Original Article

Hyperfamiliarity in Dementia and Mild Cognitive Impairment

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Abstract

Introduction: Hyperfamiliarity, a phenomenon in which feelings of familiarity are evoked by novel stimuli, is well described in epilepsy and the lesioned brain. Abnormality of familiarity in Alzheimer's disease (AD) and mild cognitive impairment (MCI) have also been described in the literature, but more from a neuropsychological approach perspective. Currently, there is a lack of study on the real-life experience of familiarity abnormality in dementia and MCI. Our aim was to compare the occurrence of hyperfamiliarity among dementia and MCI. Materials and Methods: We recruited 73 participants, 29 with AD, 10 with vascular dementia, 7 with MCI and 27 healthy controls, and administered a questionnaire to assess hyperfamiliarity frequency. Results: Hyperfamiliarity was observed in real-life in cognitive impairment, but was unrelated to its severity or underlying aetiology. Conclusion: This study highlights the similar rate of occurrence of hyperfamiliarity in the daily life of individuals with cognitive impairment. Future research should examine neuropsychological correlations and mechanisms that contribute to such observations.

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Key words: Alzheimer's disease, Delusional misidentification syndrome, Vascular dementia

Introduction

Hyperfamiliarity, a phenomenon in which novel stimuli evoke feelings of familiarity, has been described in dementia, temporal lobe epilepsy (TLE) and the lesioned brain.[1-4] There is currently no universal term for the phenomenon of hyperfamiliarity. Labels have been used to describe spurious feelings of familiarity, including 'false memory', 'false recall', 'recognition without identification' and indeed, 'hyperfamiliarity'.[3,5-7] Predominant theories on the cognitive processes behind hyperfamiliarity are highly similar. These theories postulate that hyperfamiliarity occurs when there is recognition without recollection—that is, though a stimulus is perceived to be familiar (i.e. it is recognised), there is no retrieval for contextual information regarding the stimulus (i.e. there is no recollection). However, the theories differ regarding which parts of the brain are responsible.[2,4,8-10]

While the specific causes of hyperfamiliarity are still ambiguous, existing research has identified general trends regarding its aetiology and its relationship with cognitive function. In dementia, research has largely associated deficits in the frontal and temporal lobes with hyperfamiliarity.[2,7,11-14] Additionally, research suggests that the severity of hyperfamiliarity is not linked with cognitive decline. For example, studies found that in recognition tests that involved word lists, the likelihood of falsely recognising words increased with the presence of Alzheimer's disease (AD) but was not related to the severity of AD.[1,3] In TLE and the lesioned brain, hyperfamiliarity has been described as having both a right and left hemispheric focus, as well as an association with impairments in the temporal areas.[8,15-17] These broad and occasionally ambiguous trends highlight the need for further research on hyperfamiliarity.

To date, studies on familiarity deficits in dementia and mild cognitive impairment (MCI) have been mainly based on a neuropsychological approach. It remains uncertain whether the deficits are reflected or manifested in patients' daily life. Our study aimed to fill this knowledge gap by conducting an investigation on the occurrence of hyperfamiliarity

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experienced in daily life by individuals with dementia or MCI. We included both dementia and MCI in order to study the effect and relationship of different stages or severity of cognitive impairment towards the real-life phenomenon of hypefamiliarity. We hypothesised that hyperfamiliarity is common in both dementia and MCI, and its presence is not related to the status or severity of cognitive impairment.

Materials and Methods

Patients who presented to the neurology outpatient clinic of a large tertiary hospital in Singapore with a clinical diagnosis of AD, MCI or vascular dementia (VD) were approached and recruited into the study. Diagnosis of AD was in accordance with the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV),[18] while diagnosis of VD fulfilled the NINDS-AIREN criteria[19] and diagnosis of MCI fulfilled the Peterson criteria.[20] A total of 73 participants were recruited for the study, and written consent was obtained either from the participants themselves or from their informants. Recruited participants included 29 with AD, 10 with VD, 7 with MCI (6 amnestic MCI multiple domain, 1 non-amnestic MCI single domain) and 27 healthy control participants.

Informants were approached to rate the severity of hyperfamiliarity of the patients. To participate in the study, informants were required to have spent at least 9 hours per week with the participant for the past 12 months and be familiar with the participant's habits. Healthy controls (age- and gender-matched) were defined as participants with no personal history of cognitive impairment or subjective cognitive complaints; they were mostly spouses of patients with their children serving as informant for the questionnaire. Patients with delusional misidentification syndrome (DMS) were excluded from participation. This study was approved by the SingHealth Institutional Review Board.

A questionnaire assessing participants' demographics and hyperfamiliarity-related symptoms was administered verbally to the informants. The demographics included age, gender, dementia diagnosis and Mini Mental State Examination (MMSE) score. Background of the informants such as relationship with patients was not included in the questionnaire. Hyperfamiliarity was measured on 3 domains: people (e.g. passers-by on the street), places (e.g. shopping malls) and objects (e.g. cars on the road). For each domain, informants were required to give a subjective score ranging from '0' to '5' based on the frequency of hyperfamiliarity being expressed within the past month. The scale measures how many times, on average, the participant experiences an occurrence of hyperfamiliarity per 10 opportunities. A rating of '0' indicates no occurrence of hyperfamiliarity, a rating of '1' indicates 1 to 2 occurrences, a rating of '2' indicates 3 to 4 occurrences and so on, with the highest rating of '5' indicating 9 to 10 occurrences of hyperfamiliarity out of 10 opportunities. The frequency scores for all 3 domains were added to obtain the participant's total hyperfamiliarity frequency score. The instruction given to informants was as below: Please give 1 rating for the period of within the past month of your care recipient's symptoms for below: 1) Patient claims to recognise or be familiar with people on the street he/she has not met before, 2) Patient claims to recognise or be familiar with new places even though he/she has not been there before, 3) Patient claims to recognise or be familiar with objects he/she encounters (for example, cars on the street, trees by the road) even though he/she has not previously encountered them before. The questionnaire is attached in Appendix 1.

Statistical Method

The hyperfamiliarity scores were binned into 2 categories; first category with only score of 0 and the other category with scores of 1 to 5. A Chi-square test was first applied to compare hyperfamiliarity scores among the 4 groups (AD, VD, MCI, and healthy controls). It was then applied to compare hyperfamiliarity scores among the 3 disease groups only. Spearman's rank correlation coefficient was used to measure the correlation of the hyperfamiliarity domain scores of people, places, objects and total score with MMSE score. Finally, multiple linear regression was used to determine whether MMSE score is a predictor for hyperfamiliarity total score, adjusting for covariates of age and gender. MMSE was used as a predictor in this study in order to examine the relationship of cognitive status, as reflected by MMSE score, with severity of hyperfamiliarity.

Results

Table 1 summarises the demographics of the 3 disease groups and the healthy control group.

In the comparison between all 4 groups, statistically significant differences were found in the hyperfamiliarity domains of people and objects, as well as in total score ($P < 0.05$), but not in the hyperfamiliarity domain of places ($P = 0.249$). For the hyperfamiliarity domain of people, the MCI group had a lower rate of score 0 (i.e. no occurrence of hyperfamiliarity) than did the control group. For the hyperfamiliarity domain of objects, the VD and MCI groups had lower rates of score 0 than did the control group. For total score of hyperfamiliarity, the AD, VD and MCI groups had lower rates of score 0 than did the control group. However, no statistically significant differences were found in any of the 3 hyperfamiliarity domains when comparing only among the AD, VD and MCI groups. These results are summarised in Table 2 and Figure 1. We adopted this 2

Table 1. Demographics of the Various Groups

Demographic	AD (n = 29) n (%)	VD (n = 10) n (%)	MCI (n = 7) n (%)	Controls (n = 27) n (%)
Male gender	13 (44.8)	5 (50.0)	5 (71.4)	11 (40.7)
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Age	79.3 (5.9)	73.7 (9.4)	75.7 (9.4)	74.5 (12.0)
MMSE score	16.5 (4.7)	15.0 (4.5)	21.0 (4.7)	NA

AD: Alzheimer's disease; MCI: Mild cognitive impairment; MMSE: Mini Mental State Examination; NA: Not applicable; SD: Standard deviation; VD: Vascular dementia

Table 2. Distribution of Hyperfamiliarity Score of 0 (i.e. No Occurrence of Hyperfamiliarity) in the Various Groups

Hyperfamiliarity Domains	AD (n = 29) n (%)	VD (n = 10) n (%)	MCI (n = 7) n (%)	Controls (n = 27) n (%)	4-Group Comparisons *P* Value*	3-Disease-Group Comparisons *P* Value†
People	27 (93.1)	10 (100.0)	5 (71.4)	27 (100.0)	0.024‡	0.103
Places	24 (82.8)	9 (90.0)	6 (85.7)	27 (100.0)	0.249	0.940
Objects	29 (100.0)	8 (80.0)	6 (85.7)	27 (100.0)	0.014‡	0.058
Total score	25 (86.2)	7 (70.0)	3 (42.9)	27 (100.0)	0.001‡	0.048

AD: Alzheimer's disease; MCI: Mild cognitive impairment; VD: Vascular dementia
*Chi-square test comparing all 4 groups.
†Chi-square test comparing the 3 disease groups AD, VD and MCI.
‡*P* values represent statistical significance at $P < 0.05$.

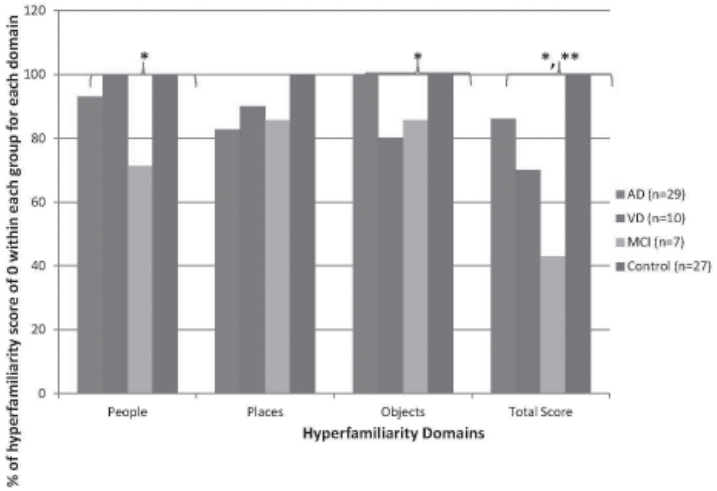

Fig. 1. Distribution of hyperfamiliarity score of 0 (i.e. no occurrence of hyperfamiliarity) in the various groups.

separate Chi-square tests approach for 2 main reasons; firstly, control group showed no occurrence of hyperfamiliarity as opposed to the 3 disease groups; secondly, to avoid multiple testing (example, single Chi-square followed by multiple pairs posthoc testing).

There was no significant correlation between any of the 3 domain scores or the total score of hyperfamiliarity and MMSE score (people: $P = 0.809$, places: $P = 0.489$; objects: $P = 0.115$, total: $P = 0.154$).

Multiple linear regression showed that MMSE was not a significant predictor for hyperfamiliarity total score (regression coefficient, β (95% CI): 0.05 (-0.03, 0.14), $P = 0.202$) even after adjustment for age and gender.

Discussion

The results suggest that hyperfamiliarity occurred in a similar rate in dementia-related cognitive impairment. Consistent with previous research, hyperfamiliarity was associated with cognitive impairment, but there was no relation between cognitive status—as indicated by MMSE

scores—and frequency of hyperfamiliarity.[1,3] To date, evidence in the literature of familiarity deficits in MCI has been controversial.[21] However, the MCI group in our study showed a significant trend in abnormal familiarity, which was comparable to those found in the dementia groups. These findings from a real-life perspective are in keeping with and supportive of the neuropsychological-based or approach studies that have indicated abnormal familiarity during memory recollection in MCI.[22] The statistical insignificance found in place domain was probably due to small sample size; less travelling in cognitively impaired patients might also have contributed to the lower rate of hyperfamiliarity in this domain.

DMS is an important form of abnormal familiarity that has been well described in dementia. It comprises a group of syndromes that are characterised by delusions of misidentification toward people, places or objects. Examples of DMS include Capgras syndrome, the belief that a loved one has been replaced by an impostor, and Fregoli syndrome, the belief that several people are in fact 1 person in disguise.[23] Face-selective self-misidentification secondary to a right occipitotemporal hypometabolism has also been reported.[24] In dementia, DMS is most commonly associated with dementia with Lewy bodies (DLB) and AD.[25,26] For instance, facial-specific DMS and hyperfamiliarity even towards animacy has been reported in AD.[27] It has been hypothesised that hyperfamiliarity is related to DMS in that they both involve the same pathophysiological mechanisms, with hyperfamiliarity being a lesser representation of DMS.[28,29] In our study, patients with DMS were excluded from analysis in order to investigate hyperfamiliarity independently and examine whether it shares any clinical resemblance with DMS.

Interestingly, there was no significant difference in incidence of hyperfamiliarity between the various dementia/MCI diagnoses. Since DMS has a strong association with AD and DLB, and not with VD and MCI, our finding of uniformity in hyperfamiliarity incidence between the 3 diagnosis groups suggests that hyperfamiliarity and DMS probably do not involve the exact same pathophysiological mechanisms. Of course, it would be too simplistic to draw such a conclusion based on these results. It is possible that hyperfamiliarity could be due to a number of causes and that multiple types of hyperfamiliarities exist, of which some share similar pathologies with DMS. For instance, Schacter et al[14] described patient BG, whose hyperfamiliarity was eliminated when the patient was presented with categorised stimuli and was tested with stimuli from non-studied categories. Schacter et al[14] argued that BG's hyperfamiliarity might be due to an over-reliance on memory for broad characteristics with impaired memory for specific items. Additionally, Vuilleumier et al[17] described patient JR, whose hyperfamiliarity appeared to be context-specific. For example, JR's hyperfamiliarity decreased while on public transport, but increased when she was on her university's campus. These findings again suggest that hyperfamiliarity involves multiple cognitive processes and thus can arise from deficits at any of the processing stages. The idea that hyperfamiliarity has multiple causes—or even that multiple types of hyperfamiliarities exist—could explain why hyperfamiliarity was not found to be specific to any particular dementia/MCI diagnosis in this study, even though DMS appears to be largely specific to AD and DLB.[26]

Previous studies demonstrated evidence supporting a dual-process mechanism in the memory recognition process.[30] From our study, we can probably conclude that the familiarity process in memory recognition is more resistant to impairment during the dementing process. Participants experience similar rates of hyperfamiliarity in their daily life, regardless of aetiology or severity of cognitive impairment. Meanwhile, factual memory recollection appeared to be more prone to degradation in the dementing process. It involves, but is not limited to, an effective and accurate information retrieval and matching process that is also required to be context-specific. This likely indicates the more widespread involvement of neuronal structures in this process. Thus, even a subtle injury may induce hyperfamiliarity secondary to an overriding familiarity process. This probably explains the common occurrence of hyperfamiliarity during daily life in all cognitive impairment participants while there was no significant difference in occurrence among the 3 diagnosis groups, as any injury along the pathway of factual memory recollection will produce a highly similar clinical outcome in terms of memory recognition experience.

We also noted the MCI group had the worst performance among the 3 groups in terms of rate of total numbers of patients scoring 0 in the questionnaire, followed by the VD group. In this study, we did not look into the neuroimaging finding of the MCI patients that could possibly have concomitant subcortical ischaemia similar to the VD group. We are still not sure whether executive dysfunction, a common finding in subcortical ischaemia, could positively affect hyperfamiliarity. Future studies should examine and correlate subcortical lesions with clinical hyperfamiliarity. However, we do need to be cautious and take note that only a very small sample size is present in the MCI group.

This study has a few limitations. First, it was limited by its small sample size and its retrospective nature coupled by relatively low occurrence of reported hyperfamiliarity among the groups. Second, diagnosis of AD was based on DSM-IV criteria, thus details regarding concomitant vascular burden in the AD group were not examined. This could confound the findings due to potential overlapping mechanisms of memory recollection deficits between the

AD and VD groups. Third, full neuropsychological data for the participants is lacking and therefore not examined; hence, poor self-monitoring or executive dysfunction was not adjusted for the results. Lastly, we didn't examine the demographic differences of informant between the groups, this might influence the way how they rate hyperfamiliarity. The multiple regression analysis would be more complete if further adjusted by informant's background differences. Nevertheless, the informants were usually the primary caregivers who know the patients the best thus this bias should be minimal.

Conclusion

Hyperfamiliarity is likely a generic or non-specific phenomenon in terms of aetiology or cognitive status correlation when applied in the dementing process. Current conceptualisation of hyperfamiliarity poses challenges in defining the aims and outcome measurement of study that relates to it. Future research should examine the full neuropsychological data of larger samples to further delineate the interactions or contributions of the various cognitive domains to hyperfamiliarity; and probably a more focus approach such as only studying AD in order to better conceptualise hyperfamiliarity so that the gap of understanding of real-life experience and neuropsychological finding of hyperfamiliarity could be further narrowed. Future study should also investigate the occurrence of hyperfamiliarity in other types of dementing illness such as Parkinsonian dementia or frontotemporal dementia.

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Appendix 1
Questionnaire of Hyperfamiliarity in Dementia and Mild Cognitive Impairment Study

Hyperfamiliarity in Dementia and Mild Cognitive Impairment Study

DEMOGRAPHICS

Patient's diagnosis: _____

(To be filled in by doctor): Stage_____ MMSE_____/_____(Date)

Number of years since onset of symptoms: _____

How many hours a week do you spend with care recipient? _____hours

QUESTIONNAIRE

A. Has the patient been diagnosed with delusional misidentification syndrome (DMS)?

If **YES**, which type? Please circle one.

a. Capgras Syndrome
b. Fergoli Syndrome
c. Intermetamorphosis
d. Subjective Doubles
e. Mirrored self-misidentification
f. Reduplicative paramnesia
g. Cotard Syndrome
h. Other: _____

If **NO,** proceed below.

B. Please rate the frequency of the following situations on a scale of 0 to 5 according to the following criteria:

0 – does not occur at all	**1** – occurs 1, 2 times out of 10	**2** – occurs 3, 4 times out of 10
3 – occurs 5, 6 times out of 10	**4** – occurs 7, 8 times out of 10	**5** – occurs 9, 10 times out of 10

Please give one rating for the period before onset of your care recipient's symptoms and one rating for the present period (within the past month).

	Before onset of dementia/ MCI symptoms	Presently (Within past month)
1. Patient claims to recognize or be familiar with **people** on the street he/she has not met before. Please indicate who the false sense of familiarity is normally directed at (e.g. people on the street, healthcare workers): _____		
2. Patient claims to recognise or be familiar with new **places** even though he/she has not been there before. Please indicate where the false sense of familiarity is normally directed at (e.g. shopping malls, friends/ relatives' homes): _____		
3. Patient claims to recognise or be familiar with **objects** he/she encounters (e.g. cars on the street, trees by the road) even though he/she has not previously encountered them before. Please indicate what the false sense of familiarity is normally directed at (e.g. cars on the street, products on sale when shopping): _____		