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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-VGKCC-Ab-LE (Chan, Henley, Rossor, & Warrington, 2007). Given the rarity of VGKCC-Ab-LE, it is important to examine the replicability of such dissociations employing the same tests and patient selection criteria.

In a recent paper, we reported on the brain abnormalities underlying anterograde amnesia in a large cohort of VGKCC-Ab-LE patients (n = 24) (Loane et al., 2019). Our patients scored lower than healthy controls (CTRs) in verbal/visual recall and verbal recognition. However, the selection criteria employed by Lad et al. (2019) were different, highlighting the possibility that an appropriate subset of our cohort would replicate their findings. Among those criteria were: (a) structural MRI conducted >1 year post-acutely; (b) atrophic hippocampi and spared parahippocampal gyri in the stable chronic phase. However, the definition of atrophy was based on visual inspection. In contrast, the data we reported in Loane et al. (2019) allow us to apply this criterion in a more precise fashion, since we had conducted gold-standard manual volumetry of medial temporal lobe structures; (c) VGKCC-Ab level > 1,000 pmol/L at diagnosis. This value is very high relative to commonly used cut-offs [100 pmol/L (Celicanin et al., 2017; Zuliani et al., 2007); 150 pmol/L (Barajas, Eric Collins, Cha, & Geschwind, 2010); 400 pmol/L (Irani et al., 2010; Vincent et al., 2004)]; (d) a clinical phenotype consistent with LGI1-LE. While the paper relied on neurological assessment to determine the presence of an "LGI1-type," our data allow us to select cases that tested positive exclusively for LGI1-Ab.

We first identified four patients with LGI1-Ab-LE, focal hippocampal atrophy [right and/or left hippocampus: $z < -1.96$ relative to a group of 48 age-matched CTRs (Argyropoulos et al., 2019), reflecting significant volume reduction ($p < .05$); right/left entorhinal/perirhinal/parahippocampal cortex volumes: $z > -1.29$], assessed > 1 year post-symptom onset ("HPC patients"). Consistent with the post-acute profile of our cohort as a whole (Loane et al., 2019), these patients showed preserved semantic memory and language, visuospatial, motor, and executive function. Since Lad et al. (2019) had employed age- and sex-matched CTRs on an individual basis, we compared our 4 male HPC patients with the 26 male CTRs of our study (patients' age at assessment: mean = 63.43; SD = 8.99 years; male CTRs' age: mean = 60.20; SD = 10.06 years; patients vs. male CTRs: $t = -0.60$, $p = 0.551$). We also conducted comparisons against population means, wherever available, in order to enhance the generalizability of our findings.

Unlike Lad et al. (2019), HPC patients showed clearly impaired verbal recognition, along with impaired delayed verbal recall (Table 1). Regarding retrograde amnesia, they showed impairment in both autobiographical and personal semantic memory. 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; "HPC_2 patients"); consistent with (Loane et al., 2019), no 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 HPC_2 patients (all rhos/ps, $-0.234 \leq rho \leq 0.580$; $p \geq .228$); (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 *U*s/*p*s, $U > 33$; $p > .271$)

		Doors and People Test															
		Recall								**Recognition**							
		Verbal				**Visual**				**Verbal**						**Visual**	
										Immediate						**Immediate**	
		Immediate (z)		**Delayed (raw scores)**		**Immediate (z)**		**Delayed (raw scores)**		**(z)**		**Set A (raw scores)**		**Set B (raw scores)**		**(z)**	
Patient group	**Vs.**	**t/Wt**	***p***	***U***	***p***	**t/Wt**	***p***	***U***	***p***	***t***	***p***	***U***	***p***	***U***	***p***	***t***	***p***
HPC (n = 4/4)	Male CTRs (n = 25/26)	−0.13	.895	**20.0**	**.043**	1.32	.198	44.0	>.999	**−2.72**	**.011**	16.5	.118	4.0	.055	0.32	.754
	Population mean	−0.63	.573	n/a	n/a	0.59	.594	n/a	n/a	**−5.43**	**.012**	n/a	n/a	n/a	n/a	1.15	.332
HPC_2 (n = 6/7)	CTRs (n = 38/39)	−1.30	.199	**28.5**	**.001**	**−2.83**	**.007**	90.0	.326	**−3.33**	**.002**	37	.021	21.0	.078	0.27	.791
	Population mean	−1.54	.183	n/a	n/a	−0.65	.547	n/a	n/a	**−3.53**	**.017**	n/a	n/a	n/a	n/a	1.18	.291
HPC-intact (n = 4/5)	CTRs (n = 38/39)	**−2.05**	**.047**	**22.0**	**.008**	−0.69	.538	**47.0**	**.040**	−0.75	.458	32	.733	9.5	.579	−0.52	.607
	Population mean	**−4.02**	**.028**	n/a	n/a	−0.07	.946	n/a	n/a	0.12	.912	n/a	n/a	n/a	n/a	0.74	.515
		Autobiographical memory interview (raw scores)															
		Autobiographical								Personal semantic							
		Total		Childhood		Early adulthood		Recent		Total		Childhood		Early adulthood		Recent	
Patient group	Vs.	Test	*p*	Test	*p*	Test	*p*	Test	*p*	Test	*p*	Test	*p*	Test	*p*	Test	*p*
HPC (n = 4/4)	Male CTRs (n = 23/26) (U)	**5.0**	**.001**	**14.0**	**.011**	**5.0**	**.001**	**10.0**	**.004**	**17**	**.047**	31.0	.313	27.0	.194	**14.5**	**.026**
	Population mean (t)	−2.36	.099	−2.18	.117	−2.93	.061	−1.96	.145	−1.68	.192	−0.34	.756	2.78	.069	−2.04	.134
HPC_2 (n = 7/7)	CTRs (n = 36/39) (U)	**16.5**	**<.001**	**37.0**	**.001**	**12.5**	**<.001**	**28.0**	**<.001**	**63.5**	**.038**	114	.699	90.5	.228	**47.5**	**.005**
	Population mean (t)	**−3.70**	**.010**	**−3.18**	**.019**	**−4.97**	**.003**	**−2.86**	**.029**	−2.27	.064	−0.32	.758	0.34	.742	**−2.73**	**.034**
HPC-intact (n = 5/5)	CTRs (n = 36/39) (U)	**25.0**	**.005**	58.5	.190	**46.0**	**.031**	**28.5**	**.004**	**35.5**	**.027**	45.5	.070	68.0	.390	64.5	.303
	Population mean (t)	−1.88	.133	−0.71	.519	−1.12	.325	**−2.87**	**.045**	−2.03	.112	−0.90	.419	<0.001	>.999	−1.35	.249

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); HPC_2: 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/HPC_2 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; HPC_2: mean = 62.32; *SD* = 12.76 years; HPC-intact: mean = 67.81; *SD* = 9.56;

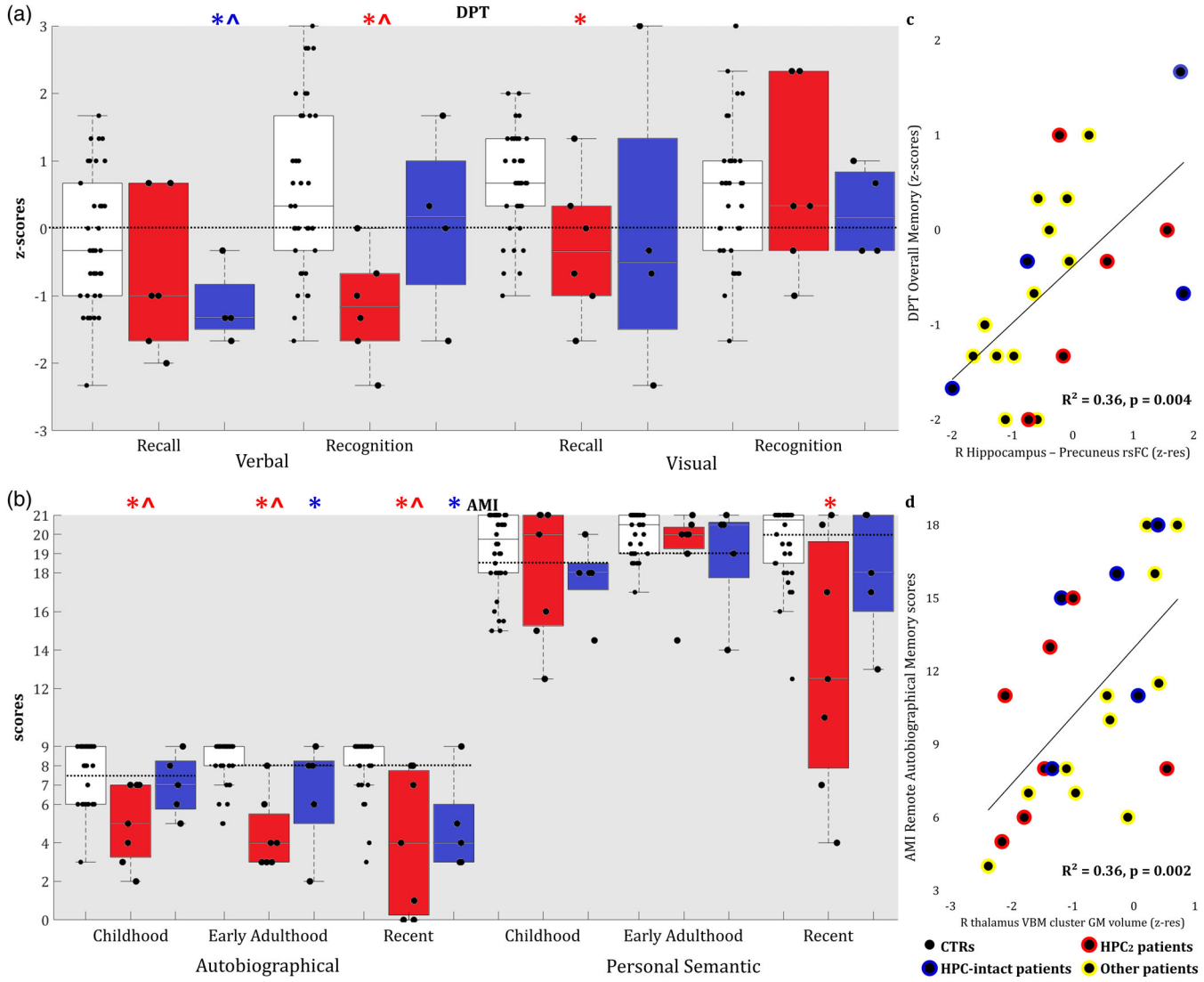

FIGURE 1 (a) Patients' and CTRs' scores on the four different subtests of the DPT (People: Immediate verbal recall; Names: immediate verbal recognition; Shapes: immediate visual recall; Doors: immediate visual recognition); (b) patients' and CTRs' scores on the AMI; (c) overall memory scores for the 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*/*ps*, $|r| < .32$; $p > .14$); (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*/*ps*, $r < .35$; $p > .10$). AMI: Autobiographical Memory Interview (Kopelman et al., 1989); CTRs: healthy controls; DPT: Doors and People Test (Baddeley et al., 1994); GM: grey matter; HPC_2: 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]

all comparisons: $|t| < 1.29$, $p > .2$). We tested the prediction that HPC_2 patients would show selective recall deficits along with impaired autobiographical but spared personal semantic memory, whereas HPC-intact patients would show little evidence for retrograde/anterograde amnesia.

Our comparisons revealed a very different pattern: both HPC_2 and HPC-intact patients showed impaired visual and/or verbal recall, but HPC_2 patients also showed impaired verbal recognition (Figure 1a). HPC_2 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-VKGCC-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, & Aggleton, 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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CONFLICT OF INTEREST

The authors declare no competing biomedical financial interests or potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Georgios P. D. Argyropoulos and Christopher R. Butler were responsible for study concept and design, data acquisition and analysis, drafting the manuscript, and preparing figures.

PATIENT CONSENT

All participants provided written informed consent according to the Declaration of Helsinki.

ETHICS APPROVAL

Ethical approval was received from South Central Oxford Research Ethics Committee (REC no: 08/H0606/133).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on OSF: https://osf.io/g63r7/?view_only=31170ae79784425d95686f1958eb4711.

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