BRAIN COMMUNICATIONS

Cognitive profiles in persons with depressive disorder and Alzheimer's disease

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Alzheimer's disease and depressive disorder are frequent in old age. Both may be associated with depressed mood and cognitive impairment. Therefore, finding a strategy to clarify the diagnosis underlying subjective complaints of impaired cognition and depressed mood in older persons is of utmost interest. We conducted a cross-sectional retrospective observational clinical cohort study using patient records from 2014 to 2018. From 3758 patients, we included patients aged 60 years and older with a Mini-Mental-Status Examination score of 24 and above. Final analysis included all patients in whom Alzheimer's disease biomarker analysis was performed (cerebrospinal fluid markers of Alzheimer's disease or positron emission tomography imaging; $n = 179$) and patients with depressive disorder in whom Alzheimer's disease was ruled out by analysis of biomarkers suggestive of Alzheimer's disease ($n = 70$). With case–control matching for age, education and gender, performance of patients with Alzheimer's disease was worse in acquisition, consolidation and recall of verbal information and false-positive answers. None of the results, however, sufficed to differentially diagnose individual patients with Alzheimer's disease or depressive disorder. With more severe symptoms of depression, patients with biomarker-verified Alzheimer's disease performed worse in executive testing but were not additionally impaired in verbal episodic memory performance. We conclude that distinguishing between Alzheimer's disease and depressive disorder is unreliable on clinical grounds and behavioural testing alone. Diagnosing the cause of subjective complaints about deteriorating cognitive function or depressed mood requires additional biomarker assessment, whereas cognitive assessment is needed to define appropriate targets of symptomatic treatment in patients with Alzheimer's disease and depressive disorder.

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Abbreviations: AD = Alzheimer's disease; ADL = activities of daily living; AUC = area under the curve; CSF = cerebrospinal fluid; CVLT = California Verbal Learning Test; dAD = Alzheimer patients with depressive syndrome; DD = depressive disorder; ECT = electroconvulsive therapy; GDS = Geriatric Depression Scale; MCI = mild cognitive impairment; MMSE = Mini-Mental Status Examination; nAD = Alzheimer patients without depressive syndrome; phospho-tau = phosphorylated tau

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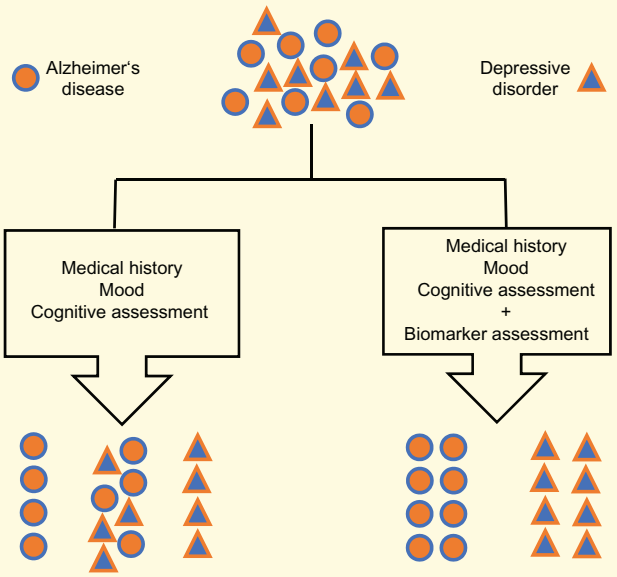
Graphical Abstract



Introduction

Two of the most common health conditions among older persons are Alzheimer's disease (AD) and depressive disorder (DD) (Ritchie and Lovestone, 2002; Alexopoulos, 2005). Both AD and DD may go along with cognitive and affective symptoms. Distinguishing between AD and DD has important therapeutic implications and current and future treatment options warrant to establish an accurate diagnosis as early as possible.

Lesions of medial temporal lobe at the onset of AD result in deficits of episodic memory and spatial orientation (Hodges, 2000). Spread of the disease to the frontal and parietal cortex further impairs executive functions, planning, attention, working memory and visuo-spatial functions (Hodges, 2000). Depressive symptoms are frequent in patients with AD (Fischer, 1996; Kobayashi and Kato, 2011) and may even be present at its onset (Verdaguer *et al.*, 2020).

Depressive disorder is characterized by depressed mood, diminished drive and anhedonia. Despite being frequently reported, characteristics of cognitive impairment in DD are less well understood and no particular pattern is associated with the severity of DD. Accruing evidence over recent years demonstrates that patients with DD may be impaired in several cognitive tasks such as short-term memory, sustained and selective attention, alertness, cognitive flexibility and executive functions (Williams *et al.*, 2000; Landrø *et al.*, 2001; Weiland-Fiedler *et al.*, 2004; Paelecke-Habermann *et al.*, 2005; Lanza *et al.*, 2020). Moreover, different memory processes such as encoding and retrieval are also impaired (Elderkin-Thompson *et al.*, 2007; Taconnat *et al.*, 2010; Mesholam-Gately *et al.*, 2012). It is unclear whether memory deficits are an independent cognitive symptom of DD or secondary to executive dysfunction (Fossati *et al.*, 2002).

The attempt to differentiate between AD and DD on clinical and behavioural grounds is inconclusive (Elderkin-Thompson *et al.*, 2003; Butters *et al.*, 2004; Elderkin-Thompson *et al.*, 2007, 2009; Beblo *et al.*, 2011; Elderkin-Thompson *et al.*, 2011; Mesholam-Gately *et al.*, 2012; Paula et al., 2013). Thus, a conceptual transition to use a biological framework applying biochemical or imaging biomarkers to diagnose AD has been suggested (Dubois *et al.*, 2007; Kester *et al.*, 2009; Blennow *et al.*, 2015; Jack *et al.*, 2018).

A recent consensus article concluded that AD is ruled out if cerebrospinal fluid (CSF)-biomarkers of AD are negative (Molinuevo *et al.*, 2014). Longitudinal data additionally demonstrate that a decrease of Abeta1-42 precedes cognitive impairment (Jack *et al.*, 2013; Villemagne *et al.*, 2013; Young *et al.*, 2014). Thus, normal levels of Abeta1-42 exclude underlying AD as a cause of cognitive impairment. Levels of tau-protein can further support the diagnosis and help to distinguish between patients with age-associated neurodegenerative or even vascular disease (Andreasen *et al.*, 2001; Goossens *et al.*, 2017; Paterson *et al.*, 2018). In cases where CSF-biomarkers are unavailable positron emission tomography (PET) biomarkers can be used to verify or exclude AD (Rice and Bisdas, 2017).

Analysis of biomarker information thus allows to select patients in whom the diagnosis of AD has to be considered as verified. Similarly, AD is ruled out if biomarker assessment is inconspicuous, i.e. no evidence of tau- or Abeta-pathology. As far as we are aware, biomarkers

have not been used to rule out AD pathology in patients with DD. Our goal was to investigate whether the cognitive profile of patients with verified AD is distinct from the cognitive profile of patients with verified DD. We also assessed the impact of depressive symptoms on the cognitive profile of patients with verified AD.

Materials and methods

Our observational clinical cohort study used patient's records of the gerontopsychiatric services at Ulm University at Bezirkskrankenhaus Günzburg from 2014 to 2018. The study was approved by the ethics committee of Ulm University (289/18) and was conducted according to the guidelines outlined in the declaration of Helsinki (2013).

Study sample

Geriatric Psychiatry services of Ulm University at Bezirkskrankenhaus Günzburg serve as a primary service for a rural catchment area of about 650 000 people. Patients are referred to this unit by surrounding hospitals, general practitioners as well as medical specialists in private practice. Among most frequent complaints presented by the patients are mood changes and memory impairment; however, lacking introspection on behalf of the patients often conflicts with the referral diagnosis or report by proxies. For this reason, a detailed neuropsychological assessment of patients presenting with either mood or cognitive complaints is included in our standard practice (exclusion criteria, Fig. 1). Further diagnostic procedures were initiated in three cases: (i) patients presented with a slowly progressing cognitive decline over many months, (ii) neuropsychological assessment indicated at least a moderate decline in episodic memory and (iii) patients remained worried after initial diagnostic steps and requested further diagnostic measures. The indeterminateness of the decision-making algorithm reflects the hitherto existing vague knowledge on the pattern of cognitive impairment due to DD and AD. We ruled out organic causes of cognitive impairment by performing CSF tap. In cases where CSF tap was contraindicated (e.g. due to anticoagulation) or patients refused the procedure, fluorodeoxyglucose-PET or Am-PET was performed instead. Additional fluorodeoxyglucose-PET or Am-PET was also initiated when clinical judgement and CSF tap results differed.

Depressed mood was diagnosed phenotypically using criteria outlined in the ICD-10. Similar to a previously reported approach (Kessler *et al.*, 2010), no organic exclusions or diagnostic hierarchy rules were applied in the diagnostic process.

Records of all in- and outpatients aged >60 years from 2014 to 2018 were included in the analysis. Age cut-off was set by following WHO recommendations ('At the moment, there is no United Nations standard numerical criterion, but the UN agreed cut-off is 60+ years to refer to the older population.'; https://www.who.int/healthinfo/survey/ageingdefnolder/en/).

Differentiation between AD and DD is of particular importance in early stages of disease. A recent meta-analysis found that a cut-off score of 24 in the Mini-Mental State Examination (MMSE) is most appropriate to differentiate between normal and impaired cognition (Creavin *et al.*, 2016). An elaborate definition of patients' cognitive profiles above this threshold would facilitate an accurate diagnostic process even in the very mild stages of the disease. Other subgroups of these patients have been published previously (Lanza *et al.*, 2020). This study aimed to select only the patients in whom biomarkers were concordant and characteristic for AD (inclusion criterion: Abeta1-42 < 550 pg/ml, total tau > 300 pg/ml and phospho-tau > 61 pg/ml). Same method was applied to rule out underlying AD pathology in patients with DD (inclusion criterion: Abeta1-42 > 550 pg/ml, total tau < 300 pg/ml and phospho-tau < 61 pg/ml). Applying these inclusion and exclusion criteria, 179 patients with diagnosis of AD and 70 patients with diagnosis of DD were analysed.

Demographic variables and neuropsychological data for all patients with verified diagnosis are summarized in Table 1.

Neuropsychological assessments

Clinical Scales

Mini-Mental Status Examination. The MMSE (Folstein *et al.*, 1975) is an assessment of global cognitive function and comprises questions on orientation, attention, short-term memory, language and basic motor skills. The score ranges from 0 to 30. A score below 24 indicates a cognitive impairment.

Geriatric Depression Scale. In this short version of the Geriatric Depression Scale (Burke *et al.*, 1991, 1992), depressive symptoms are assessed using 15 yes/no questions. A score of >5 indicates depression (van Den *et al.*, 2001).

Clock drawing test. The clock drawing test (Shulman *et al.*, 1993) requires participants to draw a face of a clock, indicating time '10 min after 11'. It is used as a screening test for cognitive impairment and spatial dysfunction. Scores range from 1 (perfect clock) to 6 (no clock is recognizable).

Specific neuropsychological tests

California Verbal Learning Test. The California Verbal Learning Test (CVLT) (Niemann *et al.*, 2008) is a verbal memory test and assesses immediate and delayed, free and cued recall, as well as recognition. A list of 16 words falling into four different categories (fruit, clothing, drinks and tools) is read five times. After each round, participants are asked to recall as many words as

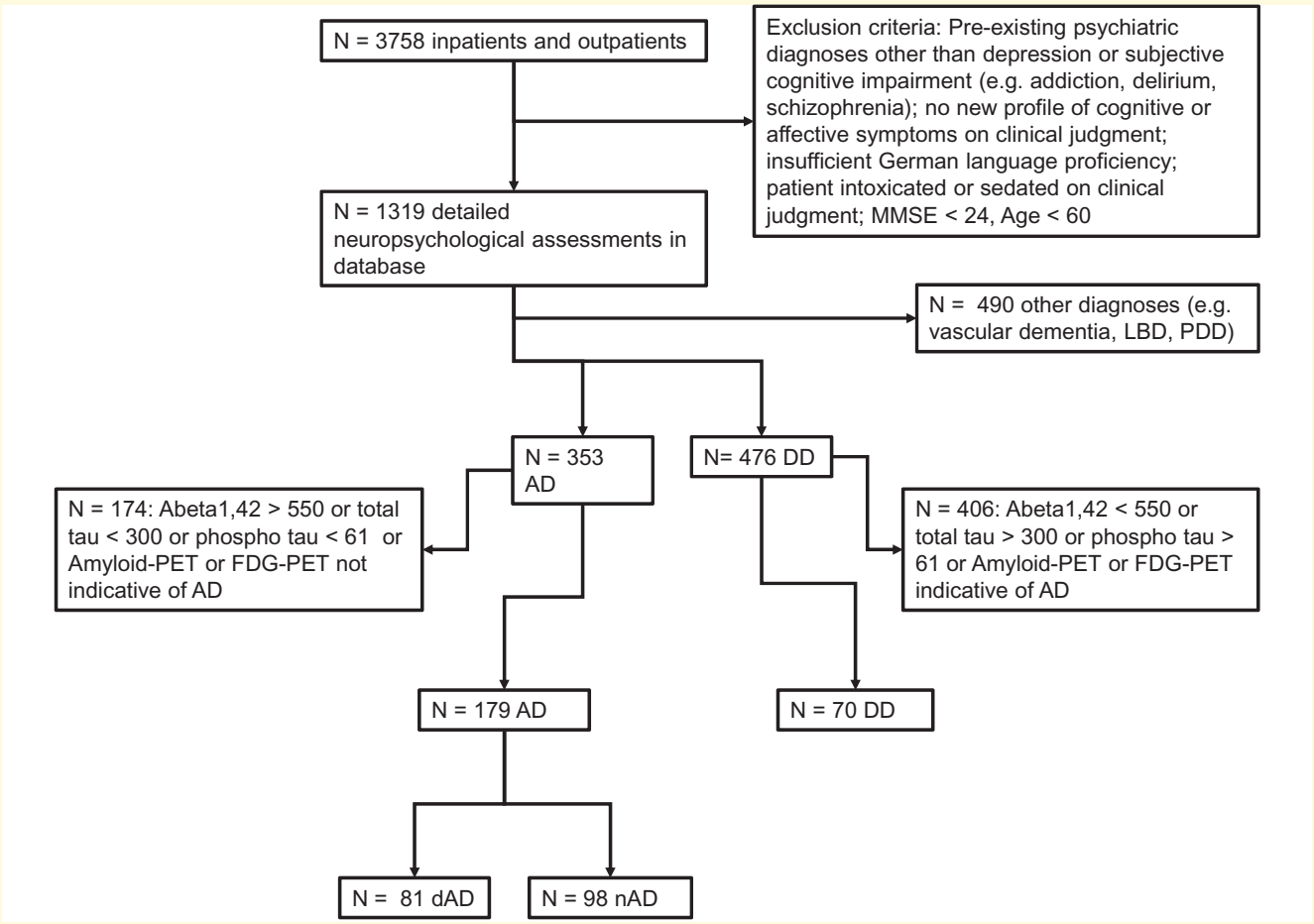


Figure 1 Selection process and exclusion criteria.
AD: Alzheimer's disease; DD: depressive disorder; dAD: AD patients with depressive syndrome; nAD: AD patients without depressive syndrome.

Table 1 Demographics and neuropsychological data of all AD and DD

Neuropsychological assessment	AD ($n = 179$) Median/IQR	DD ($n = 70$) Median/IQR	*P*-value	R^2
Age (years)	78.0/72.0–83.0	73.6/60.0–88.0	**0.000**	0.05
GDS	4.0/2.0–7.75	6.0/4.0–11.0	**0.000**	0.06
MMSE	26.0 ± 25.0–28.0	27.0 ± 25.0–29.0	**0.046**	0.02
CVLT1	3.0/2.0–4.0	3.0/2.0–5.0	**0.004**	0.03
CVLT5	5.0/4.0–7.0	7.0/5.0–9.75	**0.000**	0.10
CVLT total recall	22.0/18.0–28.0	28.0/23.0–35.8	**0.000**	0.10
CVLT delayed recall	1.0/0.0–4.0	4.0/3.0–7.0	**0.000**	0.17
CVLT delayed cued recall	4.0/2.0–6.0	7.0/5.0–9.0	**0.000**	0.15
CVLT recognition	14.0/12.0–15.0	14.0/12.3–15.0	0.964	<0.01
CVLT false positive	8.0/4.0–11.0	2.5/1.0–5.0	**0.000**	0.11
Digit span forward	7.0/5.5–8.0	6.5/5.0–8.0	0.514	<0.01
Digit span backward	4.0/3.0–5.0	4.0/3.0–5.8	0.481	<0.01
Block span forward	6.0/5.0–6.0	6.0/5.0–7.0	**0.019**	0.02
Block span backward	5.0/3.0–6.0	5.0/4.0–6.0	0.456	<0.01
Clock drawing	3.0/2.0–4.0	2.5/1.0–3.0	**0.004**	0.03
TMT-A	77.0/56.0–112.0	58.0/38.5–97.5	**0.001**	0.05
TMT-B	210.0/164.0–268.0	162.0/109.0–245.0	**0.001**	0.04
Semantic fluency	13.0/10.5–17.0	14.5/12.0–20.0	**0.020**	0.02
Phonematic fluency *P*	5.0/3.0–8.0	6.0/3.0–8.0	0.364	<0.01
Phonematic fluency *S*	8.0/4.0–10.0	7.0/5.0–10.0	0.819	<0.01

Abbreviations: AD, Alzheimer's disease; CVLT, California Verbal Learning Test; DD, depressive disorder; GDS, Geriatric Depression Scale; MMSE, Mini-Mental Status Examination; TMT-A, Trail-Making Test A; TMT-B, Trail-Making Test B.

possible. Immediate recall is followed by a free and cued delayed recall after 5 and 20-min intervals. At the end, participants are presented with a yes/no recognition task. Depending on age, sex and education, the score of delayed recall and recognition range from 10 to 15 and 14 to 16, respectively.

Digit and visual span (Wechsler Memory Scale Revised). The digit span test (Härting *et al.*, 2000) comprises forward and backward tasks. In the digit span, forward participants are instructed to repeat a sequence of digits in the order, in which they were presented. The task is terminated when the longest sequence of eight digits is reached or when participants incorrectly repeat two sequences of the same length. In the digit span backward, the same procedure is applied for repeating the digits in reversed order. Visual span was assessed using spatial sequences tapped on Corsi-block. Same as in digit span, visual span had forward and backward tasks. One point is given for each correct answer with scores ranging from 0 to 12 for digit span and visual span backward and from 0 to 14 for visual span forward. Mean digit span scores for healthy older persons are about 7–9 and 6–8 forward and backward, respectively. Mean visual span scores for healthy older persons are about 5–8 forward and 7–9 backward (Gron *et al.*, 2002; Widmann *et al.*, 2012).

Trail-Making Tests A and B (TMT-A and TMT-B). The Trail-Making Test (TMT) (Reitan and Wolfston, 1985) assess visual attention and mental flexibility. Participants are required to connect encircled numbers in ascending order from 1 to 25 (TMT-A) and 25 encircled numbers and letters in an alternating ascending/alphabetic order (TMT-B). Participants are asked to work as quickly and accurately as possible. A large discrepancy between the time needed to complete TMT-A and TMT-B is an indicator of deficits in mental flexibility. Mean scores for TMT-A and TMT-B for healthy older persons range from 25 to 50 s and 50 to 110 s, respectively (Gron *et al.*, 2002; Widmann *et al.*, 2012).

Fluency tasks (Regensburg Verbal Fluency Test; RWT). RWT (Aschenbrenner *et al.*, 2000) assesses semantic and phonetic verbal fluency. The task requires to name as many words as possible belonging to a category 'animals' (semantic fluency) and words starting with letter 'P' and with letter 'S' (phonemic fluency). One minute is given to complete each task. Mean scores for semantic and phonetic fluency are about 18–28 (Riepe *et al.*, 2010) and 6–8, respectively (Gron *et al.*, 2002; Widmann *et al.*, 2012).

Statistical analyses

All statistical data analyses were performed using SPSS (SPSS 25.0 for Windows, Armonk, NY, 2017). The normality of distribution was assessed with the Kolmogorov–Smirnov Test. Since majority of parameters were not normally distributed, the non-parametric Mann–Whitney–*U*-test was used to calculate the group differences. Effect sizes were calculated as R^2 to indicate the proportion of variance shared by the two variables. Values of $R^2 = 0.01$ indicate a small effect size, $R^2 = 0.09$ indicate a medium effect size and $R^2 = 0.25$ a large effect size (Cohen, 1992).

Data availability

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary material.

Results

Cognitive symptoms in patients with AD and patients with DD

Cognitive performance in patients with AD and DD is summarized in Table 1. Performance in both patients with AD and patients with DD is below normal. Results in healthy controls have been reported in a previous analysis (Lanza *et al.*, 2020).

Cognitive symptoms in patients with AD and patients with DD

Patients with AD and DD were matched for age (±3 years), education (±one school level) and MMSE score (±1 point). On average, patients with AD were significantly worse in the CVLT 5 ($P = 0.000$), total recall over all learning trials ($P = 0.000$), delayed recall ($P = 0.000$), delayed cued recall ($P = 0.000$) and false-positive answers ($P = 0.000$). Similarly, clock drawing test ($P = 0.044$), and the TMT-A ($P = 0.021$) was worse than in patients with DD. The results are summarized in Table 2.

Cerebrospinal fluid levels of Abeta1-42 ($P = 0.000$), total tau ($P = 0.000$), phospho-tau ($P = 0.000$) and ratio Abeta1-42/Abeta1-40 ($P = 0.000$) were different in patients with AD and DD as a consequence of the selection process (Supplementary Table 1).

The parameter that strikes out to differentiate the most, the free delayed recall has a medium to strong effect size with $R^2 = 0.21$. Receiver operating characteristic analysis revealed an AUC of 0.762 (Fig. 2).

Cognitive symptoms in patients with AD with and without concomitant depressive symptoms

To better understand depressive syndrome within AD patients and its impact on CSF values, we separated this group into two subgroups according to score in the GDS, one group being AD patients with depressive syndrome (dAD, $n = 81$;

Table 2 Matched data for sex, education, age and MMSE in patients with AD versus DD

Neuropsychological assessment	AD ($n = 63$) Median/IQR	DD ($n = 63$) Median/IQR	*P*-value	R^2
Age (years)	76.0/70.0–80.0	75.0/69.0–80.0	0.756	<0.01
GDS	5.0/2.0–8.5	6.0/4.0–10.0	**0.045**	0.03
MMSE	26.0 ± 25.0–28.0	27.0 ± 25.0–29.0	0.138	0.02
CVLT1	3.0/2.0–4.0	3.0/2.0–4.0	0.075	0.03
CVLT5	5.0/4.0–7.0	7.0/5.0–9.0	**0.000**	0.13
CVLT total recall	21.0/18.0–28.0	27.5/22.8–34.3	**0.000**	0.11
CVLT delayed recall	1.0/0.0–3.8	4.0/2.8–7.0	**0.000**	0.21
CVLT delayed cued recall	4.0/2.0–6.0	6.5/5.0–9.0	**0.000**	0.16
CVLT recognition	14.0/11.3–15.0	14.0/12.8–15.0	0.520	<0.01
CVLT false positive	6.5/3.3–12.8	2.5/1.0–5.3	**0.000**	0.10
Digit span forward	7.0/6.0–8.0	6.0/5.0–8.0	0.371	0.01
Digit span backward	4.0/3.0–5.0	4.0/3.0–5.3	0.649	<0.01
Block span forward	6.0/5.0–7.0	6.0/5.0–7.0	0.168	0.02
Block span backward	5.0/3.0–6.0	5.0/4.0–6.0	0.833	<0.01
Clock drawing	3.0/2.0–4.0	3.0/2.0–3.0	**0.044**	0.03
TMT-A	71.0/54.0–119.0	58.5/40.5–101.0	**0.021**	0.04
TMT-B	199.0/154.0–249.0	170.5/119.5–248.0	0.077	0.03
Semantic fluency	14.0/11.0–17.0	15.0/12.0–20.0	0.078	0.03
Phonematic fluency *P*	5.0/3.0–7.0	6.0/3.0–8.0	0.138	0.02
Phonematic fluency *S*	7.5/5.0–10.8	7.0/5.0–10.0	0.768	<0.01

Abbreviations: AD, Alzheimer's disease; CVLT, California Verbal Learning Test; DD, depressive disorder; GDS, Geriatric Depression Scale; MMSE, Mini-Mental Status Examination; TMT-A, Trail-Making Test A; TMT-B, Trail-Making Test B.

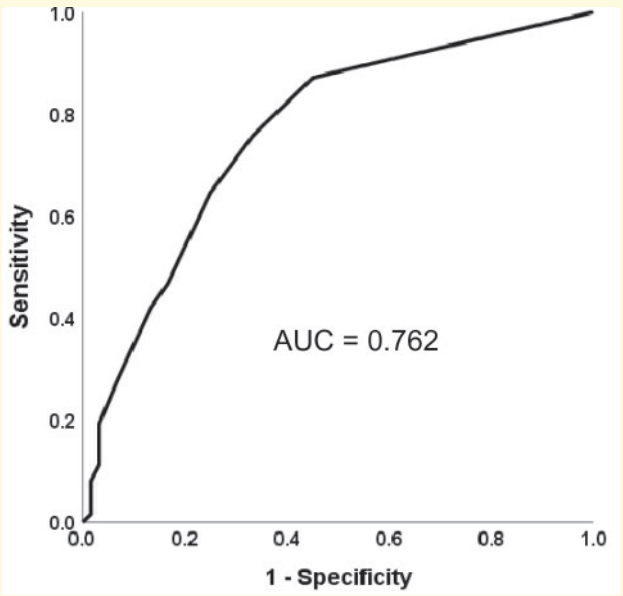


Figure 2 Area under the curve of free delayed recall.

GDS > 4), the other group being AD patients without depressive syndrome (nAD, $n = 98$; GDS < 4).

Calculation of group differences of dAD versus nAD showed significant differences for ratio Abeta1-42/Abeta1-40 ($P = 0.030$), whereas all other CSF markers were alike (Supplementary Table 2).

Verbal working memory and executive function differed between nAD than dAD. The results are summarized in Table 3.

Discussion

Clinically, cognitive and affective symptoms may be present in patients with AD as well as in patients with DD. Neither clinical assessments nor standardized behavioural testing of mood or cognition allows a differential diagnosis. The missing clinical and behavioural gold standards precluded establishing profiles of cognitive impairment due to AD and DD. To our knowledge, this study is the first to use biomarker-verified groups of AD and DD to characterize their respective cognitive profiles.

Our results demonstrate that with similar global cognitive function as assessed with the MMSE, the impairment of verbal episodic memory is much more pronounced in patients with AD than in patients with DD. This applies to established memory measures such as total and delayed recall as well as to false recognitions (Sejunaite *et al.*, 2017, 2018). We hypothesize that due to greater impairment of brain structures crucial for memory storage, patients with AD suffer from greater memory deficits than those with DD (Gron *et al.*, 2002). Although on a group level, the effect sizes of the differences in these measures in AD and DD are moderate, they do not suffice to diagnose individual patients. The receiver operating characteristic curve demonstrates a sensitivity of about 0.6 at a specificity of about 0.8 for distinction between AD and DD using free delayed recall. Thus, even the variable that distinguishes best between AD and DD having a strong effect size for group comparison does not suffice to diagnose single patients.

Executive dysfunction has further influence on memory processes such as encoding, retrieval and learning

Table 3 Neuropsychological assessments in patients with nAD and dAD

Neuropsychological assessment	nAD (GDS ≤ 4) Median/IQR	dAD (GDS > 4) Median/IQR	*P*-value	R^2
GDS	2.0/1.0–3.0	8.0/6.0–11.0	**0.000**	**0.74**
MMSE	26.0 ± 25.0–28.0	27.0 ± 25.0–28.0	0.451	<0.01
CVLT1	3.0/2.0–4.0	3.0/2.0–4.0	0.670	<0.01
CVLT5	5.0/4.0–7.0	5.0/4.0–7.0	0.615	<0.01
CVLT total recall	21.0/18.0–28.0	22.0/18.0–28.0	0.811	<0.01
CVLT delayed recall	1.0/0.0–3.0	1.0/0.0–5.0	0.241	0.01
CVLT delayed cued recall	4.0/2.0–6.0	3.5/2.0–6.3	0.813	<0.01
CVLT recognition	14.0/12.3–15.0	14.0/12.0–16.0	0.790	<0.01
CVLT false positive	8.0/3.0–11.8	7.0/4.0–11.0	0.853	<0.01
Digit span forward	7.0/5.5–8.0	7.0/5.0–8.0	0.482	<0.01
Digit span backward	4.0/3.0–5.0	4.0/3.0–5.0	**0.048**	**0.02**
Block span forward	6.0/5.0–6.0	6.0/5.0–6.0	0.401	<0.01
Block span backward	5.0/3.0–6.0	5.0/3.0–6.0	0.311	0.01
Clock drawing	3.0/2.0–4.0	3.0/2.0–4.0	**0.050**	**0.02**
TMT-A	70.5/51.3–97.8	92.0/65.0–121.5	**0.004**	**0.05**
TMT-B	199.0/155.3–264.8	215.0/177.0–279.0	**0.050**	**0.03**
Semantic fluency	13.0/11.0–17.8	13.0/10.0–16.5	0.534	<0.01
Phonematic fluency P	5.0/3.0–8.0	5.0/3.0–7.0	0.819	<0.01
Phonematic fluency S	8.0/5.0–11.0	7.0/4.0–10.0	0.075	0.02

Abbreviations: CVLT, California Verbal Learning Test; dAD, Alzheimer patients with depressive syndrome; GDS, Geriatric Depression Scale; MMSE, Mini-Mental Status Examination; nAD, Alzheimer patients without depressive syndrome; TMT-A, Trail-Making Test A; TMT-B, Trail-Making Test B.

(Elderkin-Thompson *et al.*, 2007; Taconnat *et al.*, 2010) and may cause additional memory deficits (Fossati *et al.*, 2002). It has been argued that impairment of executive function is one of the hallmarks of cognitive deficits in patients with DD (Elderkin-Thompson *et al.*, 2004; Dotson *et al.*, 2008). However, a recent study found other processes of memory learning and retrieval to be also impaired (Lanza *et al.*, 2020). Overall, group differences in executive function are smaller than memory recall, making these parameters ill-suited to distinguish AD and DD. At least, partly this may be caused by the increased variability of cognitive performance in patients with DD (Gallagher *et al.*, 2015). The overall interpretation is in good harmony with previous reports that a distinct pattern of cognitive impairment in AD and DD cannot be found (desRosiers *et al.*, 1995; Dierckx *et al.*, 2007). This study is the first to support this conclusion in patients with verified AD and verified DD. Thus, the difference between AD and DD regarding cognitive performance is dimensional rather than categorical.

Depressed mood is frequent in patients with AD (Weiner *et al.*, 1997; Wiels *et al.*, 2020). During the course of the disease, nearly half of the patients experience clinically significant depressive syndrome (Starkstein *et al.*, 2005). For this reason, we analysed subgroups of patients with verified AD with and without concomitant depressive symptoms. This study demonstrates that in patients with verified AD concurring depressive symptoms manifest with an additional impairment of executive function, whereas verbal episodic memory is equally impaired in patients with AD with and without concomitant depressive symptoms. Increased impairment of executive function in this subgroup needs to be considered as an additional target that goes beyond the treatment of cognitive symptoms in AD patients, in general.

The format of the medical records used in the study caused some limitations. The number of previous depressive episodes or the age of onset of depressive syndrome could not be reliably determined. This might be relevant, since recent studies have shown, that with each depressive episode, cognitive impairment may persist even after depressive syndrome has vanished (Butters *et al.*, 2000; Beblo *et al.*, 2011). Similarly, exact records on received medication and treatment at the time of neuropsychological assessment was unavailable.

Conclusion

Cognitive impairment and depressive syndrome may be simultaneously present in both AD and DD. Therefore, differential diagnosis solely on clinical and behavioural grounds is unreliable. On the group level, free delayed recall correctly classifies 70% of cases. However, this is insufficient for clinical diagnosis of individual patients. Biomarker analysis is needed to verify the diagnoses of AD and DD. This also applies to the studies appraising depressed mood or impaired cognition as being risk factors for either AD or DD. Standardized neuropsychological and mood assessment in patients with verified AD is important to define targets for a comprehensive therapy of AD. Even clinical trials for both AD and DD need to include this comprehensive approach to not underestimate the treatment effects.

Supplementary material

Supplementary material is available at *Brain Communications* online.

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Competing interests

The authors report no competing interest.

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