

Early detection of Alzheimer's disease: a new working memory paradigm

Max Toepper*, Thomas Beblo, Christine Thomas and Martin Driessen

Centre of Psychiatry and Psychotherapy Bethel, Department of Geriatric Psychiatry, Ev. Hospital Bielefeld, Bielefeld, Germany

SUMMARY

Objectives Early detection of Alzheimer's disease (AD) offers the chance to decelerate the patients' cognitive decline and to prolong a self-determined, independent life. Neuropsychological testing is one key approach to establish an early diagnosis. Whereas more global cognitive abilities can be preserved until further progression of the disease, specific executive abilities such as dual-task or active inhibition processes decline very early. Our recently developed working memory paradigm, the Block Suppression Test (BST), requires an active inhibition of irrelevant stimuli and thus should differentiate between Alzheimer patients and controls in early disease stages more accurately than classical screening instruments.

Methods In a pilot study we applied the BST, the MMSE, the clock drawing test, a digit-word transformation task as well as verbal and spatial memory span tasks to a group of 13 patients with Alzheimer's disease and 13 elderly controls and compared the instruments' capability to differentiate between patients and controls.

Results The BST showed the highest sensitivity among all applied tests with a perfect differentiation of healthy subjects and patients. The patients' backward spans were significantly reduced, in the inhibition condition they showed proportionally worse performances.

Conclusions Our results reveal a specific inhibition deficit in mild AD rather than a global working memory breakdown. The BST thus was superior for early diagnosis. However, these findings must be replicated in a larger sample to prove the BST's applicability for the early diagnostic assessment of AD and other dementias. Copyright © 2007 John Wiley & Sons, Ltd.

KEY WORDS — Alzheimer's disease; suppression; inhibition; memory spans; sensitivity; neuropsychological tests; working memory; early diagnosis; Corsi task

INTRODUCTION

Alzheimer's disease (AD) affects millions of people every year with increasing prevalence. An early detection and therapy of the illness helps to decelerate the patients' cognitive decline, prolongs a self-determined, independent life and, thus, would reduce the immense care-giving expenses. Since cognitive deficits are the first symptoms to occur, neuropsychological testing is one key approach on the early

diagnosis of dementia. In clinical settings larger test batteries are often not practicable because time and personnel are barely sufficient. Therefore, there is a need of shorter tests that have a satisfying extent of accuracy. The most widely used screening instruments assess general cognitive functioning (Mini Mental State Examination, MMSE) or construction (Clock Drawing Test). However, due to low difficulty, sensitivity of these tests remains rather small. Based on the original Corsi task (Corsi, 1972), we recently developed a new paradigm to assess working memory, the block suppression test (BST; Beblo *et al.*, 2004). This test requires subjects not only to reproduce but also to inhibit information. The duration of the BST is below 10 min and it is very easy to administer.

*Correspondence to: M. Toepper, Centre of Psychiatry and Psychotherapy Bethel, Department of Geriatric Psychiatry, Ev. Hospital Bielefeld, Remterweg 69-71, D-33617 Bielefeld, Germany. E-mails: max@iworks.de; max.toepper@evkb.de

Previous research often reveals working memory deficits related to a dysfunction of the central executive in early stages of AD (Baddeley *et al.*, 1991; Sala and Logie, 2001). Whereas simple memory spans are relatively preserved until further progression of the disease (Carlesimo *et al.*, 1998), central executive abilities such as inhibition processes decline very early (Greene *et al.*, 1995; Collette *et al.*, 1999; Perry and Hodges, 1999; Albert *et al.*, 2001; Baddeley *et al.*, 2001). While some studies reveal widespread inhibition deficits (Spieler *et al.*, 1996; Collette *et al.*, 2002), others show that not all inhibition processes must be deficient. In particular, active inhibition seems to be impaired in early AD (e.g. Stroop task) whereas more automatic inhibition processes (e.g. return tasks) are basically preserved (Amieva *et al.*, 1998, 2004). These findings provide evidence for a specific deficit in active inhibition rather than a global inhibitory breakdown.

In the present study, subjects had to reproduce a certain sequence of visually presented blocks (Corsi task) and, in addition, suppress the appearance of every second stimulus (BST). Thus, the BST requires an active inhibition of irrelevant information and since those processes are deficient in early stages of the disease, patients should already have difficulties. Therefore we expect disproportionately decreasing performances of the AD patients in the inhibition condition compared to relatively preserved memory spans both, in the verbal and visuospatial modality. This should result in an improved sensitivity of the BST compared to traditional neuropsychological instruments that assess rather global cognitive functioning.

METHODS

Subjects

The study included 13 patients (nine women) with the established diagnosis of Alzheimer's disease and 13 healthy subjects (nine women). Their mean age was 77 years (patients: 78 ± 7.6 years; controls: 76 ± 7.9 years), basic school education was 8.9 years in average (patients: 8.8 ± 1.0 years; controls: 8.9 ± 1.5 years). Groups did not differ significantly with respect to these variables (see Table 1).

All patients met the ICD-10 criteria of Alzheimer's disease. First symptoms had occurred within the last 2 years and the MMSE score was above 19 (mean score of the patient and control group was 24.6 ± 3.0 and 29.4 ± 0.87 respectively). Apart from AD, none of the subjects had any psychiatric or neurologic

diagnoses. Five patients took cholinesterase inhibitors since more than four weeks. Neuropsychological testing was administered under standardized conditions, a differential medication effect is therefore not expected. All other subjects were free of psychotropic medication. All subjects provided their informed written consent. The study did not extend standard clinical assessment and, therefore, did not implicate any ethical dilemmas.

Instruments

Beside the Corsi task and a digit span task, we applied the BST and its verbal version, the digit suppression test (DST). These tests require the storage and reproduction of consecutively presented items (block or digit, respectively) and, in addition, the suppression of every second stimulus appearing. Test duration was less than 10 min.

Two different scores were collected: raw scores and memory spans. While the memory span describes the longest sequence of reproduced items, raw scores were calculated by summing the number of correct trials. Starting with three consecutively presented blocks or digits, subjects had to store and reproduce two sequences of the same length. As soon as at least one of both trials was performed correctly, sequence length rose. The test was aborted if both trials of the same sequence length were incorrect.

In addition, the MMSE (Folstein *et al.*, 1975), the Clock Drawing Test (Shulman *et al.*, 1993), four items for digit-word transformation (DemTect; Kessler *et al.*, 2000) as well as the ICD-10 diagnosis checklist for Alzheimer's dementia were administered.

Statistics

Mann-Whitney *U*-Tests and *t*-Tests were used to compare neuropsychological test results. Repeated measures ANOVAs were applied to compare memory spans (factor 1) and groups (factor 2), posthoc one-way ANOVAs were utilized to identify the origin of the interaction effects. Furthermore, sensitivity and specificity were calculated to compare the quality of the applied instruments in differentiating between patients and controls. All levels of significance were $\alpha = 0.05$ and two-tailed.

RESULTS

Control subjects performed better than patients in all applied tests except for the verbal span forward. With regard to the screening instruments, AD patients

Table 1. Sample characteristics

| | Controls | AD patients | Total | <i>p</i> |
|-------------------------------------|---------------|---------------|---------------|----------|
| Number of subjects | 13 | 13 | 26 | |
| Mean age (in years (range)) | 76.38 (65–90) | 78.46 (65–92) | 77.42 (65–92) | n.s. |
| Sex (female/male) | 9/4 | 9/4 | 18/8 | n.s. |
| School education | | | | |
| 8 years | 9 | 8 | 17 | n.s. |
| 10 years | 3 | 5 | 8 | |
| 13 years | 1 | 0 | 1 | |
| Handedness (right; left; bi-manual) | 12; 0; 1 | 12; 0; 1 | 24; 0; 2 | n.s. |

Table 2. Raw scores of AD patients compared to healthy controls

| Raw scores (mean ± SD) | Controls (<i>n</i> = 13) | AD patients (<i>n</i> = 13) | Statistics (<i>t</i> (df), <i>p</i>) |
|------------------------------|---------------------------|------------------------------|--|
| Digit span task forward | 7.15 ± 1.14 | 6.92 ± 1.75 | <i>t</i> (24) = -0.40, <i>p</i> = 0.695 |
| Digit span task backward | 6.23 ± 1.09 | 4.46 ± 1.27 | <i>t</i> (24) = -3.82, <i>p</i> = 0.001 |
| Digit suppression test (DST) | 8.46 ± 1.94 | 4.15 ± 1.68 | <i>t</i> (24) = -6.06, <i>p</i> < 0.001 |
| Corsi task forward | 7.23 ± 1.09 | 5.31 ± 1.18 | <i>t</i> (24) = -4.31, <i>p</i> < 0.001 |
| Corsi task backward | 6.15 ± 0.80 | 4.08 ± 1.12 | <i>t</i> (24) = -5.46, <i>p</i> < 0.001 |
| Block suppression test (BST) | 8.77 ± 1.59 | 2.38 ± 1.56 | <i>t</i> (24) = -10.35, <i>p</i> < 0.001 |

scored lower on the MMSE ($T(13.98) = -5.48$, $p < 0.001$), the clock drawing test ($U = 29.00$, $p = 0.002$) and the digit-word transformation task ($t(18.17) = -3.07$, $p = 0.007$). Concerning both, raw scores (see Table 2) and memory spans (Table 3), patients showed significantly worse performances on the digit span task backward, the Corsi task (forward and backward) as well as the spatial and verbal suppression tasks (BST and DST).

Furthermore, compared to memory spans forward and backward, the patients showed disproportional deficits in the BST and DST (see Figure 1). ANOVA results showed significant main effects of Test and Group as well as a significant Test × Group interaction effect for spatial (Test: $F(2; 48) = 76.11$, $p < 0.001$; Group: $F(1; 24) = 49.59$, $p < 0.001$; Test × Group: $F(2; 48) = 9.83$, $p < 0.001$) and verbal (Test: $F(2; 48) = 109.53$, $p < 0.001$; Group: $F(1; 24) = 17.11$,

$p < 0.001$; Test × Group: $F(2; 48) = 3.91$, $p = 0.027$) modality. Posthoc analyses additionally indicated that there were no significant Test × Group interactions for memory spans forward versus backward.

In order to compare BST and DST with the applied screening instruments we set a cut off lower than the performance of the 'worst' control subject. Thus, all controls were correctly classified as 'healthy', consistent with a specificity of 100%. Applying a specificity of 100%, we compared the sensitivity of the tests, i.e. the percentage of correctly classified patients. Due to the higher ability to differentiate between patients and controls, we used raw scores for the analysis of sensitivity and specificity.

In this study, only the BST classified 100% of the patients correctly (see Figure 2). In comparison, the MMSE had a sensitivity of 85%, the DST a sensitivity of 62% and the Clock Drawing Test according to the

Table 3. Verbal and spatial spans of AD patients compared to healthy controls

| Memory spans (mean ± SD) | Controls (<i>n</i> = 13) | AD patients (<i>n</i> = 13) | Statistics (<i>t</i> (df), <i>p</i>) |
|--------------------------------|---------------------------|------------------------------|---|
| Verbal span forward | 6.15 ± 0.90 | 6.00 ± 0.91 | <i>t</i> (24) = -0.43, <i>p</i> = 0.669 |
| Verbal span backward | 4.46 ± 0.52 | 3.69 ± 0.75 | <i>t</i> (24) = -3.04, <i>p</i> = 0.006 |
| Verbal suppression span (DST) | 3.92 ± 0.49 | 2.69 ± 0.63 | <i>t</i> (24) = -5.54, <i>p</i> < 0.001 |
| Spatial span forward | 5.23 ± 0.44 | 4.23 ± 0.73 | <i>t</i> (24) = -4.26, <i>p</i> < 0.001 |
| Spatial span backward | 4.62 ± 0.51 | 3.46 ± 0.78 | <i>t</i> (24) = -4.49, <i>p</i> < 0.001 |
| Spatial suppression span (BST) | 4.15 ± 0.55 | 2.08 ± 0.76 | <i>t</i> (24) = -7.96, <i>p</i> < 0.001 |

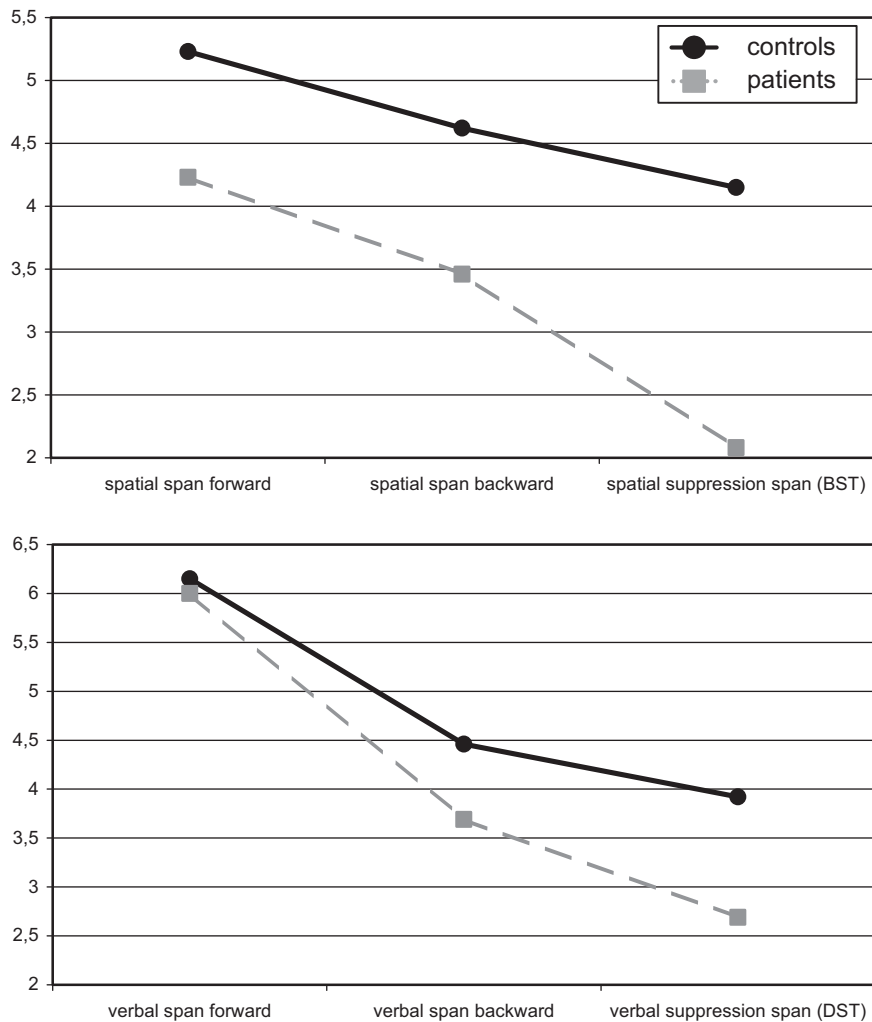


Figure 1. Spatial and verbal memory spans of AD patients and healthy controls (alternative: Disproportional inhibitory deficits of AD patients in spatial and verbal modality)

criteria of Shulman a sensitivity of 31%. All other neuropsychological tests (memory spans, digit-word transformation) showed classifications worse than BST and MMSE.

DISCUSSION

The main finding of our study comprised the BST being more appropriate in the early diagnosis of AD than classical screening instruments such as the MMSE or the Clock Drawing Test. In this pilot study, only the BST was able to correctly discriminate between controls and patients: all patients were correctly identified as 'ill' and all controls were correctly identified as 'healthy'. In comparison, two

patients showed normal performances in the MMSE and even more patients correctly performed the Clock Drawing Test. A reason for this predominance in discriminating between patients and controls might be that the BST measures a specific deficit that is known to be impaired in early AD (Perry *et al.*, 2000; Perry and Hodges, 2003). By contrast, more global cognitive abilities, as measured by classical screening instruments, are preserved until later stages (Hopper *et al.*, 2001; Almkvist, 1996).

Our results display a normal verbal span forward in the Alzheimer group. This finding is often described (Carlesimo *et al.*, 1994) and can be interpreted as a normally functioning articulatory loop according to Baddeley's working memory model. In contrast,

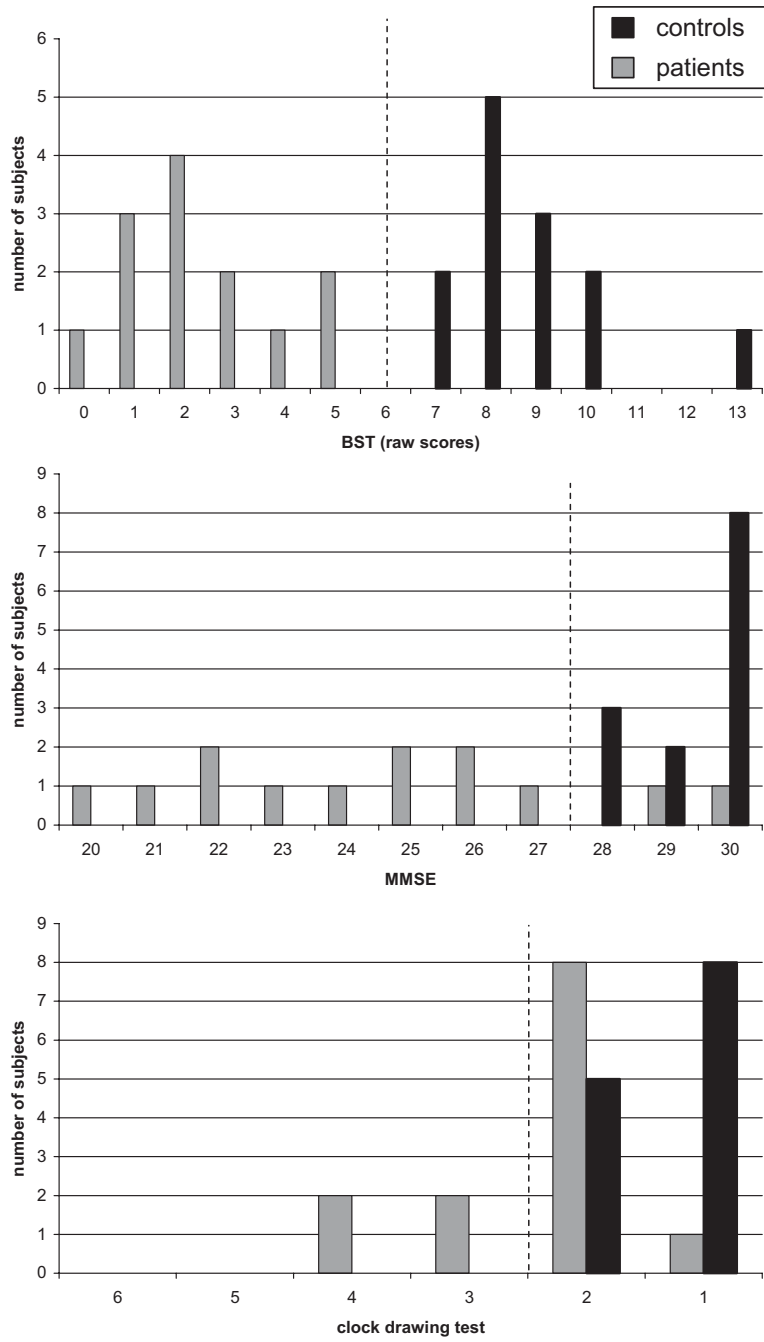


Figure 2. Sensitivity and specificity of BST, MMSE and clock drawing test

patients have difficulties on tasks that require more executive control (Carlesimo *et al.*, 1998). Consistent with Carlesimo's results, our patients also showed significantly reduced backward verbal and spatial spans. These findings give evidence for deficient processing resources of the Central Executive in early stages of Alzheimer's disease.

In contrast to other studies (Lines *et al.*, 1991), we did not find a preserved spatial span. Compared to healthy controls, patients performed significantly worse on the standard Corsi task. Thus, this test seems to require more executive resources than the repetition of number sequences. A plausible explanation for this finding might be that dealing with numbers is a very common activity in everyday life compared to the storage of block sequences. But contrary to this assumption, AD patients also showed deficits on tasks that require short-term memory processes concerning the location of faces (Clague *et al.*, 2005). A better explanation would be the assumption of an already disturbed spatial slave system: Early stages of Alzheimer's disease are characterized by a functional isolation of hippocampal structures (Braak and Braak, 1997; Braak *et al.*, 2006), for example the CA3 subregion that supports processes associated with spatial short-term memory (Kesner *et al.*, 2004). In addition, Ballmaier *et al.* (2004) revealed a widespread parietal grey matter loss in early stages of Alzheimer's disease that could be responsible for deficient spatial storage processes as well.

Furthermore, we found disproportional deficits of the AD patients when their performances in the BST, and also the DST, were compared to memory spans forward and backward. These results give evidence for a specific inhibition deficit. Collette *et al.* (2002) discuss inhibitory dysfunction in Alzheimer's disease in the context of hypometabolism in posterior (temporal and parietal) and anterior (frontal) cerebral areas. In their study, the authors compared two groups of AD patients: patients with hypometabolism in posterior and patients with hypometabolism in both posterior and anterior brain structures. Groups showed no differences on all inhibition tasks which leads to the conclusion that inhibitory dysfunction can occur in the absence of frontal hypometabolism as well. Thus, a disconnection between anterior and posterior brain structures might be a better explanation for the observed deficits.

However, it cannot be ruled out, that the higher cognitive load under suppression conditions is responsible for the low performances of the AD patients. Whether the deficit is specific inhibitory or

KEY POINTS

- The Block suppression test is a recently developed working memory paradigm that requires the active inhibition of irrelevant stimuli. Thus, the BST seems to be suitable for the assessment of the early inhibitory deficit in Alzheimer's disease.
- Compared to memory spans forward and backward, Alzheimer patients showed disproportionately worse performances when the suppression of distractors was additionally required.
- Compared to traditional neuropsychological screening instruments as MMSE or clock drawing test, the Block Suppression Test (BST) shows a higher sensitivity in detecting Alzheimer's disease.
- The Block suppressions test's ability to detect early Alzheimer's disease has to be confirmed in a larger sample.

the result of an executive breakdown with increasing task demands must be shown by further research implying experimental and neurophysiologic methods. Experimentally one could develop a task of comparable difficulty and executive demands that does not require inhibition. Neurophysiologically one could examine which brain structures are additionally activated under suppression conditions. A study implying the second idea has already started in cooperation with the Bender Institute of Neuroimaging in Giessen, Germany.

In summary, our results suggest, that the BST might be a very economic instrument for early Alzheimer detection in clinical praxis. However, as we performed a pilot study with a small sample size, our findings have to be regarded as preliminary and must be replicated in larger samples including longitudinal diagnosis confirmation before further theoretical and practical conclusions can be drawn. Noteworthy, the BST was only compared to other screening instruments, but neither to other established but more time-consuming measures (Mathuranath *et al.*, 2000; Marcos *et al.*, 2006), nor to an episodic memory test in particular. To further investigate the potential diagnostic benefits of the BST, a continuative project including a wider sample is necessary. Thereby, the BST's capability to discriminate different forms of dementia and late-life depression is of special interest.

REFERENCES

- Albert MS, Moss MB, Tanzi R, Jones K. 2001. Preclinical prediction of AD using neuropsychological tests. *J Int Neuropsychol Soc* **7**: 631–639.
- Almkvist O. 1996. Neuropsychological features of early Alzheimer's disease: preclinical and clinical stages. *Acta Neurol Scand Suppl* **165**: 63–71.
- Amieva H, Lafont S, Rainville C, et al. 1998. Analysis of inhibitory dysfunction in patients with Alzheimer's disease and normal elderly adults in two verbal tasks. *Brain Cogn* **37**: 58–60.
- Amieva H, Phillips LH, Della Sala S, Henry JD. 2004. Inhibitory functioning in Alzheimer's disease. *Brain* **127**: 949–964.
- Baddeley AD, Baddeley HA, Bucks RS, Wilcock GK. 2001. Attentional control in Alzheimer's disease. *Brain* **124**: 1492–1508.
- Baddeley AD, Bressi S, Della Sala S, et al. 1991. The decline of working memory in Alzheimer's disease. A longitudinal study. *Brain* **114**: 2521–2542.
- Ballaier M, O'Brien JT, Burton EJ, et al. 2004. Comparing gray matter loss profiles between dementia with Lewy bodies and Alzheimer's disease using cortical pattern matching: diagnosis and gender effects. *Neuroimage* **23**: 325–335.
- Beblo T, Macek C, Brinkers I, et al. 2004. A new approach in clinical neuropsychology to the assessment of spatial working memory: the block suppression test. *J Clin Exp Neuropsychol* **26**: 105–114.
- Braak H, Braak E. 1997. Frequency of stages of Alzheimer-related lesions in different age categories. *Neurobiol Aging* **18**: 351–357.
- Braak H, Rub U, Schultz C, Del Tredici K. 2006. Vulnerability of cortical neurons to Alzheimer's and Parkinson's diseases. *J Alzheimers Dis* **9**: 35–44.
- Carlesimo GA, Fadda L, Lorusso S, Caltagirone C. 1994. Verbal and spatial memory spans in Alzheimer's and multi-infarct dementia. *Acta Neurol Scand* **89**: 132–138.
- Carlesimo GA, Mauri M, Graceffa AM, et al. 1998. Memory performances in young, elderly, and very old healthy individuals versus patients with Alzheimer's disease: evidence for discontinuity between normal and pathological aging. *J Clin Exp Neuropsychol* **20**: 14–29.
- Clague F, Dudas RB, Thompson SA, et al. 2005. Multidimensional measures of person knowledge and spatial associative learning: can these be applied to the differentiation of Alzheimer's disease from frontotemporal and vascular dementia? *Neuropsychologia* **43**: 1338–1350.
- Collette F, Van der Linden M, Salmon E. 1999. Executive dysfunction in Alzheimer's disease. *Cortex* **35**: 57–72.
- Collette F, Van der Linden M, Delrue G, Salmon E. 2002. Frontal hypometabolism does not explain inhibitory dysfunction in Alzheimer disease. *Alzheimer Dis Assoc Disord* **16**: 228–238.
- Corsi PM. 1972. Human memory and the medial temporal region of the brain. *Dissertation Abstracts International* **34**: 819B.
- Folstein MF, Folstein SE, McHugh PR. 1975. 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* **12**: 189–198.
- Greene JD, Hodges JR, Baddeley AD. 1995. Autobiographical memory and executive function in early dementia of Alzheimer type. *Neuropsychologia* **33**: 1647–1670.
- Hopper T, Bayles KA, Kim E. 2001. Retained neuropsychological abilities of individuals with Alzheimer's disease. *Semin Speech Lang* **22**: 261–273.
- Kesner RP, Lee I, Gilbert P. 2004. A behavioral assessment of hippocampal function based on a subregional analysis. *Rev Neurosci* **15**: 333–351.
- Kessler J, Calabrese P, Kalbe E, Berger F. 2000. DemTect: a new screening method to support diagnosis of dementia. *Psycho* **26**: 343–347.
- Lines CR, Dawson C, Preston GC, et al. 1991. Memory and attention in patients with senile dementia of the Alzheimer type and in normal elderly subjects. *J Clin Exp Neuropsychol* **13**: 691–702.
- Marcos A, Gil P, Barabash A, et al. 2006. Neuropsychological markers of progression from mild cognitive impairment to Alzheimer's disease. *Am J Alzheimers Dis Other Demen* **21**: 189–196.
- Mathuranath PS, Nestor PJ, Berrios GE, et al. 2000. A brief cognitive test battery to differentiate Alzheimer's disease and frontotemporal dementia. *Neurology* **55**: 1613–1620.
- Perry RJ, Hodges JR. 1999. Attention and executive deficits in Alzheimer's disease. A critical review. *Brain* **122**(3): 383–404.
- Perry RJ, Hodges JR. 2003. Dissociation between top-down attentional control and the time course of visual attention as measured by attentional dwell time in patients with mild cognitive impairment. *Eur J Neurosci* **18**: 221–226.
- Perry RJ, Watson P, Hodges JR. 2000. The nature and staging of attention dysfunction in early (minimal and mild) Alzheimer's disease: relationship to episodic and semantic memory impairment. *Neuropsychologia* **38**: 252–271.
- Sala SD, Logie RH. 2001. Theoretical and practical implications of dual-task performance in Alzheimer's disease. *Brain* **124**: 1479–1481.
- Shulman KI, Gold DP, Cohen CA, Zuccherro CA. 1993. Clock-drawing and dementia in the community: a longitudinal study. *Int J Geriatr Psychiatry* **8**: 487–496.
- Spieler DH, Balota DA, Faust ME. 1996. Stroop performance in healthy younger and older adults and in individuals with dementia of the Alzheimer's type. *J Exp Psychol Hum Percept Perform* **22**: 461–479.