On the nose: Olfactory disturbances in patients with transient epileptic amnesia

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Objective: While olfactory hallucinations are relatively rare in epilepsy, a high prevalence (up to 42%) has been reported in one form – Transient Epileptic Amnesia (TEA). TEA is characterized by recurring amnestic 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 patients with 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, and assessment of accelerated long-term forgetting and autobiographical memory.

Results: Olfactory hallucinations were reported in 55% of patients with TEA. A significant reduction in smell identification (UPSIT) was found between patients with TEA and healthy controls (p < 0.001). 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.

Conclusions: Impairments in odor identification are common in patients with TEA and exceed changes that occur in normal aging. Olfactory hallucinations occur in approximately half of patients with TEA, 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.

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1. Introduction

Although olfactory hallucinations can occur in temporal lobe epilepsy (TLE), the prevalence generally appears low [1], with estimates ranging from <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 characterized by recurring amnestic 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 seizures 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 patients with TEA. Olfactory ability appears to be a sensitive marker in various neurological or neuropsychiatric groups, including schizophrenia, Parkinson’s Disease, Alzheimer’s Disease and other dementia syndromes [17–19].

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Previous studies of olfactory processing in TLE have indicated that while odor detection may be unimpaired, other judgments, such as odor identification, are significantly reduced compared to age-matched healthy controls [20–24]. No formal investigations of olfactory ability, however, has been conducted specifically in patients with 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 patients with 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 aging 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]. Odor discrimination in particular has been associated with functioning of the piriform cortex, orbitofrontal cortex, and hippocampus [28], with loss of smell (anosmia) correlated with gray matter changes within the piriform cortex, insular cortex, orbitofrontal cortex, medial prefrontal cortex, hippocampus, parahippocampal gyrus, supramarginal gyrus, nucleus accumbens, subcallosal gyrus, and medial and dorsal prefrontal cortex [29]. Previous investigations in patients with TEA suggest that volume reductions can occur in two of these regions: namely the hippocampus in patients with TEA, drawing upon both subjective report and objective basis for both olfaction and memory change.

The aim of this study, therefore, was to investigate changes in olfaction in patients with TEA, drawing upon both subjective report and objective measures. Specifically, we hypothesized 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 behavioral 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 tumors 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.

Table 1

<table>
<thead>
<tr>
<th>Demographics</th>
<th>TEA history</th>
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<tbody>
<tr>
<td>Age (y)</td>
<td>M = 70.59 (SD = 8.14)</td>
</tr>
<tr>
<td>Sex distribution</td>
<td>42 males: 13 females</td>
</tr>
</tbody>
</table>
| Smoking history | Ever smoked: 34 (61.8%)
|                | Current smoker: 3 (5.5%) |
| Age at seizure onset (y) | M = 61.51 (SD = 7.47)
| TEA duration (y) | M = 8.82 (SD = 6.50)
| Estimated number of amnestic attacks | M = 17.85 (SD = 18.05) |

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 were obtained from data previously collected in East Anglia.1 Fifty healthy control (HC) participants were selected to match TEA participants with respect to gender distribution (HC gender: 38 M, 12F; \( \chi^2 = 0.002, p = 0.965 \)), age (HC mean age = 69; \( t (104) = -0.93, p = 0.354 \)), and current smoking status (HC current smokers = 7; \( \chi^2 = 2.22, p = 0.136 \)).

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 behavioral 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 “palinosmia.”

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 odor one at a time, then immediately sniff and select one of four choices to indicate what the odor 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 categorize each participant’s smell as: normal (scores of 34–40), mildly

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1 Data 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.
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