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Review

Clinical Heterogeneity in Alzheimer's Disease: A Possible New Amnesic Phenotype

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Abstract. We rediscovered a phenotype of AD known in the early 1900s as presbyophrenia, but then forgotten, and renamed as confabulation-misidentification phenotype. The phenotype includes diencephalic amnesia whose prototype is Korsakoff syndrome. The main features are anterograde and retrograde amnesia with marked disorientation and confabulation, executive impairments, reduced insight and attention deficits, misidentification, minor hallucination and other delusions, behavioral disturbances, and early anxiety. In this article, we summarize what we have discovered about the new phenotype and what is still missing to confirm this diencephalic variant of AD.

Keywords: Alzheimer's disease, confabulation, diencephalic amnesia, Korsakoff syndrome, misidentification, presbyophrenia

INTRODUCTION

In two previous articles, we presented a single case [1] and a cohort study of seventeen patients [2] diagnosed with biomarkers-confirmed AD who had the same novel clinical phenotype. Actually, a very similar dementia phenotype was already known in the early 20th century and was named presbyophrenia [3–5], but it began to go unmentioned from the 1920s onward [3, 4]. The main features of presbyophrenia were memory deficits, confabulation and disorientation associated with delusional misidentification, hyperactivity, euphoria or irritability, frank mania in some cases, and preserved social conducts [3–5]. Therefore, it seems that we have rediscovered a presbyophrenic-like phenotype, that we called confabulation-misidentification phenotype (CM-phenotype) according to its two most salient features [2].

In this article we summarize the main findings collected about this possible new presentation of AD (CM-AD). The aim is twofold: 1) to provide clinicians with a description of the CM-phenotype so as to timely guide them in further effective case identification and differential diagnosis; 2) to highlight what

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is still missing to substantiate the concept of a new diencephalic variant of AD.

SYNDROME

The CM-phenotype is a primarily amnesic syndrome, but the features of amnesia are different from classical amnesia in ADs (CA-AD) [2]. CM-ADs also invariably present at onset with recent memory disturbances, as in the CA-phenotype, but recent memory difficulties are immediately associated with confabulations, retrograde memory difficulties, and finally with marked disorientation especially temporal in early stages, and also topographical in more later stages. In particular, confabulation is one of the two core clinical features of the phenotype together with misidentification. Frequently, it occurs as spontaneous confabulations reported by relatives in addition to provoked confabulations that emerge during testing. In some patients, spontaneous confabulation is even the first symptom of the whole clinical picture [1]. The cognitive picture at early stages is also characterized by impairment of executive functions, reduction of insight, and attention deficits, in some cases associated with mild psychomotor slowness and fluctuations. Language and praxis impairments are also present, especially at intermediate stages. Conversely, visuoperceptive and visuospatial-visuoconstructive deficits are not present in the early stages and are not salient features in more advanced stages.

Behavioral disturbances mostly occur at mild-to-moderate and moderate dementia stages in CM-AD, however, some of them start early in some patients [1, 2]. More in detail, we described a main cluster of psychotic features [2], mostly characterized by misidentification. Misidentification is less frequent than confabulation and is common especially from intermediate stages on. However, it could emerge early in some patients. Moreover, it has been identified as the first symptom in one patient [2]. The cluster is also characterized by other delusions and hallucinations, that are common at mild-to-moderate stages. However, delusions are unstructured, and hallucinations are always sporadic, usually not severe, and sometimes comparable to illusions or misinterpretations. Finally, feeling of presence is rare [2].

A second noteworthy cluster of behavioral disorders includes some features of hyperactivity-disinhibition syndrome. Considering a progression from early to more advanced stages, the cluster is characterized by mild logorrhea and verbal distractibility, mild euphoria/fatuity and social disinhibition, irritability and aggression, agitation, and finally hyperphagia [2].

The CM-phenotype also exhibits relevant features of adynamic syndrome, particularly apathy. In addition, sleep disorders, including nocturnal hyperactivity and wandering, are present from the mild-to-moderate stages. Finally, both anxiety and depression are common from the mild-to-moderate stages of dementia. However, anxiety seems more frequent than depression in the early stages [2]. In Table 1 we summarize the main clinical features of the CM-phenotype.

NEUROANATOMICAL SUBSTRATE

In a previous study, we found that AD patients with the CM-phenotype show anterior temporal, fronto-insular, and temporomesial atrophy in the early stages [2]. In addition, our preliminary data suggest that CM-ADs may show greater atrophy in some right anterior areas (e.g., fronto-insular) than CA-ADs [2]. This finding is in line with previous studies of neurological patients with delusional misidentification syndromes who had predominantly right brain damage [6], and with studies of AD patients with delusions who presented right prefrontal cortex hypometabolism [7]. Our previous studies also suggest that CM-ADs have less atrophy in some posterior areas (i.e., parietal, dorso-parietal, and precuneus) compared with CA-ADs, coherently with the absence of early major visuoperceptive, visuospatial, and apraxic deficits [2]. At FDG-PET scan CM-ADs show reduced cortical temporo-parietal, focal temporal, and frequently temporo-mesial glucose hypometabolism [2]. In addition, CM-ADs show more frequently symmetrical hypometabolism than CA-ADs, whereas CA-ADs often show asymmetric temporal hypometabolism with greater left than right. This finding is in line with the higher frequency of language deficits and depression in CA-AD than in CM-AD in the early stages [2]. Unfortunately, our FDG-PET study did not confirm asymmetrical right-sided involvement in some anterior regions as suggested by the atrophy study [2]. Regarding cerebral vascularity, CM-ADs show mild vascular burden both periventricular (PV) and considering white matter hyperintensities (WMH) similar to those of CA-AD [2].

Table 1
Cognitive and behavioral features of the possible CM-phenotype of AD

Feature	Stage	Some characteristics
Confabulation	Early* (it can be the first symptom in some patients)	Both spontaneous and provoked confabulation
Misidentification	Early OR Intermediate§ (It can be the first symptom in some patients)	Misidentification often included multiple concurrent manifestations in the same patient (e.g.: persons, places, TV celebrities, animals).
Anterograde amnesia	Early	
Retrograde amnesia	Early	More confusions, errors in dating and transpositions than lacunas
Temporal disorientation	Early	
Topographical disorientation	Early OR Intermediate	
Executive impairment	Early	
Reduction of insight	Early	
Attention deficits	Early	
Other delusions	Early OR intermediate	Themes were overall theft, persecution and jealousy.
Not recurrent hallucination	Early OR intermediate	– The content is generally not familiar persons (e.g.: a girl, some children, unspecified neighbors) and small animals. – Both visual and auditory (e.g.: voices of persons, rumors outside the house door, the telephone ring). – It seemed occur equally during the night and day.
Hyperactivity	Early OR intermediate	
Hyperfagia	Intermediate and later	
Irritability/aggression	Early OR intermediate	
Logorrhea/verbal distractibility	Early	
Euphoria/fatuity (mild)	Early	
Social disinhition (mild)	Early	
Apathy	Early OR intermediate	
Nocturnal hyperactivity/wandering	Early OR intermediate	
Anxiety	Early	
Depression	Early OR intermediate	

*Early: MCI (CDR = 0.5) and/or mild dementia (CDR = 1). §Intermediate: mild-to-moderate (CDR between 1-2) and/or moderate dementia (CDR = 2). Later stages: >moderate dementia (CDR > 2).

ETIOLOGY

Patients with the CM-phenotype were frequently found to carry *APOE* ε4, most of them ε3/ε4 [2]. Moreover, the percentage of patients carrying ε4 was higher in the group of CM-ADs than in the CA-ADs [2]. In addition, all patients had a picture of amyloid-β (Aβ), tau and phospho-tau concentrations in CSF compatible with a diagnosis of AD [1, 2]. Furthermore, no difference in biomarkers was found between patients with CM- and CA-AD [2]. In Table 2 we report the main differences between the CA- and CM-phenotype found in our previous studies [1, 2]. Table 3 shows the syndromes of some degenerative and nondegenerative diseases that we believe may overlap with the CM-phenotype when differential diagnosis is performed.

DISCUSSION

Is the CM-phenotype really a syndrome?

In two previous articles, we described a small group of patients diagnosed with biomarker-supported AD who had a common set of cognitive and behavioral features that we termed the CM-phenotype [1, 2]. These data are not sufficient to determine whether the CM-phenotype should be considered a variant of AD, rather than simply a description of a set of patients with AD who differ

Table 2
Main differences on cognitive, behavioral, APOE genotype and brain imaging emerged between confabulation-misidentification (CM)- and classical amnesic (CA)-phenotype of AD in the early stages (i.e., MCI and mild dementia)

	Cognitive features	Behavioral features	Other features
CM>CA	spontaneous confabulation*	behavioral disturbances total (NPI)*	Total APOE ε4 carriers
	provoked confabulation*	misidentification*	more right frontoinsular atrophy at MRI than HCs*
	retrograde memory deficits	other delusion*	bilateral [18F]-FDG-PET hypometabolism
	temporal disorientation*	hallucination*	medial temporal [18F]-FDG-PET hypometabolism
	topographical disorientation executive function deficits attention deficits reduction of insight*	aggression social disinhibition* hyperactive-disinhibition signs logorrhea* apathy	
CM=CA	insidious onset progressive course rate of worsening amnesia as first symptom time from onset to first visit (about 30 months) MMSE score cognitive tests scores		cardiovascular risk factors family history of dementia age of onset (72-73 years) M/F percentage degree of education manual dominance normal NE ADL score IADL score
CA>CM	language deficits	depression	APOE ε3/ε3 carriers
	visuoconstructional impairment (Rey-Osterrieth figure copy)		more right parietal, bilateral dorsal parietal and bilateral precuneus atrophy at MRI than HC*
			asymmetric left > right [18F]-FDG-PET hypometabolism

*Indicates statistically significant differences. Abbreviations: NPI = Neuropsychiatric Inventory; APOE = apolipoprotein-E; HC = healthy controls; MRI = magnetic resonance imaging; [18F]-FDG-PET=18F-fluorodeoxyglucose-positron emission tomography; MMSE = mini-mental-state-examination; NE = neurological examination; ADL = activities of daily living; IADL = instrumental activities of daily living.

slightly from the typical phenotype. There are at least three reasons for this null result.

First, to support that the CM-phenotype can be described as a syndrome it is necessary that symptoms occur in association, as we described in previous works [1, 2]. Coherently, some studies found that confabulations in AD are often associated with delusions [8, 9] or delusions and aggression [10], consistent with the symptoms' cluster of the CM phenotype. Moreover, some studies on patients with AD who show psychotic symptoms, by applying factor and cluster analyses to behavioral data, identified a misidentification subtype that is well distinguished from a paranoid subtype and a nonpsychotic subtype [11, 12]. The misidentification subtype is characterized by misidentifications, misidentification delusions, and hallucinations exactly as in the case of CM-phenotype [11, 12]. Finally, the association of the CM-phenotype symptoms was well known in the early 1900s as presbyophrenia [3–5].

Second, to support the existence of the CM-phenotype it is necessary that it is clearly distinguished from the classical phenotype and does not show only small variations from it. In this regard, the most salient symptoms of the CM-phenotype, i.e., confabulation and misidentification, are also considered relatively common in typical AD. This overlap may undermine the existence of the CM-phenotype as a distinct syndrome. However, especially considering confabulation there are important differences in the manifestation of this symptom between CM- and CA-phenotype, concerning the time of onset, the type of confabulation, and their content. Indeed, confabulations in classical AD become more frequent with the progression of dementia [13], from infrequent at the early stages [13–15] to relatively more frequent at

Table 3
Differential diagnosis. Possible distinguishing features and overlaps of the CM phenotype with other similar syndromes of AD and other neurodegenerative and non-neurodegenerative diseases

	Distinguishing features	Main overlaps with CM-phenotype
Frontal behavioral/dysexecutive variant of AD [71]	– EOAD (especially behavioral variant) – not retrograde amnesia – not disorientation	– executive impairment – reduction of insight – attention deficits – hyperactive– disinhibition syndrome – akinetic-apathetic syndrome
DLB syndrome [72]	– early visuocostrunctional impairment – early visuospatial impairment – extrapyramidal syndrome – REM-behavior-disorders (RBD) – hypersomnia – marked fluctuations – severe neuroleptic sensitivity	– misidentification – confabulation – hallucination – executive impairment – reduction of insight – attention deficits – other delusions
Behavioral variant FTD [73]	– onset before 65 years – not anterograde amnesia – not retrograde amnesia – not disorientation – not hallucination	– executive impairment – reduction of insight – attention deficits – hyperactive-disinhibition syndrome – akinetic-apathetic syndrome
Korsakoff syndrome [28, 29]	-peripheral neuropathy – history of alcoholism – cerebellar symptoms	-anterograde amnesia – retrograde amnesia – disorientation – confabulation – executive impairment – reduction of insight – attention deficits – hyperactive-disinhibition syndrome – akinetic-apathetic syndrome
Hyperactive delirium [74]	-sudden onset – reversible – waxing and waning – alteration in consciousness	-anterograde amnesia – retrograde amnesia – disorientation – confabulation – executive impairment – reduction of insight – attention deficits – misidentification – other delusion– hallucination – hyperactive-disinhibition syndrome
Limbic encephalitis [75, 76]	– subacute onset – seizures – abnormalities on T2-weighted MRI imaging (MTL) – altered consciousness – EEG abnormalities (temporal lobes) – movement disorders – autonomic dysfunctions	– amnesia – executive impairments – attention deficits (confusion) – neuropsychiatric manifestations – behavioral disturbances – affective disorders

Abbreviations: EOAD = early-onset Alzheimer's disease. DLB = dementia with Lewy bodies. FTD = frontotemporal dementia. MTL = medial temporal lobe.

the advanced stages [13, 16, 17]. Furthermore, at the early stages of classical AD confabulations are almost exclusively provoked [18], whereas spontaneous confabulations [18] occur predominantly or exclusively at the advanced stages of the disease [19]. Finally, confabulations at the early stages of classical AD are almost simple intrusions [20] into memory test content, e.g., production of unstudied words in word-list recall, or habits [21], i.e., personal semantic contents recalled in place of forgotten episodic information. By contrast, confabulations in the CM-phenotype are very frequent at the early stages of dementia [2] and in some cases are the first symptom of the whole clinical picture [1]. More importantly, at the early stages of CM-phenotype mainly spontaneous confabulations appear in addition to those provoked on testing [1, 2]. Finally, considering the content of confabulations, it consists of not only habits, but also and especially

misplacements, memory fabrications and confusions [1].

Even when considering misidentifications, we found differences between classical AD and CM-AD [2]. First, our data show that misidentifications regardless of the stage of onset, are more frequent in CM- (59%) [2] than in CA-AD (a median prevalence among different studies of 25.6%) [12, 22–26]. Furthermore, in classical AD, similar to confabulations, misidentifications become increasingly frequent when progressing from early to more advanced stages of dementia [24, 27]. Conversely, misidentification in the CM-phenotype is a frequent symptom already at mild dementia stages (41.2% in our sample) [2] and is also present at the MCI stage (23.5% in our sample) [2]. Finally, in one patient misidentification was the first symptom in the whole clinical picture [2].

In addition, in a previous study in which we compared patients with CM- and CA-phenotypes, we found multiple differences in further cognitive and behavioral aspects (see Table 2), that seemed to be maintained even at follow-up points [2].

Third, to sustain the hypothesis of a new dementia syndrome, it is mandatory to prove that it has an underlying specific neuroanatomical basis. In this regard, presbyophrenia was found to be very similar to Korsakoff syndrome (KS) [3–5]. KS is considered the prototype of diencephalic amnesia and has a precise neuroanatomical correlate that is clearly distinguishable from the hippocampal involvement of classic AD [28, 29]. Hence, the similarity between presbyophrenia and KS suggests that the CM-phenotype has specific anatomical features and is a peculiar presentation of AD.

Next steps to substantiate diencephalic variant of AD

It should be emphasized that we were able to identify the CM-phenotype mainly by adopting a thorough clinical examination developed by our group, by taking a detailed patient's clinical history, and by observing signs and symptoms of cognitive dysfunction during the interview and visit [30, 31]. Conversely, the standard battery of neuropsychological tests was found to be unable to bring out the phenotype. Thus, the observational examination of cognitive and behavioral features seems crucial for early diagnosis of the CM-phenotype. In this regard, the detection of spontaneous confabulations can be difficult, as they are often entirely plausible and not bizarre accounts [1]. Therefore, it is essential that the interview with the relative includes specific questions about confabulations and/or that specific tests are used to induce confabulations in patients [32, 33]. Moreover, the interview with the patient should preliminarily investigate retrograde memory (e.g., questions about medical history, job, family, etc.) to stimulate the appearance of confabulation. In addition, retrograde memory deficits are one of the main features of amnesia in the CM-phenotype. Based on the evidence that in some patients with CM phenotype, spontaneous confabulation preceded the onset of recent memory disorder [1], it is particularly important to investigate the occurrence of confabulation in addition to memory disorder to early detect CM-AD. Interestingly, the finding that confabulations precede amnesia is consistent with the idea that memory must be at least partially unimpaired, and hippocampus preserved for spontaneous confabulations to occur [34, 35]. Moreover, considering the relationship between psychotic symptoms and cholinergic deficits in AD [36–39], the early detection of CM-AD might lead CMs to benefit more significantly than other ADs from early therapy with cholinesterase inhibitors.

The need of deep clinical examination seems crucial not only for early diagnosis of the CM-phenotype in clinic, but also for its study in research. Indeed, both confabulation and misidentification are not frequently assessed in a standardized neuropsychological test battery, which makes it hard to retrospectively identify the CM-phenotype in existing datasets. This, in turn, severely hamper the scientific community to contribute to a conceptualization of this new phenotype.

The call for extensive clinical studies to recognize CM-phenotype is even more urgent considering the fact that in our case series CM-phenotype appears to be much more frequent than the other known variants of AD. Specifically, we retrieved 50 patients with early-stage AD from the registry of AD outpatients with positive biomarkers in the CSF enrolled consecutively over a 10-year interval in our Geriatrics unit [2]. Among them, 30 (60%) had a classical amnesic phenotype, 17 (34%) a CM-phenotype, 1 (2%) a logopenic variant, 1 (2%) a corticobasal syndrome-AD, and 1 (2%) a PCA-syndrome [2]. However, this result should be considered with caution, as the CM-phenotype estimate is probably amplified in our sample. In fact, in our Geriatrics unit we perform few spinal taps due to the advanced age of patients, and

cases with particular symptoms are more likely than classic AD to perform the examination.

Taken together, all these considerations inform us that one of the main goals of future research is to confirm the occurrence of the CM-phenotype in a larger sample of patients. Actually, we found in the scientific literature a recent study that presents patients with AD who show a phenotype very similar to the CM-phenotype, but it is only two cases [40]. Furthermore, since we (re)discovered the CM-phenotype by studying elderly patients in a geriatric setting, the cases we observed were exclusively late-onset AD (LOAD) due to selection bias. Thus, it remains to be evaluated whether the same phenotype also occurs in early-onset AD (EOAD). In addition, our description of the CM phenotype is mainly based on clinical observations collected at the first visit and lacks data from comprehensive longitudinal studies to be confirmed [2].

Regarding the neuroanatomical substrate, we assessed atrophy only by visual rating scales on MRI images [2, 41, 42], while the FDG-PET imaging was performed only on a subset of participants. Thus, a clearer characterization of the neuroanatomical network underlying the syndrome is still lacking. Our preliminary data of possible greater right hemispheric involvement in some anterior brain regions (i.e., frontoinsular), more symmetrical involvement at the temporal level, and less posterior involvement (i.e., dorso-parietal and precuneous) than in CA-AD could open the way for further studies. Moreover, based on previous evidence [7, 12, 22, 28, 29, 34, 43], we speculated that a limbic-diencephalic network (involving thalamic nuclei, mammillary bodies, medial and posterior orbitofrontal cortex, hippocampus, parahippocampal gyrus, transentorhinal cortex, and amygdala) might be the neuroanatomical substrate of the CM phenotype [2]. Interestingly, this hypothesized network is consistent with a well-known model of the limbic system [44].

Our study of biomarkers in CSF strongly supported an etiologic diagnosis of AD in patients presenting with the CM-phenotype [2]. However, considering that the CM-phenotype resembles DLB syndrome, it might be crucial to study the possible association of Lewy bodies pathology with AD in the CM phenotype. Furthermore, given the known affinity of TPD-43 pathology for limbic structures (amygdala, hippocampus, middle frontal gyrus) in the elderly (limbic-predominant age-related TDP-43 encephalopathy, LATE) [45] and the probable limbic involvement in the CM-phenotype, it seems noteworthy to study the possible contribution of TDP-43 pathology to CM-AD. In addition, given the known propensity of APOE $\varepsilon 4$ for medial temporal lobe damage [46], it seems important to replicate our preliminary data of a higher frequency of the $\varepsilon 4$ genotype in CM- than in CA-ADs. This finding is in line with the lesser posterior atrophy and the more frequent and symmetrical temporo-mesial hypometabolism found in CM-ADs [2]. Moreover, it is consistent with previous studies that found a correlation between the number of *APOE* $\varepsilon 4$ alleles and the occurrence of delusions in AD [47–51]. Establishing the higher frequency of the $\varepsilon 4$ genotype in CM-ADs might be crucial also because the use of new anti-Aβ antibody drugs for AD might result in a greater danger for cerebrovascular adverse events (ARIAs) in CM-AD [52]. In this case, this would be another important reason to make an early diagnosis of CM-AD. Finally, the probable involvement of the limbic system in the CM-phenotype suggests the importance of studying the possible association especially with the neuropathological substrate of AD known as limbic predominant [53–55].

Given the close overlap between misidentification subtype [11, 56, 57] and features of CM-phenotype, a further important question for future research is whether CM-phenotype and misidentification subtype are actually the same syndrome. Some data seem to support this interpretation. Regarding symptoms, consistent with the CM-phenotype, a study on misidentification subtype pointed out that patients showed a memory disorder from the onset [56]. In another study, the authors reported that misidentifications were associated with content-related confabulations and delusional memories and that this association entailed an underlying failure of episodic retrograde memory (i.e., memory for past personal events) [58].

Regarding anatomical aspects, our studies on CM-phenotype [1, 2] did not allow a valid comparison with studies on misidentification subtype [12] as we only did a preliminary assessment of atrophy using visual rating scales in a small subgroup of participants [2]. However, the marked mesial and anterior temporal involvement in the CM-phenotype revealed by imaging data [2] seems to coincide with the involvement of limbic and paralimbic regions (especially the hippocampus and its projections such as the parahippocampal gyrus and the transentorhinal cortex) found in the misidentification subtype [12, 58–65]. Furthermore, our studies [2] found preliminary hints of possible greater right hemispheric involvement

in some regions (i.e., right fronto-insular). These findings are in line with data about preferential right hemispheric involvement in the misidentification subtype [12, 59, 61, 64, 66–69]. Finally, despite our imaging studies [2] did not show marked anterior involvement as found in studies on misidentification subtype [12, 59–62, 65, 66, 69], multiple signs from clinical examination of the CM-phenotype (i.e., confabulations, logorrhea, euphoria/fatuity, mild social dishnibition, reduction of insight, executive deficits, attention deficits,) are consistent with frontal and fronto-parietal involvement [1, 2].

Despite the commonalities, misidentification subtype and CM-phenotype differ according to some aspects. In particular, patients with misidentification subtype, but not patients with the CM-phenotype (see Table 2) [2], show more severe global cognitive impairment and also faster rate of cognitive decline than the other subtypes [12, 56, 57, 65, 70]. Furthermore, studies on the misidentification subtype show deficits in visuoperceptive and visuospatial tasks [56, 62, 63, 65] and signs of involvement of right posterior temporo-occipital regions corresponding to the ventral visual pathway [62, 65, 69]. By contrast, in our CM-phenotype studies [2], compared to data on CA-ADs, there is no evidence neither of preminent visuoperceptive and visuospatial disorders, nor signs of involvement of posterior brain regions (see Table 2). However, results on differences between CM-phenotype and misidentification subtype should be considered with caution. Indeed, despite few exceptions [58, 70], most studies on misidentification subtype include patients at more advanced stages of dementia compared to CM-phenotype patients we included in our studies [1, 2].

An intriguing possibility is that the CM-phenotype and the misidentification subtype are the same syndrome but studied at different times in the progression of dementia. Thus, differences in some aspects between the two phenotypes could be explained by the changes that a single dementia syndrome undergoes over time during its evolution. Following this hypothesis, we can speculate that an initial limbic-paralimbic and only partially frontal, or thalamus-frontal involvement, associated with the appearance of amnesia and spontaneous confabulations, is followed by a more pronounced frontal and right-sided involvement, associated with the appearance of executive deficits and delusions including misidentifications. Then, at later stages of dementia progression, consistent with connections between frontal and parietal regions, and between hippocampus/parahippocampus and the ventral visual pathway [62], there could be the involvement of more posterior, fronto-parietal or fronto-parieto-occipital, and temporal-occipital regions, associated with the appearance of visuospatial and visuoperceptive disturbances.

CONCLUSION

To conclude, we believe that our findings about the CM-phenotype can help further refine the clinical description of AD. This, in turn, has crucial research and clinical implications. Indeed, our discovery open the way for future longitudinal studies on larger samples of patients aiming at confirming our preliminary data, including those on neural substrates, and speculations about phenotypic heterogeneity in degenerative dementias. From a clinical point of view, a clearer and more complete presentation of AD spectrum could improve early diagnosis and rehabilitation.

AUTHOR CONTRIBUTIONS

Carlo Abbate, Ph.D. (Conceptualization; Data curation; Investigation; Methodology; Writing – original draft; Writing – review & editing); Alessia Gallucci (Formal analysis; Funding acquisition; Methodology; Writing – review & editing); Pietro Davide Trimarchi (Data curation; Formal analysis; Investigation; Methodology; Software); Emanuela Piacquadio (Data curation; Investigation); Giulia Caramanti (Data curation; Investigation); Anna Parma (Data curation; Investigation); Giorgio Giulio Fumagalli (Data curation; Formal analysis; Methodology; Writing – review & editing); Silvia Inglese (Data curation; Investigation); Paola Maria Rita Parisi (Funding acquisition; Project administration; Supervision); Federica Tartarone (Funding acquisition; Project administration; Supervision); Fabrizio Giunco (Funding acquisition; Project administration; Supervision).

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CONFLICT OF INTEREST

The authors have no conflict of interest to report.

DATA AVAILABILITY

The data supporting the findings of this study are available within our previous articles [1, 2] and their supplementary material which are available in the public domain: https://pcontent.iospress.com/articles/journal-of-alzheimers-disease/jad220919 and https://doi.org/10.1080/13554794.2016.1239743

REFERENCES

[1] Abbate C, Trimarchi PD, Rotondo E, Inglese S, Nicolini P, Rossi PD, Arosio B, Mari D (2016) Spontaneous confabulations in amnestic-mild cognitive impairment due to Alzheimer's disease: A new (yet old) atypical variant? *Neurocase* **22**, 451-460.

[2] Abbate C, Trimarchi PD, Fumagalli GG, Gallucci A, Tomasini E, Fracchia S, Rebecchi I, Morello E, Fontanella A, Parisi P, Tartarone F, Giunco Fabrizio, Ciccone S, Nicolini P, Lucchi T, Arosio B, Inglese S, Rossi P (2023) Diencephalic versus hippocampal amnesia in Alzheimer's disease: The possible confabulation-misidentification phenotype. *J Alzheimers Dis* **91**, 363-388.

[3] Berrios GE (1985) Presbyophrenia: Clinical aspects. *BJPsych* **147**, 76-79.

[4] Berrios GE (1986) Presbyophrenia: The rise and fall of a concept. *Psychol Med* **16**, 267-275.

[5] Zervas IM, Fliesser JM, Woznicki M, Fricchione GL (1993) Presbyophrenia: A possible subtype of dementia. *J Geriatr Psychiatry Neurol* **6**, 25-28.

[6] Devinsky O (2009) Delusional misidentifications and duplications: Right brain lesions, left brain delusions. *Neurology* **72**, 80-87.

[7] Sultzer DL, Brown CV, Mandelkern MA, Mahler ME, Mendez MF, Chen ST, Cummings JL (2003) Delusional thoughts and regional frontal/temporal cortex metabolism in Alzheimer's disease. *Am J Psychiatry* **160**, 341-349.

[8] Lee E, Kinomura S, Meguro K, Akanuma K, Meguro M, Fukuda H (2009) Confabulations on episodic and semantic memory questions are associated with different neurologic backgrounds in Alzheimer disease. *Cogn Behav Neurol* **22**, 81-88.

[9] Lee E, Meguro K, Hashimoto R, Meguro M, Ishii H, Yamaguchi S, Mori E (2007) Confabulations in episodic memory are associated with delusions in Alzheimer's disease. *J Geriatr Psychiatry Neurol* **20**, 34-40.

[10] Lee E, Akanuma K, Meguro M, Ishii H, Yamaguchi S, Meguro K (2007) Confabulations in remembering past and planning future are associated with psychiatric symptoms in Alzheimer's disease. *Arch Clin Neuropsychol* **22**, 949-956.

[11] Cook SE, Miyahara S, Bacanu S-A, Perez-Madrinan G, Lopez OL, Kaufer DI, Nimgaonkar VL, Wisniewski SR, DeKosky ST, Sweet RA (2003) Psychotic symptoms in Alzheimer disease: Evidence for subtypes. *Am J Geriatr Psychiatry* **11**, 406-413.

[12] Reeves SJ, Gould RL, Powell JF, Howard RJ (2012) Origins of delusions in Alzheimer's disease. *Neurosci Biobehav Rev* **36**, 2274-2287.

[13] Talberg I-M, Almkvist O (2001) Confabulation and memory in patients with Alzheimer's disease. *J Clin Exp Neuropsychol* **23**, 172-184.

[14] Pelati O, Castiglioni S, Isella V, Zuffi M, de Rino F, Mossali I, Franceschi M, Pelati O (2011) When Rey-Osterrieth's complex figure becomes a Church. Prevalence and correlates of graphic confabulations in dementia. *Dement Geriatr Cogn Dis Extra* **1**, 372-380.

[15] van der Linde R, Stephan BCM, Matthews FE, Brayne C, Savva GM (2010) Behavioral and psychological symptoms in the older population without dementia–relationship with socio-demographics, health and cognition. *BMC Geriatrics* **10**, 87.

[16] Dalla Barba G, Nedjam Z, Dubois B (1999) Confabulation, executive functions, and source memory in Alzheimer's disease. *Cogn Neuropsychol* **16**, 385-398.

[17] Cooper JM, Shanks MF, Venneri A (2006) Provoked confabulations in Alzheimer's disease. *Neuropsychologia* **44**, 1697-1707.

[18] Kopelman MD (2010) Varieties of confabulation and delusion. *Cogn Neuropsychiatry* **15**, 14-37.

[19] El Haj M, Larøi F (2017) Provoked and spontaneous confabulations in Alzheimer's disease: An examination of their prevalence and relation with general cognitive and executive functioning. *Psychiatry Clin Neurosci* **71**, 61-69.

[20] Attali E, De Anna F, Dubois B, Dalla Barba G (2009) Confabulation in Alzheimer's disease: Poor encoding and retrieval of over-learned information. *Brain* **132**, 204-212.

[21] La Corte V, Serra M, Attali E, Boiss´e M-F, Dalla Barba G (2010) Confabulation in Alzheimer's disease and amnesia: A qualitative account and a new taxonomy. *J Int Neuropsychol Soc* **16**, 967-974.

[22] Ropacki SA, Jeste DV (2005) Epidemiology of and risk factors for psychosis of Alzheimer's disease: A review of 55 studies published from 1990 to 2003. *Am J Psychiatry* **162**, 2022-2030.

[23] Harciarek M, Kertesz A (2008) The prevalence of misidentification syndromes in neurodegenerative diseases. *Alzheimer Dis Assoc Disord* **22**, 163-169.

[24] Savva GM, Zaccai J, Matthews FE, Davidson JE, McKeith I, Brayne C (2009) Prevalence, correlates and course of behavioural and psychological symptoms of dementia in the population. *BJPsych* **194**, 212-219.

[25] Steinberg M, Shao H, Zandi P, Lyketsos CG,Welsh-Bohmer KA, Norton MC, Breitner JCS, Steffens DC, Tschanz JoAT, Cache County Investigators (2008) Point and 5-year period prevalence of neuropsychiatric symptoms in dementia: The Cache County Study. *Int J Geriatr Psychiatry* **23**, 170-177.

[26] Sweet RA, Bennett DA, Graff-Radford NR, Mayeux R (2010) Assessment and familial aggregation of psychosis in Alzheimer's disease from the National Institute on Aging Late Onset Alzheimer's Disease Family Study. *Brain* **133**, 1155-1162.

[27] Devanand DP, Jacobs DM, Tang M-X, Del Castillo-Castaneda C, Sano M, Marder K, Bell K, Bylsma FW, Brandt J, Albert M, Stern Y (1997) The course of psychopathologic features in mild to moderate Alzheimer disease. *Arch Gen Psychiatry* **54**, 257-263.

[28] Kopelman MD, Thomson AD, Guerrini I, Marshall EJ (2009) The Korsakoff syndrome: Clinical aspects, psychology and treatment. *Alcohol Alcohol* **44**, 148-154.

[29] Arts NJ, Walvoort SJ, Kessels RP (2017) Korsakoff's syndrome: A critical review. *Neuropsychiatr Dis Treat* **13**, 2875-2890.

[30] 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.

[31] Trimarchi PD, Sanfilippo E, Gallucci A, Inglese S, Tomasini E, Fontanella A, Rebecchi I, Fracchia S, Parisi PMR, Tartarone F, Giunco F, Abbate C (2023) Signs and symptoms method in neuropsychology: A standardized observational examination of cognitive functions can be effective in detecting mild cognitive impairment. *Neuropsychology* **37**, 846-857.

[32] Dalla Barba G (1993) Confabulation: Knowledge and recollective experience. *Cogn Neuropsychol* **10**, 1-20.

[33] Dalla Barba G, Brazzarola M, Marangoni S, La Corte V (2020) Screening for confabulations with the confabulation screen. *Neuropsychol Rehabil* **30**, 116-129.

[34] Gilboa A, Moscovitch M (2002) The cognitive neuroscience of confabulation. A review and a model. In *The handbook of memory disorders*, Baddeley A, Kopelman M, Wilson B, eds. John Wiley & Sons, Chichester, pp. 315-342.

[35] Dalla Barba G, La Corte V (2013) The hippocampus, a time machine that makes errors. *Trends Cogn Sci* **17**, 102-104.

[36] Cummings JL, Back C (1998) The cholinergic hypothesis of neuropsychiatric symptoms in Alzheimer's disease. *Am J Geriatr Psychiatry* **6**, S64-S78.

[37] Cummings JL, Kaufer D (1996) Neuropsychiatric aspects of Alzheimer's disease: The cholinergic hypothesis revisited. *Neurology* **47**, 876-883.

[38] Cancelli I, Beltrame M, D'Anna L, Gigli GL, Valente M (2009) Drugs with anticholinergic properties: A potential risk factor for psychosis onset in Alzheimer's disease? *Expert Opin Drug Saf* **8**, 549-557.

[39] Garcia-Alloza M, Gil-Bea FJ, Diez-Ariza M, Chen CPL-H, Francis PT, Lasheras B, Ramirez MJ (2005) Cholinergic–serotonergic imbalance contributes to cognitive and behavioral symptoms in Alzheimer's disease. *Neuropsychologia* **43**, 442-449.

[40] Belli E, Nicoletti V, Radicchi C, Bonaccorsi J, Cintoli S, Ceravolo R, Tognoni G (2020) Confabulations in cases of dementia: Atypical early sign of Alzheimer's disease or misleading feature in dementia diagnosis? *Front Psychol* **11**, 553886.

[41] Harper L, Fumagalli GG, Barkhof F, Scheltens P, O'Brien JT, Bouwman F, Burton EJ, Rohrer JD, Fox NC, Ridgway GR, Schott JM (2016) MRI visual rating scales in the diagnosis of dementia: Evaluation in 184 post-mortem confirmed cases. *Brain* **139**, 1211-1225.

[42] Fumagalli GG, Basilico P, Arighi A, Mercurio M, Scarioni M, Carandini T, Colombi A, Pietroboni AM, Sacchi L, Conte G, Scola E, Triulzi F, Scarpini E, Galimberti D (2020) Parieto occipital sulcus widening differentiates posterior cortical atrophy from typical Alzheimer disease. *Neuroimage Clin* **28**, 102453.

[43] Schnider A (2003) Spontaneous confabulation and the adaptation of thought to ongoing reality. *Nat Rev Neurosci* **4**, 662-671.

[44] Catani M, Dell'Acqua F, Thiebaut de Schotten M (2013) A revised limbic system model for memory, emotion and behavior. *Neurosci Biobehav Rev* **37**, 1724-1737.

[45] Nelson PT, Dickson DW, Trojanowski JQ, Jack CR, Boyle PA, Arfanakis K, Rademakers R, Alafuzoff I, Attems J, Brayne C, Coyle-Gilchrist IT (2019) Limbic-predominant age-related TDP-43 encephalopathy (LATE): Consensus working group report. *Brain* **142**, 1503-1527.

[46] Young CB, Johns E, Kennedy G, Belloy ME, Insel PS, Greicius MD, Sperling RA, Johnson KA, Poston KL, Mormino EC and Alzheimer's Disease Neuroimaging Initiative (2023) APOE effects on regional tau in preclinical Alzheimer's disease. *Mol Neurodegener* **18**, 1.

[47] Weiner MF, Vega G, Risser RC, Honig LS, Cullum CM, Crumpacker D, Rosenberg RN (1999) Apolipoprotein E epsilon 4, other risk factors, and course of Alzheimer's disease. *Biol Psychiatry* **45**, 633-638.

[48] Scarmeas N, Brandt J, Albert M, Devanand DP, Marder K, Bell K, Ciappa A, Tycko B, Stern Y (2002) Association between the APOE genotype and psychopathologic symptoms in Alzheimer's disease. *Neurology* **58**, 1182-1188.

[49] Chang JB, Wang PN, Chen WT, Liu CY, Hong CJ, Lin KN, Liu TY, Chi CW, Liu HC (2004) ApoE epsilon4 allele is associated with incidental hallucinations and delusions in patients with AD. *Neurology* **63**, 1105-1107.

[50] Spalletta G, Bernardini S, Bellincampi L, Federici G, Trequattrini A, Caltagirone C (2006) Delusion symptoms are associated with ApoE epsilon4 allelic variant at the early stage of Alzheimer's disease with late onset. *Eur J Neurol* **13**, 176-182.

[51] van der Flier WM, Staekenborg S, Pijnenburg YA, Gillissen F, Romkes R, Kok A, Bouwman FH, Scheltens P (2007) Apolipoprotein E genotype influences presence and severity of delusions and aggressive behavior in Alzheimer disease. *Dement Geriatr Cogn Disord* **23**, 42-46.

[52] Hampel H, Elhage A, Cho M, Apostolova LG, Nicoll JAR, Atri A (2023) Amyloid-related imaging abnormalities (ARIA): Radiological, biological and clinical characteristics. *Brain* **146**, 4414-4424.

[53] Ferreira D, Nordberg A, Westman E (2020) Biological subtypes of Alzheimer's disease: A systematic review and meta-analysis. *Neurology* **94**, 436-448.

[54] Jellinger KA (2021) Pathobiological subtypes of Alzheimer disease. *Dement Geriatr Cogn Disord* **49**, 321-333.

[55] Charil A, Shcherbinin S, Southekal S, Devous MD, Mintun M, Murray ME, Miller BB, Schwarz AJ (2019) Tau subtypes of Alzheimer's disease determined *in vivo* using flortaucipir PET imaging. *J Alzheimers Dis* **71**, 1037-1048.

[56] Perez-Madriñan G, Cook SE, Saxton JA, Miyahara S, Lopez OL, Kaufer DI, Howard J. Aizenstein HJ, DeKosky ST, Sweet RA (2004) Alzheimer disease with psychosis: Excess cognitive impairment is restricted to the misidentification subtype. *Am J Geriatr Psychiatry* **12**, 449-456.

[57] Wilkosz PA, Miyahara S, Lopez OL, DeKosky ST, Sweet RA (2006) Prediction of psychosis onset in Alzheimer disease: The role of cognitive impairment, depressive symptoms, and further evidence for psychosis subtypes. *Am J Geriatr Psychiatry* **14**, 352-360.

[58] Bruen PD, McGeown WJ, Shanks MF, Venneri A (2008) Neuroanatomical correlates of neuropsychiatric symptoms in Alzheimer's disease. *Brain* **131**, 2455-2463.

[59] Forstl H, Burns A, Levy R, Cairns N (1994) Neuropathological correlates of psychotic phenomena in confirmed Alzheimer's disease. *Br J Psychiatry* **165**, 53-59.

[60] Ismail Z, Nguyen MQ, Fischer CE, Schweizer TA, Mulsant BH, Mamo D (2011) Neurobiology of delusions in Alzheimer's disease. *Curr Psychiatry Rep* **13**, 211-218.

[61] Ismail Z, Nguyen MQ, Fischer CE, Schweizer TA, Mulsant BH (2012) Neuroimaging of delusions in Alzheimer's disease. *Psychiatry Res Neuroimaging* **202**, 89-95.

[62] Reeves SJ, Clark-Papasavas C, Gould RL, Ffytche D, Howard RJ (2015) Cognitive phenotype of psychotic symptoms in Alzheimer's disease: Evidence for impaired visuoperceptual function in the misidentification subtype. *Int J Geriatr Psychiatr* **30**, 1147-1155.

[63] McLachlan E, Bousfield J, Howard R, Reeves S (2018) Reduced parahippocampal volume and psychosis symptoms in Alzheimer's disease. *Int J Geriatr Psychiatr* **33**, 389-395.

[64] D'Antonio F, Di Vita A, Zazzaro G, Canevelli M, Trebbastoni A, Campanelli A, Ferracuti S, de Lena C, Guariglia C, Boccia, M (2022) Cortical complexity alterations in the medial temporal lobe are associated with Alzheimer's disease psychosis. *Aging Neuropsychol Cogn* **29,** 1022-1032.

[65] Pearce D, Gould RL, Roughley M, Reynolds G, Ward EV, Bhome R, Reeves S (2022) Paranoid and misidentification subtypes of psychosis in dementia. *Neurosci Biobehav Rev* **134**, 104529.

[66] Forstl H, Burns A, Jacoby R, Levy R (1991) Neuroanatomical correlates of clinical misidentification and misperception in senile dementia of the Alzheimer type. *J Clin Psychiatry* **52**, 268-271.

[67] Serra L, Perri R, Cercignani M, Spano B, Fadda L, Marra C, Carlesimo GA, Caltagirone C, Bozzali M (2010) Are the behavioral symptoms of Alzheimer's disease directly associated with neurodegeneration? *J Alzheimers Dis* **21**, 627-639.

[68] Nakano S, Yamashita F, Matsuda H, Kodama C, Yamada T (2006) Relationship between delusions and regional cerebral blood flow in Alzheimer's disease. *Dement Geriatr Cogn Disord* **21**, 16-21.

[69] Lee YM, Chung Y-I, Park J-M, Lee B-D, Moon E, Jeong H-J, Kim J-H, Kim H-J, Mun C-W, Kim T-H, Kim Y-H, Kim E-J (2016) Decreased gray matter volume is associated with the subtypes of psychotic symptoms in patients with antipsychotic-naive mild or moderate Alzheimer's disease: A voxel-based morphometry study. *Psychiatry Res Neuroimag* **249**, 45-51.

[70] D'Antonio F, Reeves S, Sheng Y, McLachlan E, de Lena C, Howard R, Bertrand J (2019) Misidentification subtype of Alzheimer's disease psychosis predicts a faster cognitive decline. *CPT Pharmacometrics Syst Pharmacol* **8**, 308-315.

[71] Ossenkoppele R, Pijnenburg YAL, Perry DC, Cohn-Sheehy BI, Scheltens NME, Vogel JW, Kramer JH, van der Vlies AE, La Joie R, Rosen HJ, van der Flier WM, Grinberg LT, Rozemuller AJ, Huang EJ, van Berckel BNM, Miller BL, Barkhof F, Jagust WJ, Scheltens P, Seeley WW, Rabinovici GD (2015) The behavioral/dysexecutive variant of Alzheimer's disease: Clinical, neuroimaging and pathological features. *Brain* **138**, 2732-2749.

[72] Donaghy PC, McKeith IG (2014) The clinical characteristics of dementia with Lewy bodies and a consideration of prodromal diagnosis. *Alzheimers Res Ther* **6**, 46.

[73] Barker MS, Gottesman RT, Manoochehri M, Chapman S, Appleby BS, Brushaber D, and ALL FTD Consortium Foroud T, Kaufer D, Kremers W, Leger G, Onyike C, Ritter A, Roberson ED, Weintraub S (2022) Proposed research criteria for prodromal behavioural variant frontotemporal dementia. *Brain* **145**, 1079-1097.

[74] Springer B (2024) Hyperactive delirium with severe agitation. *Emerg Med Clin North Am* **42**, 41-52.

[75] Bien CG (2022) Limbic encephalitis. In *Handbook of Clinical Neurology*, vol 187, the temporal lobe, Miceli G, Bartolomeo P, Navarro V, eds. Elsevier, Amsterdam, pp. 467-487.

[76] Witt JA, Helmstaedter C (2021) Neuropsychological evaluations in limbic encephalitis. *Brain Sci* **11**, 576.