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Contribution of autobiographic memory impairment to subjective memory complaints in focal epilepsy

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ABSTRACT

"My memory is terrible!" is a common refrain among people with epilepsy, but such complaints are not reliably linked to poor performances on standard tests of memory. Negative affect like depression and anxiety are the most robust predictor of these complaints; however, neither do they entirely account for the phenomenon. The contribution of autobiographic memory impairment to subjective memory complaints in focal epilepsy has not been well-explored despite autobiographic memory impairments being common in patients with epilepsy, and the face validity of relating day-to-day memory failings to such a personally relevant form of memory. The current study sought to clarify whether autobiographic memory dysfunction contributes to subjective complaints in epilepsy, above and beyond negative affect, objective memory impairment, and epileptological factors in a large sample of patients with drug-resistant focal epilepsy relative to healthy controls ($N = 135$). Patients were stratified into groups with mesial temporal (MT; $n = 40$) versus nonmesial temporal (NMT; $n = 46$) foci. Compared to controls ($n = 46$), both patient groups reported more bitter subjective memory complaints ($p < 0.001$, large effect size), demonstrated poorer episodic ($p = 0.001$, large effect size) and semantic autobiographical recall ($p = 0.004$, medium effect size), and had higher levels of depressive symptomatology ($p = 0.011$, medium effect size), and trait neuroticism ($p = 0.015$, medium effect size). Contrary to expectations, multiple regression analyses revealed that autobiographic memory function was not an independent predictor of subjective memory complaints in either group with epilepsy. In people with epilepsy with MT foci, objective verbal memory dysfunction, neuroticism, and female gender predicted memory complaints ($R^2 = 0.70$, $p = 0.015$), whereas only neuroticism predicted memory complaints in people with epilepsy with NMT foci ($R^2 = 0.21$, $p = 0.001$). Although patients' poor recall of their autobiographical memories did not contribute to their concerns about their day-to-day memory function, the findings indicate that the location of the epileptogenic focus can provide clues as to the underlying contributors to subjective memory complaints in focal epilepsy. Important clinical implications to stem from these findings include the need for clinicians to adopt a patient-tailored, multifactorial lens when managing memory complaints in people with epilepsy, taking into account both psychological and cognitive factors.

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1. Introduction

A common refrain across global epilepsy centers is patients complaining of memory problems [1–4]. This may seem reasonable given that memory decrement has long been recognized as an archetypal cognitive feature of the disorder; this is especially true for temporal lobe epilepsy (TLE) that disrupts brain networks fundamental to memory [5,6]. Underscoring the potential prognostic value of such complaints, in Alzheimer's disease subjective memory concerns have been directly linked to the neuropathological substrate (high β-amyloid burden) and faster rates of cognitive decline [7–11].

In epilepsy, however, while some research suggests that subjective memory complaints are concordant with impairments on standard neuropsychological tests of memory [12–15], other studies do not identify

Abbreviations: AEDs, Antiepileptic Drugs; AMI, Autobiographical Memory Interview; AMI-AI, Autobiographical Memory Interview Autobiographical Incident; AMI-PS, Autobiographical Memory Interview Personal Semantic; AMN, Autobiographic Memory Network; CEP, Comprehensive Epilepsy Program; EPQ-R, Eysenck Personality Questionnaire-Revised; fMRI, Functional Magnetic Resonance Imaging; IQ, Intelligence Quotient; MCQ, Memory Complaint Questionnaire; MT, Mesial Temporal; NDDI-E, Neurological Disorders Depression in Epilepsy Inventory; NMT, Non-Mesial Temporal; PFC, Prefrontal Cortex; RAVLT, Rey Auditory-Verbal Learning Test; RCFT, Rey–Osterrieth Complex Figure Test; TLE, Temporal Lobe Epilepsy; WMS-IV, Wechsler Memory Scale-Fourth Edition.

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such a link (e.g., [1,4,16–18]). Subjective memory complaints seem to be a more reliable marker of memory network dysfunction in patients whose seizure foci impinge on the memory-critical mesial temporal (MT) region (MT epilepsy) [6], with a previous study showing that complaints are linked to reduced performances on memory tests in MT patients, but not people with epilepsy with non-MT foci (NMT epilepsy) [19]. More robustly, previous studies link low mood and trait neuroticism (i.e., a tendency to negative affects like sadness, anxiety, and anger) to memory concerns in epilepsy (e.g., [1,20,21]). This may reflect cognitive symptoms of rumination, indecision, and reduced concentration that are prominent features of mood disorder in the population with epilepsy [22]. Together, the previous literature illustrates how difficult it can be for the busy clinician to gauge the diagnostic significance of subjective memory complaints in epilepsy, complicating investigative and treatment decisions.

The lack of a compelling connection between patient complaints and impairments detectable on traditional neuropsychological memory tests may stem from the underuse of naturalistic measures that reflect the types of day-to-day memory failings that typically concern people with epilepsy, such as, forgetting names of acquaintances. Autobiographic memory tests overcome this problem by drawing on memory for personally-relevant semantic facts (e.g., home addresses, names of acquaintances, dates), and salient episodes across the lifespan (e.g., that 6th birthday party you had at the zoo) [23], whereas standard memory tests only assess the ability to learn and retain simple, decontextualized information over a short period of time, such as the number of words that can be recalled from a list after a 20-minute delay. To our knowledge, the contribution of autobiographic memory to subjective memory complaints has only once been explored, in a paper profiling the cognition of the relatively rare TLE subtype, transient epileptic amnesia (TEA) [24]. It found that together with depression/anxiety symptoms, impoverished autobiographic memory recall predicted 51% of the variance of subjective remote memory scores in this TEA sample. Its contribution to focal epilepsies more commonly encountered in tertiary epilepsy clinics remains unknown, however, despite growing evidence that autobiographic memory is frequently compromised in patients with heterogeneous focal epilepsies [25–27], and can occur in the context of normal performances on standard memory tests [28]. Autobiographic memory is thought to be poor across temporal and extratemporal focal epilepsies because of the widely distributed topography of the autobiographic memory network [29,30]. It encompasses midline regions (mesial prefrontal cortices; mesial temporal structures; retrosplenial and posterior cingulate cortex), lateral cortices (ventrolateral prefrontal cortex; anterolateral temporal cortex; temporoparietal junction), and the cerebellum [29]. It draws together regions specialized for retrieval, autonoetic consciousness, emotion, and mental imagery in order to create a rich, temporally specific autobiographical recollection [31]. The current study examined whether autobiographic memory impairments predict subjective memory complaints in focal epilepsy, above and beyond the already known affective, cognitive, and epileptological predictors. We also aimed to delineate specific models of memory complaints for MT and NMT epilepsy subgroups.

We hypothesize that compared to healthy controls, patients with MT and NMT epilepsy will both (i) report significantly higher subjective memory complaints, depressive symptoms, and neuroticism, and (ii) will have significantly worse autobiographic recall, with no differences in performance between the two epilepsy groups; patients with MT epilepsy will show significantly worse verbal and visual memory test performance relative to both controls and patients with NMT epilepsy. We hypothesize that because of its seemingly superior ecological validity, poor autobiographic memory function will be a stronger predictor of subjective memory complaints for both patients with MT and NMT epilepsy than traditional objective measures of verbal and visual recall. Exploratory analyses will delineate distinct sets of affective, cognitive, and epileptological predictors of subjective memory complaints for patients with MT versus NMT focal epilepsy.

2. Methods

2.1. Participants

Overall, 135 adults participated in this study: 89 people with drug-resistant focal epilepsy recruited from the Comprehensive Epilepsy Program (CEP) at Austin Health (Melbourne, Australia), and 46 neurologically normal caregivers of these patients constituting a healthy control group. All participants were aged 18 years or older, had no prior history of neurosurgery and an Intelligence Quotient (IQ) estimated to be above 70, or else no indication of intellectual impairment as judged by a neuropsychologist (G.R.). Healthy controls were eligible for the study if they additionally reported no history of neurological impairment, or other serious medical or psychiatric conditions. The study was approved by the relevant Human Research Ethics Committees, and all participants gave written, informed consent.

Epileptogenic foci were identified using established methods, including clinical history, video-electroencephalography monitoring, 3-Tesla magnetic resonance imaging (MRI), interictal [18F] fluorodeoxyglucose positron emission tomography, ictal and interictal blood flow Single Photon Emission Computerized Tomography, and neuropsychological evaluation [32]. On the basis of this information, patients were categorized into two groups: patients with MT foci ($n = 40$; 40% left lateralized) and NMT foci ($n = 49$; 44.9% left lateralized). Of the NMT group, 15 had lateral temporal foci, nine had frontal foci, five had parietal foci, four had anterior quadrant foci, four had posterior quadrant foci, and one had a subcortical focus.

The demographic characteristics of the sample are summarized in Table 1. There was a significant difference in the age of patients with MT epilepsy, patients with NMT epilepsy, and healthy controls, $F(2, 132) = 9.850$, $p < .001$, $\eta_p^2 = 0.130$, large effect size (see Table 1). Planned contrasts revealed that people in the MT and NMT groups were younger than healthy controls, $t(132) = 4.290$, $p < .001$, with no differences in the age of patients with MT versus NMT epilepsies ($p = .379$). There were no significant differences between patients with MT epilepsy, patients with NMT epilepsy, and healthy controls for gender, handedness, years of education, or IQ ($p > .05$ for all comparisons). There were also no significant differences between the patient groups in terms of epilepsy characteristics ($p > .008$ for all comparisons).

2.2. Measures and procedure

All participants completed measures assessing subjective memory complaints, mood, neuroticism, and autobiographical memory. Only patients with epilepsy completed testing on standard neuropsychological measures of verbal and visual memory, as these measures are validated in the population with epilepsy and have powerful age-stratified normative data. As such, it was deemed unnecessary to subject the healthy control participants to this component of testing, and patient scores were instead assessed relative to normative data.

2.2.1. Subjective memory measures

The Memory Complaint Questionnaire (MCQ) [4,33] is a 30-item self-report measure that gauges an individual's beliefs about their everyday memory functioning. The MCQ was specifically designed to study memory complaints in TLE, with the development of test items derived from a large database of systematically recorded verbatim accounts of memory difficulties spontaneously offered by patients with TLE to clinical neuropsychology in a well-established comprehensive epilepsy program. Each item is scored on a 5-point Likert scale. Scores are summed, with total scores ranging from 30 (low) to 150 (severe memory complaints). In a sample of people with epilepsy, the MCQ

Table 1
Demographic and clinical characteristics of the sample.

	People with epilepsy ($n = 89$)		
	MT ($n = 40$)	NMT ($n = 49$)	Healthy controls ($n = 46$)
Age at Testing (Years)	42.13 (13.29) [20–67]	39.63 (12.43) [18–69]	51.22 (14.04) [22–82]
Gender, *Male*	18 (45%)	20 (40.8%)	11 (23.9%)
Years of Education	13.59 (3.53) [9–24]	13.36 (3.08) [5–21]	13.28 (3.24) [9–21]
FSIQ	101.13 (13.14)[a] [63–132]	102.48 (11.29)[a] [72–130]	104.13 (13.48)[a] [71–132]
Preferred Writing Hand, *Right*	39 (97.5%)	46 (93.9%)	38 (82.6%)[a]
Age at Onset (Years)	24.93 (15.71)[a] [1.1–63]	18.93 (10.86) [2–46]	
Duration (Years)	17.85 (13.33) [3–48]	20.87 (12.92) [2–52]	
Monthly Seizure Frequency	19.73 (32.67) [1–150]	26.31 (65.07) [1–400]	
Lesion on MRI, *Yes*	25 (62.5%)	33 (67.3%)	
Laterality of focus, *Left*	16 (40%)	22 (44.9%)	
No of AEDs	2.24 (0.88)[b] [1–4]	2.22 (0.92) [1–4]	

Note. Values are mean (SD) [range] or number (%). AEDs = antiepileptic drugs; FSIQ = Full Scale IQ; MT = mesial temporal lobe epilepsy; NMT = nonmesial temporal lobe epilepsy. $^{***}p < .001$.
[a] There was 1 case of missing data.
[b] There were 2 cases of missing data.

has good test–retest reliability ($r = 0.86$) and internal consistency both test and retest (Cronbach's $\alpha = 0.84$ and 0.86, respectively).

2.2.2. Affective measures

The Neurological Disorders Depression in Epilepsy Inventory (NDDI-E) [34] is a 6-item self-report questionnaire designed to assess current depressive symptomatology, with each item rated on a 4-point Likert scale. Total scores range from six (nil) to 24 (severe). Scores greater than 15 strongly indicate major depression in people with epilepsy [34–36]. Gilliam et al. [34] reported that internal consistency for the NDDI-E in a sample of people with epilepsy was acceptable (Cronbach's $\alpha = 0.85$) and that two-week test–retest reliability was also adequate ($r_s = 0.78$). The NDDI-E correlates strongly with a well-validated measure of depression (i.e., the Beck Depression Inventory; $r_s = 0.78$), providing evidence for construct validity.

The Eysenck Personality Questionnaire-Revised (EPQ-R) [37] is a 48-item personality questionnaire. The neuroticism subscale comprises 12 Yes/No items that survey the occurrence of neurotic cognitions and behaviors (i.e., trait depressive and anxiety features). Total scores range from 0 (low) to 12 (high). Caruso et al. [38] reported adequate reliability for this subscale (Cronbach's $\alpha = 0.83$) in a meta-analysis of reliability coefficients from across 69 samples of heterogeneous populations.

2.2.3. Autobiographical memory measures

The Autobiographical Memory Interview (AMI) [39] is a semi-structured interview that assesses autobiographic memory function across childhood, early adulthood, and recent life periods. The Personal Semantic schedule (AMI-PS) requires recall of specific personal facts for each life period such as names, dates, and addresses. The Autobiographical Incident schedule (AMI-AI) requires the participant to recall multiple specific personal events from each life period, with episodes scored in terms of their level of detail and specificity in time and place. Scores between 54–63 and 19–27 are within the normal range of performance for the PS and AI schedules, respectively [40]. Interrater reliability is $r =$ 0.83–0.86, with good sensitivity to organic disease.

2.2.4. Objective cognitive measures

2.2.4.1. General intellectual capability. Estimation of IQ ($M = 100$, $SD =$ 10) was derived from the Wechsler Test of Adult Reading (WTAR) [41]. The WTAR is a widely used clinical measure designed to assess premorbid functioning in adults aged 16–89 years. It requires participants to provide one pronunciation of a list of 50 irregularly spelled words. The WTAR raw score (i.e., the total number of correct pronunciations) is converted to a standard score based on the individual's age, using manual-provided normative tables [42]. The WTAR has excellent internal consistency across all age groups in both U.S. and U.K. standardization samples (i.e., Cronbach's $\alpha = 0.90$–0.97 and 0.87–0.95, respectively) and also has very good test–retest reliability (>0.90 over 2–12 weeks), with minimal practice effects. The WTAR demonstrates high correlations with Full Scale IQ scores derived from the WAIS-III ($\sim r = 0.73$) [41,42].

2.2.4.2. Verbal memory. The Rey Auditory-Verbal Learning Test (RAVLT) [42] is a widely used word-list learning task designed to assess auditory-verbal new learning and recall. It comprises a list of 15 nouns (List A) that participants are required to acquire and recall over five learning trials, with free recall of these words demanded following an interference trial of an alternate list of 15 nouns (List B), and again following a 30-minute delay. Verbal memory was assessed using the RAVLT delayed recall score (i.e., total number of words recalled, ranging from 0 to 15), which were subsequently converted to scaled scores (i.e., $M =$ 10, $SD = 3$) using Australian normative data stratified by age and gender [42]. The RAVLT delayed recall score has adequate test–retest reliability over one to three-year intervals ($r = 0.57$–78) [43,44]. It has been shown to be sensitive to neurological dysfunction and memory deficits in people with epilepsy [45,46].

2.2.4.3. Visual memory. The Rey–Osterrieth Complex Figure Test (RCFT) [42] is a measure of visuospatial constructional ability and visual memory. It requires participants to copy a two-dimensional complex figure and later reproduce this figure from memory after a 30-minute delay [47]. Visual memory was assessed using the RCFT delayed recall score (i.e., accuracy and quantity of recall design), which was scored using the Osterrieth [48] system. Scores range from 0 (low accuracy) to 36 (high accuracy), with raw scores converted to scaled scores (i.e., $M =$ 10, $SD = 3$) using normative data stratified by age reported in the RCFT manual [49]. The RCFT delayed recall score has adequate test–retest reliability in healthy subjects ($r = 0.89$, 6-month interval [49]; $r = 0.79$, 8-month interval) [50].

2.2.4.4. Working memory. The Symbol Span subtest of the Wechsler Memory Scale, 4th edition (WMS-IV) [51] was included as a metric of the executive function and employed as a measure of working memory. Scaled scores (i.e., $M = 10$, $SD = 3$) were derived from age-matched normative data outlined in the WMS-IV Manual [51]. The manual also outlines in detail the test's psychometric properties.

2.3. Statistical analyses

Data were analyzed using IBM SPSS Statistics version 25.0, with a statistical significance criterion set at $p \leq .05$ (two-tailed). Effect sizes were described according to Cohen's [52] criteria. Variables were inspected prior to analysis to ensure that the assumptions of parametric statistics were upheld, and when violated substituted nonparametric alternatives such as the Brown–Forsyth test [53]. Bonferroni correction was applied to multiple comparisons where appropriate. Little's missing completely at random test yielded a nonsignificant result ($\chi^2(8) = 4.96, p = .762$), indicating that missing data did not have a systematic impact on the results.

To examine group differences on demographic variables, we conducted a between-subject analysis of variance (ANOVA) with planned comparisons between (i) patients with MT epilepsy and NMT epilepsy versus healthy controls; and (ii) patients with MT epilepsy versus NMT epilepsy. Pearson's chi-square analysis with Fisher's Exact Test was used for categorical variables. Independent sample *t*-tests were used to examine patient group differences on clinical variables (i.e., epilepsy characteristics) and objective cognitive measures, and one-sample *t*-tests were used to compare patient scores on objective cognitive measures relative to established normative data.

To test the hypotheses that relative to healthy controls, people with MT and NMT epilepsy would (i) report significantly higher subjective memory complaints, depressive symptoms, and neuroticism, and (ii) have significantly worse episodic and semantic autobiographic recall, we conducted a series of between-subject ANOVAs with planned comparisons between the following: (i) patients with MT and NMT epilepsy versus controls; and (ii) patients with MT epilepsy versus patients with NMT epilepsy. Partial eta squared (η_p^2) and Cohen's d_s were used as the measure of effect size. Bivariate correlation coefficients were utilized to identify potential predictors of subjective memory complaints, as measured by the MCQ, in each patient group.

Variables that correlated significantly with the MCQ were then entered as predictors in two separate hierarchical regression analyses to identify the best predictors of subjective memory complaints in the MT and NMT groups, respectively.

3. Results

3.1. Cognitive and psychological difficulties demonstrated in MT and NMT epilepsy

3.1.1. Patients with MT and NMT epilepsy both endorse bitter subjective memory complaints

There was a significant difference in the MCQ scores of patients with MT epilepsy, patients with NMT epilepsy, and healthy controls, $F_{BF}(2, 118.18) = 11.66$, $p < .001$, $\eta_p^2 = 0.165$ large effect size (see Table 2). As expected, planned contrasts revealed that patients in the MT and NMT groups reported more severe subjective memory complaints compared with healthy controls, $t(106.98) = 5.13$, $p < .001$, $d_s = -0.931$, large effect size. However, there were no significant differences between the MCQ scores of patients with MT and NMT epilepsy ($p = .833$), indicating that both groups held a similarly high level of concern about their memory.

3.1.2. Autobiographic memory dysfunction evident in both patients with MT and NMT epilepsy

There was a significant difference in the total AMI-AI scores of patients with MT epilepsy, patients with NMT epilepsy, and healthy controls, $F_{BF}(2, 123.73) = 5.97$, $p = .003$, $\eta_p^2 = 0.088$, medium effect size (see Table 2). Planned contrasts revealed that consistent with expectations, MT and NMT groups demonstrated significantly poorer autobiographical recall across the lifespan when compared with controls, $t(84.35) = 0.487$, $p = .001$, $d_s = 1.088$, large effect size. There was no significant difference in the total AMI-AI scores between patients with MT and NMT epilepsy ($p = .627$), indicating that both groups had similarly poor episodic autobiographic memory recall. Follow-up inspection of AMI-AI scores stratified into the three time periods (i.e., childhood, early adult, and recent life events) revealed significant differences in the AMI-AI scores of patients with MT epilepsy, patients with NMT epilepsy, and healthy controls for memories from childhood, $F(2, 131) = 3.66$, $p = .029$, and early adult time periods, $F_{BF}(2, 122.32) = 4.24$, $p = .017$. Planned contrasts revealed that MT and NMT groups demonstrated significantly poorer autobiographical recall for childhood and early adult time periods when compared with controls (i.e., $t(131) = 2.622$, $p = .010$, and $t(111.77) = 2.99$, $p = .003$, respectively), with no differences between patient groups ($p = .426$ and .482, respectively). There were no differences in the AMI-AI of patients with MT epilepsy, patients with NMT epilepsy, and healthy controls for recent life events ($p = .095$); however, inspection of planned contrasts revealed that MT and NMT groups demonstrated significantly poorer autobiographical recall for recent life events when compared with controls (i.e., $t(130) = 2.065$, $p = .041$), with no differences between patient groups ($p = .550$).

There was also a significant difference in the total AMI-PS scores of patients with MT epilepsy, patients with NMT epilepsy, and healthy controls, $F_{BF}(2, 93.08) = 4.53$, $p = .013$, $\eta_p^2 = 0.089$, large effect size (see Table 2). Planned contrasts revealed that consistent with expectations, patients in the MT and NMT groups demonstrated significantly poorer recall of personal semantic memories across the lifespan compared with controls, $t(108.29) = 2.91$, $p = .004$, $d_s = 0.53$, medium effect size. There was no significant difference in AMI-PS scores between patients with MT and NMT epilepsy ($p = .137$), indicating that both groups had similarly poor personal semantic autobiographical memory. Follow-up inspection AMI-PS scores stratified into the three time periods (i.e., childhood, early adult, and recent life events) revealed significant differences in the AMI-PS scores of patients with MT epilepsy, patients with NMT epilepsy, and healthy controls for memories from early adult, $F_{BF}(2, 110.26) = 6.35$, p = .002, and recent time periods, $F(2, 130) = 3.35$, $p = .038$. Planned contrasts revealed that MT and NMT groups demonstrated significantly poorer autobiographical recall for early adult life events when compared with controls, $t(128.26) = 4.17$, $p < .001$, with no differences between patient groups ($p = .696$). In contrast, patients with MT epilepsy demonstrated significantly poorer autobiographical recall for recent life events than patients with NMT epilepsy, $t(130) = -2.17$, $p = .032$, with no differences between patient groups collectively and healthy controls ($p = .124$). There were also no differences in the AMI-PS of patients with MT epilepsy, patients with NMT epilepsy, and healthy controls for recall of childhood memories ($p = .447$).

3.1.3. Patients with MT and NMT epilepsy endorse high levels of affective symptoms

There was a significant difference in the NDDI-E scores of patients with MT epilepsy, patients with NMT epilepsy, and healthy controls, $F(2, 121) = 3.53$, $p = .032$, $\eta_p^2 = 0.055$, small–medium effect size (see Table 2). Planned contrasts revealed that as expected, both epilepsy groups reported significantly higher levels of depressive symptomatology on the NDDI-E relative to the healthy controls, $t(121) = 2.59$, $p = .011$, $d_s = 0.497$, medium effect size. There was no significant difference in the levels of symptomatology reported by people with MT versus NMT epilepsy ($p = .432$).

Significant between group differences were also found with respect to neuroticism scores, $F(2, 131) = 3.107$, $p = .048$, $\eta_p^2 = 0.045$, small effect size. As expected, planned contrasts revealed that both epilepsy

Table 2
Descriptive statistics for autobiographical memory variables and cognitive and affective measures in patients with MT epilepsy, patients with NMT epilepsy, and healthy controls.

	Patients with MT epilepsy ($n = 40$)	Patients with NMT epilepsy ($n = 49$)	Healthy controls ($n = 46$)
MCQ	92.05 (22.85) [43–134]	93.02 (19.92) [55–129]	74.91 (17.32)*** [49–128]
AMI-PS Total score	53.54 (6.95)[a] [32.5–63]	55.50 (4.70)[a] [41.5–61.5]	57.10 (4.07)** [46.5–62.5]
AMI-PS Childhood score	17.69 (3.40) [8–21]	18.22 (2.07)[a] [11.5–21]	18.37 (2.58) [8–21]
AMI-PS Early Adult score	18.21 (2.33)[a] [14–21]	18.42 (2.70)[a] [8–21]	19.76 (1.49) [14–21]
AMI-PS Recent score	17.90 (2.86)[a] [6–21]	18.87 (1.77)[a] [13–21]	18.97 (1.49) [15–20.5]
AMI-AI Total score	16.90 (3.91)[a] [8–26]	16.42 (5.29)[a] [4–27]	19.37 (3.90)* [8–26]
AMI-AI Childhood score	5.53 (1.87) [2–9]	5.85 (2.22)[a] [0–9]	6.61 (1.61) [2–9]
AMI-AI Early Adult score	5.59 (2.00)[a] [1–9]	5.25 (2.49)[a] [1–9]	6.48 (1.76) [1–9]
AMI-AI Recent score	5.74 (1.71)[a] [2–9]	5.52 (1.76)[a] [2–9]	6.28 (1.70) [2–9]
NDDIE	12.84 (3.14)[b] [6–20]	12.23 (3.97)[c] [6–20]	10.80 (3.16)[d,*] [6–19]
EPQ-R – Neuroticism	5.63 (3.43) [0–12]	5.82 (3.62) [0–12]	4.11 (3.64)[a,*] [0–12]
RAVLT Delay SS	10.72 (3.01)[e] [3–14][g]	10.72 (2.72)[f] [3–15][g]	
RCFT Delay SS	8.43 (4.78)[h] [−1–20][j]	9.17 (4.29)[i] [0–18][k]	
WMS-IV Symbol Span SS	9.91 (2.43)[i] [6–15]	10.37 (2.84)[l] [5–17]	

Note. Values are mean (SD) and [range]. AMI-AI = Autobiographical Memory Interview Autobiographic Incidents; AMI-PS = Autobiographical Memory Interview Personal Semantic; EPQ-R = Eysenck Personality Questionnaire, revised; MCQ = Memory Complaints Questionnaire; NDDI-E = Neurological Disorders Depression Inventory for Epilepsy; RAVLT = Rey Auditory Verbal Learning Test; RCFT = Rey–Osterrieth Complex Figure Test; SS = Scaled Score; WMS-IV = Wechsler Memory Scale, Fourth Edition.

* $p < .05$.
** $p < .01$.
*** $p < .001$.
[a] There was 1 case of missing data.
[b] There were 3 cases of missing data.
[c] There were 2 cases of missing data.
[d] There were 6 cases of missing data.
[e] There were 19 cases of missing data.
[f] There were 15 cases of missing data.
[g] There was 1 case with a Scaled Score < 4.
[h] There were 12 cases of missing data.
[i] There were 7 cases of missing data.
[j] There were 4 cases with a Scaled Score < 4.
[k] There were 5 cases with a Scaled Score < 4.
[l] There were 11 cases of missing data.

groups reported significantly higher neuroticism scores on the EPQ-R relative to healthy controls, $t(131) = -2.461$, $p = .015$, $d_s = 0.468$, medium effect size. No significant differences in EPQ-R neuroticism subscales scores were observed between patients with MT and NMT epilepsy ($p = .802$), indicating that both groups had similarly high levels of neuroticism.

3.1.4. Heterogeneous objective cognitive deficits in MT and NMT epilepsy

There were no significant differences identified between patient groups in terms of objective measures of memory (RAVLT; RCFT) and working memory (Symbol Span), or between the scaled scores on each measure and the population mean (i.e., $M = 10$) for either patient group ($p > .017$ for all comparisons; see Table 2). Inspection of the range of patient scores across these measures for both groups revealed heterogeneity within the samples, whereby despite the group-level mean scores being comparable to normal performance, a meaningful subset of patients' scores fell in the "borderline impaired" and "profoundly impaired" ranges (i.e., scaled score < 4; see Table 2) at a higher frequency than is to be expected in a normally distributed population. The distribution of scores across these measures for both patient groups is presented in Supplementary Figs. 1–3.

3.2. Predictors of subjective memory differ across types of focal epilepsy

In patients with MT epilepsy, stronger subjective memory complaints were associated with poorer objective verbal recall (RAVLT), and poorer personal semantic and episodic autobiographic memory across the lifespan (AMI-PS and AMI-AI; see Table 3). Increased MCQ scores in the MT group were also significantly associated with elevated neuroticism scores ($p = .173$) and gender ($r_s = 0.34$, $p = .03$). Further investigation of the latter revealed that female patients with MT epilepsy reported a significantly higher number of subjective memory complaints than male patients with MT epilepsy, $t(38) = 2.47$, $p = .02$, $d_s = 0.78$, large effect size.

In contrast, there were no significant correlations between subjective memory complaints and any autobiographic memory variables nor objective memory or working memory measures in the patient group with NMT epilepsy (all $p's > 0.05$). In these patients, increased MCQ scores were significantly associated with elevated scores on both the neuroticism and depression measures.

Exploratory analyses revealed that correlations between the MCQ and autobiographic memory variables were significantly stronger in the MT group compared to the NMT group, $Z = -4.18$, $p < .001$. Of

note, only the lifespan metrics of autobiographic memory function were included (AMI-AI and AMI-PS total scores). This was a statistical decision to maximize power through the avoidance of multiple comparisons that would be introduced by including extra variables composed of the stratified temporal subscores derived from the total scores of the AMI-AI and AMI-PS. Furthermore, the reliability of these subscores, relative to their composite scores, is unknown and avoidance of multiple comparisons with these subscores ensured the analysis remained statistically robust [40]. No significant relationships between any of the epilepsy variables and subjective memory complaints were identified in either patient groups with MT or NMT epilepsy (all p's > .05).

3.2.1. Model of subjective memory complaints in MT epilepsy

To identify the strongest predictors of subjective memory complaints in MT epilepsy, cognitive, affective, and autobiographical memory variables that were found to be significantly associated with MCQ scores in the MT group (see Table 3) were sequentially entered into a hierarchical regression analysis, along with significantly associated demographic variables (e.g., gender). In cases of multicollinearity between predictors, only the stronger correlate of MCQ was retained [53]; as such, because of moderate–high correlations between AMI-PS scores and both the RAVLT delay score ($r = 0.59$, $p = .004$) and the AMI-AI score ($r = 0.56$, $p < .001$), this variable was subsequently excluded from the model.

With only the RAVLT delay trial entered as a predictor, the model was significant and accounted for 32.7% of the variance in MCQ scores, $R^2 = 0.33$, $R^2_{Adjusted} = 0.29$, $F(1, 19) = 9.24$, $p = .007$, $\eta^2_p = 0.327$, large effect size. Scores on the EPQ-R neuroticism and the AMI-AI subscales were included in the model at Step 2, and together, they accounted for an additional 23.2% of the variance, which resulted in a significant increase in R^2; $R^2 = 0.56$, $R^2_{Adjusted} = 0.48$, $F_{chg}(2, 17) = 4.48$, $p = .027$, $\eta^2_p = 0.436$, large effect size. With the inclusion of gender at Step 3, the final model accounted for an additional 13.9% of the variance and again resulted in a significant increase in R^2; $R^2 = 0.70$, $R^2_{Adjusted} = 0.62$, $F_{chg}(1, 16) = 7.38$, $p = .015$, $\eta^2_p = 0.316$, large effect size. Upon further inspection of the unique and independent relationships between each of the predictors and MCQ scores in the final model, it was revealed that only the RAVLT 30-minute delay scores ($\beta = -0.607$, $p = .001$), neuroticism scores ($\beta = 0.432$, $p = .009$), and gender ($\beta = 0.376$, $p = .015$), made a significant unique contribution to MCQ scores, whereas AMI-AI scores did not make a significant contribution ($p > .05$; see Fig. 1).

3.2.2. Model of subjective memory complaints in NMT epilepsy

Subjective memory complaints were not associated with any autobiographic memory variables in patients with NMT epilepsy (see Table 3). Instead, they were associated with elevated depressive symptomatology on the NDDI-E and increased neuroticism on the EPQ-R. No epilepsy variable had a significant relationship to MCQ scores either. Based on these results, a hierarchical regression model examining the comparative importance of neuroticism and depression in predicting MCQ scores in patients with NMT epilepsy was planned; however, in light of moderate–high correlations between the NDDI-E and EPQ-R neuroticism subscales ($r = 0.55$, $p < .001$), only one relationship could be examined in detail to avoid multicollinearity. Consequently, a simple linear regression model was computed and EPQ-R neuroticism subscale scores were entered as the sole predictor as they were the marginally stronger correlate of MCQ scores (see Table 3). The final model was significant with EPQ-R neuroticism scores accounting for 20.6% ($\beta = 0.454$) of the variance in MCQ scores, $R^2 = 0.21$, $R^2_{Adjusted} = 0.19$, $F(1, 47) = 12.22$, $p = .001$, $\eta^2_p = 0.206$, large effect size (see Fig. 1).

Table 3
Correlations between subjective memory complaints and autobiographical memory variables, cognitive and affective measures, and epilepsy variables in patients with MT and NMT epilepsy.*

	Patients with MT epilepsy ($n = 40$)	Patients with NMT epilepsy ($n = 49$)
	MCQ score	
Autobiographic memory variables		
AMI-PS Total Score	−0.42[a,**]	−0.02[a]
AMI-AI Total Score	−0.33[a,*]	−0.12[a]
Objective cognitive variables		
RAVLT Delay SS	−0.57[b,**]	−0.10[c]
RCFT Delay SS	0.06[d]	−0.04[e]
WMS-IV Symbol Span Scaled Score	−0.23[e]	−0.28[f]
Affective variables		
NDDI-E	0.23[g]	0.452[h,**]
EPQ-R – Neuroticism	0.47[**]	0.454[**]
Epileptological variables		
Age at onset	0.22[a]	0.16
Duration of epilepsy	−0.13	−0.15
Monthly seizure frequency	−0.20	−0.12
Number of current AEDs	−0.17[h]	−0.03

AEDs = antiepileptic drugs; AMI-AI = Autobiographical Memory Interview Autobiographic Incidents; AMI-PS = Autobiographical Memory Interview Personal Semantic; EPQ-R = Eysenck Personality Questionnaire, revised; MCQ = Memory Complaints Questionnaire; NDDI-E = Neurological Disorders Depression Inventory for Epilepsy; RAVLT = Rey Auditory Verbal Learning Test; RCFT = Rey–Osterrieth Complex Figure Test; SS = Scaled Score; WMS-IV = Wechsler Memory Scale, Fourth Edition.

* $p < .05$.
** $p < .01$.
[a] There was 1 case of missing data.
[b] There were 19 cases of missing data.
[c] There were 15 cases of missing data.
[d] There were 12 cases of missing data.
[e] There were 7 cases of missing data.
[f] There were 11 cases of missing data.
[g] There were 3 cases of missing data.
[h] There were 2 cases of missing data.

4. Discussion

Subjective memory concerns are often voiced by people with epilepsy and are known to have consequences for educational attainment, employment, social life, self-esteem, and hope for the future [54].

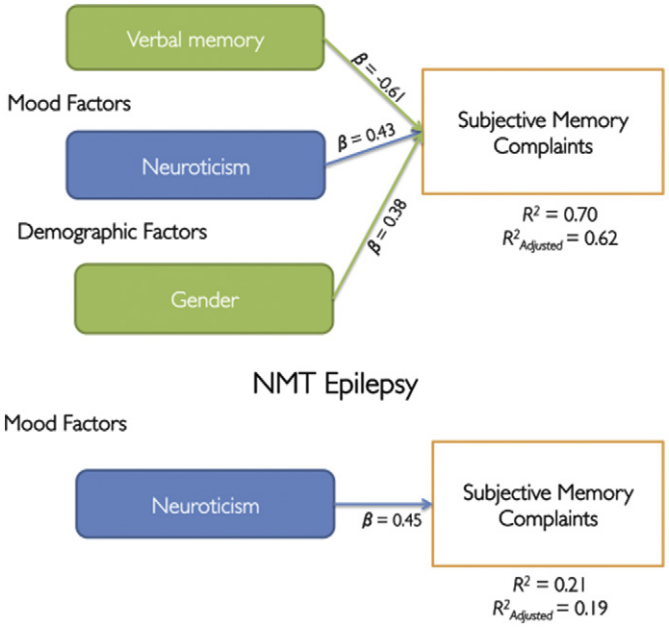

Fig. 1. Predictors of subjective memory complaints in MT and NMT epilepsy.

However, their diagnostic value for detecting an underlying neurocognitive disorder has remained ambiguous. This study examined the affective, cognitive, and epileptological underpinnings of subjective memory complaints in patients with seizure foci in the encoding-critical mesial temporal region, compared to those with foci elsewhere in the brain. It extends our previous work [19] by incorporating a naturalistic measure of everyday, personally relevant memory (autobiographical memory), whose relationships to memory complaints were previously unexplored.

Contrary to expectation, autobiographical memory disturbance did not account for subjective complaints in people with either MT or NMT epilepsy. This surprising finding indicates that although autobiographical memory is frequently compromised in patients with focal epilepsy, naturalistic measures such as the AMI may not add useful information in interpreting subjective concerns.

In the MT group, objective verbal memory dysfunction, female gender, and an elevated tendency to experience negative affect (i.e., neuroticism) were the best predictors of subjective concerns. In contrast, the subjective memory complaints of patients with NMT epilepsy are underpinned by elevated neuroticism. Taken together, our findings highlight that the location of the epileptogenic focus can provide clues to the origin of subjective memory complaints. In patients with MT epilepsy, they are likely underpinned by a combination of cognitive and psychiatric factors, whereas in patients with NMT epilepsy, psychiatric factors are the primary contributor. These differences carry important and specific clinical implications for nuanced management of memory complaints in these distinct patient groups.

4.1. Diagnostic utility of subjective memory complaints in focal epilepsy

Objective verbal memory dysfunction was found to contribute to subjective memory complaints in patients with MT foci only. This finding expands on our previous work showing that memory complaints are equally bitter in people with MT and NMT epilepsy, but objective memory dysfunction only predicts the complaints of patients with MT epilepsy [19]. Together, these findings suggest that in people with MT epilepsy, subjective memory complaints could potentially be a marker of underlying memory disorder [1,20], dovetailing with dementia research showing that subjective memory complaints can be prognostic of underlying mesial temporal disease and degenerative memory disorder [7–11]. As such, subjective complaints in this group require careful examination by a clinical neuropsychologist with expertise in epilepsy [55]. The findings also suggest that traditional memory tests may be reasonable markers of personally meaningful memory failures in MT epilepsy and may not be esoteric psychometric tools of little ecological validity. It is important to note, however, that these preliminary findings require further replication in order to firmly establish the relative contribution of verbal versus visual objective memory performances to subjective memory complaints in this population.

The current study showed that verbal memory dysfunction contributed to subjective memory complaints in MT epilepsy, whereas our previous work found visuospatial memory dysfunction underpinned memory concerns in MT epilepsy [19]. This indicates that subjective concerns may be underpinned by either verbal or visual memory dysfunction in this subgroup of people with epilepsy. Although speculative, it is reasonable to suggest that some memory complaints by patients with MT epilepsy reflect the subjective detection of a decline in their verbal or visual memory capability relative to their previous level of functioning [56], or perhaps features of accelerated long term forgetting not captured by the current study's methodology and known to be a feature of mesial temporal lobe disease [24,57]. As such, further research utilizing a repeated measures design is required to firmly establish the role of longitudinal objective memory performances on patients' subjective memory complaints.

More speculatively, our findings could also reflect the role of MT structures in the subjective appraisal of one's own memory (a.k.a., metamemory). One of the specific contributions of the MT lobes to episodic memory is that the perirhinal cortices imbue a memory engram with a sense of familiarity [6]. The sense of familiarity can be explicit, as occurs when the initial encoding-related neural activation pattern is reinstated within the MT lobe during recall, allowing visceral reexperiencing of a past event [58,59]. Familiarity can be also implicit, and is related to a "feeling of knowing" [60] that evokes the sense that you would be able to provide a correct answer if given cues or prompts. In this way, the specificity of memory dysfunction predicting subjective memory concerns only in the MT group could reflect an impoverished sense of familiarity accompanying recall, which would not be a feature of NMT memory dysfunction. A lack of familiarity or sense-of-knowing accompanying recall of your memories is unsettling, and may have prompted disconcerted patients with MT epilepsy to offer subjective concerns to clinicians. While experimental validation of this interpretation was beyond the scope of the current study, it represents an interesting avenue for future research.

4.2. Robust effects of emotional distress on subjective memory complaints in epilepsy

The current study confirms that state (mood) and trait emotional distress (i.e., neuroticism) gives rise to memory concerns in many people with epilepsy, irrespective of the location of the epileptogenic focus [13,16–21,61–63]. In an extension of previous findings, the current study confirms that subjective memory complaints in patients with either MT or NMT epilepsy are underpinned by a vulnerability to depression as well as neuroticism [19]. Neuroticism is a personality trait characterized by a predisposition to experience distress and negative emotional states, such as, depression, anxiety, anger, and guilt [64]. Individuals high on neuroticism are hypervigilant and prone to psychopathology [65], with their cognitive style characterized by irrational thinking, low self-esteem, poor coping mechanisms, and increased somatic complaints [66]. Speculatively, it may be that subjective memory complaints in epilepsy serve as a more socially "acceptable" way for some medicalized individuals to convey their emotional distress, functioning as a "cry for help" in a population potentially already feeling stigmatized by their seizures [67].

Subjective memory concerns reported by many people with epilepsy could also reflect cognitive symptoms that are intrinsic to affective disturbance [68], such as, distractibility, reduced attention, and pathological rumination [22], with the significance of these symptoms likely to be exacerbated by any underlying neurotic personality traits [69]. For example, people high in neuroticism are more predisposed to attach undue significance to relatively benign moments of forgetfulness, potentially misinterpreting brief attentional lapses as a marker of memory deterioration [63]. Our clinical experience suggests that this can give rise to a vicious cycle, whereby hypervigilance for memory lapses leads to attentional dysfunction that is subsequently misinterpreted as memory failure, which feeds increased hypervigilance. This observation dovetails with Hermann's [70] concept of the memory introspection paradox: "the poorer one's memory aptitude, the more difficult it will be to remember what one's memory is really like." (p. 448). Thus, subjective memory complaints in some patients may, paradoxically, reflect an intact memory system, and a neurotic bias toward remembering episodes of forgetting.

For clinical practice, our findings suggest that any person with epilepsy complaining about their memory should be empathically but directly questioned as to the presence of broad symptoms of emotional distress and mood disturbance, in addition to the specific circumstances of their memory lapses. This process could be facilitated with the use of an epilepsy-specific screening questionnaire for depression such as the NDDI-E [34], which canvasses symptoms distinct from the common cognitive symptoms known to overlap with depression and epilepsy, thus reducing the likelihood of conflating the diagnosis of depression with cognitive disorder in this population.

4.3. Influence of gender in the memory complaints of people with MT epilepsy

The current study found that females with MT epilepsy report worse subjective memory complaints relative to their male counterparts. This is consistent with the well-established finding that women show an increased willingness to report health-related problems [71], with masculinity norms thought to constitute a barrier to men's engagement in health-seeking behavior [72]. In particular, our findings parallel those of the head injury literature, which have highlighted that females are more likely than men to report elevated postconcussive symptoms, such as, memory lapses following a head strike [73–76]. While speculative, it is reasonable to infer that identification of gender differences in only patients with MT epilepsy likely reflects the underlying disruption to mesial temporal structures critical for memory function in these patients [70], with the women in this MT group more willing to report objective problems with their memory than men.

4.4. What's really driving subjective memory complaints in patients with NMT epilepsy?

The current study has identified a number of cognitive, affective, and demographic factors that underpin subjective memory complaints in patients with MT and NMT epilepsy. However, in those with NMT foci, neuroticism was the sole contributing factor and this only accounted for approximately 20% of the variance. This leaves a substantial proportion of the variance unexplained, and potentially accounted for in part by other known contributors of memory complaints in epilepsy, such as, illness perceptions, which were not explored in the current study [77]. Nevertheless, our findings in the NMT group are broadly commensurate with those of prior studies in epilepsy more generally, which have typically explained approximately 20–36% of variance in subjective memory complaints in people with epilepsy [19,20,62,63].

This finding has two important implications: first, it makes our delineation of 70% of the variance underpinning subjective memory complaints in the MT group a marked improvement on previous studies. Second, it suggests that there is a great deal of inter- and intraindividual variability in the factors underpinning the experiences of poor memory by patients with NMT epilepsy, and our reliance on group-level multivariate statistics to capture these effects is inadequate here. Given that the NMT group included patients with diverse seizure foci relative to the MT group, analysis of the factors that give rise to their memory complaints is likely too crude to capture the nuanced nature of these experiences and the differing impact of their various foci on memory and metamemory function [78]. As such, it is important that future studies tease out these more nuanced effects by stratifying people with epilepsy into more homogenous groups based on the seizure focus.

4.5. Future directions

Given that our patient sample comprised focal (predominately drug-resistant) people with epilepsy, further exploration of the contribution of autobiographical memory to subjective memory complaints in milder or less commonly encountered groups of patients with epilepsy is warranted. The null influence of autobiographic memory on subjective memory complaints in people with focal epilepsy should also be replicated using other robust tools commensurate with the ones employed by our study.

4.6. Conclusions

In a busy epilepsy clinic, it is highly likely that some patients will disclose concerns about their memory. The results of this study suggest that these complaints should trigger enquiries about the presence of emotional distress, which may help to improve the currently poor recognition and treatment of mood disorders in epilepsy [22,79,80]. Patients with MT lobe foci in particular will often warrant comprehensive cognitive testing [55], with this study showing that self-reported concerns are a valid trigger for this process. There is no one-size-fits-all approach for assessing and treating memory complaints in patients with epilepsy. Our findings underscore the need to validate the patient's concerns, and to address them with an individualized approach. Taking a few extra minutes to probe the nature of a patient's subjective memory complaints will lead to important insights into what further assessment, psychoeducation, or treatment the patient requires.

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Declaration of competing interest

None.

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