) and Azari et al. (1992) namely display the existence of a modification in the functional interactions between the hemispheres. Besides these data, some authors have thoroughly studied the question of an interhemispheric disconnection in AD. For example, interhemispheric coherency studies were performed by Wada et al. (1998b). Lower coherence was observed between the hemispheres in 10 mild to moderate AD patients compared to controls, suggesting a disturbance of the interhemispheric functional connectivity in AD.

Being the major commissure linking the two hemispheres, the exploration of the corpus callosum and its associated functions might be of interest within the framework of an interhemispheric disconnection in AD. MRI studies have shown an atrophy of the corpus callosum in AD patients compared to controls (Pantel et al., 1999; Teipel et al., 1999; see also Hampel et al., 1998; Janowski et al., 1996). Teipel et al. (1999) found smaller total callosal areas in 12 mild to moderate AD patients and the most severe changes were observed in the callosal rostrum and splenium (anterior and posterior part of the corpus callosum) relative to healthy controls. These changes seemed to be independent of any primary pathology of the white matter since they occur in AD with only minimal white matter changes. Using MRI, Pantel et al. (1999) also noticed atrophy in all the subsections of the corpus callosum in AD (13.4% in mild to moderate AD patients) compared to age-matched healthy controls. They interpreted the changes of global and regional size of the corpus callosum as being due to the degeneration of the pyramidal neuron axons of cortical layer III, from which callosal fibers arise. In their study, severity of dementia was significantly correlated with the size of the middle sections of the corpus callosum (rostral body and midbody). Furthermore, in AD patients, the size of the rostral midbody of the corpus callosum was correlated with frontal lobe volume, the size of the midbody with temporal lobe volume, and the size of the splenium with parietal lobe volume. This pattern of correlations was not observed in control participants. It should, however, be noted that a correlation was also observed between age and the corpus callosum, especially with its anterior part. In conclusion, these data suggest that the corpus callosum might be a marker of the progressive neocortical disconnection in AD. Indeed, regional callosal atrophy observed in AD patients is seen even after excluding a primary white matter degeneration and correlated significantly with corresponding cerebral lobe volumes.

Besides its value as a potential marker of AD, the corpus callosum might also be a useful tool for the differential diagnosis of dementia. Yamauchi et al. (2000) compared three different kinds of demented patients to a group of 23 control participants: 11 patients with frontotemporal dementia (FTD), 9 patients with probable progressive supranuclear palsy (PSP) and 16 probable AD. No significant difference was found between groups for sex distribution, level of education or age and the three groups were mild to moderate demented patients. The duration of the disease was similar between the AD and FTD groups but was different between these latter groups and PSP patients who displayed a significantly longer mean duration of disease. Consequently, results from the comparison between PSP and other dementias should be interpreted with caution. In the three groups of patients, a decrease of total callosal area (from the anterior border of the rostrum to the caudal end of the splenium) was observed compared to controls. However, a specific part of the corpus callosum was significantly smaller in each of these dementia types compared to others: the anterior quarter callosal area in FTD, the middle-anterior quarter area in PSP and finally the posterior quarter area in AD. Yamauchi et al. concluded that these characteristic patterns of callosal atrophy might reflect the differential patterns of neocortical involvement in the different kinds of dementia. Lyoo et al. (1997) also showed a differential pattern of corpus callosum atrophy between AD ($n = 162$) and MID ($n = 28$) compared to control participants ($n = 36$). In the early stages of dementia, patients with AD present a decreased size of the corpus callosum in the posterior midbody, isthmus and splenium while the area of the genu is decreased in MID, relative to the values obtained in the healthy comparison group. However, both in AD and MID, measures of all regions of the corpus callosum decrease as the dementia progresses.

In conclusion, these electrophysiological and neuroimaging data provide evidence of disconnection problems in AD. These problems are observed either within (for example, diminished antero-posterior connectivity) or between (for example, reduction of the corpus callosum) the cerebral hemispheres when using various techniques such as EEG, PET, or even MRI. As for the neuropathological data, these results showed that the deterioration in an AD brain is not global. Indeed, loss of coherency is observed in AD between posterior and anterior cortical areas but not within either the prefrontal or posterior regions.

Finally, some data showed differentiation between AD and other dementia regarding, for example, the location of the corpus callosum atrophy. All these studies have explored the disconnection hypothesis but still need to be replicated and extended to determine whether the disconnection is anatomical or is the consequence of neuronal loss in the areas being connected.

NEUROPSYCHOLOGICAL DATA

Very few neuropsychological studies have directly examined the disconnection hypothesis in AD. Most often, the disconnection interpretation still remains a *post hoc* explanatory process. However, Lakmache et al. (1998) conducted a study aimed at exploring interhemispheric transfer in AD patients. In this study, they selected an experimental procedure that generally evaluates the processing by either each hemisphere separately (intrahemispheric condition) or the combined activation of both the hemispheres via the corpus callosum (interhemispheric condition). The authors designed various tasks to evaluate different parts of the corpus callosum.

First, they used a motor test to assess the integrity of the anterior part of the corpus callosum, which connects the frontal lobes and the motor areas. The task used by Lakmache et al. required a bimanual and hence, interhemispheric coordination. A diagonal model line was presented and the participants were asked to draw a line matching this model as closely as possible. To draw the line, two buttons are needed, one button to control the horizontal (x axis) and the other to direct the vertical (y axis) displacement of the pencil. Consequently, the task could only be executed by using both hands and coordinate the movement of the two hands to draw a diagonal line matching the model. The dependent variable was the deviation of the line drawn from the sample line. Indeed, poor matching to the model would evidence a disturbance in bimanual coordination. In these conditions, when participants were given a time limit to draw their line, AD patients made significantly more errors than controls: either they could not finish the task or they showed erratic performance. This problem of interhemispheric coordination was present in AD patients while no difference was noticed between them and controls in a task designed to control the manual dexterity of the patients.

Second, performance on different somesthesic tests was evaluated to assess the integrity of the trunk of the corpus callosum, connecting the parietal and temporal regions. Four tests were administered in this condition, the first one was a finger identification test. Out of sight, the experimenter touched a particular location on the patient's hand, and the patient had to indicate with his/her thumb the place where he had felt the touch. In the intrahemispheric condition, the participants were asked to show the location on the same hand as the stimulation. In the interhemispheric condition, they had to show the location on the other hand. A second somesthesic test consisted in comparing three-dimensional shapes (such as a star or a square, . . .) and was constructed on the intra- versus interhemispheric design (explore and recognize with the same hand versus with different hands). In these tasks, performance of AD patients was affected only in the interhemispheric condition. A third somesthesic task required participants to name sixty familiar objects (comb, spoon, . . .), explored with their right or left hand. Performance of controls and AD patients did not differ when the objects were handled with the right hand, but AD patients had a poorer performance when the objects were palpated with the left hand. This performance is also illustrative of interhemispheric problems in AD since the naming test involves access to language centers which are generally lateralized in the left hemisphere. When an object is palpated with the left hand, information about this object is projected in the right hemisphere and thus must be transferred to the left hemisphere so that the object can be named (interhemispheric condition). The intrahemispheric condition is when the object is palpated with the right hand because in this case no transfer through the corpus callosum is needed since information is directly projected in the left hemisphere. A last somesthesic task was also used to assess the somesthesic interhemispheric transmission by contrasting an intra- and an interhemispheric condition of reaction time to a stimulus. The stimulus was a puff of air delivered to one of the hands. The subject had to respond either with the stimulated hand (intrahemispheric condition) or with the other (interhemispheric condition) by pressing a response key. Although AD patients exhibited longer reaction times compared to controls in all the conditions, this effect was more pronounced in the interhemispheric condition, in which the stimulus was projected to one hemisphere and the response was produced by the other.

Finally, visual comparison tasks were administered to test for a transfer disturbance between visual areas of both hemispheres through the posterior part of the corpus callosum. In the color comparison task, a same/different judgment had to be made between two colored circles (red or green) presented tachitascopically. These two circles were projected either in the same hemisphere or each in a different hemisphere, the latter condition involving an interhemispheric transfer. Performance did not differ between the two groups in the intrahemispheric condition, but AD patients' performance significantly declined

in the interhemispheric condition. A second visual task consisted in a letter comparison task. Participants had to state as quickly as possible whether two letters were the same or different. These pairs of letters were projected either in the same hemisphere (intra) or one in each hemisphere (inter). In control participants, no difference was found between the intra- and interhemispheric situation, whereas AD patients' performance declined in the latter condition. A decline in AD patients was also observed in judgment accuracy when letters were presented in the left hemifield (right hemisphere), with this condition requiring an interhemispheric transfer. Finally, it should be noted that no differences were found in the task designed to assess the visual interhemispheric transmission time. This task requires the participant to respond to a flash of light projected either in the left or right hemifield. In the intrahemispheric condition, the light and the response (pressing a response key with the hand) were processed by the same hemisphere while in the interhemispheric situation, they involved the opposite hemisphere (the information is received by one hemisphere and should be transferred to the other hemisphere controlling the hand which has to answer).

On the whole, these results showed callosal deficits in AD. Indeed, AD patients performed poorly when coactivation of both hemispheres was required in the interhemispheric condition, while performance was preserved in the respective intrahemispheric conditions. In this regard, it should be noted that the assessment of the motor interhemispheric transfer is not compared to an intrahemispheric condition. Moreover, differences between AD and controls for the motor interhemispheric coordination task are observed only when a time limit is set in this task but not in a free time condition. Consequently, other factors than a disturbance of the transfer of motor information between the hemispheres might explain the difficulties observed in AD patients. Finally, another limit of this study is the small sample of patients (10 mild to moderate AD patients). Consequently, these results need to be replicated and extended.

Mohr et al.'s (1990) findings using a dichotic listening paradigm also seem relevant with regard to the integrity of the corpus callosum in AD. In their procedure, conflictual stimuli (pairs of words) were presented simultaneously in the right and the left ear, under three conditions. In the first condition, subjects had to recall all the stimuli, regardless of the side where the stimulus was presented (free recall). In the two other conditions, they were asked to recall either the word presented to the right ear (RER condition) first, or the word presented to the left ear (LER condition) first. The order of these two latter conditions was counterbalanced among participants. In the free recall condition, controls recalled more correct items heard by the right ear than by the left ear (right ear advantage). In the LER and RER conditions, controls' performance revealed an advantage for the left ear in the LER condition, and an advantage for the right ear in the RER condition, when compared to the proportion of correct items recalled. On the other hand, the performance of 22 mild to severe AD patients was characterized by inferior accuracy regardless of the condition and by the presence of a right ear advantage in all three recall conditions. In the LER condition, AD patients recalled a greater number of correct items for the stimuli presented to the right ear than to the left ear. The disappearance of the left ear advantage in the LER condition has been interpreted by Mohr et al. (1990) as reflecting an inability of AD patients to shift their attention. However, the right-ear advantage persistence in AD patients could be explained by the easier access to the language areas of the information presented to the right ear (left hemisphere) and a perturbation that the "left information" undergoes when passing from one hemisphere (right) to the other (left). Two other studies (e.g., Grady et al., 1989; Grimes et al., 1985) have also administered dichotic listening tasks to AD patients. For example, Grady et al. (1989) observed a dichotic listening impairment in a group of 32 mild to moderate AD patients compared to controls. Moreover, Grady et al. (1989) examined whether impaired dichotic task performance in AD is related to difficulties in the perception of degraded speech of stimuli presented monaurally. They observed that performance on degraded speech tasks was impaired in AD patients but was only correlated minimally with the dichotic task performance in this group compared to healthy controls. This result suggests that auditory processing of difficult stimuli is impaired in AD but that dichotic impairment reflects another deficit in these patients. Consequently, Grady et al. proposed different interpretations of the dichotic listening impairment observed in AD. Firstly, they suggested that the left temporal association cortex metabolic dysfunction and atrophy observed in AD might perturb the auditory processing of speech especially for the processing of two stimuli presented simultaneously resulting in an impaired performance on dichotic listening tasks. It should be noted that Grimes et al. (1985) observed a correlation between performance for information from the right ear on the dichotic task and the cerebral glucose metabolism at resting state in the left temporal cortex. Secondly, the existence of an increased asymmetry (Haxby et al., 1985) and decreased functional coupling between homologous regions (Horwitz et al., 1987) observed in AD might result in a disturbance of the communication between the right and left hemiphere and thus affect performance on dichotic tasks. Finally, they suggested

that dichotic performance might be influenced by a more general attentional deficit in AD. A disturbance in a network of fronto-parietal areas would explain this attentional impairment that would affect dichotic tasks performance in AD.

In summary, the interhemispheric transfer disturbance highlighted in AD is in agreement with a disconnection process. However, further neuropsychological studies are clearly needed not only to confirm these data, but also to explore other types of disconnection deficits, namely those involving intrahemispheric connections (for example, the frontal and parietal areas; Horwitz et al., 1987). The consequences that a disconnection might have on the cognitive functioning of a subject will be discussed in the next section.

DISCONNECTION AND COGNITIVE FUNCTIONING IN AD PATIENTS

Most cognitive tasks are multidetermined, and consequently, optimal performance in these tasks involves the intervention of different processes and brain areas across a large neural network (see, for example, the network involved in episodic memory; Nyberg and Cabeza, 2000). Performance would then not only depend on the integrity of different cerebral areas, but would also rely on the integrity of the connections between them. In the same vein, Morris (1996) argues that "a breakdown in coherence would disrupt the ability of the information processing system to direct and coordinate the cognitive components of complex tasks efficiently, particularly those involving divided attention" (p. 239). What Morris means by coherence is a synchronization between the activity of different cerebral areas. The situation of dual tasks may help to illustrate the problem resulting from a breakdown in coherence. From a neurobiological point of view, a dual task condition involves the synchronous activity of different cerebral areas. Hence, if the transmission between these areas is less efficient, the coordination of mental activity would be affected. Several authors (e.g., Baddeley et al., 1986, 2001; Collette et al., 1999b) have shown that AD patients have more difficulties on dual tasks than control participants. In the Baddeley et al. (1986) study, a visuomotor pursuit task and a digit span task were administered to participants, first separately (simple task condition), and then simultaneously (dual task condition). Compared to control subjects' performance, a greater decrease in the AD patients' performance was observed when tasks were performed simultaneously, although the difficulty of the tasks performed separately was equated across the groups. Moreover, a follow-up examination of some of the AD patients revealed that their performance on the dual task deteriorated, while it was maintained in the simple task condition (Baddeley et al., 1991). In line with Morris (1994), it could be argued that in the dual task condition, a transfer breakdown (expressed by a loss of coherency) should disrupt the capacity of the system to synchronize activity of different cerebral areas, thus resulting in poor performance. However, studies concerning dual task performance deficits in AD still need to clarify whether the deficits are the consequence of a coordination problem rather than a global reduction of cognitive resources or a deficit in executive functions such as shifting.

Furthermore, it appears that an interhemispheric disconnection may have a more important impact on effortful tasks (tasks requiring attentional resources to be performed) than on automatic ones. Indeed, one of the main results from interhemispheric disconnection studies was to show that a simple task, involving few resources, is processed more efficiently by only one hemisphere, in contrast with effortful tasks, where a distribution between the two hemispheres is more advantageous (e.g., Weissman and Banich, 2000). When processing demands are important, areas from both hemispheres can be recruited through these interhemispheric interactions and thus a decrease of performance in these tasks might be interpreted as the result of an inability to distribute processing across the hemispheres. The data discussed previously, which tend to show an interhemispheric disconnection in AD, together with the Weissman and Banich experiment, might at least partly explain why in early AD patients, control (or executive) processes are defective while automatic processes are preserved (Collette et al., 1999b, 2003; Fabrigoule et al., 1998; Laflèche and Albert, 1995).

The so-called "executive functions" rely on a set of processes (inhibition, planning, flexibility, control, etc.) which enhance the subject's adaptation to new situations when routines are not sufficient. For some authors, the neurobiological substrates of executive functioning are located in the frontal lobes (e.g., Shallice, 1988). But others consider that the activation of different areas as well as connections between these areas are needed for adequate executive functioning (Collette et al., 2003; Fuster, 1993; Weinberger, 1993). In this prospect, we examined the performance of two groups of AD patients on executive functions tasks (Collette et al., 2002). In the first group, hypometabolism was restricted to posterior cerebral areas (parietal and temporal), while in the second group, hypometabolism encompassed both frontal and posterior areas. The executive functions testing administered to the participants included a series of task assessing inhibitory processes such as the go/no-go task (Zimmerman and Fimm, 1994),

the Stroop task (Stroop, 1935), the Hayling task (Burgess and Shallice, 1996), verbal fluency and the selective attentional task "D2" (Brickenkamp, 1966). Our results showed that AD patients' performance was inferior to control subjects' on all executive tasks whether they presented a frontal lobe hypometabolism or not. These results suggest that executive dysfunction in AD is not related to a frontal lobe impairment, but rather a consequence of partial disconnection between posterior and anterior cerebral areas.

Perry and Hodges (1999) also evoked the possibility that AD patients' attentional/executive deficits could be associated with a disconnection problem. Many attentional tasks imply fast and simultaneous integration of multiple types of information and therefore necessitate the integrity of corticocortical tracts. In this context, the attentional/executive disorders associated with AD would result from a disruption in the exchange of information between neuronal networks linked by corticocortical tracts. For example, Azari et al. (1992) proposed that the loss of functional connectivity observed in AD between frontal and parietal cortices might explain the attentional deficits of these patients.

Considering the working memory (phonological loop and central executive) deficits observed in AD patients, we proposed a possible trajectory of cognitive impairment in AD, with an early stage being the consequence of disconnection mechanisms (Collette et al., 1999a). That study was based on Baddeley's (1986) working memory model and examined the integrity of the phonological loop and central executive components of working memory in a group of mild to moderate AD patients. Since the phonological loop functioning is considered to be relatively automatic whereas the central executive is involved in control processes, we hypothesized that AD patients in the first stages of the disease would exhibit impairments in tasks assessing the central executive with a preservation of the phonological loop's subcomponents (phonological store and articulatory rehearsal mechanism). The articulatory rehearsal mechanism and the phonological store were examined by comparing the span performance for short and long words and for phonologically similar and dissimilar words. The contribution of long-term memory to span performance was explored by comparing the span performance for words and non-words. A superiority of the performance for words versus non-words span tasks would reflect this contribution. Two tasks were used to evaluate the central executive functioning: the alpha span task (Belleville et al., 1998) and the dual task paradigm proposed by Greene et al. (1995). The alpha span task compared the recall of information in serial order (implying only the temporary storage of information) or in alphabetical order (implying storage and manipulation of information) while the dual task paradigm compared the performance in a digit span task and in a cancellation task carried out separately to the performance when the two tasks were carried out simultaneously. The results showed that, as a group, AD patients presented poor performance in all tasks assessing the phonological loop, the contribution of long-term memory to span performance, and the central executive. Moreover, the span level of AD patients was related to the severity of the disease, as measured by the Mattis Dementia Rating Scale (Mattis, 1973). Therefore, further analyses were conducted using two groups of patients based on their span level. These analyses showed that only the subgroup of patients with a low span performance (consequently more severely demented patients) showed deficits affecting the different components of the phonological loop. On the other hand, both subgroups of (less and more demented) AD patients showed deficits affecting central executive functioning and the contribution of long-term memory to span performance. Thus, these data indicate that high-span level and less demented patients have impairments involving executive processes as well as the integration of different types of information (especially information stored in long-term and working memory), while the low-span level and more demented patients showed deficits involving more basic and automatic processes. Globally, these results support Fabrigoule et al.'s (1998) view that there exists an early impairment of the control process in AD, the automatic processes (such as those involved in phonological loop functioning) being affected later in the disease. In addition, it was suggested that the executive dysfunction observed in less demented AD patients might be partly due to a breakdown in connections between the main cortical association areas (Collette et al., 1999a).

Episodic memory is another relevant cognitive domain with regard to disconnections in AD. Episodic memory is dedicated to the long-term storing of personally experienced events and episodes associated with a particular spatial and temporal context. The existence of memory disorders is clearly the most prevalent and prominent feature of the early stages of AD (Collette et al., 2003). Recent studies indicate that episodic memory is subserved by a large network of cerebral regions (including the hippocampus formation, frontal areas, temporal-parietal association cortex, the cerebellum, and the anterior cingulate cortex; Nyberg and Cabeza, 2000; Van der Linden et al., 2001). Consequently, defective connections between the different regions of the network might cause episodic memory deficits in early AD. In this prospect, Schröder et al. (2001) have obtained results suggesting that memory dysfunction in AD results from a deviant

pattern of cortical activity rather than a specific perturbation of one single area. According to this study, a right prefronto-temporal network would potentially underlie the AD memory deficits. In the same vein, Lekeu et al. (2003) explored the brain correlates of free versus cued recall performance in AD patients using an adaptation (Van der Linden et al., in press) of the Free and Cued Selective Reminding procedure developed by Grober and Buschke (1987). Statistical parametric mapping (SPM 99) was used to establish clinico-metabolic correlations between performance at free and cued verbal recall, and resting brain metabolism in 31 AD patients. The results showed that the patients' performance on free recall was related to metabolic activity in right frontal regions [Brodmann's area (BA) 10 and BA 45], suggesting that performance reflected a strategic retrieval attempt. Poor retrieval performance in AD was attributed to a loss of functional correlation between medial temporal and frontal regions in AD patients. Indeed, interregional correlations analyses revealed greater correlations in elderly controls than in AD patients between the right inferior frontal gyrus and left middle frontal gyri, right inferior temporal gyrus, right inferior parietal lobule and left parahippocampal gyrus. Scores of AD patients on the cued recall task were correlated to residual metabolic activity in bilateral parahippocampal regions (BA 36), suggesting that AD patients' performance reflected retrieval of semantic associations without recollection. Indeed, imaging data have shown that acquisition of new semantic associations would depend on surrounding hippocampal structures (perirhinal, parahippocampal and entorhinal regions) while the hippocampus along with frontal areas would support the acquisition of the episodic (contextual) information (Tulving and Markowitsch, 1998). More specifically, in the cued recall part of the task, AD patients would thus produce the first item semantically associated that came to mind and would not have access to the contextual features of the target item to check the information. In conclusion, it would appear that memory deficits in early AD patients might be due to a dysfunctioning affecting the medial temporal structures as well as to a lack of connectivity between these regions and frontal areas.

CONCLUSIONS

Numerous neuropathological, neurophysiological, and neuroimagery data are consistent with the existence of a disconnection disorder in AD. Neuropathological markers of AD seem to be selectively distributed within the brain and to coincide with the beginnings and endings of corticocortical tracts. Consequently, a disconnection is created through the disruption of afferent/efferent relations between brain areas. This situation is particularly well illustrated looking at the distribution of the neuropathological markers of AD in the hippocampal formation. Indeed, these markers are found in areas serving as gateways between the hippocampal formation and the rest of the brain. As a consequence, the hippocampal formation is isolated from the rest of the brain. Besides these neuropathological data, other evidence supporting a disconnection perspective comes from neurophysiological and neuroimaging studies showing abnormal functional connectivity in AD patients. In these studies, a loss of functional connectivity has been displayed by a decreased EEG or MEG coherency in AD as well as with magnetic resonance diffusion tensor imaging and PET techniques (either at rest or while the subject performed a task). In particular, some studies have focused on interhemispheric relations and have evidenced a disruption of interhemispheric connectivity by these electrophysiological and neuroimaging techniques. Moreover, these callosal disconnections are also supported by neuropsychological data in AD patients.

More generally, many neuropsychological findings indirectly suggest that disconnections might explain part of the symptomatology of AD. According to Arendt (2001), AD would consist in a breakdown of mechanisms regulating modifications of synaptic connections, which play a crucial role in the "higher order" (cognitively demanding) functions of the brain. In the author's view, cerebral organization of mental activity is based on the combination of flexible and rigid connections. Rigid connections ensure the stability of the principal characteristics of functions while flexible connections determine the "unique, non repeatable characteristic of an experienced mental act" (p. 725). These flexible connections are responsible for the high degree of structural plasticity, which is found in brain regions involved in higher order functions such as the hippocampus, neocortical association areas and the cholinergic basal forebrain neurons. As we have seen before, these latter structures are also those that display a strong vulnerability in AD. Consequently, Arendt formulated the problems of AD as a disruption of the brain's capacity to modify its own structural organization and "functioning as an adaptive response to functional demands" (p. 728). This view clearly emphasizes the role of connections in AD pathology.

Applications of the disconnection hypothesis to the understanding of AD still need to be developed. Neuropsychological studies on this topic are still few and only concerned with the interhemispheric aspect of connectivity. Lakmache et al. (1998) have provided evidence of disruption of interhemispheric connections in AD compared to

controls. However, these interhemispheric relations need further investigation. In this regard, a differential diagnosis perspective has to be adopted in this interhemispheric evaluation. Indeed, MRI studies have shown a characteristic pattern of callosal atrophy in AD dementia compared to other types of dementia (Lyoo et al., 1997; Yamauchi et al., 2000). Therefore, neuropsychological studies should evaluate other dementias with interhemispheric tasks to isolate a typical pattern of interhemispheric tasks in AD. However, these neuropsychological studies should be not only focused on interhemispheric relations but also on intrahemispheric connectivity. The exploration of intrahemispheric connectivity in AD would probably pass through a better understanding of the role of the heteromodal cortices and should lead to the creation of tasks specially designed to assess the integrity of these cortices.

In these future connectivity studies, special attention should also be given to aging as age-related differences have been observed on interhemispheric relations (for a review, see Reuter-Lorentz and Stanczak, 2000) and intrahemispheric connectivity. MRI studies have reported specific age-related effects on the corpus callosum (see, for example, Janowski et al., 1996), particularly in the anterior region (Weis et al., 1991). From a cognitive point of view, aging has also been associated with differences in interhemispheric relations. For example, Moes et al. (1995) have shown that healthy elderly participants have a significantly poorer performance than young controls on a bimanual coordination task similar to the one used by Lakmache et al. (1998) in their study on AD patients. Furthermore, aging effects on intrahemispheric connectivity should also be taken into account. Cabeza et al. (1997) have shown reduced functional connectivity in the elderly compared to young participants while they were performing an episodic memory task. They consequently interpreted age-related memory problems in terms of disconnection. Using diffusion tensor imaging, O'Sullivan et al. (2001) also argue that a mechanism of age-related cognitive decline would be the reduction in integrity of white matter tracts.

Further interesting studies related to this disconnection topic are neuroimaging studies. In these studies, functional connectivity analysis should be more systematically performed on neuroimaging results obtained in AD. The interest of these analyses is particularly evident in Grady et al.'s (2001) study described earlier. These analyses examining functional connectivity have revealed the role of the hippocampus in the memory performance of normal controls and the absence of correlation between the right prefrontal cortex and the hippocampus in AD patients, which suggests that AD performance on the memory task might be, at least in part, the consequence of a disconnection problem. In short, studies of functional connectivity in AD patients performing a task are not only interesting for bringing to light a disconnection problem in AD, but are also informative regarding the complex nature of normal brain functioning.

Another promising technique regarding connectivity is transcranial magnetic stimulation (TMS), which is a safe and non-invasive method for the stimulation of cortical areas through the scalp and the disruption of processing for brief periods, thus creating a temporary, "virtual brain lesion." The combination of TMS with neuroimaging techniques offers a tool for assessing the state of the functional connectivity by studying the distributed effects of TMS on the neuronal networks involved in a specific behavior (for a review on TMS, see Pascual-Leone et al., 2000). For example, Mottaghy et al. (2000) have applied repetitive transcranial magnetic stimulation while subjects performed a working memory task. Applying these stimulations to the dorsolateral prefrontal cortex (DLPFC), they observed dynamical changes in a network of interacting cerebral areas (repetitive stimulations to the right DLPFC significantly decreased activity in right prefrontal and bilateral parietal areas) as well as behavioral changes (significant decrease of working memory performance). These results revealed the interest of this method for studying working memory organization. This method might be informative about the working memory disruption in AD because the TMS technique allows a connectivity view of brain functioning.

In conclusion, disconnection is a plausible explanation for some of the cognitive deficits observed in AD such as episodic memory or executive function impairment, as well as difficulties that AD patients encounter in their daily lives. Indeed, efficient connections between different cortical areas are even more important in daily life than in the deliberately simplified laboratory settings. For instance, numerous dual task situations are present in daily life and thus problems resulting from an impairment at this level will have important repercussions on the quality of the patient's life. More generally, behavioral disturbances in AD might also be attributed to a disconnection. In a paper about frontal-lesioned patients, Baddeley et al. (1997) observed that patients showing dual-task impairment also evidenced more important behavioral disorders. Moreover, we have hypothesized that the central executive dysfunction (resulting in difficulty to perform two tasks simultaneously) would result from a disconnection process. Therefore, the disconnection hypothesis might also offer a background for discussing the behavioral problems observed and the difficulties encountered in the daily life of these AD patients.

ACKNOWLEDGMENTS

Fabienne Collette is a Post-doctoral Researcher at the Belgian National Fund for Scientific Research (FNRS).

REFERENCES

Arendt, T. (2001). Alzheimer's disease as a disorder of mechanisms underlying structural brain self-organization. *Neuroscience* **102:** 723–765.

Arriagada, P. V., Growdon, J. H., Hedley-Whyte, E. T., and Hyman, B. T. (1992). Neurofibrillary tangles but not senile plaques parallel duration and severity of Alzheimer's disease. *Neurology* **42:** 631–639.

Azari, N. P., Rapoport, S. I., Grady, C. L., Schapiro, M. B., Salerno, J. A., Gonzales-Aviles, A., et al. (1992). Patterns of interregional correlations of cerebral glucose metabolic rates in patients with dementia of the Alzheimer type. *Neurodegeneration* **1:** 101–111.

Baddeley, A. D. (1986). *Working Memory*, Oxford University Press, Oxford.

Baddeley, A. D., Baddeley, H. A., Bucks, R. S., and Wilcock, G. K. (2001). Attentional control in Alzheimer's disease. *Brain* **124:** 1492–1508.

Baddeley, A. D., Logie, R., Bressi, S., Della Sala, S., and Spinnler, H. (1986). Dementia and working memory. *Q. J. Exp. Psychol.* **38:** 603–618.

Baddeley, A., Della Sala, S., Papagno, C., and Spinnler, H. (1997). Dual-task performance in dysexecutive and nondysexecutive patients with a frontal lesion. *Neuropsychology* **11:** 187–194.

Baddeley, A. D., Bressi, S., Della Sala, S., Logie, R., and Spinnler, H. (1991). The decline of working memory in Alzheimer's disease: A longitudinal study. *Brain* **114:** 2521–2542.

Belleville, S., Rouleau, N., and Caza, N. (1998). Effects of normal aging on the manipulation of information in working memory. *Mem. Cognit.* **26:** 572–583.

Berendse, H. W., Verbundt, J. P. A., Scheltens, Ph., van Dijk, B. W., and Jonkman, E. J. (2000). Magnetoencephalography analysis of cortical activity in Alzheimer's disease: A pilot study. *Clin. Neurophysiol.* **11:** 604–612.

Besthorn, C., Förstl, H., Geiger-Kabisch, C., Sattel, H., Gasser, T., and Schreitter-Gasser, U. (1994). EEG coherence in Alzheimer disease. *Electroencephalogr. Clin. Neurophysiol.* **90:** 242–245.

Brickenkamp, R. (1966). *Le test D2 d'attention concentrée*, Editest, Paris.

Buldyrev, S. V., Cruz, L., Gòmez-Isla, T., Gomez-Tortosa, E., Havlin, S., Le, R., et al. (2000). Description of microcolumnar ensembles in association cortex and their disruption in Alzheimer and Lewy body dementias. *Proc. Natl. Acad. Sci. USA* **97:** 5039–5043.

Burgess, P. W., and Shallice, T. (1996). Response suppression, initiation and strategy use following frontal lobe lesions. *Neuropsychologia* **34:** 263–273.

Cabeza, R., McIntosh, A. R., Tulving, E., Nyberg, L., and Grady, C. L. (1997). Age-related differences in effective neural connectivity during encoding and recall. *Neuroreport* **8:** 3479–3483.

Collette, F., Van der Linden, M., Bechet, S., and Salmon, E. (1999a). Phonological loop and central executive functioning in Alzheimer's disease. *Neuropsychologia* **37:** 905–918.

Collette, F., Van der Linden, M., and Salmon, E. (1999b). Executive Dysfunction in Alzheimer's Disease. *Cortex* **35:** 57–72.

Collette, F., Van der Linden, M., Juillerat, A. C., and Meulemans, T. (2003). A cognitive neuropsychological approach to Alzheimer's disease. In: Mulligan, R., Van der Linden, M., and Juillerat, A. C. (eds.), *The Clinical Management of Early Alzheimer's Disease*, Erlbaum, Mahwah, NJ.

Collette, F., Van der Linden, M., Delrue, G., and Salmon, E. (2002). Frontal hypometabolism does not explain inhibitory dysfunction in Alzheimer's disease. *Alzheimer Dis. Assoc. Disorder.* **17:** 228–238.

Damasio, A. R., Van Hoesen, G. W., and Hyman, B. T. (1990). Reflections on the selectivity of neuropathological changes in Alzheimer's disease. In: Schwartz, M. N. (ed.), *Modular Deficits in Alzheimer Type Dementia*, MIT Press, Cambridge, pp. 83–100.

Davis, H., Mast, T., Yoshie, N., and Zerlin, S. (1966). The slow response of the human cortex to auditory stimuli: recovery process. *Electroencephalogr. Clin. Neurophysiol.* **21:** 105–113.

Davis, H., Osterhammel, P. A., Wier, C. C., and Gjerdingen, D. B. (1972). Slow vertex potentials: interactions among auditory, tactile, electric and visual stimuli. *Electroencephalogr. Clin. Neurophysiol.* **33:** 537–545.

De Lacoste, M. C., and White, C. L. (1993). The role of cortical connectivity in Alzheimer's disease pathogenesis: A review and model system. *Neurobiol. Aging* **14:** 1–16.

Fabrigoule, C., Rouch, I., Taberly, A., Letenneur, L., Commenges, D., Mazaux, J. M., et al. (1998). Cognitive process in preclinical phase of dementia. *Brain* **121:** 135–141.

Finger, S. (1994). *Origins of Neuroscience: A history of explorations into brain function*, Oxford University Press, New York.

Friston, K. J. (1999). Schizophrenia and the disconnection hypothesis. *Acta Psychiatr. Scand.* **99:** 68–79.

Frith, C. D., Friston, K. J., Herold, S., Silbersweig, D., Fletcher, P., Cahill, C., et al. (1995). Regional brain activity in chronic schizophrenic patients during the performance of a verbal fluency task. *Br. J. Psychiatry* **167:** 343–349.

Fuster, J. M. (1993). Frontal lobes. *Curr. Opin. Neurobiol.* **3:** 160–165.

Geschwind, N. (1965). Disconnection syndromes in animals and man. *Brain* **88:** 237–294.

Golob, E. J., Miranda, G. G., Johnson, J. K., and Starr, A. (2001). Sensory cortical interactions in aging, mild cognitive impairement, and Alzheimer's disease. *Neurobiol. Aging* **22:** 755–763.

Gòmez-Isla, T., and Hyman, B. T. (1997). Connections and cognitive impairment in Alzheimer's disease. In: Hyman, B. T., Duyckaerts, C., and Christen, Y. (eds.), *Connections, Cognition, and Alzheimer's Disease*, Springer, Berlin, pp. 149–166.

Gòmez-Isla, T., Price, J. L., McKeel, D. W., Morris, J. C., Growdon, J. H., and Hyman, B. T. (1996). Profound loss of layer II entorhinal cortex neurons occurs in very mild Alzheimer's disease. *J. Neurosci.* **16:** 4491–4500.

Gòmez-Isla, T., Hollister, R., West, H., Mui, S., Growdon, J., Petersen, R. C., et al. (1997). Neuronal loss correlates with but exceeds neurofibrillary tangles in Alzheimer's disease. *Ann. Neurol.* **41:** 17–24.

Grady, C. L., Grimes, A. M., Patronas, N., Sunderland, T., Foster, N. L., and Rapoport, S. I. (1989). Divided attention, as measured by dichotic speech performance, in dementia of the Alzheimer type. *Arch. Neurol.* **46:** 317–320.

Grady, C. L., Furey, M. L., Pietrini, P., Horwitz, B., and Rapoport, S. I. (2001). Altered brain functional connectivity and impaired short-term memory in Alzheimer's disease. *Brain* **124:** 739–756.

Greene, J. D. W., Hodges, J. R., and Baddeley, A. D. (1995). Autobiographical memory and executive functions in early dementia of Alzheimer type. *Neuropsychologia* **33:** 1647–1670.

Grimes, A. M., Grady, C. L., Foster, N. M., Sunderland, T., and Patronas, N. J. (1985). Central auditory function in Alzheimer's disease. *Neurology* **35:** 352–358.

Grober, E., and Buschke, H. (1987). Genuine memory deficits in dementia. *Dev. Neuropsychol.* **3:** 13–36.

Hampel, H., Teipel, S. J., Alexander, G. E., Horwitz, B., Teichberg, D., Schapiro, M. B., et al. (1998). Corpus callosum atrophy is a possible indicator of region- and cell type-specific neuronal degeneration in Alzheimer Disease. *Arch. Neurol.* **55:** 193–198.

Haxby, J. V., Duara, R., Grady, C. L., Rapoport, S. I., and Cutler, N. R. (1985). Relations between neuropsychological and cerebral metabolic asymmetries in early Alzheimer's disease. *J. Cereb. Blood Flow Metab.* **5:** 193–200.

Horwitz, B., Duara, R., and Rapoport, S. I. (1986). Age differences in intercorrelations between regional cerebral metabolic rates for glucose. *Ann. Neurol.* **19:** 60–67.

Horwitz, B., Grady, C. L., Sclageter, N. L., Duara, R., and Rapoport, S. I. (1987). Intercorrelations of regional glucose metabolic rates in Alzheimer's disease. *Brain Res.* **407:** 294–306.

Jackson, J. H. (1874/1958). On the nature of the duality of the brain. In: Taylor, J. (ed.), *Selected Writings of John Hughlings Jackson*, Basic Books, New York, pp. 129–145.

Janowski, J. S., Kaye, J. A., and Carper, R. A. (1996). Atrophy of the corpus callosum in Alzheimer's disease versus healthy aging. *J. Am. Geriatr. Soc.* **44:** 798–803.

Laflèche, G., and Albert, M. S. (1995). Executive function deficits in mild Alzheimer's disease. *Neuropsychology* **9:** 313–320.

Lakmache, Y., Lassonde, M., Gauthier, S., Frigon, J. Y., and Lepore, F. (1998). Interhemispheric disconnection syndrome in Alzheimer's disease. *Proc. Natl. Acad. Sci. USA* **95:** 9042–9046.

Lekeu, F., Van der Linden, M., Chicherio, C., Collette, F., Degueldre, C., Franck, G., et al. (2003). Brain correlates of performance in a free/cued recall task with semantic encoding in Alzheimer's disease. *Alzheimer Dis. Assoc. Disorder*. **17:** 35–45.

Le Roc'h, K., Rancurel, G., Poitrenaud, J., Bourgin, P., and Sebban, C. (1993). Fluidité verbale et cohérence EEG dans la maladie d'Alzheimer. *Neurophysiol. Clin.* **23:** 422–433.

Leuchter, A. F., Newton, T. F., Cook, I. A., Walter, D. O., Rosenberg-Thompson, S., and Lachenbruch, P. A. (1992). Changes in brain functional connectivity in alzheimer-type and multi-infarct dementia. *Brain* **115:** 1543–1561.

Lichtheim, L. (1885). On aphasia. *Brain* **7:** 433–484.

Locatelli, T., Cursi, M., Liberati, D., Franceschi, M., and Comi, G. (1998). EEG coherence in Alzheimer's disease. *Electroencephalogr. Clin. Neurophysiol.* **106:** 229–237.

Lyoo, K., Satlin, A., Lee, C. K., and Renshaw, P. F. (1997). Regional atrophy of the corpus callosum in subjects with Alzheimer's disease and multi-infarct dementia. *Psychiatry Res.: Neuroimaging* **74:** 63–72.

Mattis, S. (1973). *Dementia rating scale*, NFER-Nelson, Winsor.

Mesulam, M. M. (1998). From sensation to cognition. *Brain* **121:** 1013–1052.

Moes, P., Jeeves, M. A., and Cook, K. (1995). Bimanual coordination with aging: Implications for interhemispheric transfer. *Dev. Neuropsychol.* **11:** 23–40.

Mohr, E., Cox, C., Williams, J., Chase, T. N., and Fedio, P. (1990). Impairment of central auditory function in Alzheimer's disease. *J. Clin. Exp. Neuropsychol.* **12:** 235–246.

Morris, R. G. (1994). Working memory in Alzheimer-Type dementia. *Neuropsychology* **8:** 544–554.

Morris, R. G. (1996). Neurobiological correlates of cognitive dysfunction. In: Morris, R. G. (ed.), *The Cognitive Neuropsychology of Alzheimer-type Dementia*, Oxford University Press, Oxford, pp. 223–254.

Morrison, J., Scherr, S., Lewis, D., Campbell, M., Bloom, F., Rogers, J., et al. (1986). The laminar and regional distribution of neocortical somatostatin and neuritic plaques: Implications for Alzheimer's disease as a global neocortical disconnection syndrome. In: Scheibel, A., Wechsler, A., and Brazier, M. (eds.), *The Biological Substrates of Alzheimer's Disease*, Academic Press, Orlando, pp. 115–131.

Mottaghy, F. M., Krause, B. J., Kemna, L. J., Töpper, R., Tellmann, L., Beu, M., et al. (2000). Modulation of the neuronal circuitry subserving working memory in healthy human subjects by repetitive transcranial magnetic stimulation. *Neurosci. Lett.* **280:** 167–170.

Nyberg, L., and Cabeza, R. (2000). Brain imaging of memory. In: Tulving, E., and Craik, F. I. M. (eds.), *The Oxford Handbook of Memory*, Oxford University Press, Oxford, pp. 501–519.

O'Sullivan, M., Jones, D. K., Summers, P. E., Morris, R. G., Williams, S. C. R., and Markus, H. S. (2001). Evidence for cortical "disconnection" as a mechanism of age-related cognitive decline. *Neurology* **57:** 632–638.

Pantel, J., Schröder, J., Jauss, M., Essig, M., Minakaran, R., Schönknecht, P., et al. (1999). Topography of callosal atrophy reflects the distribution of regional cerebral volume reduction in Alzheimer's disease. *Psychiatry Res.* **90:** 181–192.

Pascual-Leone, A., Walsh, V., and Rothwell, J. (2000). Transcranial magnetic stimulation in cognitive neuroscience: Virtual lesion, chronometry, and functional connectivity. *Curr. Opin. Neurobiol.* **10:** 232–237.

Pearson, R. C. A., Esiri, M. M., Hiorns, R. W., Wilcock, G. K., and Powell, T. P. S. (1985). Anatomical correlates of the distribution of the pathological changes in the neocortex in Alzheimer's disease. *Proc. Natl. Acad. Sci. USA* **82:** 4531–4534.

Peled, A. (1999). Multiple constraint organization in the brain: A theory for schizophrenia. *Brain Res. Bull.* **49:** 245–250.

Perry, R. J., and Hodges, J. R. (1999). Attention and executive deficits in Alzheimer's disease: A critical review. *Brain* **122:** 383–404.

Petersen, R. C., Smith, G. E., Waring, S. C., Ivnik, R. J., Tangalos, E. G., and Kokmen, E. (1999). Mild cognitive impairment: clinical characterization and outcome. *Arch. Neurol.* **56:** 303–308.

Reuter-Lorentz, P. A., and Stanczak, L. (2000). Differential effects of aging on the functions of the corpus callosum. *Dev. Neuropsychol.* **18:** 113–137.

Rose, S. E., Chen, F., Chalk, J. B., Zelaya, F. O., Strugnell, W. E., Benson, M., et al. (2000). Loss of connectivity in Alzheimer's disease: An evaluation of white matter tract integrity with colour coded MR diffusion tensor imaging. *ET J.* **69:** 528–530.

Schröder, J., Buchsbaum, M. S., Shihabuddin, L., Tang, C., Wie, T. C., Spiegel-Cohen, J., et al. (2001). Patterns of cortical activity and memory performance in Alzheimer's disease. *Biol. Psychiatry* **49:** 426–436.

Shallice, T. (1988). *From Neuropsychology to Mental Structures*, Cambridge University Press, Cambridge.

Sperry, R. W. (1961). Cerebral organization and behavior. *Science* **133:** 1749–1757.

Stroop, J. R. (1935). Studies of interference in serial verbal reactions. *J. Exp. Psychol.* **6:** 643–661.

Teipel, S. J., Hampel, H., Pietrini, P., Alexander, G. E., Horwitz, B., Daley, E., et al. (1999). Region-specific corpus callosum atrophy correlates with the regional pattern of cortical glucose metabolism in Alzheimer's disease. *Arch. Neurol.* **56:** 467–473.

Tulving, E., and Markowitsch, H. J. (1998). Episodic and declarative memory: role of the hippocampus. *Hippocampus* **8:** 198–204.

Uylings, H. B. M., and de Brabander, J. M. (2002). Neuronal changes in normal human aging and Alzheimer's disease. *Brain Cogn.* **49:** 268–276.

Van der Linden, M., and Coyette, F., and Members of GREMEM (GRECO) (in press). Elaboration d'une version verbale de la procédure de rappel libre/rappel indicé de Grober et Buschke. In: Van der Linden, M., Deweer, B., Adam, S., Coyette, F., and Poitrenaud, J. (eds.), *L'évaluation de la mémoire épisodique: Mise au point et étalonnage de quatre épreuves*, Solal, Marseille.

Van der Linden, M., Meulemans, Th., Marczewski, Ph., and Collette, F. (2001). The relationships between episodic memory, working memory, and executive functions: The contribution of the prefrontal cortex. *Psychol. Belg.* **40:** 275–297.

Van Hoesen, G. W. (1990). The dissection by Alzheimer's disease of cortical and limbic neural systems relevant to memory. In: McGaugh, J. L., Weinberger, N. M., and Lynch, G. (eds.), *Brain Organization and Memory: Cells, Systems and Circuits*, Oxford University Press, Oxford, pp. 234–261.

Van Hoesen, G. W. (1997). Ventromedial temporal lobe anatomy, with comments on Alzheimer's disease and temporal injury. *J. Neuropsychiatry Clin. Neurosci.* **9:** 331–341.

Wada, Y., Nanbu, Y., Kikuchi, M., Koshino, Y., Hashimoto, T., and Yamaguchi, N. (1998a). Abnormal functional connectivity in Alzheimer's disease: Intrahemispheric EEG coherence during rest and photic stimulation. *Eur. Arch. Psychiatry Clin. Neurosci.* **248:** 203–208.

Wada, Y., Nanbu, Y., Koshino, Y., Yamaguchi, N., and Hashimoto, T. (1998b). Reduced interhemispheric EEG coherence in Alzheimer's disease: Analysis during rest and photic stimulation. *Alzheimer Dis. Assoc. Disord.* **12:** 175–181.

Weinberger, D. R. (1993). A connectionist approach to the prefrontal cortex. *J. Neuropsychiatry Clin. Neurosci.* **5:** 241–253.

Weis, S., Jellinger, K., and Wegner, E. (1991). Morphometry of the corpus callosum in normal aging and Alzheimer's disease. *J. Neural Transm. Suppl.* **33:** 35–38.

Weissman, D. H., and Banich, M. T. (2000). The cerebral hemispheres cooperate to perform complex but not simple tasks. *Neuropsychology* **14:** 41–59.

Wernicke, C. (1874/1977). Der aphasische symptomencomplex: Eine psychologische studie auf anatomischer basis. In: Eggert, G. H. (ed.), *Wernicke's Works on Aphasia: A Sourcebook and Review*, Mouton, The Hague, pp. 91–145.

Yamauchi, H., Fukuyama, H., Nagahama, Y., Katsumi, Y., Hayashi, T., Oyanagi, C., et al. (2000). Comparison of the pattern of atrophy of the corpus callosum in frontotemporal dementia, progressive supranuclear palsy and Alzheimer's disease. *J. Neurol. Neurosurg. Psychiatry* **69:** 623–629.

Zimmerman, P., and Fimm, B. (1994) *Tests d'évaluation de l'attention (TEA)*, Psytest, Würselen.