Hyperfamiliarity in Amnestic and Vascular Mild Cognitive Impairment

Pei Shi Chia, Shahul Hameed, Kok Pin Yong, Ling Ling Chan, Simon Kang Seng Ting

ABSTRACT: Objective: Hyperfamiliarity is a phenomenon where new stimuli are perceived as familiar. Previous studies have demonstrated familiarity disorder in mild cognitive impairment (MCI), but mostly from the perspective of a neuropsychological approach, and the exact correlation of MCI aetiologies with the phenomenon remains uncertain. Based on current evidence suggesting a frontal-subcortical pathway contributing to familiarity processing, we hypothesize that individuals with a vascular aetiology of MCI will likely suffer more familiarity deficits. This study aims to examine the real-life hyperfamiliarity symptoms in amnestic versus vascular MCI. Methods: Informants of 11 amnestic and 9 vascular cognitive impairment patients were interviewed about the frequency of hyperfamiliarity symptoms in the previous month. MRI brain images of vascular cognitive impairment patients were analysed as well. Results: Patients with vascular cognitive impairment with no dementia (VCIND) showed a significantly higher frequency of hyperfamiliarity for people but not places or objects. Within VCIND patients, overall basal ganglia hyperintensities, particularly in the putamen, were found to significantly correlate to hyperfamiliarity. Conclusions: Patients with VCIND suffer more real-life hyperfamiliarity during people recognition compared to patients with amnestic mild cognitive impairment (aMCI), despite a comparative global decline in cognitive. This is likely due to impaired memory retrieval and matching processes resulting from subcortical ischaemic lesions.

INTRODUCTION

Hyperfamiliarity is paramnesia in which an individual experiences abnormal familiarity when presented with novel stimuli.1 This is commonly linked to such neurological conditions as dementia.2-5 While familiar stimuli recognition tends to be intact, unknown ones trigger hyperfamiliarity.1,6 Normally, when a familiar stimulus is encountered, it triggers recognition without contextual or episodic information, and retrieval is then required to recall such information. Hyperfamiliarity with novel stimuli is thought to occur when recognition is wrongly triggered, but retrieval of other information cannot occur as the stimulus has never been encountered previously.7

Research has highlighted several brain regions thought to be responsible for familiarity disorder, which appears under such various terms as false recognition or recall. Frontal lobe impairment has been implicated multiple times in abnormal false recognition.4,8,9 In dementia patients, hyperfamiliarity manifested as high levels of false positives during recognition tasks and also in daily life. This was associated with damage to the fronto-temporal circuits.4

In addition to the frontal lobe, patients with extrahippocampal medial temporal lobe lesions also displayed hyperfamiliarity, but...
to a lesser extent. The perihinal cortex is specifically believed to be involved in producing familiarity,10 and when over-stimulated in epilepsy patients during seizures contributes to the occurrence of hyperfamiliarity.3 While the medial temporal lobe is thought to contribute to false recognition, the prefrontal cortex seems to be responsible for monitoring memory retrieval and thus limiting false recognition.13 This suggests that familiarity disorder likely results from functional mismatch among the neuroanatomical structures mentioned above.

Recognition requires both recollection, for conscious retrieval of information, as well as familiarity, the detection of previously encountered stimuli. Deficits in familiarity have been observed in amnestic mild cognitive impairment (aMCI).14-16 A term used to describe an earlier phase of cognitive decline. It is often a precursor of Alzheimer’s disease (AD), though not all cases progress to this stage. Memory deficits are a common clinical feature.17

Vascular cognitive impairment with no dementia (VCIND), however, is cognitive impairment attributed to vascular pathology. The term is used to refer to patients who have been affected by vascular disease and subsequently developed cognitive deficits. Often, radiological evidence is needed to determine vascular brain changes.18 Vascular brain changes impact the brain differently, resulting in a type of cognitive impairment different from the amnestic version. Unlike aMCI, neuroimaging often reveals signs of vascular disease, such as ischaemic lesions or white matter hyperintensities in VCIND.19 These often result in a certain pattern of symptoms. It is important to note, however, that various vascular diseases lead to different signs in neuroimaging. Impairments in VCIND can differ depending on the type and severity of vascular disease as well. With strokes, cognitive domains affected can depend on the neuroanatomical location and severity of the lesion in the brain.20,21

Given the difference in aetiology, the cognitive profiles of both aMCI and VCIND present differently. The distinction in diagnosis between VCIND and aMCI is based on the clinical profiles of vascular dementia and AD.18 Behaviourally, patients with VCIND tend to present with impaired attention and executive function as well as psychomotor retardation22-24 during neuropsychological testing. On the other hand, patients with aMCI display impairment in anterograde episodic memory.25 Novel stimuli are often poorly encoded and thus quickly forgotten.26,27 However, distinguishing the two just by their clinical features is no easy task, as there are overlapping features despite the different neuropathological origins.28

To date, familiarity disorder in mild cognitive impairment (mMCI), particularly VCIND, has not been well studied, and its aetiology is not understood. Our previous study showed that hyperfamiliarity in cognitive impairment exists comparably despite level of severity of impairment in AD, vascular dementia (VD) and MCI.28 Although observed in patients with MCI, the previous study did not look into the relationship between the aetiology of MCI (amnestic or vascular) contributing to such an observation. Previous studies have suggested that fronto-subcortical dysfunction produces familiarity disorders,4,8,9,13 which is an area often affected by the vascular pathological changes present in VCIND. Subcortical VCIND accounts for 40% of all VCIND cases, making it the most common form.29 Given this, we hypothesize that hyperfamiliarity will be more prevalent among patients with VCIND than in patients with aMCI. In the present study, we aim to measure the difference between the real-life occurrence of hyperfamiliarity in VCIND and aMCI.

**Methods**

**Participants**

Patients who presented to the neurology outpatient clinic of a tertiary hospital in Singapore with a clinical diagnosis of either aMCI or VCIND were identified as candidates. The diagnosis of aMCI was based on the criteria posited by Peterson and Morris,31 while the diagnosis of VCIND was made during consensus meetings of a group of neurologists and neuropsychologists based on the following criteria: (1) cognitive decline as reported by the patient or his/her caregiver; (2) objective evidence of cognitive decline as confirmed by neuropsychological tests in at least one cognitive domain that is below 1.5 standard deviations of established normative means; (3) intact general cognitive functioning and basic activities of daily living; (4) symptoms did not meet the DSM–IV diagnostic criteria dementia; and (5) evidence of a vascular cause based on MRI scans of strategic infarcts or subcortical small-vessel infarcts.

If present, the informants and/or patients’ caregivers were approached and recruited into the study. A total of 20 participants were recruited. There were 11 informants of aMCI patients and 9 informants of VCIND patients. Among the nine VCIND patients, seven had subcortical ischaemic vascular disease type, one had cortical and one had mixed cortical/subcortical-type ischaemia. Written consent was obtained from all participants. Patients with other neurological or psychiatric conditions such as epilepsy or delusional misidentification syndrome (DMS) were excluded from our study.

**Procedure**

A questionnaire based on our previous study29 was utilised to collect informants’ and patients’ demographic information, as well as to assess the severity of hyperfamiliarity symptoms. To participate in the study, informants were required to have spent at least 9 hours per week with the participant during the previous 12 months and to be familiar with the participant’s habits. It was administered to informants verbally. These demographics include informant’s age, gender and relationship with the patient. The patient’s diagnosis and Mini–Mental State Examination (MMSE) score were also collected.

Informants were asked to rate the frequency of hyperfamiliarity of patients in three domains: “people” (e.g., strangers on the street), “places” (e.g., shopping malls) and “objects” (e.g., cars on the street). For each domain, informants were given a statement on hyperfamiliarity (e.g., “Patient claims to recognize or be familiar with people on the street even though they have not met before”). They then reported how often they observed symptoms within the last month, from 0 (does not occur at all) to 5 (occurs 9 or 10 times out of 10 encounters). For our study, hyperfamiliarity was defined as any incorrect recognition of a person, place or object.

MRI brain images of the VCIND group performed within 12 months of study recruitment were retrieved. A senior neuroradiologist blinded to patient diagnosis scored the ischaemic visual ratings (IVRs) of signal hyperintensities for VCIND patients based on the fluid-attenuated inversion recovery sequence images.
The presence and severity of hyperintensities were scored according to a comprehensive scale created by Scheltens and colleagues,1,2 which includes periventricular, white matter and basal ganglia hyperintensities, as well as infra-tentorial foci of the hyperintensity.

Written consent was obtained from all participants, and the study was approved by the Singhealth Centralised Institutional Review Board.

**Statistical Method**

Wilcoxon’s rank sum test with continuity correction for continuous variables and the chi-squared test for categorical variables were applied to compare the demographics and hyperfamiliarity scores between the two groups. For this analysis, hyperfamiliarity scores were further dichotomised into two categories: those with scores of 0 (negative for hyperfamiliarity) and those with scores of 1-5 (positive for hyperfamiliarity). This was done, as the majority of participants reported only a score of 1 (occurs 1 to 2 times out of 10).

Spearman’s rank correlation coefficient was employed to measure the correlation between total hyperfamiliarity scores as well as scores in the “people” domain, and the IVR scores for hyperintensities of the VCIND group. The “object” and “place” domains were not analysed due to the low presence of these scores.

**RESULTS**

Wilcoxon’s rank sum test and the chi-squared test for patient and informant demographics (e.g., age, gender, relationship of informant with patient) showed no group differences between aMCI and VCIND patients.

In the comparison between both groups, statistically significant differences were found only in the hyperfamiliarity domain of “people,” as well as in total score (p < 0.05), but not in the hyperfamiliarity domains of “places” and “objects” (p = 0.881, p = 0.257, respectively). For the hyperfamiliarity domain of “people,” as well as in terms of total score, the VCIND group had significantly more participants who were positive for hyperfamiliarity, compared to the aMCI group. Table 1 summarizes the demographics of the two groups, and Table 2 presents the results of the data analysis.

Spearman’s rank correlation coefficient showed that there were no significant correlations between total hyperfamiliarity and IVR scores (Table 3). However, there was a significant positive correlation between scores in the “people” domain of hyperfamiliarity and basal ganglia IVR scores (r = 0.76, p = 0.028). Within the basal ganglia, there was a strong positive correlation between scores in the “people” domain and IVR scores of the putamen (r = 0.715, p = 0.046). Other areas in the basal ganglia—such as the caudate nucleus, globus pallidus, thalamus and internal capsule—showed no significant correlations.

**DISCUSSION**

Our results demonstrate that, despite being comparable in terms of global cognitive function as measured by MMSE score, VCIND patients tended to have significantly more hyperfamiliarity symptoms in the “people” domain compared to the aMCI group, but not in the “places” and “objects” domains. This confirms the hypothesis that hyperfamiliarity is more common among patients with VCIND, though only in some aspects, likely due to the vascular pathological brain changes to neuroanatomical structures implicated in hyperfamiliarity.

Most VCIND patients had the subcortical ischaemic type, and this study also found that the basal ganglia were implicated in hyperfamiliarity. Our results suggest that a significant increase in presence and severity of hyperintensities in the basal ganglia, among patients with VCIND, though only in some aspects, likely due to the vascular pathological brain changes to neuroanatomical structures implicated in hyperfamiliarity.

**Table 1: Participant demographics**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Total (n = 20)</th>
<th>aMCI (n = 11)</th>
<th>VCIND (n = 9)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>71.8 (9.1)</td>
<td>73.3 (9.5)</td>
<td>70.0 (8.7)</td>
<td>0.360</td>
</tr>
<tr>
<td>Gender, male, n (%)</td>
<td>12 (60.0)</td>
<td>5 (45.5)</td>
<td>7 (77.8)</td>
<td>0.142</td>
</tr>
<tr>
<td>MMSE score, mean</td>
<td>24.4 (4.2)</td>
<td>23.0 (4.9)</td>
<td>26.0 (2.3)</td>
<td>0.339</td>
</tr>
<tr>
<td>Informant</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>55.2 (16.9)</td>
<td>58.1 (16.2)</td>
<td>51.1 (18.1)</td>
<td>0.386</td>
</tr>
<tr>
<td>Gender, male, n (%)</td>
<td>2 (10.0)</td>
<td>1 (9.1)</td>
<td>1 (11.1)</td>
<td>0.881</td>
</tr>
<tr>
<td>Race, Chinese, n (%)</td>
<td>13 (81.2)</td>
<td>5 (71.4)</td>
<td>8 (88.9)</td>
<td>0.375</td>
</tr>
<tr>
<td>Relationship, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spouse</td>
<td>9 (45.0)</td>
<td>5 (45.5)</td>
<td>4 (44.4)</td>
<td>0.631</td>
</tr>
<tr>
<td>Child</td>
<td>10 (50.0)</td>
<td>5 (45.5)</td>
<td>5 (55.6)</td>
<td></td>
</tr>
<tr>
<td>Sibling</td>
<td>1 (5.0)</td>
<td>1 (9.1)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Education, mean (SD)</td>
<td>12.9 (2.9)</td>
<td>12.7 (2.4)</td>
<td>13.4 (4.0)</td>
<td>0.891</td>
</tr>
</tbody>
</table>

Wilcoxon rank sum test with continuity correction for continuous variables, and chi-square test for categorical variables. aMCI = amnestic mild cognitive impairment; VCIND = vascular cognitive impairment with no dementia; SD = standard deviation.

*Values of p < 0.05 were considered statistically significant.

**Table 2: Hyperfamiliarity scores, total and by domain**

<table>
<thead>
<tr>
<th>Hyperfamiliarity</th>
<th>Total (n = 20)</th>
<th>aMCI (n = 11)</th>
<th>VCIND (n = 9)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Score, mean (SD)</td>
<td>0.40 (0.75)</td>
<td>0.09 (0.97)</td>
<td>0.48 (0.30)</td>
<td>0.026</td>
</tr>
<tr>
<td>Presence, n (%)</td>
<td>6 (30.0)</td>
<td>1 (9.1)</td>
<td>5 (56.6)</td>
<td>0.024</td>
</tr>
<tr>
<td>People</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Score, mean (SD)</td>
<td>0.15 (0.37)</td>
<td>0.0 (0.0)</td>
<td>0.33 (0.50)</td>
<td>0.043</td>
</tr>
<tr>
<td>Presence, n (%)</td>
<td>3 (15.0)</td>
<td>0 (0)</td>
<td>3 (33.3)</td>
<td>0.038</td>
</tr>
<tr>
<td>Places</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Score, mean (SD)</td>
<td>0.20 (0.67)</td>
<td>0.09 (0.30)</td>
<td>0.33 (1.0)</td>
<td>0.827</td>
</tr>
<tr>
<td>Presence, n (%)</td>
<td>2 (10.0)</td>
<td>1 (9.1)</td>
<td>1 (11.1)</td>
<td>0.881</td>
</tr>
<tr>
<td>Objects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Score, mean (SD)</td>
<td>0.05 (0.22)</td>
<td>0.0 (0.0)</td>
<td>0.11 (0.33)</td>
<td>0.269</td>
</tr>
<tr>
<td>Presence, n (%)</td>
<td>1 (5.0)</td>
<td>0 (0)</td>
<td>1 (11.1)</td>
<td>0.257</td>
</tr>
</tbody>
</table>

aMCI = amnestic mild cognitive impairment; VCIND = vascular cognitive impairment with no dementia; SD = standard deviation.

*Values of p < 0.05 were considered statistically significant.
Table 3: Summary of the ischaemic visual rating scores for VCIND patients

<table>
<thead>
<tr>
<th>VCIND group, n = 9</th>
<th>Ischaemic visual rating scores</th>
<th>Hyperfamiliarity, total score</th>
<th>Hyperfamiliarity, &quot;people&quot; domain score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>r</td>
<td>p</td>
</tr>
<tr>
<td>PVH, mean (SD)</td>
<td>3.25 (1.669)</td>
<td>-0.554</td>
<td>0.154</td>
</tr>
<tr>
<td>WMH, mean (SD)</td>
<td>9.63 (5.579)</td>
<td>0.125</td>
<td>0.767</td>
</tr>
<tr>
<td>BGH, mean (SD)</td>
<td>8.75 (3.845)</td>
<td>0.466</td>
<td>0.245</td>
</tr>
<tr>
<td>Caudate, mean (SD)</td>
<td>1.63 (1.061)</td>
<td>-0.284</td>
<td>0.495</td>
</tr>
<tr>
<td>Putamen, mean (SD)</td>
<td>2.00 (1.604)</td>
<td>-0.141</td>
<td>0.739</td>
</tr>
<tr>
<td>Globus pallidus, mean (SD)</td>
<td>1.00 (1.309)</td>
<td>0.366</td>
<td>0.372</td>
</tr>
<tr>
<td>Thalamus, mean (SD)</td>
<td>2.25 (1.488)</td>
<td>0.448</td>
<td>0.266</td>
</tr>
<tr>
<td>Internal capsule, mean (SD)</td>
<td>1.88 (1.553)</td>
<td>0.309</td>
<td>0.475</td>
</tr>
</tbody>
</table>

VCIND = vascular cognitive impairment with no dementia; SD = standard deviation; PVH = periventricular hyperintensities; WMH = white matter hyperintensities; BGH = basal ganglia hyperintensities; r = Spearman’s rank correlation coefficient measuring correlation of hyperfamiliarity score of “people” domain with respective ischaemic scores.

particularly the putamen, means a higher likelihood of patients having hyperfamiliarity symptoms, particularly in the “people” domain. This is consistent with previous studies which indicated that these subcortical structures participate in memory function. It has been established that small-vessel ischaemic strokes tend to affect such subcortical structures as the basal ganglia and thalamus.33 Alexander and colleagues,34 for example, demonstrated that the basal ganglia are involved in memory formation and recall. This is consistent with recent studies which indicated that these particular subcortical structures participate in memory formation, together with the hippocampus.35 There is also recent evidence to suggest striatum involvement in memory recognition from a familiarity (perceived recognition) perspective.36 The putamen itself has also been found to play a role in working memory, particularly in encoding and maintenance.37 Putamen lesions as a result of stroke also demonstrate its involvement in maintenance of information in working memory,38,39 as well as in discarding irrelevant information.40 The putamen has also been found to contribute to episodic memory function.41 Compromised subcortical integrity in these areas, as a result of small-vessel ischaemia, could have contributed to the higher frequency of real-life false event memory recollection reflected in our study. Previous studies have also demonstrated evidence supporting a dual-process mechanism in the memory recognition process,42 in which the frontal subcortical pathway is important in effective memory retrieval and the matching process. Subcortical ischaemia, which tends to impair the frontal subcortical regions,33 results in executive dysfunction and may be responsible for the occurrences of the hyperfamiliarity observed in real life among VCIND patients.

Another possible explanation as to why participants with aMCI would not show as many symptoms of hyperfamiliarity may be due to the neuropathological profile of aMCI. Patients with aMCI have been known to display more atrophy of the hippocampus when compared to normal controls.43,44 A recent study also demonstrated that the volumes of the hippocampal regions and entorhinal cortex have been shown to be more atrophied in patients with aMCI compared to patients with non-amnestic MCI.45 However, the perirhinal cortex, which has previously been implicated in familiarity disorder,3,11 was relatively spared. This may explain anatomically why patients with aMCI would be less affected by familiarity disorder.

Unlike the “people” domain, the two groups did not differ significantly in terms of scores in the “place” and “object” domains, however. Furthermore, there were no significant correlations between IVR scores and total hyperfamiliarity scores, despite a strong significant correlation between hyperfamiliarity scores in the “people” domain and IVR scores in the basal ganglia and putamen. This is likely diluted from the effect of the “place” and “object” domain scores, as they were extremely low. This suggests that people familiarity is probably processed distinctly from places or objects. It is possible that the hyperfamiliarity effect may exist predominantly for faces, since facial recognition occurs via unique mechanisms compared to object or place recognition. Evidence suggests a dedicated pathway in terms of facial processing, as a double dissociation between face and object recognition has been demonstrated in the literature. For instance, individuals with brain trauma have reported prosopagnosia with intact object recognition,46,47 while others have suffered impaired object recognition with unaffected face recognition.48-50 Furthermore, neuroimaging research has identified specific regions in the brain that react particularly to face stimuli, such as the fusiform face area in the fusiform gyrus.51-55 In literature, activity in the putamen was found to predict recognition when encoding and matching faces to names.56 This is consistent with our finding that the severity of ischaemia in the putamen positively correlates with the frequency of hyperfamiliarity occurring, but only in the “people” domain. Overall, hyperfamiliarity for faces has been largely observed in the literature,3,7,57,58 with little to no research dedicated to hyperfamiliarity for objects or places. This may explain why hyperfamiliarity was only significantly frequent in the “people” domain, as well as being the only domain to correlate significantly with severity of basal ganglia and putamen hyperintensities in VCIND patients. The small sample size also could have contributed to the low frequency of hyperfamiliarity symptoms in the “object” and “place” domains.

This study has some limitations, the largest of which being the small sample size, given the availability of VCIND and aMCI...
patients at the time. It may be more prudent then to consider this a pilot study, but any future endeavours will include more participants. The present study was largely dependent on a small sample of informants and their report on patients’ hyperfamiliarity symptoms. Some informants were spouses who lived together with and thus spent more time with patients, compared to informants who were patients’ children who lived apart but visited regularly. Thus, informants’ reports may vary or not be entirely accurate. However, the informants were usually the primary caregivers, and it was found that the between-group demographics (such as age, gender, relationship with patient and years of education) were also comparable. Thus, this should not present as a severe limitation. In addition, patients’ exposure to the external environment was not monitored, which could vary and influence the frequency of encountering situations where hyperfamiliarity could be present. However, patients with cognitive impairment generally tend to have limited exposure. Future studies should include this as a variable to be controlled by assessing frequency of interaction with the external environment. While normative data do not exist for hyperfamiliarity within the general population, a sample of healthy controls comparable in demographics (N = 24) from the previous study with no neurological conditions reported no symptoms of hyperfamiliarity in the current applied questionnaire. Thus, using this as a baseline, we can infer that hyperfamiliarity is likely elevated in the clinical groups being applied questionnaire. Thus, using this as a baseline, we can infer hyperfamiliarity symptoms in daily life or used as a predictor of future occurrences in a longitudinal setting. Future studies should also look into the correlation between types of VCIND and clinical phenomenology to further characterize the brain–behavior relationship in producing real-life hyperfamiliarity. This may better establish the aetiology of hyperfamiliarity, particularly with regard to pathological vascular brain changes.

Thus, this study found that patients with VCIND encountered more hyperfamiliarity in daily life, particularly when seeing unfamiliar people, in comparison to patients with aMCI. This effect is observed despite a comparative global decline in cognitive function. This is likely due to impaired memory retrieval and matching processes as a result of subcortical ischaemic lesions caused by vascular disease.

ACKNOWLEDGMENTS

This study was supported by an NNI–HREF grant (NRH13/004) and an NNI Centre Grant (NCG PB02).

DISCLOSURES

Pei Shi Chia, Shahul Hameed, Kok Pin Yong, Ling Ling Chan and Simon Kang Seng Ting hereby state that they have nothing to disclose.

STATEMENT OF AUTHORSHIP

P.S. Chia collected the data and wrote the paper. L.L. Chan scored the neuroimaging data. S. Hameed supervised data collection. K.P. Yong obtained the grant for the study. S. Ting designed the study, supervised data collection and was responsible for the statistical design of the study and for carrying out the statistical analysis, and assisted with writing the article.

SUPPLEMENTARY MATERIAL

To view supplementary material for this article, please visit https://doi.org/10.1017/cjn.2016.403

REFERENCES

12. Gonsalves BD, Kahn I, Curran T, Norman KA, Wagner AD. Memory strength and repetition suppression: multimodal imaging


50. Moscovitch M, Winocur G, Behrmann M. What is special about face recognition? Nineteen experiments on a person with visual


