LETTER TO THE EDITOR

Does hippocampal atrophy explain anterograde and retrograde amnesia following autoimmune limbic encephalitis?

Dear Editor,

Autoimmune limbic encephalitis associated with antibodies to components of the voltage-gated potassium channel complex (VGKCC-Ab-LE) often leads to focal hippocampal atrophy and persistent episodic memory impairment (Butler et al., 2014; Loane et al., 2019). In an interesting study of 7 VGKCC-Ab-LE patients with hippocampal damage, Lad, Mullally, Houston, Kelly, and Griffiths (2019) reported (a) impaired recall, in the face of preserved recognition memory, as disclosed by the Doors and People Test (DPT; Baddeley, Emslie, & Nimmo-Smith, 1994). This was interpreted as consistent with frameworks attributing recollection processes to hippocampal function (Yonelinas, 2002); (b) impairment of autobiographical (“episodic”) memory in the face of preserved personal semantic memory, without temporal gradient (Autobiographical Memory Interview—AMI; Kopelman, Wilson, & Baddeley, 1989). This was interpreted as inconsistent with systems consolidation accounts (Squire, Genzel, Wixted, & Morris, 2015) and dovetails with reports on temporally ungraded retrograde amnesia (Post-AMT/AMI memory for events in all three periods assessed (childhood, recent events)). However, their impaired personal semantic memory was driven by their low scores in the recent epoch: they showed no evidence of personal semantic memory impairment for childhood or early adulthood, but impairment for recent events. On the contrary, patients showed impaired autobiographical memory for events in all three periods assessed (childhood, early adulthood, recent events).

Given that our different findings could potentially be attributed to the lower sample size, we then (a) included another 3 LGI1-Ab-LE cases that satisfied all criteria above except for the fact that: 1 patient had been assessed 1 year [instead of >1 year as in Lad et al. (2019)] post-symptom onset, and another 2 had presented with acute VGKCC-Ab levels < 1,000 pmol/L (but still >400 pmol/L; “HPC2 patients”); consistent with (Loane et al., 2019), negative correlation was observed, even at trending levels, between the acute VGKCC-Ab levels and DPT/AMI scores or right/left hippocampal volumes across those 7 HPC2 patients (all rhos/ps, −0.234 < rho ≤ 0.580; p ≥ .228); (b) identified another 5 (1 female) LGI1-Ab-LE patients with no atrophy in the hippocampus or the parahippocampal gyrus...
**TABLE 1** Comparisons of the different LGI1-Ab-LE patient groups with CTRs or the population mean on the Doors and People Test (Baddeley et al., 1994) and the Autobiographical Memory Interview (Kopelman et al., 1989); none of the patient groups differed from CTRs on the recall-recognition discrepancy scores (all Us/ps, U > 33; p > .271)

| Patient group     | Vs.                  | Doors and People Test | Recognition | Autobiographical memory interview (raw scores) | Autobiographical Memory Interview (raw scores) |
|-------------------|----------------------|-----------------------|-------------|-----------------------------------------------|-----------------------------------------------|
|                   |                      | Recall                |             |                                              |                                              |
|                   |                      | Verbal                |             |                                              |                                              |
|                   |                      | Immediate (z)         |             |                                              |                                              |
|                   |                      | Delayed (raw scores)  |             |                                              |                                              |
|                   |                      | Immediate (z)         |             |                                              |                                              |
|                   |                      | Delayed (raw scores)  |             |                                              |                                              |
| HPC (n = 4/4)     | Male CTRs (n = 25/26) | −0.13 .895            | 20.0 .043   | 1.32 .198                                     | 44.0 >.999                                    |
|                   | Population mean      | −0.63 .573            | n/a n/a     | 0.59 .594                                     | n/a n/a                                       |
| HPC2 (n = 6/7)    | CTRs (n = 38/39)     | −1.30 .199            | 28.5 .001   | −2.83 .007                                     | 90.0 .326                                     |
|                   | Population mean      | −1.54 .183            | n/a n/a     | −0.65 .547                                     | n/a n/a                                       |
| HPC-intact (n = 4/5) | CTRs (n = 38/39) | −2.05 .047            | 22.0 .008   | −0.69 .538                                     | 47.0 .040                                     |
|                   | Population mean      | −4.02 .028            | n/a n/a     | −0.07 .946                                     | n/a n/a                                       |
| HPC (n = 4/4)     | Male CTRs (n = 23/26) | 5.0 .001              | 140.0 .011  | 5.0 .001                                       | 10.0 .004                                      |
|                   | Population mean (t)  | −2.36 .099            | −2.18 .117  | −2.93 .061                                     | −1.96 .145                                     |
| HPC2 (n = 7/7)    | CTRs (n = 36/39)     | 16.5 .001             | 37.0 .001   | 12.5 .001                                      | 28.0 <.001                                     |
|                   | Population mean (t)  | −3.70 .010            | −3.18 .019  | −4.97 .003                                     | −2.86 .029                                     |
| HPC-intact (n = 5/5) | CTRs (n = 36/39) | 25.0 .005             | 58.5 .190   | 46.0 .031                                      | 28.5 .004                                      |
|                   | Population mean (t)  | −1.88 .133            | −0.71 .519  | −1.12 .325                                     | −2.87 .045                                     |

Abbreviations: CTRs: healthy controls; HPC: LGI1-Ab-LE patients with hippocampal and no parahippocampal atrophy that meet the selection criteria employed by Lad et al. (2019); HPC2: LGI1-Ab-LE patients with hippocampal and no parahippocampal atrophy; HPC-intact: LGI1-Ab-LE patients without hippocampal or parahippocampal atrophy; LGI1-Ab-LE: autoimmune limbic encephalitis associated with autoantibodies targeting leucine-rich glioma-inactivated protein 1; n = a/b: number of patients or CTRs originally reported in Loane et al. (2019) who had completed the Doors and People Test and/or the Autobiographical Memory Interview; Set A/Set B: HPC/HPC2 patients’ lower scores in verbal recognition memory could not be exclusively attributed to their performance in the more difficult Set B; bold values: p < .05; t/Wt: Student/Welch (unequal variance) t test; U: Mann–Whitney U (the raw scores for CTRs were not normally distributed); vs. population mean: in a series of one-sample t tests we compare patients’ scores with z = 0 (Doors and People Test) or with the mean/minimum and maximum values of acceptable range (Autobiographical Memory Interview); z: age-scaled standardized scores.
("HPC-intact")—all 5 patients showed intact semantic memory, language, executive, motor, and visuospatial function. We iterated the comparisons on the DPT and the AMI between these groups and all 39 CTRs (male and female) reported in Loane et al. (2019) (age at assessment: CTRs: mean = 60.86; SD = 11.61 years; HPC2: mean = 62.32; SD = 12.76 years; HPC-intact: mean = 67.81; SD = 9.56;

**FIGURE 1**  (a) Patients’ and CTRs’ scores on the four different subtests of the DPT (People: Immediate verbal recall; Names: immediate verbal recognition; Shapes: immediate visual recall; Doors: immediate visual recognition); (b) patients’ and CTRs’ scores on the AMI; (c) overall memory scores for the DPT correlated across our cohort of 24 VGKCC-Ab-LE patients (22/24 completed the DPT; 23/24 had viable resting-state fMRI datasets) with their reduced interhippocampal (r = .43, p = .0496) and corticohippocampal (right hippocampus – precuneus cluster) rsFC (r = .60, p = .004), consistent with the findings in Loane et al. (2019); hippocampal (left or right) volumes did not correlate with overall memory scores or with immediate verbal/visual recall/recognition scores across patients (all rs/p, |r| < .32; p > .14); (d) remote autobiographical memory (AMI) impairment was a function of thalamic volume reduction (r = .60, p = .002; cluster identified in Loane et al. (2019); the correlation is consistent with that reported in a group of 38 patients with autoimmune LE in Argyropoulos et al. (2019); hippocampal (left or right) volumes did not correlate with remote autobiographical memory scores across patients (both rs/p, r < .35; p > .10). AMI: Autobiographical Memory Interview (Kopelman et al., 1989); CTRs: healthy controls; DPT: Doors and People Test (Baddeley et al., 1994); GM: grey matter; HPC2: LGI1-Ab-LE patients with hippocampal and no parahippocampal atrophy; HPC-intact: LGI1-Ab-LE patients without hippocampal or parahippocampal atrophy; LGI1-Ab-LE: autoimmune limbic encephalitis associated with autoantibodies targeting leucine-rich glioma-inactivated protein 1; R: right (hemisphere); rsFC: resting-state functional connectivity; VBM: voxel-based morphometry; VGKCC-Ab-LE: voltage-gated potassium channel complex autoantibody-related limbic encephalitis; z: age-scaled standardized scores in the DPT; z-res: volumes are residualized against age, sex, total intracranial volume and scanning protocol; connectivity values are residualized against age, sex, and seed volume across participants; *: vs CTRs: p < .05; ^: vs z = 0 (DPT) or vs mean (minimum and maximum values of acceptable range) (AMI); dashed horizontal lines: z = 0 (DPT) or mean (minimum and maximum values of acceptable range) (AMI) [Color figure can be viewed at wileyonlinelibrary.com]
Our comparisons revealed a very different pattern: both HPC2 and HPC-intact patients showed impaired visual and/or verbal recall, but HPC2 patients also showed impaired verbal recognition (Figure 1a). HPC2 patients scored lower in both autobiographical and personal semantic memory than CTRs, as did HPC-intact patients (Figure 1b). Nevertheless, impaired personal semantic memory was driven by low scores in the recent epoch only. Moreover, patients’ low scores in the recent epoch for both autobiographical and semantic memories should not be attributed to retrograde amnesia, since the recent epoch largely overlapped with the postmorbid period. The selective impairment in autobiographical aspects of remote memory shown in Lad et al. (2019) may thus not be inconsistent with our findings.

Overall, our data show that focal hippocampal atrophy after VGKCC-Ab-LE does not necessarily cause selective deficits in recall memory. Instead, impairment may extend to certain types of recognition memory, as observed in cases of more dense amnesia following hippocampal damage (e.g., Manns & Squire, 1999). Custom-made behavioral paradigms that quantify the contributions of familiarity and recollection in recognition memory following focal damage within the medial temporal lobes should be employed instead (e.g., Argyropoulos et al., 2020; Bowles et al., 2007), ideally for distinct material types. For instance, the hippocampus may enhance verbal recognition by activating pre-existing associations with (and thus enriching contextual memory for) each verbal memorandum, hence increasing the probability of its successful recognition (Bird & Burgess, 2008). Individual differences in the extent to which HPC patients rely on familiarity to perform in recognition memory tasks pre- and, a fortiori, post-morbidly should also be taken into account. However, anterograde and retrograde amnesia may occur post-VGKCC-Ab-LE in the absence of hippocampal/parahippocampal atrophy. We propose that the interpretation of memory deficits reported here and in Lad et al. (2019) should also take into account structural/functional abnormalities in the extended hippocampal system (Bubb, Kinnavane, & Agleton, 2017), in line with Argyropoulos et al. (2019) and Loane et al. (2019). Across our patient cohort, overall memory scores (DPT) were a function of reduced interhippocampal and corticohippocampal resting-state functional connectivity (Figure 1c). Likewise, remote autobiographical memory (AMI) impairment was a function of thalamic volume reduction (Figure 1d). We thus believe that assessment of network abnormalities that may follow hippocampal damage is crucial to resolve debates about the neural basis of anterograde and retrograde amnesia. Since the profile of small patient groups with “focal” hippocampal amnesia may readily be biased by the idiosyncratic features of each study, we call for cross-center studies that employ a broad range of neuropsychological tests to assess episodic memory and also capitalize on the variability of hippocampal damage and symptom severity across larger cohorts.
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