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On the nose: olfactory disturbances in Transient Epileptic Amnesia

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Abstract

Objective—While olfactory hallucinations are relatively rare in epilepsy, a high incidence (up to 42%) has been reported in one form – Transient Epileptic Amnesia (TEA). TEA is characterised by recurring amnesic seizures and is commonly associated with persistent interictal memory deficits. Despite reports of changes in smell, olfactory ability has not been objectively assessed in this group. The aim of this study was to measure olfactory ability in TEA and explore whether olfactory symptoms relate to other clinical variables.

Methods—Fifty-five participants with TEA were recruited from The Impairment of Memory in Epilepsy project database. The presence of olfactory symptoms was obtained via case notes and clinical interview. Participants completed questionnaires to evaluate their olfaction and memory function subjectively. Olfactory ability was measured using the University of Pennsylvania Smell Identification Test (UPSIT). TEA participants' performance was compared to 50 matched healthy control participants. A subset of TEA participants (n=26) also completed a battery of memory tests including standard neuropsychological measures, accelerated forgetting and autobiographical memory.

Results—Olfactory hallucinations were reported in 55% of TEA cases. A significant reduction in smell identification (UPSIT) was found between TEA and healthy controls ($p < .001$). Epilepsy variables, including history of olfactory hallucinations, were not predictive of olfactory ability. Patients reported ongoing memory difficulties and performed below normative values on objective tests. While no correlation was found between objective measures of memory and olfactory performance, subjective complaints of route finding difficulty was associated with UPSIT score.

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Conflicts of interest

The authors declare that they have no financial or other conflicts of interest in relation to this research and its publication.

Conclusions—Impairments in odour identification are common in TEA and exceed changes that occur in normal ageing. Olfactory hallucinations occurs in approximately half of TEA cases, but do not always coincide with reduced sense of smell. Olfactory impairment and interictal memory problems both occur frequently in TEA but are not closely associated.

Keywords

Transient epileptic amnesia; Epilepsy; Memory; Olfaction

1 Introduction

Although olfactory hallucinations can occur in temporal lobe epilepsy (TLE), the prevalence generally appears low [1], with estimates ranging from less than 1% of cases reviewed [2] up to approximately 7% [3,4]. An exception to this has been reported in patients with a relatively recently defined form of TLE, Transient Epileptic Amnesia (TEA)[5]. TEA is characterised by recurring amnesic seizures in which memory functioning is disrupted over a brief period while other cognitive functions remain predominantly intact [6]. In the majority of patients, some attacks also involve more classical epileptic features, such as olfactory hallucinations, automatisms or brief periods of unresponsiveness [7]. In addition to their ictal amnesia, most patients with TEA report some degree of persistent, interictal memory difficulty, usually autobiographical amnesia [8,9], accelerated long term-forgetting [10–13] or topographical amnesia [5].

While a recent retrospective series of patients with TEA reported olfactory hallucinations in only 2 of their 30 participants [14], in the largest prospective study to date, 42% of the 50 cases reported having experienced olfactory or gustatory hallucinations when directly asked [5]. In keeping with some other reports [6,9,15,16], the evidence overall suggests that olfactory symptoms are relatively common in TEA.

Olfactory ability appears a sensitive marker in various neurological or neuropsychiatric groups, including schizophrenia, Parkinson's Disease, Alzheimer's Disease and other dementia syndromes [17–19]. Previous studies of olfactory processing in TLE have indicated that while odour detection may be unimpaired, other judgements, such as odour identification, are significantly reduced compared to age matched healthy controls [20–24]. No formal investigations of olfactory ability, however, has been conducted specifically in TEA, despite the higher rate of olfactory disturbances. It is therefore unknown whether the presence of olfactory hallucinations is associated with impairment of olfactory abilities, or whether olfactory symptoms in TEA relate to other clinical features, such as the degree of memory disturbance or severity of epilepsy.

Associations between memory and olfaction have been proposed both in the normal ageing population [25] and in dementia [26]. From a structural standpoint, this is supported by overlapping brain structures, with both memory and olfactory processing involving areas such as the hippocampus, amygdala, and frontal lobes [27]. Odour discrimination in particular has been associated with functioning of the piriform cortex, orbitofrontal cortex and hippocampus [28], with loss of smell (anosmia) correlated with grey matter changes within the piriform cortex, insular cortex, orbitofrontal cortex, medial prefrontal cortex,

hippocampus, parahippocampal gyrus, supramarginal gyrus, nucleus accumbens, subcallosal gyrus, medial and dorsal prefrontal cortex [29]. Previous investigations in TEA suggest that volume reductions can occur in two of these regions: namely the hippocampus and orbitofrontal cortices [30], providing a potential anatomical basis for both olfaction and memory change.

The aim of this study, therefore, was to investigate changes in olfaction in TEA, drawing upon both subjective report and objective measures. Specifically, we hypothesised that patients with TEA would demonstrate an objective reduction in smell, which may be more pronounced for those with a history of olfactory hallucinations. In addition, we aimed to explore whether olfactory symptoms relate to other clinical variables, with a particular interest in any relationship between memory and olfaction given the prominence of these symptoms in this population.

2 Method

2.1 Participants

Invitations to the study were sent to all currently registered research participants of the TIME (The Impairment of Memory in Epilepsy) project, who had previously met criteria for a diagnosis of Transient Epileptic Amnesia [6]. This diagnosis was established via a clinical assessment with an experienced behavioural neurologist (AZ or CB), with evidence of epilepsy confirmed through epileptiform abnormalities on clinical EEG, reports of concurrent epileptic features (e.g. lip smacking) and /or a positive treatment response to anticonvulsant therapy.

Fifty-five participants agreed and were judged eligible to complete the study, with cases excluded if there was clearly documented loss of smell due to other medical causes, such as nasal surgery or significant head injury, or if the person had also been diagnosed with a dementia. Results of clinical MR brain imaging scans conducted in 46 participants confirmed the absence of any tumours or other structural lesions which might account for sensory loss, though two patients had changes in the right medial temporal lobe (one high T2 signal change in right hippocampus, one probable cavernoma in right hippocampus). Four further patients underwent CT scans of the brain with essentially normal results.

Fifteen participants originally took part in the 2007 cohort, with their history of olfactory symptoms first reported there [5]. The remaining participants were subsequently recruited through neurology clinics across the UK via the British Neurological Surveillance Unit (a service of the Association of British Neurologists) and as a result of direct referral to AZ and CB. Thus, the onset of epilepsy had been within 5 years in approximately one third of patients, 5-10 years previously in one third, and 11-35 years previously in the final third.

The overall sample demonstrated clinical characteristics typical of TEA, with symptoms typically emerging during midlife, with an average age of onset of 61.5 years. The majority (76%) were male (See Table 1). Review of clinical EEG reports, available in 51 of the 55 participants, indicated clear epileptiform activity in 12 (24%), non-specific abnormalities in 13 (25%), and normal recordings in 26 (51%) of participants.

To evaluate TEA participant olfactory performance, healthy control data was obtained from data previously collected in East Anglia¹. Fifty healthy control (HC) participants were selected to match TEA participants with respect to gender distribution (HC gender: 38M, 12F; χ^2 , $p = .965$), age (HC mean age = 69; $t(104) = -0.93$, $p = .354$) and current smoking status (HC current smokers = 7; χ^2 , $p = .136$).

The study was approved by the Multicentre Research Ethics Committee, United Kingdom (MREC 03/10/77). All participants gave written, informed consent.

2.2 Retrospective case review –olfactory history

To identify participants with a history of olfactory hallucinations, we reviewed clinical information in the TIME case notes. This primarily involved searching letters generated from a structured interview administered by an experienced behavioural neurologist from the TIME team (AZ or CB) with each participant and an accompanying family member. Questions regarding olfactory hallucinations or reduced smell were specifically included. In addition, where available, any earlier correspondence written by a treating clinician was also inspected, particularly for participants who entered the TIME project many years after onset. A note was made of any mention of the presence of olfactory or gustatory hallucinations (either during seizures or at other times), changes in sensitivity to smells (either a decrease or increase) or the experience of a lingering or persistent smell, either real or imaginary, a phenomenon we describe using the term “palinomia”.

2.3 Olfaction and Memory Questionnaire measures

All TEA participants completed a questionnaire pack containing the following measures:

1. University of Pennsylvania Smell Identification Test (UPSIT): a well-established, highly reliable 40-item multiple-choice test [31–33]. Participants scratch a label to release an odour one at a time, then immediately sniff and select one of four choices to indicate what the odour smelt like. Participants were asked to refrain from completing the test if they had a cold, influenza or nasal allergies that interfered with their sense of smell. In addition to the total score, normative tables provided within the UPSIT were used to record each individual's percentile rank (based on age and gender) and to diagnostically categorise each participants' smell as: normal (scores of 34–40), mildly impaired (30–33), moderately impaired (26–29), severely impaired (19–25) or anosmic (18 and below).
2. Very Long Term Memory Questionnaire (VLTMQ) [34] 13-item scale in which participants rate how often they have forgotten various types of personally salient events or facts (where 0 = never to 3 = many times), generating a maximum score of 39.
3. Everyday memory questionnaire (EMQ) [35]: an 18-item scale to estimate the frequency of everyday memory failures (e.g. misplacing objects in the home,

¹Data supplied by Professor Chris Hawkes, based on $n=310$ healthy controls aged 17–93 years, collected at Ipswich Hospital, Suffolk UK and Queens Hospital, Romford, Essex UK.

forgetting names) occur (from 0= not at all to 5 = more than once a day). The maximum score is 90.

4. Self-evaluation of smell and memory functioning: participants were asked to indicate 'yes' or 'no' to questions asking if they had reduced smell, heightened smell, and whether they had experienced olfactory hallucinations (either during seizures or at other times). Information was also collected relating to smoking habits. In addition, participants were asked to rate a range of characteristic memory difficulties on a 10-point scale (where 0 is 'no difficulty at all', and 10 is 'impossible') (see Supplementary Material).

2.4 Neuropsychological memory assessment

Approximately half of the TEA participants (n=26) underwent a standardised neuropsychological battery used previously by Butler et al [5]. This included the Wechsler Abbreviated Intelligence Scale (WASI) as a measure of general intellectual functioning, the Graded Naming Test to assess semantic memory, the Controlled Oral Word Association Test and Trail Making Test as measures of executive functioning, as well as measures of verbal and visual memory: immediate free recall, 30-minute delayed recall, and recognition of the first story (Anna Thompson) from the Logical Memory subtest of the Wechsler Memory Scale –III [36]; 30-minute delayed recall of the Rey Complex Figure Test [37]; and the Words and Faces subtests from the Recognition Memory Test [38]. Performance on each of the 6 memory measures was converted into a z score based on control data previously collected Butler et al [5] and then averaged to generate an overall memory impairment index (Z AvMem).

To assess accelerated long term forgetting (ALF), participants were administered a modified version of the Rey Auditory Verbal Learning Test. Here, participants learn the 15-item word list to a set criterion (either 80% or 90%)², with memory tested at 30 minutes and then at 1 week via telephone. Raw scores for the 1-week recall performance were converted to z scores using normative data from the TIME project (Z ALF).

Lastly, the Modified Autobiographical Memory Interview (MAMI) was used to measure autobiographical memory. Participants were asked to retrieve specific episodic memories from each decade of their life. Episodes were then rated from 0 to 5 (where 0 indicates a failure to recall a relevant memory and 5 indicates successful retrieval of a specific episode in which event details are described). Average performance for episodic recall was calculated across all decades and then converted to a z score based on pre-existing TIME control data (Z MAMI).

2.5 Statistical analysis

IBM SPSS Statistics 22.0 and STATA were used for data analysis. Between-group comparisons of olfactory performance were performed using independent sample t-tests.

²Learning criterion of 90% was applied for 10 participants in order to comply with protocols used in a longitudinal follow up of the 2007 cohort. Z scores were calculated based on normative data collected by Butler et al [12]. Learning criterion of 80% was applied to the remaining participants, with z scores calculated based on separate normative data collected through the TIME project.

Sociodemographic variables were compared using either parametric or non-parametric tests, as appropriate. The relationship between UPSIT and clinical variables of TEA (duration, estimated number of attacks, and presence of olfactory hallucinations) was examined using linear regression models. As it is known within wider populations that age, gender and current smoking status can impact upon olfactory performance[39], we firstly checked if models required adjustment for these variables within our TEA sample. Univariate analysis did not find any significant relationships with UPSIT score within this older, predominantly male, predominantly non-smoking sample. Univariate analyses were then conducted for each of the three TEA variables to identify any variables to include in a stepwise multivariable model. One-way analysis of variance was also conducted to examine any effect of EEG result (normal, non-specific abnormalities, or epileptiform activity) on UPSIT score and memory measures (Z AvMem, Z ALF, Z MAMI, EMQ, VLTMQ). Agreement between subjective ratings of smell and objective impairment on the UPSIT was assessed using the kappa reliability statistic. Lastly, associations between UPSIT and both subjective (EMQ, VLTMQ, memory ratings) and objective memory measures (Z AvMem, Z ALF, Z MAMI) were tested using non-parametric correlational analysis. Statistical significance was judged as any p values $<.05$.

3 Results

3.1 Retrospective case review results

Review of clinical notes indicated that olfactory hallucinations were mentioned in 30 (55%) of the TEA participants as part of the clinical presentation. Typically this involved reports of a “funny smell” either immediately preceding or during the course of the amnesic attacks, although in 5 cases the same smell was reported to arise at other times. Where a judgement was expressed, smells were regarded as unpleasant ($n=4$). Most commonly, these hallucinatory odours were described as “strange” ($n=7$) or resembling a “burning” or “cooking” smell ($n=6$). Other descriptions included: garlic ($n=1$), cleaning fluid ($n=1$), metallic ($n=1$), courgettes ($n=1$), fishy ($n=1$) or sweet ($n=1$). In some instances, patients reported these odours as hallucinatory tastes, reflecting the common confusion between the two senses[40]. In a further 9 cases, patients reported gustatory hallucinations, which were described as either “unpleasant” or “odd”. Given the lack of further details of these experiences we are unable to confirm whether these were truly gustatory or if (as we suspect) these were also olfactory in nature.

Aside from brief olfactory hallucinations that typically occurred during seizures, in 10 cases participants reported a lingering or persistent smell (palinostmia). These could include both odours believed to be present and detectable by others but which lingered abnormally (in 5 of the 10 cases), or enduring hallucinations (in 8 of the 10 cases).

For most participants, the emergence of olfactory hallucinations corresponded with the onset of amnesic seizures, although in two cases these reportedly commenced 6-24 months prior to the onset of the amnesic attacks.

In 13 cases (24%), participants reported a reduced sense of smell to the clinician, including 4 cases where olfactory hallucinations were not a reported feature. A perceived heightened

sense of smell was mentioned in 5 participants (9%), 4 of whom had described experiencing enduring smells. In 2 individuals, both types of changes had been reported over time, with instances where smells were difficult to perceive, but other occasions where smells seemed excessively intense and perseverative.

3.2 Current objective olfactory performance - UPSIT

Consistent with our first hypothesis, TEA participants overall were significantly poorer at identifying smells on the UPSIT when compared with healthy matched controls (TEA mean = 23.75 ± 7.80 , HC mean = 30.06 ± 5.48 ; $t(97.02) = 4.83$; $p < .001$, $d = 0.94$ see Figure 1a). Based on age and gender norms provided with the UPSIT manual, TEA patients on average performed at the 27th percentile, with approximately a third (29% - 16 cases) scoring below the 10th percentile for their age and gender. Although 4 TEA participants demonstrated a normal sense of smell, 78% demonstrated at least moderate impairment in their ability to identify odours, as defined by the UPSIT categorisations (see Figure 1b).

By contrast, the majority of the healthy control sample (60%) performed within the normal or mildly impaired range based on the UPSIT test norms, with mean performance at the 43rd percentile for their age and gender. Only 8% (4 cases) fell below the 10th percentile on age and gender norms. Accordingly, the distribution of scores across the impairment categories was significantly different between TEA and HC participants ($X^2(4) = 18.84$, $p = .001$).

Despite the overall reduction in UPSIT score for TEA participants, results for individual items revealed that certain odours were still well recognised, regardless of impairment level. These included: smoke (87% of TEA participants correct), baby powder (85%), raspberry (84%), onion and peanut (both 80%). See Figure 2 in Supplementary Material.

Linear regression indicated that duration of TEA or number of amnesic seizures were not predictive of UPSIT score (b coef = -0.19 , $SE = 0.16$, $p = .247$, b coef = -0.02 , $SE = 0.06$, $p = .726$ respectively). Contrary to expectation, there was also no evidence that a history of olfactory hallucinations was predictive of olfactory ability, as measured by the total UPSIT score (b coef = -0.65 , $SE = 2.13$, $p = .761$). The distribution of UPSIT impairment categories was similar when comparing those who had a history of olfactory hallucinations as those who did not ($X^2 = 1.07$, $p = .784$), with approximately half of participants in each group demonstrating severe impairments or anosmia (48% of those without a history and 53% of those with a positive history). Within the 30 cases with a history of olfactory hallucination, 5 people performed either within the normal range or were only mildly impaired, indicating that the presence of hallucinations was not always associated with substantial reductions in smell. There was also no effect of EEG classification (normal, non-specific abnormalities, or epileptiform activity) on the UPSIT score ($F(2,50) = .342$, $p = .712$).

3.3 Current subjective reports of olfactory change

Almost half (49%) of the TEA participants reported some change in sense of smell. In 19 participants (35%), this was reported as a current reduction in olfaction while in 8 (15%) hypersensitivity to smell was reported.

Interestingly, while 65% of TEA participants did not believe that their smell had been reduced, 26 of these participants (72%) were at least moderately impaired on the UPSIT (with 58% severely impaired or anosmic). Of those reporting hypersensitivity to smells, 2 were mildly impaired, 1 moderately impaired, and the remaining 5 severely impaired or anosmic.

The level of agreement between patient self-report of reduced smell and impairment on the UPSIT (defined as moderate and above) was evaluated using a kappa statistic. Only a slight level of agreement was found ($\kappa = 0.13$)[41], indicating a relatively poor level of accuracy in self-report.

3.4 Current subjective memory difficulty

All TEA participants indicated some characteristic memory difficulty on their self-evaluation ratings of memory: 47% reported at least moderate difficulty with events over the past few weeks (that is, a difficulty level at least 5 out of 10), with 80% reporting difficulty with more distant past. 22% reported difficulty with memory for day to day events. Approximately one third of participants reported difficulties with recalling familiar routes (36%) or familiar landmarks (33%). Consistent with this, both the mean EMQ and mean VLMTQ were significantly greater than normal (i.e. more than two standard deviations above the normative mean values).

All self-reported memory measures were significantly correlated with each other (all $\rho > .34$, all $p < .01$), such that those who reported greater difficulties in one aspect of memory reported greater difficulty in other aspects of memory. When comparing performance on the UPSIT with self-reported memory problems, memory for familiar routes appeared significantly related ($\rho = -.32$, $p = .019$; see Table 2), with greater topographic difficulty reported in those who were poorer at identifying smells.

3.5 Current objective memory difficulty

Neuropsychological test results for the 26 participants available for testing are shown in Table 3. There were no significant differences in demographic (current age: $p = .280$, gender: $p = .587$) or clinical variables (age of TEA onset: $p = .081$; duration: $p = .511$; estimated number of amnesic attacks: $p = .972$; olfactory hallucinations: $p = .923$) when comparing those participants who completed the neuropsychological assessment from those who did not.

Overall, participants performed well on general measures of intelligence, semantic memory, executive function and visuospatial skills. There was no elevation in symptoms of anxiety or depression. Performance on the memory measures, however, indicated some reductions compared with previously collected normative data (see Table 3). On standard memory tests, average performance of TEA patients was approximately 1.5 standard deviations below the control mean. The largest memory impairments, however, were found for autobiographical memory (where Z MAMI scores indicated average performance 4 standard deviations below the control mean).

When comparing each of the subjective memory measures with the objective measures, a significant correspondence was found between accelerated forgetting (Z ALF) and self-

reported everyday memory failures (EMQ; $\rho = -.60$, $p = .002$ – such that poorer 1 week recall was associated with a higher rate of everyday memory failures). Overall performance on standard memory measures (Z Av Mem) was related to self-ratings of both day-to-day and distant memory difficulties ($\rho = -.45$, $p = .021$; $\rho = -.42$, $p = .035$ – with poorer general memory performance associated with reports of greater episodic memory difficulty). When comparing performance on the UPSIT with the objective memory scores (Z Av Mem, Z ALF, Z MAMI), however, no significant relationships emerged ($\rho = .131$, $p = .523$; $\rho = .28$, $p = .18$; $\rho = .08$, $p = .70$, respectively). Thus there did not appear to be any association between objective measures of memory and olfactory performance. There was also no group differences found for any subjective (EMQ, VLTMQ) or objective (Z Av Mem, Z ALF, Z MAMI) memory measures, when analysed according to the EEG classification (all $p > .09$).

4 Discussion

Our findings indicate that olfactory symptoms are very common among patients with TEA. Olfactory hallucinations were reported in 55% of cases overall; around half reported a current subjective alteration of the sense of smell, generally a reduction; a smaller proportion, 10%, reported an unusual persistence of real or imagined smells, palinostmia. In keeping with the high frequency of subjective olfactory disturbance, an objective measure of olfactory identification, the UPSIT, confirmed a significant reduction in the sense of smell in patients with TEA at the group level: 51% showed anosmia or severe impairments to sense of smell, as against 20% of controls of the same age. Epilepsy variables, such as duration of TEA, total number of amnesic seizures, or history of olfactory hallucinations, were not predictive of the degree of olfactory disturbance. As expected from previous work, both subjective and objective memory measures in patients with TEA point to a persistent interictal impairment of memory, particularly affecting autobiographical memory for events from previous months and years. We detected a correlation between subjective complaints of impaired topographical memory (route finding) and objective olfactory impairment. However, there was no correlation between performance on any of our objective measures of memory and olfactory impairment. We discuss each of these findings in turn.

4.1 Subjective olfactory disturbances

Consistent with previous reports in epilepsy, olfactory disturbances in TEA patients included both decreases in smell and reports of increased sensitivity [40]. Most common, however, were experiences of olfactory hallucinations. These were typically considered unpleasant and associated with burning or cooking odours, akin to descriptions provided in other forms of epilepsy [42]. Although previous estimates regarding the incidence of olfactory auras in epilepsy have varied markedly, ranging from less than 1% to greater than 30% [40], the majority of studies report relatively low numbers. When including different forms of epilepsy, one large sample ($n=686$), reported olfactory hallucinations in 3.6% of cases [43]. Figures increase slightly when studies focus specifically on TLE ($n=217$), with reports of 5.5% with olfactory disturbances[3], or about 10% [42]. By contrast, and in keeping with the previous study by Butler and colleagues[5], we found a high proportion of TEA patients experiencing olfactory hallucinations – approximately half of all cases. Although this differs

to a recent retrospective study in TEA [14], this discrepancy is most likely a result of differences in data collection, as our clinical interviews with participants specifically included questions about olfactory features. Previous work has shown that olfactory hallucinations in epilepsy are particularly associated with seizure foci in amygdala [3] or orbitofrontal cortex [44]. This may be relevant in explaining the high frequency of olfactory hallucinations in TEA, given the orbitofrontal cortex appears the most atrophic brain region [30]. Future studies incorporating brain imaging may help confirm this relationship.

4.2 Objective olfactory decline

The overall finding of reduced performance on the UPSIT compared with healthy older controls is the first objective demonstration of the presence of olfactory deficits in TEA patients. This result is consistent with previous studies of TLE, where reduced ability in identifying odours has been found. In fact, a recent study in TLE which also used the UPSIT reported very similar performances (with means of 22.08 out of 40 vs our 23.75)[20]. Although olfactory ability is known to decrease with age[45], the proportion of TEA participants showing severe impairments to smell was more than double what might be expected within the general population. Akin to more typical forms of TLE, these impairments in TEA most likely arise from either damage or disruption to connections within the complex network of temporal regions involved in olfactory processing [23].

4.3 Relationship between objective olfactory ability and clinical characteristics

Although the proportion of participants who experienced olfactory hallucinations was equivalent to the proportion showing severe impairments in odour identification, no significant relationship emerged between the two. Some participants with a history of hallucinations still performed within the normal or mild impairment range of the UPSIT. This suggests that these distorted experiences of smells do not necessarily adversely impact the ability to identify smells. No group differences in smell were found according to participants' EEG result. We also found no correspondence between olfactory performance and duration of TEA or total number of amnesic seizures. The lack of association between smell performance and these measures of epilepsy severity, has been reported previously in TLE[20]. This null result may reflect that changes in olfaction occur early on, commencing with, or perhaps preceding, the onset of amnesic attacks. As a result, the number of attacks and presence of olfactory hallucinations may have little impact on such changes.

4.4 Patient accuracy and awareness of olfactory changes

While a subset of patients were very aware of their reduced sense of smell, it was notable that a substantial proportion of participants had not detected the change. Overall, there was poor agreement between self-reported reduced smell and objective findings. Anecdotally, for some participants, completion of the smell test highlighted for the first time that a difficulty existed, with comments by some participants that all odours smelt the same, or no odour could be detected at all. Some patients reported heightened detection of smell, or an abnormal lingering, and yet showed reduced ability to correctly identify smells. Confusion also existed regarding hallucinatory experiences which are described as “odd tastes”, but which reflect olfactory experiences (e.g. reports of a “courgette *taste*”).

There is little information in the literature about the accuracy of older adults when judging their sense of smell. While some studies suggest that this is poorly judged[46], others suggest that we should only expect milder losses to go unnoticed[47]. Regardless, clinicians should be aware that while reduced smell is a common feature of this condition, subjective self-report of changes may not be reliable. The presence of olfactory hallucinations, however, remains a common feature of TEA and should be routinely questioned (together with questions regarding any odd tastes).

4.5 Subjective and objective memory performance

Consistent with previous findings[5], participants reported ongoing memory difficulties and showed reductions on memory testing when compared with normative data. This was most clearly demonstrated for autobiographical memory, both in self-reported difficulty recalling events from the distant past, and objective scores on the modified Autobiographical Memory Interview. Some reductions were also found on overall performance across standard memory tests, which were moderately correlated with self-ratings of difficulties in day-to-day and distant memory. In one third of participants, difficulties with topographic memory were reported.

4.6 Relationship between olfactory and memory performance

When relating olfactory performance with memory, no significant relationships were detected between olfaction and the objective measures of memory included within our study. This is in contrast to associations found in previous studies of both cognitively normal older adults [48] and those with mild cognitive impairment [25,49] or Parkinson's Disease [50,51]. Within epilepsy studies, however, relationships between UPSIT and measures of neuropsychological function have not been clearly established [52]. Thus, while disturbances in olfactory and episodic memory ability appear common in TEA, there does not appear to be a simple, direct relationship between them.

A significant relationship did emerge, however, between self-reported difficulty with route-finding and the UPSIT. While the reason for this relationship is unclear, it could be that smell identification and topographical memory performance share a greater overlap regarding neural networks involved. We acknowledge, however, that as an exploratory study, we did not correct for multiple comparisons, and therefore it is possible that the relationship may have arisen by chance. Future research which also includes objective tests of topographical memory, ideally combined with brain imaging, may help to confirm and clarify any potential relationship.

4.7 Limitations and future directions

The current study focused on a large sample of TEA patients to verify if subjective reports of olfactory change were objectively supported, and examine associations between olfactory ability and other clinical and cognitive variables within TEA. While we did not use a concurrent control group, TEA participants were compared both with published UPSIT test normative data and a well-matched UK sample of healthy older adults – with both indicating reductions in olfaction compared to what would be expected within the general population. Future studies, however, may seek to recruit a healthy control group to also investigate

awareness of olfactory changes, and how this may relate to cognitive function. In addition, inclusion of a concurrent, matched TLE group would provide the opportunity to determine any differences in the level of olfactory impairment.

4.8 Conclusion

This first systematic investigation of olfactory disturbances in TEA confirms that impairments in odour identification are common in TEA and exceed changes that occur in normal ageing. Approximately half of all TEA patients experienced olfactory hallucinations, although the presence of hallucinations did not predict olfactory ability. TEA patients typically experience ongoing memory difficulties, particularly with regard to autobiographical memory. While these memory difficulties appear unrelated to olfactory ability in TEA, a potential link between olfactory disturbances and topographical memory should be further explored in future.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

A) Boxplot showing olfactory performance on the University of Pennsylvania Smell Identification Test (UPSIT) by diagnosis. Healthy control participants correctly identify a significantly higher number of smells than TEA participants ($p < .001$); B) UPSIT impairment categories by group (where “normal” is defined as scores of 34-40, “mild” impairment scores are 30-33, “moderate” impairment scores are 26-29, “severe” impairment scores are 19-25 and “anosmia” scores are 18 and below). TEA and HC participants show reverse patterns in the distribution of smell impairment (with 78% of TEA participants classified as at least moderately impaired vs 80% of HC participants who are at most moderately impaired).

Table 1
Core clinical features of TEA participants

Demographics	
Age (y)	M = 70.59 (SD = 8.14)
Sex distribution	42 males : 13 females
Smoking history	Ever smoked: 34 (61.8%) Current smoker: 3 (5.5%)
TEA history	
Age at seizure onset (y)	M = 61.51 (SD = 7.47) ; 44 – 76 years
TEA duration (y)	M = 8.82 (SD = 6.50) ; 0.5 – 35.3 years
Estimated number of amnesic attacks	M = 17.85 (SD = 18.05); 2 – 68

Table 2
Self-reported difficulties with episodic memory (Mean and standard deviation and correlation with UPSIT score)

Self-reported memory difficulty	Mean (SD) (n=55)	Correlation with UPSIT (Spearman rho)	p
day to day events (/10)	2.00 (2.42)	-.08	.551
events from the past few weeks (/10)	4.08 (2.55)	-.09	.445
events from the more distant past (/10)	5.84 (2.16)	-.01	.706
familiar routes (/10)	3.35 (2.88)	-.32	.019
location of familiar landmarks (/10)	3.18 (2.88)	-.27	.069
EMQ (/ 90)	30.95 (14.07)*	-.25	.067
VLMTQ (/39)	9.39 (6.28)*	-.02	.874

* result significantly above normative values (HC mean for EMQ = 13.8; VLTMQ = 2.4)

Table 3
Neuropsychological test performance (Mean and standard deviation)

Neuropsychological Measure	TEA (n=26)	Controls (n=24) *
WASI (2-subtest IQ)	118.69 (10.34)	120.0 (14.4)
Graded Naming Test (/30)	22.00 (3.16)	23.5 (4.2)
COWAT (letters F,A,S)	41.27 (13.67)	43.8 (11.4)
Trail Making Test – Part A	35.13" (13.75)	-
Trail Making Test – Part B	101.61" (64.47)	-
Rey Complex Figure Test – copy (/36)	31.27 (4.36)	35.5 (1.1)
Hospital Anxiety Depression Scale – Anxiety	5.95 (4.09)	4.7 (2.8)
Hospital Anxiety Depression Scale – Depression	4.48 (3.94)	2.9 (1.7)
Logical Memory (Story 1) – Immediate (/25)	10.62 (4.14)	15.9 (3.8)
Logical Memory (story 1) – Delay (/25)	8.73 (4.55)	14.7 (3.8)
Logical Memory (Story 1) – Recognition (/15)	12.04 (1.64)	13.6 (1.2)
Rey Complex Figure Test – 30 min delay (/36)	12.06 (4.78)	18.6 (6.1)
Recognition Memory Test – Words (/50)	44.38 (5.71)	48.3 (1.9)
Recognition Memory Test – Faces (/50)	39.58 (5.85)	45.1 (2.9)
Z Av Memory	-1.55 (1.00)	
Z ALF	-1.25 (1.07)	
Z MAMI	-4.02 (2.57)	

* Healthy control participants from Butler et al 2007