Alzheimer's Disease and Cognitive Neuropsychology: a Two-Way Interaction

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Alzheimer's Disease (AD) represents the progressive accumulation of a constellation of cognitive deficits, making neuropsychology central to the diagnosis of AD. These cognitive deficits may occur in a wide range of domains, though recent taxonomies have focused on slowly progressive disorders of a single domain (e.g., language, memory or praxis) remaining isolated for much of the early course of the disease. In this paper we review some of the methodological matters related to patient assessment, suggesting that a cognitive approach to the diagnosis of AD should be used. In addition, we will review some of the most significant contributions that neuropsychological findings in patients with AD have made to the understanding of normal cognition.

Enfermedad de Alzheimer y Neuropsicología Cognitiva: Una Interacción de Doble Vía

La Enfermedad de Alzheimer (EA) representa la acumulación progresiva de una constelación de déficits cognitivos, por lo cual la neuropsicología es central para su diagnóstico. Estos déficits cognitivos pueden ocurrir en una amplia variedad de dominios, aunque las taxonomías recientes se han centrado en los desórdenes de lenta progresión de un dominio simple (por ejemplo, lenguaje, memoria, praxias) que permanecen aislados durante gran parte de la primera etapa del curso de la enfermedad. En este documento se revisan algunos de los aspectos metodológicos relacionados con la evaluación del paciente, sugiriendo el uso de una aproximación cognitiva al diagnóstico de la EA. Adicionalmente, se revisan algunos de las más significativas contribuciones que los resultados neuropsicológicos en pacientes con EA han hecho a la comprensión del funcionamiento de la cognición normal.

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AD is a progressive degenerative disease of unknown aetiology which was first described in 1907 by Alois Alzheimer (1907). One year before publishing this case, in 1906, Alzheimer had given a lecture at the 37th Conference of the South-West German Psychiatrists in Tübingen entitled 'A characteristic serious disease of the cerebral cortex' in which for the first time he described a form of dementia. Later on, Kraepelin began to refer to it as Alzheimer's disease (Kraepelin, 1910). As reported by Maurer, Volk, & Gerbaldo (1997), Alzheimer reported the case history of the patient without identifying her, and he described it as '..."the case of a patient who was kept under close observation during institutionalisation at the Frankfurt Hospital and whose central nervous system had been given to me by director Sioli for further examination"..."51-year-old woman" who showed "as one of her first disease symptoms a strong feeling of jealousy towards her husband. Very soon she showed rapidly increasing memory impairments; she was disoriented carrying objects to and from in her flat and hid them. Sometimes she felt that someone wanted to kill her and began to scream loudly...After four and a half years of sickness she died." ' (p.1548). The file with Alzheimer's clinical notes regarding Auguste D. has been recently found in the archive of the Department of Psychiatry in Frankfurt am Main, Germany and published by Maurer et al. (1997).

AD is the commonest cause of dementia in the elderly (Schoenberg, Kokmen, & Okazaki, 1987) with an incidence ranging from 2.5 to 5 per thousand in the general population - an incidence that has grown in recent years as a result of an increasing ageing population. As for the elderly population, AD is found in 8% to 10% of the over-65-year population, and in as many as 32% of the over-85's (Galasko, Corey-Bloom, & Thal, 1991; Jorm, 1990). Evidence from epidemiological studies seems to suggest an exponential increase in the prevalence of AD with age (Jorm, Korten, & Henderson, 1987). More recent evidence from meta-analysis research, though, questions this claim and suggests that AD is better conceptualised as an 'age-related' rather than 'ageing-related' disease, a disease which affects people within an age range rather than related to the ageing process (Ritchie & Kildea, 1995). Debate over whether AD is "ageing" or "age" related does not mask the fact that there will undoubtedly be an increase in incidence. The disease represents between 60% and 85% of all dementias (Evans, Funkenstein, Albert, Scerr, Cook, Chown, Herbert, Hennekens, & Taylor, 1989). These figures make it clear that AD represents a growing health-care problem in our society - where the proportion of the ageing population continues to increase. At present, effective treatment is not available.

However, the large investments made in the field of dementia treatment have led to enormous progress in recent years and some effective treatment may become available in the near future.

AD affects mainly the supratentorial cortical and cholinergic neurones and, histopathologically, is marked by the presence of neurofibrillary degeneration and senile plaques. Clinically, AD is characterised by its insidious onset, and almost complete absence of specific neurological signs. These features may distinguish AD from other types of dementia. Neuroradiological findings are either normal, or may show non-specific cortical or periventricular atrophy.

Despite substantial research effort into the diagnosis of AD in recent years, there is no definitive test to establish the presence of the disease (Brazzelli, Capitani, Della Sala, Spinnler, & Zuffi, 1994). Therefore, inclusion for diagnosis remains a discriminative process in which neuropsychological assessment plays an invaluable role. In the absence of support from standard diagnostic tools in neurology and neuroradiology, diagnosis is generally made on the basis of neuropsychological deficits (Spinnler & Della Sala, 1988) or behavioural observations. This methodology allows the clinician to reach an early diagnosis with an estimated degree of accuracy of between 85% and 90%, and to do so without the use of invasive techniques such as cerebral biopsy (Boller, Lopez, & Moossy, 1989). Diagnosis, therefore, relies on techniques which allow exclusion of other causes of dementia as well as identification of typical features. The degree of accuracy is higher when the diagnosis is reached after a comparison of a patient's performance on two successive test sessions, usually after a 6-8 month interval. This makes neuropsychology of critical importance in the early identification of Alzheimer's disease.

Alzheimer Dementia as a Neuropsychological Disease

Given that little, if any, contribution is provided by the neurological and neuroradiological examination of patients manifesting progressive cognitive deterioration, AD raises severe diagnostic problems in its early stages. The differential diagnosis is of paramount importance since 30% of dementias may be reversible (e.g. depressive pseudodementia, normo-tensive hydrocephalus). Differential diagnosis from other types of degenerative dementia is also an issue of great importance. Since AD natural history is still not well characterised, confusion may arise as to whether some forms of isolated slowly progressive deficits or groups of deficits represent an unusual manifestation of AD or an entirely different nosological entity. Should

effective treatment become available for other forms of dementia, differential diagnosis will rely increasingly more on the contribution of an accurate neuropsychological examination. Differential diagnosis is also important when selection for research purposes has to be made. If one wants to reach an understanding of the natural history of AD, as well as obtain reliable results in terms of understanding its behavioural manifestation, an effort should be made to increase accuracy of diagnosis *in vivo*.

Since the symptomatology in dementia is almost entirely of a neuropsychological nature - being a constellation of deficits affecting several cognitive domains - neuropsychology has a very prominent role in the diagnosis of dementia (Brazzelli et al., 1994). The progressive increase in the number of these deficits contributes substantially to the ecological severity of the dementia, leaving few unsolved diagnostic questions in the later stages of the disease. However, in the very early stages of AD, subtle deficits in a range of cognitive domains can be identified only by an accurate neuropsychological assessment including standardised measures. This assessment will provide a better understanding and characterisation of the intellectual deterioration.

AD is the most likely diagnosis when any patient presents with progressive cognitive deficits for which the onset is unclear - deficits involving functions such as memory (episodic, prospective, semantic, with deficits greatly affecting a patient's ability to cope with everyday task demands), language (word finding problems, comprehension deficits, empty speech or excessive use of circumlocutions), praxis (ideomotor apraxia, motor-perceptual deficits, dressing apraxia), or gnosis (e.g. prosopagnosia) (Nebes, 1992). The cognitive impairments are numerous, severe, progressive and enduring - and, among the cognitive changes observed in clinical practice, those deficits associated with AD are amongst the most disabling. In addition to purely cognitive signs, patients with AD can also display a constellation of so called 'non cognitive symptoms', psychiatric manifestations such as depression and anxiety, but also psychotic traits such as delusions of various type, hallucinations, misperception, maniac beliefs.

Initially, the disease affects a few cognitive domains. A superficial evaluation of these deficits would be intractable from the normal course of ageing. With time this extends to a progressive loss of competence, though there may be fleeting intervals of impressive lucidity. There is progressive involvement of more and more cognitive abilities, slowly impoverishing a larger range of intellectual capacities, and leading to the complete loss of competence in all cognitive domains. Recent research on neuropsychology

of AD has therefore transcended from an elementary stage in which the purpose was gross description of the types of deficit caused by this disease, to a more analytic stage. Consequently, current research, grounded in established cognitive theories, is converging on a systematic appraisal of distinctive features characterising the cognitive profile of AD.

Even when thoroughly investigated, definite diagnosis of AD cannot be reached *in vivo*, only investigation at autopsy can confirm AD. It is true that, in the living patient, AD is relatively easy to diagnose in its late stages (5-8 years post-onset), but it raises problems for the clinician in the early stages. These problems may be overcome if the course of diagnosis follows a 'cascade schedule' (Della Sala & Venneri, 1997; Spinnler, 1999; Spinnler & Della Sala, 1988) consisting of different stages of progressively finer filtering. The following steps are suggested: (1) a preliminary enquiry into the patient's personal history of difficulties suggestive of dementia; (2) formal neuropsychological testing; (3) neurological, neuroradiological (CT and MRI scans) and neurophysiological examinations (EEG, PET, and SPECT). In stage 1, the presence of the dementia is provisionally established; in stage 2 a diagnosis of probable dementia of Alzheimer type is made; at stage 3, neurological and neuroradiological findings allow the exclusion of other possible aetiological alternatives. This approach to diagnosis represents a substantial improvement in comparison to the usual approach - in which AD is diagnosed by default.

Clinical criteria are currently applied in clinical practice in order to reach a diagnosis of AD. The most commonly used assessment tools are those listed in the DSM-IV (APA, 1994) and those provided by the NINCDS-ADRDA (McKann, Drachman, Folstein, Katzman, Price, & Stadlan, 1984), some of the latter have been further validated in a recent study (Ala & Frey II, 1995).

A variety of brief screening instruments and test batteries are also available. However, many factors should be taken into account when using psychometrics. First of all, the discriminative power of psychometric instruments used to detect dementia. This depends upon reliability and difficulty of items included in a psychometric instrument. Reliability may be increased either by choosing homogeneous items or by lengthening the test. Item difficulty is a critical variable in cases of instruments used to detect dementia. If an instrument includes easy items, this will not allow one to distinguish between mild demented subjects and normal subjects showing poor performance, but it may be a good help in identifying moderate dementia. On the other hand, an instrument including difficult items will

detect mild dementia, but it will be far beyond the limits of the majority of severe patients (Venneri, Turnbull, & Della Sala, 1996).

Rating scales such as the MMSE (the Mini Mental State Examination, Folstein, Folstein, & McHugh, 1975)), the MSQ (the Mental Status Questionnaire, Kahn, Goldfarb, Pollack, & Beck, 1960)), DRS (the Dementia Rating Scale, Mattis, 1976), and the MODA (Milan Overall Dementia Assessment, Brazzelli et al., 1994) produce a global score which summarises a patient's cognitive competence. They are brief and easy to administer and provide sufficient information for epidemiological studies. However, caution is required in cases of poorly educated people. There is unanimous agreement among studies that education does have an effect on MMSE score (Kittner, White, Farmer, Wolz, Kaplan, Moes, Brody, & Feinleib, 1986; Kukull, Larson, Teri, Bowen, McCormick, & Pfanschmidt, 1994; Uhlmann & Larson, 1991). Unless we are to believe that lack of education might predispose individuals to dementia, these findings are good evidence that the type of data provided by this kind of brief screening instruments may be misleading, and give rise to false diagnoses of dementia.

More comprehensive test batteries also provide insight into a patient's cognitive profile, since they allow a detailed investigation of several cognitive domains, allowing a clinician to establish which cognitive abilities are impaired and preserved (Gray & Della Sala, 1996; Roth, Tim, Mountjoy, Huppert, Hendrie, Verma, & Goddard, 1986; Spinnler & Della Sala, 1988; Welsh, Butters, Hughes, Mohs, & Heyman, 1992). These batteries include tests to assess retrograde and anterograde memory processing, language, perceptual and spatial skills, and executive functions. Poor performance of demented patients reflect differences in the severity of their cognitive deficits, caused by the spreading of the degenerative process into specific cortical areas. This analytical approach is useful for research purposes, or when it is necessary to demonstrate a specific cognitive pattern to confirm the diagnosis of a particular neuropsychological syndrome. However, these instruments are unsuitable in severely deteriorated patients because of the difficulties related to their administration.

In recent years, in parallel with the invaluable contribution of neuropsychology, information provided by imaging techniques has become increasingly influential. Computerised Tomography (CT) and Magnetic Resonance Imaging (MRI) contribute significantly in identifying other possible causes of dementia, such as cerebrovascular lesions and hydrocephalus. AD causes a reduction in brain weight and volume, as well as an increase in size of the sulci and ventricles. This may be detected by

CT and MRI which show extensive atrophy. However, often extensive atrophy may be present in the brain of healthy elderly individuals, therefore resulting of poor correlation with the presence of AD. Recent findings have attached significant diagnostic validity to cortical atrophy affecting the medial part of the temporal lobes (Convit, de Leon, Golomb, Geroge, Tarshish, Bobinski, Tsui, De Santi, Wegiel, & Wisniewski, 1993; de Leon, George, Stylopoulos, Smith, & Miller, 1989; de Leon, Golomb, George, Convit, Tarshish, Mcrae, Desanti, Smith, Ferris, Noz, et al., 1993). Further, more recent findings have shown that brain volume quantification obtained by sequential scanning with MRI every six months can be useful, since AD brains appear to shrink much more quickly than normal brains (Fox, Freeborough, & Rossor, 1996) (see Figure 1).
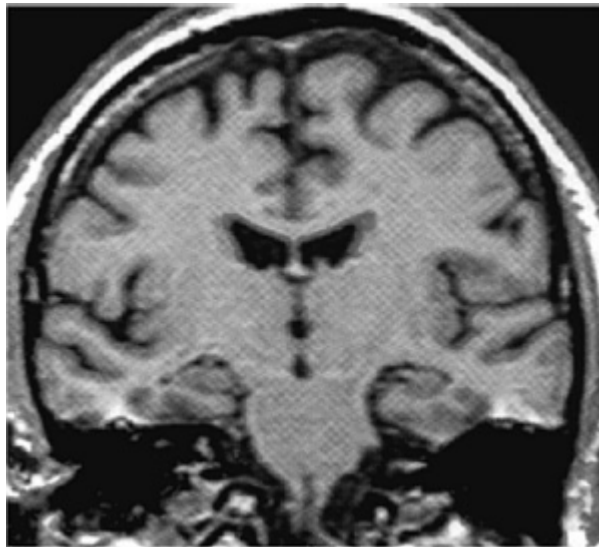

Figure 1. Coronal slice displaying the superimposed difference image (marked in red) between two registered MR scans of an AD patient acquired in succession at a 11 month interval (reproduced with permission from Fox et al., The Lancet, 348, 1996, p.96)

In addition, data acquired with dynamic imaging techniques such as Single Photon Emission Computerised Tomography (SPECT) and Positron Emission Tomography (PET) have suggested a pattern of perfusion deficits in the temporo-parietal regions (Claus, van Harskamp, Breteler, Krenning, de Koning, van der Cammen, Hofman, & Hasan, 1994; Elmstahl, Siennicki-

Lantz, Lilja, & Bjuno, 1994; Foster, Chase, Mansi, Brooks, Fedio, Patronas, & Di Chiro, 1984; Montaldi, Brooks, McColl, Wyper, Patterson, Barron, & McCulloch, 1990). There are indications that this pattern is rather specific and sensitive to distinguish AD individuals from controls (Claus et al., 1994; Foster et al., 1984). However, a recent study casts some doubts and presents evidence in favour of much higher variability and heterogeneity in the patterns of cerebral blood flow to be expected in patients with AD (Zimmer, Leucht, Radler, Schmauss, Gebhardt, & Lauter, 1997). Information provided by modern imaging techniques combined with the neuropsychological findings and clinical history significantly improve diagnostic accuracy. As shown in Figure 2, patterns of bilateral brain dysfunction in the parieto-temporal regions, detected with SPECT, may be very useful in distinguishing AD from other forms of degenerative dementia, such as Frontal Lobe Dementia, with the latter typified by deficits in the temporal and frontal regions.
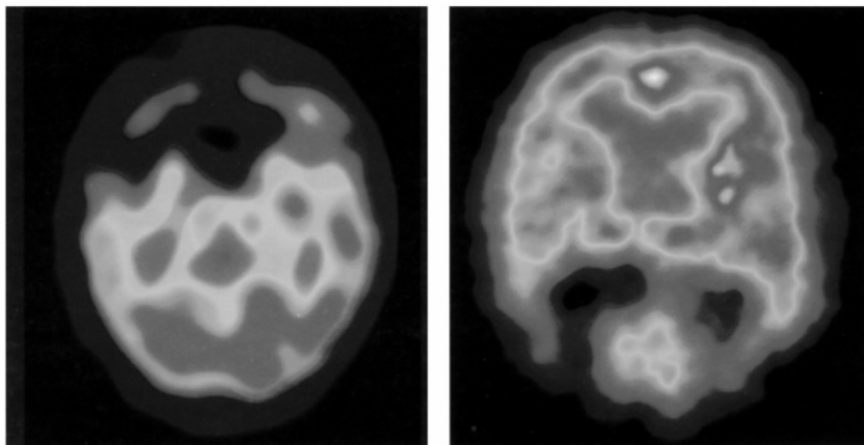

Figure 2. Comparison between HMPAO SPECT profiles of a patient with fronto-temporal dementia (on the left) and a patient with AD (on the right)

Still, without the combination of neuroimaging data with behavioural observations and a detailed neuropsychological investigation, the risk for false positives or false negatives is very high.

The cognitive approach to Dementia

A cognitive approach allows for the description and classification of the different problems arising after brain injury. Thus, although caused by quite different pathologies, cognitive impairment due to focal damage (e.g. after stroke) and that resulting from dementia share many similarities, since the same cognitive architecture is damaged in both cases. Thus, the study of cognitive symptoms in AD offers insights into the function of the normal human brain (Ellis & Young, 1988), in a similar manner as that of symptoms arising from other pathologies.

In recent years, cognitive neuropsychology has placed great emphasis on instances where there is a differential pattern of performance in two cognitive domains - regarded as 'dissociations' in function (for example, an intact ability to recognise words, with severe impairment in recognising faces). Sometimes, it is also possible to observe the opposite dissociation in function in a second patient (an intact ability to recognise faces, with severe impairment in recognising words). Such a pattern of double dissociation, observed between two patients, is generally considered to be strong evidence that the two cognitive mechanisms involved are functionally separable (i.e. that face and word recognition are run by separate cognitive systems associated with different brain regions).

Given the importance of such dissociations in verifying theories formulated in modern cognitive neuropsychology (Caramazza, 1986; Shallice, 1988), it is worth emphasising that AD patients have proved useful candidates for investigations of this kind (Baddeley, Della Sala, & Spinnler, 1991a; Becker, 1988; Della Sala, Muggia, Spinnler, & Zuffi, 1995c; Thaiss & De Bleser, 1992). As discussed earlier, heterogeneity characterises the pathological, metabolic and neuropsychological features of the degenerative process in AD, i.e. lesions can vary across different neuroanatomical sites and, more relevant for the present issue, the involvement differs among different patients (Boller, Forette, Khachaturian, Poncet, & Chrysten, 1992; Weinstein, Scheltens, Hijdra, & Van Rojen, 1995). Thus, the situation in AD, where there is a progressive accumulation of deficits in cognitive domains which are neither "pure" nor complete (Martin, Brouwers, Lalonde, Cox, Teleska, & Fedio, 1986), means that the investigation of AD patients is as useful for the study of cognitive deficits as that of more focal pathologies. In AD, contrary to what happens with focal lesions, the incomplete encroachment on regional neuronal networks might facilitate the emergence of fine-grained dissociations. At the same time a better understanding of the AD deterioration may be reached by using a cognitive approach to its study.

Studies with AD patients have already made a substantial empirical contribution to cognitive models in several domains - such as working memory (Baddeley et al., 1991a; Becker, 1988), face processing, (Della Sala et al., 1995c), language (Della Sala, Lorenzi, Spinnler, & Zuffi, 1993; Phillips, Della Sala, & Trivelli, 1996), visual perception (Della Sala, Laiacona, Trivelli, & Spinnler, 1995b; Della Sala, Spinnler, & Trivelli, 1996) and semantic memory (Barbarotto, Capitani, Spinnler, & Trivelli, 1995; Hodges, Graham, & Patterson, 1995). A concrete example supporting this claim comes from a study by Della Sala and coworkers (1995c), who have been able to support a cognitive modelling of face processing by means of evidence from AD patients. Della Sala et al., using a multiple single case approach, found statistically warranted double dissociations between tasks assessing familiar face recognition and those assessing unknown face discrimination. In this study, six out of the thirty AD patients who entered the study, were found to show dissociations: 4/6 showed a selective impairment on familiar face recognition, while the remaining two showed the reverse pattern, with a selective impairment of unknown face discrimination. Evidence from this study supported Bruce and Young's (1986) hypothesis that distinct pathways are involved in the processing of familiar and unknown faces and contradicted the hierarchical models of face processing in humans. Furthermore, Hodges et al. (1995) studied a patient with semantic dementia and found evidence that sheds light on the organisation of semantic information which is interpreted in terms of a network concept rather than a structural hierarchy.

More examples of this two-way interaction between AD and cognitive theories can be found in recent published evidence of AD patients displaying unilateral neglect in the late stages of their disease. Findings from these cases have put under question the theories suggested to explain this disorder in case of focal lesions (Bartolomeo, Dalla Barba, Boisse, Bachoud-Levi, Degos, & Boller, 1998; Venneri, Pentore, Cotticelli, & Della Sala, 1998). Unilateral neglect (a term which labels a phenomenon involving lack of awareness of stimuli appearing on the side contralateral to the cerebral lesion) is very frequent following unilateral lesions, but it should be an unusual finding in AD because of the symmetric and slowly progressive nature of this disease (Kirk & Kertesz, 1991). The occurrence of neglect in AD questions the validity of the models proposed to explain the role of the two cerebral hemispheres in distributing attention in space. Further, research into psychotic symptoms (delusions of different type) in AD have led to a better understanding not only of the origin of these disorders in patients with

AD, but also shed some light on the underlying cognitive failure resulting in delusion formation which could explain the mechanisms of delusions in other pathologies such as vascular dementia and schizophrenia (Staff, Shanks, Macintosh, Pestell, Gemmell, & Venneri, 1999; Venneri, Shanks, Staff, & Della Sala, 2000). This evidence supports the hypothesis that studies with AD patients may provide a reliable contribution to the understanding of how some cognitive processes work in normals.

A series of experiments using the dual-task paradigm further highlights how both models of cognitive functions in normals and the investigation of Alzheimer disease may be of mutual benefit. These studies have shown that when patients affected by AD are asked to perform two tasks simultaneously, their performance is particularly impaired, even when great care is taken to ensure that the level of performance on the individual tasks is equated with that of age-matched controls (Baddeley, Bressi, Della Sala, Logie, & Spinnler, 1986). A longitudinal study showed that this disadvantage became more pronounced with the progression of the disease, while performance on the single task did not show the same degree of sensitivity (Baddeley, Della Sala, & Spinnler, 1991b). A further longitudinal experiment varied difficulty within a single task (Baddeley et al., 1991b). The results showed no interaction between task difficulty and progressive deterioration in performance. These findings allowed the authors to discount the hypothesis that the rate of deterioration is simply dependent on the level of task difficulty and to suggest that, in AD patients (unlike in amnesics), many aspects of cognitive deterioration originate from a deficit in the central executive component of working memory. The outcome of this series of experiments supports the view that AD/pts may suffer from a deficit in their ability to cope with the cognitive processing necessary for carrying out two tasks simultaneously, irrespective of the difficulty of each of the single tasks (Della Sala, Baddeley, Papagno, & Spinnler, 1995a). From a more cognitive point, these findings support the notion of a central executive module within the frame of reference of the working memory model (Baddeley, 1996).

Conclusions

It is likely that biological diagnostic markers and treatment specific to the pathophysiological processes associated with AD will be available in future years. However, at present, the aim of neuropsychology is to acquire knowledge about the neuropsychological profiles resulting from different

types of dementia, and improve diagnostic accuracy. On the other hand, cognitive investigations in AD are offering an increasing contribution to clarifying how the normal brain works.

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