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PERVASIVE OLFACTORY IMPAIRMENT AFTER BILATERAL LIMBIC SYSTEM DESTRUCTION

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Abstract

What pattern of brain damage could completely obliterate the sense of olfaction in humans? We had an opportunity to address this intriguing question in patient B., who has extensive bilateral damage to most of the limbic system, including the medial and lateral temporal lobes, orbital frontal cortex, insular cortex, anterior cingulate cortex, and basal forebrain, caused by herpes simplex encephalitis. The patient demonstrated profound impairments in odor identification and recognition. Moreover, he could not discriminate between olfactory stimuli and he had severe impairments in odor detection. Reliable stimulus detection was obtained only for solutions of the organic solvent acetone and highly concentrated solutions of ethanol. In contrast to the more circumscribed olfactory deficits demonstrated in patients with damage confined to either the temporal lobes or orbitofrontal cortex (which tend to involve odor identification but not odor detection), patient B. demonstrates a strikingly severe and complete anosmia. This contrast in olfactory abilities and deficits as a result of different anatomical pathology affords new insights into the neural substrates of olfactory processing in humans.

INTRODUCTION

Olfaction is an interesting sensory modality. Expansion of olfactory sensation and associated neural processors was a principal driving force in evolution of the mammalian brain (Rowe et al., 2011), and yet in humans, the importance of olfaction is disproportionately reduced relative to senses such as vision and audition. It is the only sensory modality in which information reaches the cortex directly without being relayed to the thalamus (although some olfactory projections are sent to the thalamus). Most olfactory fibers do not cross, but project ipsilaterally in the brain. Despite its reduced role in humans, though, olfactory information can have a powerful influence on behavior, especially through its relationship with other classic “limbic” functions such as memory and emotion.

Olfactory information reaches the brain via the olfactory nerve (cranial nerve I), entering the olfactory bulb and then passing along the olfactory tract, the latter which divides into medial and lateral olfactory striae projecting to cortex (Heimer et al., 1977) (a small intermediate branch has also been described, and this may project to the perforated substance and/or run through the anterior commissure to connect the two sides of the olfactory system; Eslinger et al., 1982). The primary olfactory cortex, which is responsible for awareness or what can be

termed “conscious perception” of olfactory stimuli, includes the prepiriform cortex and periamygdaloid area in the anteromedial part of the temporal lobe known as the uncus. The entorhinal area, which comprises the anteriormost part of the parahippocampal gyrus adjacent to the uncus, functions as olfactory association cortex. The uncus and entorhinal area, together with the limen insulae, constitute the piriform area, or what is termed the lateral olfactory area. Other cortical processors of olfactory information include the intermediate olfactory area (including the anterior perforated substance, innominate substance, and diagonal band of Broca) and the medial olfactory area (septal area) on the medial surface of the frontal lobe, ventral to the genu and rostrum of the corpus callosum (Barr, 1979; Carpenter, 1972).

In a manner roughly akin to other sensory modalities such as vision and audition, the higher-level processing of olfactory information can be broken down into several more specific abilities, including odor detection, intensity judgment, discrimination, and identification. Odor detection refers to the ability to detect whether an odor is present or not. Odor intensity judgment refers to the ability to judge the intensity of an odor. Odor discrimination refers to the ability to judge differences between odors. Odor identification refers to the ability to recognize and name an odor—e.g., what the normal source is and what the odor normally is called. There is evidence that these different aspects of olfactory processing are dissociable and depend on partly distinct neural systems (Gottfried & Zald, 2005; Landis et al., 2005; Lledo et al., 2005).

The importance of the piriform cortex and orbitofrontal cortex (OFC) for olfactory processing has been supported by lesion studies (Eslinger et al., 1982; Jones-Gotman et al., 1997), and more recently by functional imaging approaches including PET (Dade et al., 1998; Royet et al., 2000, 2001; Zatorre et al., 1992, 2000), fMRI (Katata et al., 2009), and NIRS (Kokan et al., 2011) (for reviews, see Dade, Zatorre, & Jones-Gotman, 2002; Zald & Pardo, 2000). In the lesion work, for example, impairments in odor quality discrimination have been observed in monkeys following lesions of the orbitofrontal cortex (Tanabe, Iino, et al., 1975; Tanabe, Yarita, et al., 1975). Similar deficits have been reported in human subjects with lesions in orbitofrontal cortex (Potter & Butters, 1980). Patient HM, who has bilateral mesial temporal lobe damage, was reported to have defects in the ability to discriminate and identify odors in same-different discrimination and in matching-to-sample tasks, although he was preserved on basic tests of odor detection and intensity discrimination (Eichenbaum et al., 1983). Jones-Gotman et al. (1997) reported impaired odor identification (on the University of Pennsylvania Smell Identification Test) in patients with varying types of temporal lobe resections, with greatest impairment in the nostril ipsilateral to the resection.

The functional imaging work has revealed important nuances regarding odor processing, such as the existence of partially distinct neural processing systems for body odors versus non-body odors (Lundström et al., 2008) and a key role for the amygdala in the processing of aversive odors (Zald & Pardo, 1997). However, functional imaging approaches do not address the question of which neural regions are necessary for odor processing—this question is more directly tested with lesion approaches. In the available lesion work, there is evidence that damage to the OFC or to the anteromesial temporal lobe impairs the abilities to discriminate and identify odors (Eichenbaum et al., 1983; Eslinger et al., 1982; Jones-Gotman et al., 1997; Potter & Butters, 1980). However, the patients reported in these studies for the most part do not show impairments in odor detection and odor intensity judgments. Specifically, as noted above, HM had normal odor detection and intensity discrimination, and the patients with OFC lesions reported by Potter and Butters (1980) also were unimpaired on odor detection. The patients reported by Jones-Gotman et al. (1997) had normal odor detection (they were specifically screened on this criterion). Thus, the available

lesion evidence does not contain a case where a patient was entirely anosmic, in the sense of having virtually no capacity for higher-order processing of olfactory information.

We had an opportunity to explore further the neuroanatomical basis of olfactory processing by studying a patient, known as patient B., who has extensive bilateral temporal, orbitofrontal, insular, and basal forebrain damage as a result of herpes simplex encephalitis. In contrast to the olfactory deficits demonstrated in patients with damage to the anteromedial temporal lobes or to the orbitofrontal cortex alone, patient B. demonstrates a strikingly severe anosmia that covers virtually all aspects of olfactory processing. This contrast in olfactory abilities and deficits as a result of different anatomical pathology affords new insights into the neural basis of higher-order olfactory processing in humans.

METHODS

Participants

The participants in this study include patient B. and a group of normal comparison participants.

Patient B—Patient B. has extensive bilateral damage to the temporal lobe, orbitofrontal region, insula, and basal forebrain as a result of herpes simplex encephalitis incurred when he was 48 years old (for comprehensive descriptions of the patient, see Damasio et al., 1985; Damasio et al., 1989; Tranel et al., 2000). He was 60 years old at the time the olfactory experiments reported in the current article were conducted. B. is fully right-handed and has 13 years of schooling. He was a non-smoker since the onset of his brain damage.¹ Based on detailed reports obtained from his relatives (wife, children), we were able to determine that B.'s sense of smell was entirely normal prior to his neurological illness.

Results of neuroanatomical analyses, based on CT and structural MRI data, indicate damage to most of the cortical and a portion of subcortical limbic system structures in patient B. In the temporal lobe, the mesial portion, including the parahippocampal gyrus, all of the allocortices (hippocampus), and the major subcortical subcomponents of the limbic system (septum, amygdala, substantia innominata) are destroyed bilaterally (the nucleus accumbens is partially spared). Also involved is the anterolateral temporal lobe including the nonlimbic neocortical structures in Brodmann areas 38, 20, and 21 as well as the anterior part of 22. In the frontal lobe, damage includes most of the orbitofrontal cortex and basal forebrain gray matter bilaterally. On the mesial surface, the lesion extends into the anterior portion of the cingulate gyrus with destruction more marked on the right side than on the left side (Figure 1).

B. has a pervasive amnesic syndrome, encompassing virtually all aspects of anterograde declarative memory and much of the retrograde compartment as well. The retrograde amnesia spans most of B.'s life prior to his illness, sparing only generic (semantic) memory including factual knowledge and some bits and pieces of knowledge of his previous experiences devoid of detail and appropriate contextual information. On the anterograde side, with the exception of preserved learning of visuomotor skills, visuoperceptual priming, and covert (unconscious) learning of affective valence (Tranel et al., 1993; Tranel et al., 1994), B. is incapable of acquiring new information. Attention, concentration, short-term memory, elementary perceptual abilities, intellect, and most basic linguistic abilities are

¹In this context, it is interesting to note that B. did not evidence “urges” or “cravings” to smoke following his lesion onset, which is consistent with the idea that insula damage (which B. has in entirety in both left and right hemispheres) can disrupt smoking addiction by abolishing urges and cravings for nicotine (Naqvi et al., 2007).

mostly preserved (see Tranel et al., 2000, for details on the patient's neuropsychological profile).

Normal comparison participants—B.'s performance on the olfactory tests was compared to that of 19 normal comparison (NC) participants (10 men, 9 women), who were free of neurological and psychiatric disease. The NC group was mainly middle-aged (Age in years: $M = 45.2$, $SD = 3.9$; range 23 – 77), and mainly college-educated (Education in years: $M = 16.4$, $SD = 4.5$, range 12 – 20), comparable to B. in terms of these basic demographic factors (the few years more of education, on average, in the NC group is considered unlikely to appreciably affect performance on the basic olfactory tests used in the current studies).

Olfactory Experiments

Experiment 1: Identification of Common Odorants

Part A: Odor Identification – Confrontation Naming: The participant was asked to identify common odors presented individually in 3 ounce brown bottles. The stimuli included a “blank” stimulus (water) and 14 common environmental scents: fresh ground coffee, soap, pipe tobacco, juicy fruit gum, baby powder, rose (Phenethyl Alcohol – Fisher Scientific Company), peanuts, cinnamon (McCormick), wintergreen (Methyl Salicylate – EM Science), aftershave (Brut), mothballs (Naphthylene aldehyde), chocolate (Nestles), butterscotch (McCormick), and strawberry (McCormick). On each of the 15 trials involving a different sample odor, the participant was given the sample and was instructed to sniff the bottle and name (or identify) the scent. To minimize the demand for short term memory on the task, repeated sniffing of the sample was allowed. If the participant was unable to name the stimulus, they were asked to give a verbal description or definition of the odor—e.g., “What does this smell remind you of? Does it make you think of anything in particular?”² We scored the number of stimuli named correctly, and in addition, the number of stimuli identified accurately (either by the correct name or by an accurate verbal description).

Part B: Odor Identification – 4-Alternative Forced-Choice Recognition: The 15 sample stimuli were presented in successive trials and on each trial, the participant was asked to choose the name of the odor from a list of 4 odor labels. Comprising the list was the target name (e.g., “chocolate”), a semantic foil (i.e., same general class of odor, e.g., “maple syrup”), a phonemic foil (i.e., phonetically similar name, e.g., “cherry”), and an unrelated foil (i.e., “potato chips”). We scored the number of stimuli for which the correct name was chosen.

Part C: Odor Identification – Smell Identification Test: This standardized and normed test of odor identification published by Doty (1995) was administered to B. The test is presented in a scratch-and-sniff format. There are 40 stimuli, and for each, the participant scratches an odorized patch, sniffs the odor, and then chooses from 4 foils the name that best identifies the odor. The score is the number of correct responses.

Experiment 2: Method of Signal Detection—This technique was based on the signal detection method, using procedures derived from Eichenbaum et al. (1983) and Potter and Butters (1980). The stimuli were 1.3 mM n-Butanol (reagent grade, EM Science) in distilled deionized water (signal), and water alone (blank). Single stimuli were presented successively to the participant in random order on 16 trials, with half the trials containing signal (odor) and half blank (water). On each trial the participant was allowed a single sniff

²For a response to be scored as an “accurate identification” when the correct name was not provided, the participant had to generate a specific description that unambiguously identified the smell; see H. Damasio et al. (2004) for a complete description of this scoring method).

and was required to identify the stimulus as “odor” or “no odor.” No feedback regarding the accuracy of responses was given. To assess the accuracy of odor detection, d' was calculated with signal detection theory from the observed “hit” and “false alarm” rate data.

The results from Experiment 2 (see below) indicated that B. is unable to detect odors at concentrations for which normal healthy persons can accomplish odor detection without difficulty. However, two major questions remain unanswered by these findings. The first is whether detection of all olfactory stimuli is equally affected, and the second is the extent to which response bias might be interfering with B.'s performance. Experiments 3 and 4 were designed to address these two questions, through the use of additional stimuli and by applying different modes of stimulus presentation with different response requirements.

Experiment 3: Matching of Odors using Signal Detection—In Experiment 3, the participant was required to discriminate between two odors. There were 42 trials involving pairs of suprathreshold stimuli presented in rapid succession. On half the trials, the two stimuli were different from one another, and on the other half, the stimuli were the same odorant. After presentation of the stimulus pair the participant was asked to state whether the odors were the “same” or “different.” The intertrial interval was 30 seconds. Discrimination was tested for various pair combinations of the following odors: BuOH, PeOH, MeSal, EtOH, and acetone. For B. and the NC participants, signal detection theory was used to calculate d' , in order to establish accuracy of performance.

Experiment 4: Detection of Odors—The data from Experiments 2 and 3 (see below) indicate that B. has severe anosmia in the context of an overly cautious response tendency. Because this response tendency may mask some sparing of olfactory capabilities, we examined B.'s threshold for detection of 4 different pure odors using a forced choice paradigm which does not afford a cautious response style.

The stimuli for this test consisted of the “full” concentration of each of the four stock odorants (n-Butanol (1.3 mM), essence of rose (phenethyl alcohol – Fischer Scientific), ethanol, and acetone) and 3 sequential two-fold dilutions of each of these stock solutions. A 10 ml volume of each solution was matched against a blank sample (distilled-deionized water) of equal volume presented to the participant in wide mouth glass jars. There were 32 trials, with 2 trials per odorant at each of the 4 concentrations. For each of the odor-blank pairs, starting with the highest odor concentration, the participant was allowed one sniff each of the odor and the blank sample. The stimuli followed one another in rapid succession (the “signal” versus “blank” order was randomized) and the participant was asked to choose which of the two jars contained the odorant—i.e., responses were 2-alternative forced-choice. The intertrial interval was 30 seconds.

RESULTS

Experiment 1: Identification of Common Odorants

Part A: Odor Identification – Confrontation Naming—B. was unable to name correctly any of the 15 stimuli presented to him (score: 0/15). He did not provide accurate descriptions or definitions for any of the stimuli (score: 0/15). Illustrative examples of his responses are presented in Table 1. The NC participants named correctly about two-thirds of the stimuli ($M = 10.0$, $SD = 2$). In addition, the NC participants were able to identify accurately (with the correct name or a specific verbal description) nearly all of the stimuli ($M = 14.5$, $SD = 1.0$).

Part B: Odor Identification – 4-Alternative Forced-Choice Recognition—B.'s performance was at chance (score: 3/15 correct). His errors were distributed among semantic

(7), phonemic (1), and unrelated (4) foils. The NC participants had very high performances in this procedure, with an average of 92% correct ($M = 13.8$, $SD = 1.3$). Their errors were mainly the semantic foil (75% of errors); the rest were the unrelated foil (25%).

Part C: Odor Identification –Smell Identification Test—B. performed at chance on the Smell Identification Test, achieving a score of 9/40 (23%; chance is 25%). For his age, the cutoff score for the 5th percentile on this test is 16/40; thus, he is well below that level.

Experiment 2: Method of Signal Detection

On the 16 trials that used 1.3 mM butanol as the signal stimulus (mixed randomly with water as a blank stimulus on half the trials), B. responded “no odor” on all 16 trials. This yields a hit rate of 0 and false alarm rate of 0, and the resulting d' score (correcting for a 0-level false alarm rate using standard procedures; see Macmillan and Creelman, 1991) is thus 0.0. The NC participants had perfect scores for both hits (100%) and blanks (100%), yielding a hit rate of 1.0 and a false alarm rate of 0. The resultant d' score for the NC group (again, applying standard corrections) is 3.76.

We repeated this experiment in B., using 1.3 mM acetone as the signal stimulus and following the same procedure—i.e., 16 trials where the signal or blank was presented in random order and B. was asked to identify the stimulus as “odor” or “no odor” on each trial. His performance was the same as for the butanol, with responses of “no odor” on all 16 trials. Again, this yields a d' score of 0.0.

Experiment 3: Matching of Odors using Signal Detection

On the 21 trials with different odors, B. correctly reported that the odors were different on 3 trials, and on the 21 trials with the same odor, he correctly reported that the odors were the same on 17 trials. Thus, he displayed a tendency to report “same” for most of the trials, with his hit rate being .81 and false alarm rate being .86. This yields a d' score of -0.20 , indicating that B. has virtually no ability to discriminate “same” and “different” odors. The NC participants had nearly perfect scores in this experiment, with average performances of 20.2 for the 21 “same” trials and 20.0 for the 21 “different” trials. This yields a hit rate of .96, a false alarm rate of .05, and a d' of 3.40.

Experiment 4: Detection of Odors

B. performed at chance for the BuOH and PeOH odors, at all concentrations, indicating that he could not detect these odors at any concentration. For EtOH, his threshold for detection was 100%, as he only detected the odor when it was at full strength (2/2). His threshold for detection of acetone was 20%, as he detected acetone correctly on all but the lowest concentration trials (6/6 trials correct, above the lowest concentration). The NC participants detected the odorants at the following thresholds: BuOH at 20%, PeOH at 20%, EtOH at 50%, and acetone at 20%. B. was thus comparable to the comparison participants for acetone, and he was able to detect EtOH at its full concentration but not below that.

DISCUSSION

The results from these experiments demonstrate the nearly complete obliteration of B.'s olfactory capacities. B. was completely unable to identify common environmental odors, and he could not provide accurate verbal descriptions or definitions of scents. In addition, he showed no overt behavioral signs to indicate accurate recognition, and he was unable to identify odor stimuli in a forced choice recognition paradigm. He performed at chance on a standardized smell identification test. Moreover, he was completely unable to identify different odors as different and identical odors as the same, for odorant contrasts that normal

participants performed nearly perfectly. In short, other than obviously recognizing that “smells” were “smells,” his capacity to identify odors is virtually completely destroyed.

B. was also severely impaired in his ability to detect odorants. He had zero-level discrimination (d' scores of 0.0) for both butanol and acetone, in a standard signal detection paradigm. In threshold detection studies with varying levels of concentration of different odors, the only stimuli he reliably detected were EtOH at a very high concentration, and acetone at all assessed levels of concentration. Primary odorants from the floral and peppermint-like groups were never detected reliably. By contrast, normal comparison participants had no difficulty detecting these substances even at very weak concentrations.

All together, the results of these experiments indicate that B. is almost completely anosmic. He does have some preserved capacity to detect olfactory stimuli, as indicated by the findings with acetone and full concentration EtOH, and this suggests that there is some patency of olfactory processing up to the level of the olfactory bulb. The findings in B. complement data obtained in patient HM, who has bilateral temporal lobe damage but no damage to the orbitofrontal cortex (Eichenbaum et al, 1983), and data obtained in patients with discrete lesions of the prefrontal cortex (Potter & Butters, 1980). HM and the prefrontal patients resemble B. in that they cannot identify odors or discriminate between odors in a same-different paradigm. However, unlike B., these patients demonstrate normal performance on tests of odor detection and discrimination of intensity.

The medial temporal lobe including the primary olfactory cortex of the uncus is completely destroyed in B. but not in the other groups (HM and the prefrontal patients alluded to above). It is possible that the olfactory bulb itself is involved in B.; however, this is difficult to determine from neuroimaging studies alone, and anatomical studies in postmortem tissue indicate that the olfactory bulb is inconsistently involved in the destructive process of herpes simplex encephalitis (Johnson & Mims, 1968a&b; Damasio & Van Hoesen, 1985).³ Thus, we can only tentatively speculate that the preserved intensity encoding in patients with selective lesions of either the temporal or the frontal lobes is mediated by the primary olfactory cortex and quite possibly by the olfactory bulb as well. We suggest that this primary perceptual system acts in an “alerting” capacity, directing the organism's attention to the presence of an olfactory stimulus but providing little specific information as to the meaning and identity of the stimulus.

From a functional neuroanatomical perspective, olfactory associational function appears to be situated mainly in the anterior temporal and the orbitofrontal cortices. The olfactory areas of the anterior temporal lobes project to the dorsomedial nucleus of the thalamus and to the entorhinal cortex (Powell et al, 1965; Van Hoesen & Pandya, 1975a&b), and from both of these areas olfactory information is relayed to the orbitofrontal portion of the prefrontal cortex (Leonard, 1969; Potter & Nauta, 1979). In addition, the anterior temporal lobe connections to the entorhinal cortex allow access to the hippocampus, an area associated with memory formation, and to multimodal sensory information (Van Hoesen, 1982). This anatomical relationship between olfactory areas and the relationship between these areas and the hippocampus suggest that the anterior temporal lobe and its connections to the orbitofrontal lobe are organized in tandem to mediate olfactory associational processing. Information registered in this system can be compared to other incoming information from the same modality, and to stored representations from other modalities. Destruction of either area eliminates the “comparator” mechanism and results in an inability to hold new olfactory information in a manner which would allow for ongoing discriminations and for the retrieval of relevant information related to the stimulus. The olfactory findings in patient HM and in

³Unfortunately, we do not have a postmortem study of B.'s brain, out of respect for his family's wishes.

patients with prefrontal lobe damage are consistent with this hypothesis, as there are selective and complete deficits in appreciation of odor quality with lesions of either the orbitofrontal or anterior temporal areas.

It is worth mentioning here that we have studied another patient who sustained a severe case of herpes simplex encephalitis, yielding brain lesions that are very comparable to those in patient B.—and in particular, nearly complete destruction of the limbic system. This patient was reported extensively by Feinstein et al. (2010), and it is notable that the patient is completely anosmic and performs at chance level on standardized smell identification tests. These findings are consistent with those in patient B., providing a replication of the pattern whereby, with destruction of both the anteromedial temporal lobes and medial orbital prefrontal cortex, there is a nearly complete obliteration of the sense of smell.

Another structure that has been associated with odor processing is the dorsomedial nucleus of the thalamus—for example, impaired odor processing has been reported in patients with damage to this structure as a result of Korsakoff's disease (Victor et al., 1971; for a review of the literature on the role of the dorsomedial thalamic nucleus in olfaction, see Tham et al., 2009). This literature is beyond the scope of the current report, but it is important to acknowledge that structures other than the medial temporal lobes and orbital prefrontal cortex are likely involved in at least some aspects of olfactory processing.

Our study has limitations, and it is a single case (although the latter is buttressed by the Feinstein et al. case mentioned above). As noted earlier, we do not know exactly the status of the olfactory bulb in patient B. The question of whether his olfaction is patent at all cannot be entirely resolved, and it is possible, for example, that his ability to detect acetone and high concentrations of EtOH (stimuli that many normal participants actually find somewhat aversive) is mediated by peripheral endings of the trigeminal nerve in the nasal mucosa or gustatory end organs, and in turn, by intact posterior cortices mediating somatosensory and gustatory perception (although in this context, it is important to remember that B.'s entire insular cortices are destroyed bilaterally). B. has some preserved capacity to discriminate substances on the basis of taste, although his recognition of gustatory stimuli is severely impaired (Adolphs et al., 2005). As noted, patient B. is not available for further studies, and questions such as these raised here cannot be definitively answered. Nonetheless, these experiments provide clear evidence that B. has a profoundly impaired sense of smell, with one of the most severe anosmia syndromes ever reported in the literature, following bilateral limbic system destruction.

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Figure 1.
An MRI of B.'s brain, performed 9/11/91 (about 15 years after the onset of his condition), showing extensive bilateral damage to most cortical and subcortical limbic system structures.

Table 1

Examples of B.'s responses in Odor Identification – Confrontation Naming (Experiment 1, Part A)

Stimulus	B.'s Response
coffee	very strong liquid for under your arms
tobacco	sweet flower, like perfume
rose	clear soap
peanuts	hair-do
mothballs	clear smell