Original Article

Functional Neuro-Imaging and Post-Traumatic Olfactory Impairment

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ABSTRACT

Objective: To evaluate via a research literature survey the anterior neurological significance of decreased olfactory functioning following traumatic brain injuries. Materials and Methods: A computer literature review was performed to locate all functional neuro-imaging studies on patients with post-traumatic anosmia and other olfactory deficits. Results: A convergence of findings from nine functional neuro-imaging studies indicating evidence for reduced metabolic activity at rest or relative hypo-perfusion during olfactory activations. Hypo-activation of the prefrontal regions was apparent in all nine post-traumatic samples, with three samples yielding evidence of reduced activity in the temporal regions as well. Conclusions: The practical ramifications include the reasonable hypothesis that a total anosmic head trauma patient likely has frontal lobe involvement.

Key words: Anosmia, functional neuro-imaging, olfaction, traumatic brain injury

INTRODUCTION

As “clinical signs”, anosmia (complete loss of sense of smell) and reduced sense of smell occur in a wide variety of neurologic and neuropsychiatric conditions.[1,2] However, in the context of closed head trauma, it has been proposed that post-traumatic olfactory impairment can be a clinical sign associated with damage to the anterior regions of the brain following blunt-force, acceleration-deceleration trauma to the head.[3-5] Zusho[6] has observed that occipital impacts and direct frontal impacts most often caused post-traumatic anosmia, presumably through a coup-contrecoup mechanism of injury resulting in shearing injury at the level of the olfactory nerves as they penetrate the cribriform plate towards the olfactory bulb. Olfactory dysfunction is also believed to be more common in the presence of moderate to severe head injury. However, a study by Ogawa and Rutka[7] found that so-called “trivial” head injuries accounted for 11.8% of patients with olfactory changes following workplace falls or blows to the head.

Varney[8] proposed that reduced sense of smell following mild to moderately severe traumatic brain injury (TBI) is often associated with damage to the orbital-frontal cortex,[9] evidence of executive dysfunction on the Iowa Collateral Head Injury Interview,[10] and poor vocational outcome.[11,12] Furthermore, a “preliminary” single photon emission computed tomography (SPECT) study of selected patients with poor clinical outcomes following mild TBI also demonstrated evidence of reduced activation of anterior orbital-frontal and anterior temporal regions of the brain.[13] Varney’s initial hypothesis was supported by findings from a study by Callahan and Hinkebein.[14] These investigators found that
individuals with post-traumatic anosmia manifested test-based evidence of executive dysfunction and increased functional disability in daily life. Similarly, M.A. Roberts and Simco proved a brief clinical procedure for examining sense of smell in elementary-aged children and showed that children with post-traumatic anosmia were three times as likely to be rated by their parents as having clinically significant deficits in executive function on the Pediatric Inventory of Neurobehavioral Symptoms.

More recently, Fortin and colleagues found that individuals with frontal lobe involvement following TBI performed more poorly on two different tests of olfactory recognition than did patients with lesions in other loci. Mood status and severity of initial injury were not significantly associated with olfactory impairment once the effects of age were taken into account. Almost half of the patients with olfactory impairment were unaware of this problem, once again demonstrating that post-traumatic anosmia and hyposmia tend to be relatively “silent” defects.

However, research by other experts in the fields of TBI and olfactory function has failed to support Varney’s hypothesis. Furthermore, these same investigators have criticized Varney’s initial findings on a variety of methodological grounds. Additionally, since reduced sense of smell is most often tested clinically by presenting odorants and eliciting verbal report from patients, olfactory dysfunction is theoretically subject to being feigned or malingered in the context of protracted litigation following head trauma. A further serious confound is the possibility that olfactory dysfunction may be a preexisting condition that only becomes apparent following a TBI. At least in some cases poorer olfactory identification may correlate nonspecifically with deficits in the orbitofrontal regions, and consistent with this are studies linking olfactory impairments in children to Attention-Deficit/Hyperactivity Disorder, a condition with prefrontal compromise. Also, numerous studies support the premise that aggressive behavior is associated with reduced functioning of the orbital-frontal cortex. Naturally, such patients are more prone to make the poor decisions and to take the kinds of risks that lead to head injuries. We therefore caution that in all studies reviewed here, the sample of head trauma patients may already be inherently biased toward patients with olfactory dysfunction or anosmia, in which case estimates of the frequency of occurrence of post-traumatic olfactory dysfunction or anosmia following head trauma will be too high.

Accordingly, this brief review of pertinent findings from functional neuro-imaging studies of olfactory deficits was undertaken to attempt to clarify the apparent controversy over the possible significance of decreased olfactory function following TBI. This review is especially timely given recent evidence that reduced olfactory function has been found to be among the most common neurological deficits in combat veterans who have been exposed to concussion-blast. In fact, the first three cases of reported “shell shock” described during World War I all had significant olfactory deficits on their neurologic exams.

### MATERIALS AND METHODS

A PubMed computerized literature search was undertaken in an attempt to find all published functional neuro-imaging studies of patients with post-traumatic anosmia other than Varney’s initial SPECT scan study in 1995. The primary findings from this literature review will be “anosmia and functional neuro-imaging,” “anosmia and functional magnetic resonance imaging (MRI),” and “post-traumatic anosmia.”

### RESULTS

Nine functional neuro-imaging studies identified in the literature search provided evidence for reduced metabolic activity in prefrontal regions at rest or relative hypo-perfusion during olfactory activations. The findings were consistent across different imaging modalities, different methods of data analysis, and the use of different procedures for assessing olfactory function. Three of the studies also provided evidence of reduced activity in the temporal regions of the brain, as well the frontal lobes. The results are summarized in Table 1.

### DISCUSSION

The evidence from this brief but comprehensive review provides consistent support for Varney’s hypothesis that post-traumatic anosmia is often associated with dysfunction in the anterior regions of the brain in the post-acute period following impact. More specifically, the results across all nine studies showed evidence of functional compromise in the orbital-frontal regions of the brain (i.e. those portions of the cortex that are adjacent to the olfactory pathways), with three of the studies also showing evidence of functional compromise in the temporal lobes. Though complete loss of smell or anosmia following head injury was, as expected, more likely the more severe the head injury, it could also result from even a minor blow to the head (i.e. one not associated with loss of consciousness). In addition, though a number of studies have indicated that olfactory dysfunction is most often associated with frontal-occipital blows, the study of Ogawa and Rutkai failed to confirm this association. Instead the

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incidence of olfactory dysfunction in their sample (workers sustaining blunt head injuries after falls or being inadvertently struck on the job) was effectively the same for those hit on the side of the head (19.3%) as those hit in the front or the rear (22.75%). Obviously, this point merits further investigation.

We conclude that, if a clinician encounters a totally anosmic patient following head trauma, it would be advisable to adopt a high index of suspicion with regard to the possible presence of neurobehavioral symptoms and task-related deficits associated with damage to or dysfunction in the frontal lobes. This is a crucial insight for clinicians and radiologists alike because problems with executive function associated with frontal lobe damage following mild TBI can pose significant impediments to behaving competently in real-world situations,[8,11] even in the absence of major test-based neuropsychological deficits.[13,40]

Several limitations of the present survey deserve comment. First, because editorial policies typically bias against publication of null results, neuro-imaging studies with negative findings with regard to olfaction and mild TBI may not have made their way into the published research literature. Second, this literature review could not address the degree of neurobehavioral impairment associated with post-traumatic anosmia in the various samples. Third, one of the problems in evaluating patients with anosmia—especially in cases where issues of compensation are involved—is the difficulty, if not impossibility, of quantifying olfactory losses accurately. To date, the most sophisticated systems for measuring olfactory recognition, the University of Pennsylvania Smell Identification Test[41] or the “Sniffin Sticks” approach which has gained popularity in Europe and Asia,[42,43] still depend on volunteered subjective responses. It may be that in the future the use of olfactory evoked potentials, SPECT, or functional MRI may lead to greater objectivity.

At present, unfortunately, there is not enough data to compare the yield from functional neuro-imaging techniques to the efficacy of using only structural neuro-imaging techniques.[44,45] On the other hand, the methods that were employed in the studies reviewed in this article did approximate the “rough and ready” assessment conducted during a clinical neurological exam (on those rare occasions when testing of the first cranial nerve has not been “deferred”). Fourth, there was no consistent information regarding “real-world” outcomes (e.g., vocational status, functional disability status) in this group of studies. Thus, no firm conclusions can be drawn from the present data to resolve the debate between those experts who believe that post-traumatic anosmia has ecological validity as a “poor prognostic” sign and those who do not.

Although functional neuro-imaging paradigms appear to be quite ‘sensitive’ to the presence of post-traumatic impairment of olfactory function, hypo-metabolic activity or decreased perfusion in the prefrontal regions is not necessarily a ‘specific’ indicator of either TBI or executive dysfunction. As previously noted, numerous studies support the premise that aggressive behavior is also associated with reduced functioning of the orbital-frontal cortex.[26,27] Thus, multiple “clinical signs” (such as post-traumatic anosmia) or various behavioral syndromes (e.g., impulsive aggression, depression) are likely to be partially mediated by functional networks that include portions of the orbital-frontal cortex. Interestingly, however, one recent study of combat veterans with post traumatic stress disorder (PTSD) demonstrated that deficient olfactory recognition was associated with greater risk of aggression and impulsivity.[46] Furthermore, the same research group found that impulsive children with attention deficit hyperactivity disorder (ADHD) manifested poorer identification of odors when their performance was compared to that of healthy aged-matched, comparison children.[27] These researchers interpreted

### Table 1: Functional neuro-imaging studies of post-traumatic olfactory deficits

| Authors               | Year  | Type    | Olfactory testing | N | Patients | Control (N) | Analysis                                | Findings (brain area)                          |
|-----------------------|-------|---------|-------------------|---|----------|-------------|------------------------------------------|-----------------------------------------------|
| Varney et al[31]      | 1998  | SPECT   | Single item       | 18| Anosmic  | Normal (5)  | Quantitative                             | Hypoperfusion, (orbital-frontal)              |
| Levy et al[32]        | 1999  | fMRI    | Chemical vapors   | 5 | Hyposmic | Normal (2)  | Quantitative                             | Hypoactivation, (frontal-temporal)            |
| DiNardo et al[33]     | 2000  | SPECT   | Cain’s 8 items    | 5 | Anosmic  | Normal (10)| Semi-quantitative                        | Less activation                               |
| Varney et al[34]      | 2000  | PET     | Single item       | 11| Anosmic  | Normal (56)| Quantitative                             | Hypometabolism, (orbital-frontal, medial frontal) |
| Eftekhari et al[35]   | 2005  | SPECT   | Single item       | 14| Anosmic  | Normal (10)| Quantitative                             | Reduced perfusion                            |
| Mann and Vento[36]    | 2006  | SPECT   | 6 items           | 6 | “Impaired” | None        | Quantitative                             | Normal                                        |
| Eftekhari et al[37]   | 2006  | SPECT   | Cain’s 8 items    | 16| Anosmic  | Normal (13)| Semi-quantitative                        | Hypoperfusion, (orbital-frontal)              |
| Liu et al[38]         | 2008  | fMRI    | Single item       | 5 | Anosmic  | Normal (10)| Unclear                                  | Reduced activation, (frontal-limbic)          |
| Atighechi et al[39]   | 2009  | SPECT   | Cain’s 8 items    | 21| Anosmic  | Normal (62)| Semi-quantitative                        | Hypoperfusion, (frontal, temporal, parietal)  |

SPECT - Single photon emission computed tomography; fMRI - Functional magnetic resonance imaging; PET - Positron emission tomography.
this result as being consistent with previous reports of prefrontal compromise in children and adolescents with “externalizing” behavior disorders.

With regard to the implications of the present findings for forensic practice, it occasionally may prove necessary to seek some type of corroborating evidence of olfactory dysfunction, such as a SPECT scan[47] when malingering of anosmia is suspected or the results of so-called “effort-testing” are questionable. Similarly, olfactory evoked potential paradigms would appear to have some future utility in providing corroboration for the clinical complaint/finding of anosmia[48-50] as does the Olfactory Stop Reaction used with quantitative electroencephalogram (EEG) records.[51]

Although some patients are occasionally quite vociferous about the impact of reduced senses of smell and taste on their quality of life and seek specialized chemo-sensory evaluation, many adults and children with TBI, post-traumatic anosmia or hyposmia may be relatively “silent” deficits[13] leading some experts to label olfaction “the neglected sense”.[52,53] As Kivity and associates[44] have noted, “…assessment of the sense of smell and olfactory impairments is usually overlooked by patients and their clinicians.” Given the clinical data reviewed here, clinicians should be encouraged to screen for olfactory impairments…” (p. 243). As Samuel Shem[54] warned in his novel, House of God, “If you don’t take a temperature, then you can’t find a fever.”

In summary, additional research will be needed to determine the neurobehavioral correlates of post-traumatic anosmia in the field of TBI research. However, a consistent body of evidence appears to be emerging that indicates that pronounced deficits in odor recognition following TBI are associated with predictable findings on functional neuro-imaging. This conclusion, in and of itself, should be enough to elevate mandatory testing of olfaction to the status of a “standard of care,” when care-providers are called upon to assess TBI patients at increased risk for anosmia and other olfactory deficits following closed head trauma.[53] As Cain[56] pointed out over two decades ago, “The routine test of olfaction need not lead to an ambiguous outcome, a rather widely held notion (p. 515).” This conclusion is even more relevant today, given recent technical advances in testing olfaction.[2]

Conscientiously assessing olfactory function is likely to be especially important when evaluating cases of “mild” TBI due to blast-exposure (as well as blunt-force trauma), given that Ruff and colleagues found a high frequency of olfactory impairment and neuro-cognitive deficits in combat veterans with persistent headache following improvised explosive device (IED) and military ordnance concussion-blasts.[28] Furthermore, findings from initial case reports[57] and case series[58] suggest that functional neuro-imaging studies may uncover significant problems with brain function following blast-exposures even when structural imaging studies yield negative results. It would appear that studies combining functional neuro-imaging, careful measurement of olfactory function, and neurobehavioral outcome (using both test-based and real-world criteria) are likely to be fertile ground for investigating the all-too-frequent effects of blast-exposure associated with modern warfare.[59]

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