Supplementary Material

Diencephalic versus Hippocampal Amnesia in Alzheimer's Disease: The Possible Confabulation-Misidentification Phenotype

SUPPLEMENTARY METHODS

Instruments

Informant reports about cognitive and behavioral status

The semi-structured interview used in our Unit assessed the following spectrum of cognitive domains and/or features: memory (recent, past, and prospective), confabulation, temporal orientation, topographical orientation, attention, executive functions, insight, language, praxis. Behavioral disturbances examined were: personality changes, misidentification, delusion different from misidentification (including different themes like paranoid, theft, jealousy, as well as feeling of presence and the action of hiding objects or precious related to delusion of theft), hallucination, apathy, abulia, irritability, aggression (including verbal and physical aggression, opposition, self-injury, screaming, misoginia), social disinhibition, impulse control disorders (including smoking, alcohol abuse, coprolalia, hypersexuality, gaming), obsessions/compulsions, hyperactivity/psychomotor agitation (including motor restlessness, shadowing, escapes from home, object defenestration), wandering, purposeless activity, hyperphagia (including craving for sweets and binge eating), euphory/fatuity, insomnia (including initial and central insomnia, sleep-awake cycle upset, vivid dreams, nightmares, nocturnal agitation behaviors, and nocturnal wandering), hypersomnia, REM-behavior disorder (RBD), confusional arousal, lability, anxiety, and depression. Additional items covered type of onset, course, fluctuations in both attention and cognition, sundowning, and the first cognitive symptom. The interview procedure included a first part of free recall, prompted by a general question about cognitive functioning, and a second part in which the examiner systematically asked a list of questions, one for each cognitive and behavioral feature included in the interview. The informant first had to respond yes or not to each question. Then, she/he was asked to support the emergence of a feature by reporting some patient's behaviors that exemplified that feature. If the informant could not recall any examples, the examiner described to her/him at least two typical behaviors that exemplify that feature. Then, again, the informant was asked to answer yes or not. Each feature was simply rated as

present/absent. The cognitive section of the interview used in our Unit was presented as an appendix in a previous article [1].

The standard observational neuropsychological examination (NPE)

We reported the semi-structured interview used in the NPE in a previous article [2]. The interview covered a fixed number of topics, but its administration is quite flexible, leaving the examiner able to decide the order of questions and the specific combination of open questions (e.g., "please, let me know something about your medical history") and closed questions (e.g., "what day is today?"). The broad aim of the interview was to obtain an adequate understanding of the patient's behavior by collecting samples of speech, emotional behaviors, social conducts, thinking, memories, etc., from which the neuropsychologist might be able to detect pathological signs (or alternatively be reassured by the absence of pathological signs). Also, a secondary aim was to preliminary measure specific cognitive functions (e.g., insight, orientation, retrograde memory, etc.) to be potentially explored later more in detail. The list of signs in the NPE includes the signs of impairment from eight cognitive domains: orientation, psychomotor speed, attention, prefrontal functions, memory, speech and language, visuospatial abilities. We reported the NPE list of signs used in the current study in Supplementary Table 1. A more comprehensive NPE list of signs has been presented in a previous article [2]. In particular, for orientation we considered signs of temporal, spatial, personal, family, and situational disorientation; for attention, signs of both selective (e.g., verbal distractibility, attentive captures) and sustained attention impairment (e.g., drowsiness, mental fatigue, effort of mental concentration); for prefrontal functions, signs of the dysexecutive syndrome (e.g., perseveration, difficulty in planning of discourse, simplified or confused mental tracking or reasoning), adynamic syndrome (e.g., diminished motivation, reduction of initiative, lack of spontaneity), hyperactive disinhibition syndrome (e.g., logorrhea, impulsivity, social inappropriateness), and obsessive-compulsive syndrome. Moreover, reduction of insight and provoked confabulation at memory test were two further signs in the prefrontal function domain. For memory, we considered signs of anterograde (e.g., repetitions in the discourse) and retrograde amnesia (e.g., forgetting of past events); for speech and language, signs of dysfluency (e.g., effortful articulation, speech lacking normal prosodic variations), phonemic deficits (e.g., phonemic paraphasias, conduites d'approché), syntactic deficits (e.g., telegraphic speech output, omission/substitution of

grammatical morphemes), lexical semantic deficits (e.g., anomic pauses, passepartout words, circumlocutions), and comprehension deficits (e.g., answers unrelated to questions); for spatial abilities, signs of topographical disorientation (e.g., topographical disorientation in the Hospital Unit), as well as of extra-personal (e.g., the patient does not answer questions when prompted from a side of his space), personal (e.g., the arms of patient's glasses are misplaced upon one of her/his ears) and motor neglect (e.g., underuse of counter-lesional limb).

Retrospective Observational Case-Series Study

We collected the following additional data at baseline to better characterize the case-series: demographic data (sex, age, education, handedness), general cognitive status (MMSE), neurological examination, vascular risk (number of risk factors, i.e., hypertension, diabetes mellitus, dyslipidemia, ischemic heart disease, atrial fibrillation, carotid atherosclerosis, smoking, stroke/TIA, obesity, hyperhomocysteinemia), risk of vascular dementia (Hachinski scale), functional status (ADL and IADL scales), severity of cognitive decline (CDR), syndrome diagnosis (i.e., MCI or mild dementia), and *APOE* genotype. In addition, we retrieved neurological examination, general cognitive status (MMSE), and anti-dementia medication use from follow-up geriatric visits (see Table 5 in the main manuscript).

REFERENCES

[1] Abbate C, Trimarchi PD, Nicolini P, Bergamaschini L, Vergani C, Mari D (2011) Comparison of informant reports and neuropsychological assessment in mild cognitive impairment. *Am J Alzheimers Dis Other Demen* **26**, 528-534.

[2] Abbate C, Trimarchi PD, Inglese S, Tomasini E, Bagarolo R, Giunco F, Cesari M (2021) Signs and symptoms method in neuropsychology: A preliminary investigation of a standardized clinical interview for assessment of cognitive decline in dementia. *Appl Neuropsychol Adult* **28**, 282-296.

SUPPLEMENTARY RESULTS

Descriptive Data

All CM-AD patients had one geriatric follow-up visit at 12 months post-baseline, while only 11 patients (64.7%) had two follow-ups at 24 months post-baseline (Supplementary Tables 2 and 3). Unfortunately, starting from 36 months after the baseline, we had longitudinal cognitive and behavioral data from less than 50% of both the samples of AD patients (Supplementary Tables 2 and 3).

Main Cognitive and Behavioral Features of the CM-Phenotype

The cognitive profile is dominated by anterograde amnesia (100%) associated with confabulation (88.2%), disorientation—especially temporal (88.2%) at early stages, but also topographical including data from more later stages (88.2%)—and quite often by retrograde amnesia (64.7%) (Table 3 in the main manuscript). It is worth noting that confabulation emerged at early stages of MCI and mild dementia in 14 of 17 patients (82.3%), and it was the first symptom in one patient (Case#2, Table 1 in the main manuscript). Also, confabulation included spontaneous confabulations in 9 patients. Executive impairments (88.2%), reduction of insight (88.2%), and attention deficits (82.3%) constituted the second more frequent cluster of cognitive features. Also, early mild psychomotor slowness (58.8%) and later mild fluctuations (52.9%) were not uncommon. Finally, language (76.5%) and praxis (52.9%) deficits were quite common especially including data from later stages. However, they were mild and quite nonspecific at early stages. Considering the behavioral features, the whole CM-phenotype showed quite relevant behavioral disturbances. Many behavioral features were common when considering cumulative frequencies including mild-to-moderate and moderate dementia stages (Table 3 in the main manuscript). However, some of them started before the MCI or mild dementia stages in some patients (see the NPI score in the main manuscript Table 6). In particular, we registered a main neuropsychiatric features cluster, in which the most salient feature was misidentification. Misidentification was common especially considering data from intermediate stages (52.9%), but it emerged early as well in four patients (case#5, 6, 9, 17, Table 1). Moreover, it was the first symptom in one patient (case#17). In addition, misidentification often included multiple concurrent manifestations in the same patient (e.g., persons, places, TV celebrities, animals). Delusions different from misidentification were present at early stages (41.2%) and become

common including data from mild-to-moderate and moderate stages (70.6%). However, it was often mild and not structured compared to misidentification. Themes were theft, persecution, and jealousy. Hallucinations were rare at early stages (17.6%), but quite common including data from mild-to-moderate stages (64.7%). However, hallucination was ever infrequent, intermittent, sometimes presenting in a single episode, and never severe and recurring. The content of hallucination was generally not familiar persons (e.g., a girl, some children, unspecified neighbors) and small animals. Modalities were both visual and auditory (e.g., voices of persons, rumors outside the house door, the telephone ring). Hallucination seemed occur equally during the night and day. Generally, hallucination did not bother the patient. Only one patient (case#2) seemed moderately annoyed since the persons in her hallucination would assault her. In some instances, hallucinations seemed to be more similar to illusions or misinterpretations than to overt hallucinations (e.g., patient#16 told that the stars in the sky came alive and talked to her, *and* that some satellites moving in the sky were UFO that were coming and see her). In one patient there emerged feeling of presence (case#9). Hyperactive-disinhibition syndrome was a second relevant cluster of behavioral disturbances. In particular, hyperactivity/psychomotor agitation was frequent considering cumulative frequencies at mild-to-moderate stage (76.5%), while hyperphagia was common considering the more advanced stages (76.5%). In the same context, irritability and aggression emerged at early stages in some patients and were quite common (76.5% and 64.7% respectively) when considering data from intermediate dementia stages. In addition, we noted that a subgroup of patients early showed mild logorrhea and verbal distractibility, sometimes associated with mild euphoria/fatuity and social disinhibition. In parallel with the hyperactive-disinhibition syndrome, relevant features of the adynamic syndrome emerged too. In particular, apathy was common at mild stage (64.7%) and very common including data from mild-to-moderate stages on (82.3%). Besides, considering sleep, insomnia was quite frequent considering data from the mild dementia stage (64.7%) and even more frequent including data from mild-to-moderate stage (70.6%). In particular, central insomnia associated with nocturnal hyperactivity and wandering (see supplementary methods) was a prevalent feature. Finally, considering affective symptoms, anxiety and depression were not irrelevant at mild dementia stage (both 58.8%), and much common considering data from mild-to-moderate and moderate dementia stages (both 70.6%). Anxiety was more frequent at the baseline and early stages than depression.

Main Differences Between the CM- and CA-Phenotype of AD

Primary outcomes

Informant report

The relatives of the CM-ADs reported more confabulation (41.2% versus 0%, p<0.0001), misidentification (23.5% versus 0%, p=0.013), and other delusions (41.2% versus 3.3%, p= 0.002) at the baseline compared to the relatives of the CA-ADs (Supplementary Table 4). There was no further statistically significant difference. However, a similar difference with tendency to significance for the comparison between the two groups emerged for temporal disorientation (35.3% versus 6.7%, p=0.019), executive functions deficits (64.7% versus 36.7%, p=0.064), reduction of insight (47.1% versus 20%, p=0.051), and social disinhibition (17.6% versus 0%, p=0.042). In addition, raw differences in many further features were in line with the main results. In particular, topographical disorientation (41.2% versus 23.3%), apathy (41.2% versus 20%), and aggression (35.3% versus 13.3%) were similarly more frequent in the reports by the relatives of the CM-ADs compared to those of the CA-ADs (Supplementary Table 4). However, all these comparisons did not reach the statistical significance. Conversely, language deficits (23.5% versus 43.3%) and depression (17.6% versus 40%) were less frequent at the baseline in the informant reports of the CM-ADs compared to those of the CA-ADs (Supplementary Table 4). However, those last two comparisons were not statistically significant.

NPE

At the baseline NPE the neuropsychologists detected more temporal disorientation (88.2% versus 53.3%, p=0.015), and provoked confabulation at memory tests (58.8% versus 0%, p<0.0001) in the CM-AD compared to the CA-AD group. There was no further statistically significant difference. However, the same clinicians detected more signs of reduction of insight (70.6% versus 40%, p=0.044), anterograde amnesia (52.9% versus 23.3%, p=0.040), and retrograde amnesia (64.7% versus 36.7%, p=0.064) in the CM-AD compared to the CA-AD group (Supplementary Table 5), being the comparisons near to the statistical significance. Instead, psychomotor slowness and sustained attention deficits which included fluctuations did not result different between the two phenotypes. In addition, signs of the hyperactive-disinhibition syndrome appeared more numerous in the CM-AD than in the CA-AD group (41.2% versus 23.3%), but this difference did not reach the statistical significance. By contrast,

the neuropsychologists detected less signs of lexical semantic deficits in spontaneous speech in the CM-ADs compared to the CA-ADs (23.5% versus 43.3%) (Supplementary Table 5). However, also this difference was not statistically significant.

Geriatric follow-ups

We presented general data about the geriatric follow-ups in supplemental Supplementary Table 6. No differences emerged between the CM-AD and CA-AD group on number and duration of follow-ups, MMSE scores at baseline and last follow-up, and age at baseline and last follow-up (Supplementary Table 7). In particular, in both the AD groups the mean number of geriatric follow-ups was about 7 visits, mean follow-up duration about 39-40 months, mean MMSE score at baseline about 24 point, mean MMSE score at the last visit about 15-16 points, mean age at baseline about 75-76 years, and mean age at the last follow-up about 79 years (Supplementary Table 6 and 7). Treatment with anti-dementia drugs were started for 15 of 17 CM-ADs and 24 of 29 CA-ADs. Most patients used acetylcholinesterase inhibitors (AChEI), especially rivastigmine, while few of them used donepezil and whereas only three of them assumed memantine. Only one patient took both rivastigmine and memantine.

We found many non-statistically significant raw differences between the two groups of AD patients on various cognitive and behavioral features at both 12 and 24 months that were in the same direction as those that emerged at baseline (Supplementary Tables 2 and 3, and Table 5 in the main manuscript). In particular, at 12 months after the baseline, the CM-ADs showed more fluctuations (17.6% versus 3.7%), temporal (35.3% versus 25.9%) as well as topographical (64.7% versus 44.4%) disorientation, executive function deficits (41.2% versus 33.3%), misidentification (23.5% versus 7.4%), delusion not-misidentification (41.2% versus 25.9%), apathy (47.1% versus 33.3%), and aggression (35.3% versus 29.6%) than the CA-ADs. At 24 months after the baseline, the CM-ADs presented more temporal disorientation (18.2% versus 10.5%), executive function deficits (27.3% versus 10.5%), reduction of insight (27.3% versus 5.35%), misidentification (27.3% versus 10.5%), delusion not misidentification (45.4% versus 36.8%), hallucination (27.3% versus 15.8%), apathy (36.4% versus 10.5%), abulia (18.2% versus 5.3%), aggression (45.4% versus 31.6%), social disinhibition (18.2% versus 0%), hyperactivity/psychomotor agitation (45.4% versus 26.3%), and hyperfagia (18.2% versus 0%) than the CA-ADs. In countertendency, language deficits (41.2% versus 63%) and depression

(52.9% versus 63%) continued to be a little less frequent in the CM-ADs than in the CA-ADs at 12 months after the baseline. In addition, the two most salient features of the CM-phenotype, i.e., confabulation and misidentification, never emerged at the geriatric follow-ups in 20 out of 29 CA-ADs (68.9%) (negative CA-ADs) (Supplementary Table 7). All the remaining positive CA-ADs started to showed exclusively minor and infrequent confabulation and/or misidentification starting at later stages of dementia. A comparison between positive and negative CA-ADs showed more control visits ($p<0.001$), longer follow-up ($p=0.048$), and more advanced cognitive decline at MMSE ($p=0.017$) in the group of positive CA-ADs (Supplementary Table 7), supporting the view that some minor confabulation and misidentification could emerge in CA-AD, but especially at later stages.

Secondary outcomes

NPI scores, clinical variables, neurological examination

No differences emerged in type of onset, course, fluctuations and sundowning between the CM- and CA-ADs (see Table 6 in the main manuscript). Also, the neurologist did not find any relevant qualitative difference between the two groups on neurological signs and symptoms by reviewing baseline and longitudinal NEs. Mild extra pyramidal symptoms emerged in some patients especially at later dementia stages, but in all these cases they are related to the concurrent long-time antipsychotic therapy.

Supplementary Table 1. The content of the NPE. Cognitive domains, neuropsychological impairments and the corresponding signs included in the NPE.

Cognitive domain	Impairment or syndrome	Sign	Score range absent/ present
Orientation	Temporal disorientation	i. failures or confusions to remember information about current date and time (i.e., date, the day of the week, month, season and year)	[0] [1]§
	Spatial disorientation	i. failures or confusions to remember information about spatial localization (i.e., Hospital, floor, nation, country, city)	[0] [1]§
	Personal disorientation	i. loss of knowledge about oneself (e.g., one's name, date of birth, age, address, eye color, profession)	[0] [1]
	Disorientation to family members	i. failures or confusions to remember information about his/her relatives and parents (e.g., either the number or name or sex of sons, nephews, brothers, sisters)	[0] [1]
	Disorientation to situation	i. failures or confusions to remember situational information (e.g., the patient does not know what are the reasons for the consultation or what type of visit she/he is going to do)	[0] [1]
Psychomotor speed	Psychomotor slowness	i. Slow thinking ii. The slowness of speech (not due to dysfluency)	[0] [1] [0] [1]
Attention	Selective attention impairments	i. Internal distractibility (e.g., talkativeness, derailment) ii. External distractibility (e.g., attentive captures)	[0] [1] [0] [1]
	Sustained attention impairments	i. Sleepiness (e.g., somnolence, drowsiness) ii. Fluctuations in attention iii. A decrease in sustained attention (e.g., mental fatigue) iv. The effort of mental concentration	[0] [1] [0] [1] [0] [1] [0] [1]
Prefrontal functions	Dysexecutive syndrome	i. Cognitive hesitancy ii. Perseveration (e.g., perseveration of speech or action components) iii. Difficulty in the planning of discourse iv. The patient does not stay on topic v. Simplified or confused mental tracking or reasoning	[0] [1] [0] [1] [0] [1] [0] [1] [0] [1]
	Altered Insight	i. Impoverished or diminished insight	[0] [1]
	Apathetic-akinetic syndrome (adynamic syndrome)	i. Diminished motivation ii. Lack of spontaneity iii. Reduction of verbal initiative iv. Mutism v. Reduction of initiative vi. Reduced expression of emotions vii. Flattened emotion (e.g., diminished empathy)	[0] [1] [0] [1] [0] [1] [0] [1] [0] [1] [0] [1] [0] [1]
	Hyperactive-Disinhibition syndrome	i. Hyperactivity ii. Logorrhea iii. Impulsivity iv. Diminished emotional control	[0] [1] [0] [1] [0] [1] [0] [1]
		v. Aggression and opposition vi. Euphoria vii. Social inappropriateness viii. Fatuity and jocularity ix. Echolalia x. Verbal distractibility (e.g., talkativeness, derailment, tangentiality, etc.) xi. Captures of attention xii. Utilization behavior	[0] [1] [0] [1] [0] [1] [0] [1] [0] [1] [0] [1] [0] [1] [0] [1]

	Obsessive-compulsive syndrome	i. Signs of obsessive-compulsive disorder	[0] [1]
Memory	Anterograde amnesia	i. Repetition in the discourse ii. Forgetting of recent events	[0] [1] [0] [1]
	Retrograde amnesia	i. Forgetting of past events ii. Latency of recall iii. Lack of temporal and spatial attributes of memory	[0] [1] [0] [1] [0] [1]
	Frontal memory deficits	i. Confabulation	[0] [1]
Speech and language	Dysfluency	i. Effortful articulation ii. Speech lacking normal prosodic variations iii. Reduced speech output	[0] [1] [0] [1] [0] [1]
	Phonemic deficits	i. Phonemic paraphasias ii. Conduites d'approche	[0] [1] [0] [1]
	Syntactic deficits	i. Simplified syntactic clauses ii. Telegraphic speech output iii. Omission/substitution of grammatical morphemes	[0] [1] [0] [1] [0] [1]
	Lexical-semantic deficits	i. Word-finding latencies ii. Word-finding problems (e.g., anomic pauses) iii. Passepartout-words iv. Circumlocutions v. Verbal paraphasias/lexical substitutions vi. Semantic paraphasias vii. Reduction in the information content of discourse (e.g., few content words)	[0] [1] [0] [1] [0] [1] [0] [1] [0] [1] [0] [1] [0] [1]
	Comprehension deficits	i. Answers unrelated to questions ii. Questions have to be repeated (in absence of hearing loss)	[0] [1] [0] [1]
Spatial abilities	Topographical disorientation	i. Topographical disorientation in the Hospital	[0] [1]
	Extra-personal neglect	i. The patient does not answer questions when prompted from a side of his space……..…….....	[0] [1]
	Personal neglect	i. Dressing apraxia (e.g., the arms of patient's glasses are misplaced upon one of her/his ears)	[0] [1]
	Motor neglect	i. Underuse of a contralesional limb ii. Head and eyes exploration movements are limited, shortened or defective towards a region of space	[0] [1] [0] [1]

[§]Temporal and spatial disorientation were scored: 0 point (equivalent to 5/5 in the standard scoring system), 1 point (equivalent to 4/5, 3/5, 2/5, 1/5)

Supplementary Table 2. Cognitive features reported at geriatric follow-up visits (number and %).

	T12		T24		T36		T48		T60		T72>	
	CM N=17	CA N=27	CM N=11	CA N=19	CM N=8	CA N=13	CM N=5	CA N=10	CM N=3	CA N=7	CM N=3	CA N=3
Fluctuations	3 17.6%	1 3.7%	2 18.2%	4 21.1%	1 12.5%	1 7.7%	0	0	1 33.3%	0	0	1 33.3%
Sundowning	1 5.9%	3 11.1%	0	1 5.3%	0	1 7.7%	0	1 10%	1 33.3%	0	0	1 33.3%
Psychomotor slowness	1 5.9%	1 3.7%	1 9.1%	0	2 25%	2 15.4%	2 40%	0	0	0	1 33.3%	0
Confusional episodes	0	2 7.4%	1 9.1%	0	0	0	0	1 10%	0	0	0	1 33.3%
Recent memory deficits	15 88.2%	23 85.2%	5 45.4%	12 63.2%	2 25%	8 1.5%	2 40%	7 70%	1 33.3%	5 71.4%	0	3 100%
Retrograde memory deficits	2 11.8%	8 29.6%	0	1 5.3%	1 12.5%	2 15.4%	0	1 10%	0	0	1 33.3%	0
Confabulation	4 23.5%	1 3.7%	0	0	1 12.5%	3 23.1%	0	1 10%	0	0	0	1 33.3%
Temporal disorientation	6 35.3%	7 25.9%	2 18.2%	2 10.5%	2 25%	3 23.1%	2 40%	3 30%	0	2 28.6%	0	1 33.3%
Topographical disorientation	11 64.7%	12 44.4%	3 27.3%	6 31.6%	3 37.5%	4 0.8%	2 40%	2 20%	1 33.3%	4 57.1%	2 66.7%	2 66.7%
Attention deficits	5 29.4%	14 51.8%	1 9.1%	1 5.3%	1 12.5%	2 15.4%	1 20%	3 30%	0	0	0	1 33.3%
Executive function deficits	7 41.2%	9 33.3%	3 27.3%	2 10.5%	1 12.5%	1 7.7%	0	1 10%	0	1 14.3%	0	1 33.3%
Reduction of insight	10 58.8%	7 25.9%	3 27.3%	1 5.3%	0	1 7.7%	1 20%	0	1 33.3%	1 14.3%	0	1 33.3%
Language deficits	7 41.2%	17 63%	3 27.3%	5 26.3%	3 37.5%	4 30.8%	1 20%	2 20%	2 66.7%	3 42.8%	2 66.7%	2 66.7%
Praxis deficits	5 29.4%	7 25.9%	4 36.4%	2 10.5%	2 25%	5 38.5%	1 20%	2 20%	1 33.3%	2 28.6%	1 33.3%	1 33.3%

Supplementary Table 3. Behavioral features reported at geriatric follow-up visits.

	T12		T24		T36		T48		T60		T72>	
	CM N 17	CA N 27	CM N 11	CA N 19	CM N 8	CA N 13	CM N 5	CA N10	CM N 3	CA N 7	CM N 3	CA N 3
Misidentification	4 23.5%	2 7.4%	3 27.3%	2 10.5%	2 25%	2 15.4%	1 20%	2 20%	2 66.7%	0	2 66.7%	1 33.3%
Delusion not-misidentification	7 41.2%	7 25.9%	5 45.4%	7 36.8%	0	3 23.1%	2 40%	2 20%	0	1 14.3%	1 33.3%	1 33.3%
Hallucination	7 41.2%	3 11.1%	3 27.3%	3 15.8%	3 37.5%	1 7.7%	2 40%	3 30%	1 33.3%	1 14.3%	1 33.3%	1 33.3%
Apathy	8 47.1%	9 33.3%	4 36.4%	2 10.5%	1 12.5%	1 7.7%	0	1 10%	1 33.3%	0	1 33.3%	0
Abulia	1 5.9%	5 18.5%	2 18.2%	1 5.3%	0	0	1 20%	0	0	0	2 66.7%	0
Irritability	8 47.1%	14 51.8%	5 45.4%	9 47.4%	2 25%	4 30.8%	1 20%	4 40%	2 66.7%	1 14.3%	0	1 33.3%
Aggression	6 35.3%	8 29.6%	5 45.4%	6 31.6%	2 25%	0	2 40%	3 30%	0	2 28.6%	1 33.3%	1 33.3%
Social disinhibition	4 23.5%	0	2 18.2%	0	0	0	0	0	1 33.3%	0	0	0
Impulse control disorder	0	1 3.7%	0	0	0	0	0	0	1 33.3%	0	0	0
Obsession-compulsion	1 5.9%	1 3.7%	0	0	0	0	0	0	0	0	0	0
Hyperactivity	5 29.4%	7 25.9%	5 45.4%	5 26.3%	3 37.5%	3 23.1%	3 60%	3 30%	2 66.7%	1 14.3%	3 100%	1 33.3%
Wandering	3 17.6%	3 11.1%	0	2 10.5%	1 12.5%	1 7.7%	1 20%	2 20%	2 66.7%	2 28.6%	2 66.7%	2 66.7%
Purposeless activity	4 23.5%	8 29.6%	3 27.3%	9 47.4%	1 12.5%	3 23.1%	1 20%	2 20%	1 33.3%	3 42.8%	1 33.3%	1 33.3%
Hyperphagia	3 17.6%	3 11.1%	2 18.2%	0	3 37.5%	0	3 60%	0	1 33.3%	0	1 33.3%	1 33.3%
Euphory/fatuity	1 5.9%	1 3.7%	0	0	0	0	0	0	0	0	0	0
Insomnia	7 41.2%	10 37%	4 36.4%	6 1.6%	2 25%	1 7.7%	2 40%	2 20%	2 66.7%	2 28.6%	3 100%	2 66.7%
Hypersomnia	2 11.8%	5 18.5%	4 36.4%	2 10.5%	2 25%	0	2 40%	1 10%	1 33.3%	1 14.3%	0	2 66.7%
REM behavior disorder (RBD)	3 17.6%	1 3.7%	1 9.1%	2 10.5%	0	1 7.7%	0	0	0	0	0	0
Confusional arousal	2 11.8%	0	0	0	1 12.5%	0	1 20%	1 10%	0	0	0	0
Lability	2 11.8%	4 14.8%	2 18.2%	1 5.3%	0	1 7.7%	0	2 20%	0	1 14.3%	0	1 33.3%
Anxiety	6 35.3%	13 48.1%	4 36.4%	4 21.1%	1 12.5%	1 7.7%	1 20%	1 10%	1 33.3%	1 14.3%	1 33.3%	1 33.3%
Depression	9 52.9%	17 63%	6 54.5%	6 31.6%	2 25%	2 15.4%	2 40%	3 30%	1 33.3%	2 28.6%	0	1 33.3%

Supplementary Table 4. Informant reports about cognitive and behavioral status collected at baseline (T0) (Statistically significant differences are in bold).

	HC N = 40 count	CM-AD N = 17 count	CA-AD N = 30 count	HC %	CM-AD %	CA-AD %	HC versus CM-AD	HC versus CA-AD	CM-AD versus CA-AD
Cognitive features									
Recent memory deficits	23	16	28	57.5	94.1	93.3	**p=0.007**	**p=0.001**	p=1.000*
Past memory deficits	2	3	7	5	17.6	23.3	p=0.138*	p=0.032*	p=0.727*
Prospective memory deficits	2	1	2	5	5.9	6.7	p=0.151*	p=1.000*	p=0.336*
Confabulation	0	7	0	0	41.2	0.0	**p<0.0001***	nv	**p<0.0001***
Temporal disorientation	0	6	2	0	35.3	6.7	**p<0.0001***	p=0.180*	p=0.019
Topographical disorientation	2	7	7	5	41.2	23.3	**p=0.002***	p=0.032*	p=0.199
Attention deficits	4	9	17	10	52.9	56.7	**p=0.001***	**p<0.0001**	p=0.805
Executive functions deficits	6	11	11	15	64.7	36.7	**p<0.0001**	p=0.036	p=0.064
Reduction of insight	1	8	6	2.5	47.1	20.0	**p<0.0001***	p=0.037*	p=0.051
Language deficits	13	4	13	32.5	23.5	43.3	p=0.070	p=0.353	p=0.175
Praxis deficits	0	2	0	0	11.8	0.0	p=0.085*	nv	p=0.126*
Behavioral features									
Personality changes	0	0	0	0	0.0	0.0	nv	nv	nv
Misidentification	0	4	0	0	23.5	0.0	**p=0.006***	nv	**p=0.013***
Delusion (not-misidentification)	0	7	1	0	41.2	3.3	**p<0.0001***	p=0.429*	**p=0.002***
Hallucination	0	3	2	0	17.6	6.7	p=0.023*	p=0.180*	p=0.336*
Apathy	2	7	6	5	41.2	20.0	**p=0.002***	p=0.066*	p=0.176*
Abulia	0	1	2	0	5.9	6.7	p=0.298*	p=0.180*	p=1.000*
Irritability	0	4	7	0	23.5	23.3	**p=0.006***	**p=0.002***	p=1.000*
Aggression	1	6	4	2.5	35.3	13.3	**p=0.002***	p=0.157*	p=0.136*
Social disinhibition	1	3	0	2.5	17.6	0.0	p=0.075*	p=1.000*	p=0.042*
Impulse control disorder	0	0	0	0	0.0	0.0	nv	nv	nv
Obsession- Compulsion	0	1	0	0	5.9	0.0	p=0.298*	nv	p=0.362*
Hyperactivity (psychomotor agitation)	1	1	0	2.5	5.9	0.0	p=0-511*	p=1.000*	p=0.362*
Wandering	0	0	0	0	0.0	0.0	nv	nv	nv

Purposeless activity	0	0	0	0	0.0	0.0	nv	nv	nv
Hyperfagia	0	0	0	0	0.0	0.0	nv	nv	nv
Euphory/Fatuity	0	2	0	0	11.8	0.0	p=0.085*	nv	p=0.126*
Insomnia	4	3	4	10	17.6	13.3	p=0.415*	p=0.717*	p=0.692*
Hypersomnia	0	2	3	0	11.8	10.0	p=0.085*	p=0.074*	p=1.000*
Rem Behavior Disorder (RBD)	0	2	0	0	11.8	0.0	p=0.085*	nv	p=0.126*
Confusional arousal	0	0	0	0	0.0	0.0	nv	nv	nv
Lability	0	2	2	0	11.8	6.7	p=0.085*	p=0.180*	p=0,613*
Anxiety	12	6	10	30	35.3	33.3	p=0.694	p=0.766	p=0.892
Depression	10	3	12	25	17.6	40.0	p=0.734*	p=0.181	p=0.114

nv, no variability in the data.
*Fisher's exact test.

Supplementary Table 5. Signs of cognitive dysfunction emerged at the standard observational neuropsychological examination (NPE) performed at baseline (T0). (Statistically significant comparisons are in bold).

	HC N = 40 Count	CM-AD N = 17 Count	CA-AD N = 30 Count	HC %	CM-AD %	CA-AD %	HC versus CM-AD *p*	HC versus CA-AD *p*	CM-AD versus CA-AD *p*
Orientation									
Temporal disorientation	4	15	16	10.0	88.2	53.3	**p<0.0001**	**p<0.0001**	**p=0.015**
Spatial disorientation	1	3	7	2.5	17.6	23.3	p=0.075*	**p=0.017***	p=0.727*
Personal disorientation	0	1	0	0.0	5.9	0.0	p=0.298*	nv	p=1.000*
Family disorientation	0	1	1	0.0	5.9	3.3	p=0.298*	p=0.429*	p=1.000*
Situational disorientation	5	5	8	12.5	29.4	26.7	p=0.145*	p=0.131	p=1.000*
Psychomotor Slowness	4	10	18	10	58.8	60.0	**p<0.0001**	**p<0.0001**	p=0.937
Attention									
Selective Attention deficits	0	5	4	0	29.4	13.3	**p=0.001***	p=0.030*	p=0.252*
Vigilance-Sustained Attention deficits	3	5	4	7.5	29.4	13.3	p=0.043*	p=0.452*	p=0.252*
Prefrontal Functions									
Dys-Executive syndrome	1	11	21	2.5	64.7	70.0	**p<0.0001**	**p<0.0001**	p=0.708
Reduction of insight	1	12	12	2.5	70.6	40.0	**p<0.0001**	**p<0.0001**	p=0.044
Adynamic syndrome	1	1	1	2.5	5.9	3.3	p=0.511*	p=1.000*	p=1.000*
Hyperactive-Dishinibition syndrome	2	7	7	5	41.2	23.3	**p=0.004***	p=0.084*	p=0.199
Obsessive-Compulsive syndrome	0	0	0	0	0.0	0.0	nv	nv	nv
Memory									
Anterograde Amnesia	0	9	7	0	52.9	23.3	**p<0.0001**	**p=0.002***	p=0.040
Retrograde Amnesia	0	11	11	0	64.7	36.7	**p<0.0001**	**p<0.0001**	p=0.064
Confabulation at memory testing	0	10	0	0	58.8	0.0	**p<0.0001**	nv	**p<0.0001**
Speech and Language									
Dysfluency	0	0	5	0	0.0	16.7	nv	**p=0.012***	p=0.143
Phonemic deficits	0	0	1	0	0.0	3.3	nv	p=0.429*	p=1.000*
Syntactic deficits	0	1	1	0	5.9	3.3	p=0.298*	p=0.429*	p=1.000*

Lexical-Semantic deficits	2	4	13	5	23.5	43.3	p=0.058*	**p<0.0001**	p=0.175
Comprehension deficits	0	0	3	0	0.0	10.0	nv	p=0.074*	p=0.292*
Spatial Abilities									
Topographical disorientation	0	0	0	0	0.0	0.0	nv	nv	nv
Extra-Personal neglect	0	0	2	0	0.0	6.7	nv	p=0.180*	p=0.528*
Personal neglect	0	0	0	0	0.0	0.0	nv	nv	nv
Motor neglect	0	0	0	0	0.0	0.0	nv	nv	nv

nv, no variability in the data.
*Fisher's exact test.

Supplementary Table 6. Follow-up overview. Geriatric follow-up visits of the AD patients with the CM-and CA-phenotype.

Pt.	Tot. follow-ups	Date of first visit (T0) (baseline)	Date of last follow-up	Follow-up duration (mo)	MMSE at T0	MMSE at last follow-up (date)*	Age at T0	Age at last follow-up	Date of start anti-dementia treatment	Anti-dementia drug (last)
CM										
1	10	14/02/2011	15/02/2017	72	25	14 (27/04/2015)	79	85	07/10/2011	rivastigmine
2	16	27/09/2010	30/01/2019	100	25	10 (23/04/2015)	69	78	01/09/2011	rivastigmine
3	9	12/09/2011	21/01/2015	40	25	6 (21/11/2014)	76	79	14/12/2011	rivastigmine
4	3	06/09/2011	27/05/2013	21	22	22	81	82	01/11/2011	rivastigmine
5	17	13/02/2012	11/01/2019	83	24	13 (16/11/2017)	80	87	07/03/2012	rivastigmine
6	11	09/01/2012	16/05/2016	52	23	12 (07/09/2015)	77	81	10/02/2012	rivastigmine
7	7	27/05/2013	12/01/2018	56	22	21 (09/09/2015)	79	83	16/09/2013	memantine
8	12	16/11/2015	27/06/2019	43	29	28 (09/11/2018)	68	72	04/09/2017	rivastigmine
9	3	17/06/2014	27/07/2015	13	24	7 (25/02/2015)	78	79	01/10/2011	donepezil
10	5	14/09/2015	12/07/2017	22	24	19	78	80	19/01/2016	rivastigmine
11	7	16/06/2015	30/07/2018	37	27	26 (13/07/2018)	73	76	7/11/2017	donepezil
12	7	23/05/2016	15/03/2019	34	29	17	78	81	13/12/2017	rivastigmine
13	3	08/03/2016	08/02/2019	35	27	18	68	71	06/04/2018	rivastigmine
14	2	04/03/2015	10/06/2016	15	25	nr	73	74	na	-
15	4	05/07/2016	16/02/2018	19	23	20 (20/10/2017)	76	78	na	-
16	8	21/04/2017	13/11/2019	31	19	4	72	74	05/08/2017	rivastigmine/memantine
17	7	19/12/2017	02/09/2019	21	27	18	84	85	20/04/2018	rivastigmine
CA										
1	12	07/02/2011	19/12/2017	82	21	9	75	82	01/06/2011	rivastigmine
2§	13	19/10/2009	20/06/2019	116	25	12	69	79	03/12/2009	rivastigmine
3§	11	01/09/2008	17/03/2015	78	26	6 (06/02/2012)	74	81	07/07/2010	rivastigmine
4§	11	17/01/2012	20/12/2016	59	19	10	79	84	01/04/2012	rivastigmine
5	7	25/01/2010	03/02/2015	60	24	8	75	80	01/02/2010	rivastigmine
6§	14	04/02/2013	06/04/2018	62	28	8 (01/12/2016)	75	80	14/09/2015	rivastigmine
7§	4	20/03/2012	14/10/2013	19	24	24	82	83	March 2012	rivastigmine
8	6	04/09/2012	24/01/2017	52	22	13	84	88	na	-
9§	14	21/11/2010	22/12/2015	61	23	2 (11/02/2015)	72	77	01/04/2011	rivastigmine
10	7	07/05/2013	05/06/2015	25	21	8	77	79	May 2013	rivastigmine
11	8	04/06/2013	14/12/2015	30	21	12	75	77	01/11/2013	rivastigmine
12§	10	10/06/2013	08/02/2016	32	27	24	80	82	10/06/2014	rivastigmine

13[§]	5	14/05/2013	10/04/2014	11	25	12	80	81	July 2013	rivastigmine
14	2	29/04/2014	12/12/2016	32	26	13	69	72	na	-
15	3	30/07/2013	03/04/2014	8	27	24	76	77	01/11/2013	rivastigmine
16	3	13/01/2014	27/04/2015	15	22	26 (26/01/2015)	81	83	21/03/14	rivastigmine
17	5	14/10/2013	03/04/2019	66	27	23	72	78	16/12/2013	donepezil
18	9	13/06/2013	10/01/2018	55	27	19	80	85	2013	memantine
19[§]	11	10/12/2013	23/06/2017	42	23	7 (08/09/2015)	78	82	03/03/2014	rivastigmine
20	6	25/03/2014	27/05/2015	14	24	22	79	80	20/06/2014	donepezil
21	2	06/10/2015	27/01/2016	3	19	23 (19/10/2015)	75	75	26/01/2016	rivastigmine
22	6	27/01/2015	14/03/2018	38	19	13	78	81	May 2016	rivastigmine
23	4	26/02/2015	04/01/2018	34	27	(MoCA:14)	68	71	27/07/2015	rivastigmine
24	7	30/10/2015	01/03/2018	28	27	24	77	79	na	-
25	7	16/02/2016	30/04/2019	38	28	26	71	74	12/12/2017	rivastigmine
26	4	27/06/2016	21/02/2018	20	23	25	76	77	19/04/2017	rivastigmine
27	6	25/11/2016	12/10/2018	23	27	29	79	80	na	-
28	6	04/09/2017	05/06/2019	21	28	27	78	79	na	-
29	5	27/02/2018	22/02/2019	12	24	20	77	78	18/07/2018	rivastigmine

nr, not reported; na, not administered; MoCA, Montreal Cognitive Assessment; rivastig, rivastigmine; mema, memantine.

*When MMSE was missing or not administrable at the last follow-up, we reported the score of the last MMSE available and the date of administration. [§]Patients with classical amnesic phenotype who developed some confabulation and/or misidentification during follow up (positive CA-AD).

Supplementary Table 7. Follow-up analysis. Comparisons between AD patients with the CM- and CA-phenotype on some variables at the geriatric follow-up study, as well as between patients with the CA-phenotype who developed confabulation and/or misidentification during follow-up (CA-positive), and patients with the CA-phenotype who never developed confabulation and/or misidentification during follow up (CA-negative). (Statistically significant differences are in bold).

	CM N = 17	CA N = 29	*p*	CA positive N = 9	CA negative N = 20	*p*
Number of follow-ups visits	7.7 ±4.4	7.2 ±3.5	p=0.654	10.3 ±3.6	5.7 ±2.4	**p<0.001**
Follow-up duration (mo)	40.8 ±24.8	39.2 ±26.1	p=0.834	53.3 ±32.1	32.8 ±20.9	**p=0.048**
MMSE at T0	24.7 ±2.6	24.3 ±2.9	p=0.615	24.4 ±2.6	24.2 ±3.0	p=0.837
MMSE at last follow-up	15.9 ±6.9	16.7 ±7.9	p=0.735	11.7 ±7.6	19.1 ±7.0	**p=0.017**
Age at T0	75.8 ±4.6	76.2 ±3.9	p=0.748	76.5 ±4.3	76.1 ±3.9	p=0.781
Age at last follow-up	79.1 ±4.6	79.4 ±3.6	p=0.791	81.0 ±2.1	78.7 ±4.1	p=0.132

Supplementary Table 8. Neuropsychological tests performed at the time of the first multidimensional (baseline) assessment. (Statistically significant differences are in bold).

	HC N = 40 Median (IQR) [n° exams]	CM-AD N = 16* Median (IQR) [n° exams]	CA-AD N = 30 Median (IQR) [n° exams]	HC versus CM-AD	HC versus CA-AD	CM-AD versus CA-AD
Attentive matrices	52.5 (22) [40]	41 (22) [13]	36.5 (13.2) [26]	**p=0.001**	**p<0.0001**	p=0.846
Bells test	35 (4) [40]	32 (5) [13]	32 (5) [24]	**p=0.004**	**p=0.001**	p=0.791
Prose memory	12.9 (8.5) [40]	5.3 (8.4) [16]	4 (7) [29]	**p<0.0001**	**p<0.0001**	p=0.631
ROCF delayed recall	17.2 (26) [40]	5 (7.1) [14]	4 (7.7) [25]	**p<0.0001**	**p<0.0001**	p=0.963
Digit span forward	5 (5) [40]	5 (0) [13]	5 (1) [27]	p=0.190	p=0.047	p=0.602
Digit span backward	4 (2) [40]	3 (0.5) [13]	3 (2) [27]	p=0.019	**p=0.001**	p=0.693
TMT A	50 (67) [40]	63.5 (138.2) [16]	84 (62) [28]	p=0.032	**p<0.0001**	p=0.550
TMT B	113.5 (226) [40]	420 (206.5) [16]	353 (129) [27]	**p<0.0001**	**p<0.0001**	p=0.723
CPM	28 (16) [40]	21 (15.7) [16]	17 (8.5) [30]	**p<0.0001**	**p<0.0001**	p=0.484
Phonological fluency	32 (39) [40]	22 (12.5) [16]	22 (13.5) [30]	**p=0.001**	**p<0.0001**	p=0.981
Picture naming	74.5 (16) [40]	66 (11.5) [16]	64 (13) [29]	**p<0.0001**	**p<0.0001**	p=0.330
IMAT Dx	72 (3) [40]	70 (4.7) [16]	70 (4) [30]	**p=0.001**	**p=0.004**	p=0.532
IMAT Sx	72 (5) [40]	69.5 (4.2) [16]	71 (8) [29]	**p=0.008**	p=0.066	p=0.581
Figures copy	13 (4) [40]	12 (3.7) [16]	11 (3.5) [30]	**p=0.013**	**p<0.0001**	p=0.666
ROCF Copy	34 (8) [40]	30.5 (15) [16]	25 (17) [27]	**p=0.001**	**p<0.0001**	p=0.535

ROCF, Rey-Osterrieth complex figure; TMT, trail making test; CPM, Raven's colored progressive matrices; IMAT, ideomotor apraxia test.
*Data about cognitive testing of one patient with CM-phenotype (Case#16) were not available.