REVIEW

Olfactory function in psychotic disorders: Insights from neuroimaging studies

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Abstract

Olfactory deficits on measures of identification, familiarity, and memory are consistently noted in patients with psychotic disorders relative to age-matched controls. Olfactory intensity ratings, however, appear to remain intact while the data on hedonics and detection threshold are inconsistent. Despite the behavioral abnormalities noted, no specific regional brain hypoactivity has been identified in psychosis patients, for any of the olfactory domains. However, an intriguing finding emerged from this review in that the amygdala and pirifom cortices were not noted to be abnormal in hedonic processing (nor was the amygdala identified abnormal in any study) in psychotic disorders. This finding is in contrast to the literature in healthy individuals, in that this brain region is strongly implicated in olfactory processing (particularly for unpleasant odorants). Secondary olfactory cortex (orbitofrontal cortices, thalamus, and insula) was abnormally activated in the studies examined, particularly for hedonic processing. Further research, using consistent methodology, is required for better understanding the neurobiology of olfactory deficits. The authors suggest taking age and sex differences into consideration and further contrasting olfactory subgroups (impaired *vs* intact) to better our understanding of the heterogeneity of psychotic disorders.

Key words: Olfaction; Schizophrenia; Neuroimaging; Functional magnetic resonance imaging; Positron emission tomography; Single photon emission computed tomography

Core tip: Olfactory identification, familiarity, and memory deficits are consistently noted in patients with psychotic disorders relative to age-matched controls. Olfactory intensity ratings remain intact while olfactory hedonics and detection threshold show inconsistent findings. This review found no consistent differences in functional activity in amygdala and pirifom cortices in psychotic patients relative to control subjects.

Secondary olfactory cortices were abnormally activated in psychosis patients, however. Further methodologically consistent research is required for better understanding the neurobiology of olfactory deficits in psychotic disorders. The authors recommend examining sex differences contrasting olfactory subgroups (impaired *vs* intact) in future examinations.

INTRODUCTION

Olfactory input, although mostly unconsciously processed and relatively ignored, colours our appreciation for food, influences our mood and warns us of impending danger (*e.g.*, spoiled food, smoke, chemical spill *etc.*). It is only when olfaction is impaired that humans begin to realize how much olfactory stimulation influences decisions in everyday life. In fact, olfactory compromise has been linked to depression[1] and for patients with traumatic brain injury, post traumatic anosmia is negatively linked to return to work after injury[2,3]. For individuals with neurodegenerative disorders, such as Parkinson's disease[4], Dementia (*e.g.*, Alzheimer's disease[5]), or psychotic disorders[6], olfactory decline may be one of the first symptoms subjectively noted. Consequently, formal assessment of olfactory function may allow for early identification of those at risk of developing these illnesses prior to the illness onset. Understanding the neurobiology of olfactory decline may prove useful to clinicians and allow for early detection, intervention and treatment.

In psychotic disorders, including schizophrenia, olfactory deficits are observable early in the course of illness, but progress very little, if any[7]. However, these olfactory problems may be a harbinger for poorer prognosis, both symptomatically and in terms of functional outcome[8,9]. A better understanding of olfactory compromise in these disorders is fundamental to better understanding the heterogeneity of illness course and symptoms. Further elucidating the neurobiology of olfactory deficits may provide further clues to the underlying brain abnormalities in this disorder.

The purpose of this paper, therefore, is to review the literature on olfactory function in patients with schizophrenia, paying particular attention to the neuroimaging data that has accumulated.

The olfactory system

Small postage stamp sized regions of superior aspect of each nasal cavity and upper portion of the nasal septum contain the olfactory epithelium. Within this region, specialized G-protein coupled olfactory receptors bind to inhaled volatile chemicals that have dissolved in the olfactory mucosa. Once odorants are bound to receptors, action potentials are initiated and are transmitted to the brain *via* the olfactory nerves. Axons project through fenestrations within the cribriform plate of the ethmoid bone and synapse on neurons (mitral and tufted cells) within the olfactory bulb. From here, signals project predominantly through the lateral olfactory tract to the primary olfactory cortex (including the piriform and entorhinal cortices, part of the amygdala and the olfactory tubercule). Collaterals from these axons project to the anterior olfactory nucleus. A minority of fibres project *via* the medial olfactory tract and cross, *via* the anterior commissure, to the contralateral olfactory bulb. However, the vast majority of olfactory projections are ipsilateral[10].

The olfactory system is unique among the senses as it projects initially to cortical regions, rather than thalamic nuclei. Thalamic connections occur post-cortically, along with projections from piriform cortex to other limbic regions, such as the hypothalamus and hippocampus. Projections to the orbitofrontal cortex can be either direct from primary olfactory cortex, or indirect *via* the dorsomedial nucleus of the thalamus[11].

A further differentiating factor that separates the olfactory system from other senses is that the signals from primary sensory receptors to higher processing regions are predominantly sent ispilaterally, rather than having a contralateral representation. This fact allows for the assessment of the relative contribution of each hemisphere to the processing of olfactory stimuli. If stimulus presentation is restricted to one nostril only, the ipsilateral hemisphere will be preferentially (initially) engaged. This anatomic detail has been exploited by some research groups and lateralized findings have been reported[12,13].

Olfactory dysfunction can occur as a result of damage at any level of the olfactory system, from destruction of the olfactory receptors due to exposure to inhaled chemical toxins, to deficits in olfactory detection threshold as a result of olfactory nerve/tract damage during closed head injury, to distinct higher level olfactory deficits (*e.g.,* olfactory agnosia) as a result of lesions to secondary olfactory cortex[14,15].

Olfaction in schizophrenia

Between 1%-3% of the population suffers from non-affective psychotic disorders, with schizophrenia being the most common form[16]. These disorders are associated with a diverse range of abnormal mental phenomena, including hallucinations, delusions, unusual thought content, anhedonia, social withdrawal and alterations in cognitive domains such as memory, attention, language and executive function. The typical age of onset of these disorders is relatively early, with most individuals presenting with their

first psychotic episode in late adolescence or early adulthood. For many, the course of illness is one of waxing and waning of symptomatology; few make a full recovery after one episode. The issue of whether olfactory sensitivity (detection threshold/acuity) is impaired in schizophrenia has not yet been resolved, with some studies showing normal acuity[17,18], others impaired[19,20] and still others demonstrating enhanced sensitivity[21,22]. As well, the issue of whether olfactory hedonics are abnormal in patients with psychotic disorders continues to be debated[19,23-27]. There is evidence that pleasantness ratings differ by sex[28,29] and are likely related to symptom presentation[30,31]. More consistent findings have emerged when olfactory discrimination (same as/different) and olfactory memory/familiarity are assessed. Patients with psychotic disorders appear to be impaired on both of these functions[26,32,33]. Odour intensity ratings, however, appear to be intact in patients with psychotic disorders[26].

The most robust difference between patients with psychotic disorders and control subjects has been noted in studies examining olfactory identification ability. In these investigations, consistently abnormal olfactory identification has been shown in psychosis patients[7,9,18,30,34]. Olfactory identification deficits do not appear to be influenced by age of illness onset[17,34], smoking history[17,35], exposure to antipsychotic medications[13,17,32] or cannabis use[7]. Olfactory identification deficits, however, are thought to correlate with measures of verbal memory function[36,37], and negative (but not positive) psychotic symptoms[7,9,34]. Recent research has shown that olfactory compromise may be a marker for poorer outcome. Good *et al*[8] examined symptomatic outcome in a group of patients who were antipsychotic drug naive at initial olfactory testing. Poorer negative and cognitive symptom outcome was associated with a lower baseline olfactory identification (UPSIT) test score. This same group prospectively followed a group of first episode patients for 4 years[9]. Those with poorer olfactory scores at initial assessment had worse symptom outcome and reduced functional outcome at follow up. Additionally, individuals who are at risk for developing a psychotic disorder (by virtue of having a first degree relative with the disorder and/or showing attenuated psychotic symptoms), having lower olfactory test scores appears to be related to the conversion to a true psychotic disorder[6]. Taken together, these findings suggest that not only may olfactory deficits predict transition to illness, but that subgroups may be identified, early in the course of illness, who may be at risk for a more severe illness course.

Overlap between olfactory processing and pathology in schizophrenia
That patients with psychotic disorders have olfactory dysfunction is not surprising given the overlap between olfactory processing regions and areas of the brain that have been consistently noted as abnormal in these patients. Abnormalities in medial temporal regions, including the hippocampus, amygdala and parahippocampal gyrus have been observed in patients with psychotic disorders. For a review, see[38,39]. Moreover, orbitofrontal and dorsomedial nucleus of thalamus have also been found to be both structurally and functionally abnormal[40,41]. Left sided abnormalities are more commonly reported[42].

NEUROIMAGING OF THE OLFACTORY SYSTEM IN HEALTHY INDIVIDUALS
The olfactory system has been well described anatomically (see above). However, recent neuroimaging studies have revealed a more widespread network of interrelated olfactory brain regions required for different aspects of olfactory processing. For example, although the piriform cortex is reciprocally connected with the olfactory bulb, functional magnetic resonance imaging (FMRI) studies have reported that piriform cortex activation is most robust during active "sniffing" of the odorants, and not during passive odours presentation such as when subjects are instructed not to purposely inhale the odorants[43] but see also[44]. However, the primary olfactory cortex appears to habituate more quickly than other brain regions and thus may be a better reason why consistent activation is not found in this brain region in all studies. The insula and anterior cingulate cortex are not necessarily associated with olfaction *per se*; however, activation in these regions has been demonstrated relatively consistently during odour presentation, suggesting a role in higher-order olfactory processing[45] (Table 1).

Passive Odour presentation
Brain regions that are activated after presentation of odours when subjects are instructed not to sniff or nor consciously process the odorants include areas associated with primary olfactory cortex [piriform cortex (however, see above), amygdala, hippocampus, entorhinal cortex] and secondary olfactory regions (thalamus, orbitofrontal cortex, cingulate and insula)[46-49]. These regions can be thought of as "core" olfactory regions. When olfactory-cognitive load is increased, other ancillary regions are also engaged.

Odour "sniffing" vs smelling
As previously mentioned, the piriform cortex may be activated solely in the presence of active "sniffing" or nasal airflow[43,50]. A more recent positron emission tomography (PET) study, however, did not confirm these results[44].

Odour hedonics: Humans are particularly poor at naming odours *de novo* (see section below). However, odours can evoke very strong emotional reactions, even without conscious awareness. Consequently,

Table 1 Description of the olfactory methods used to examine different olfactory domains

Olfactory domain	Methods by which this domain is assessed
Passive smelling	Odorant is presented passively to the subject. Imaging done without response or overt cognitive appreciation
Olfactory detection	Similar to passive smelling, however, the subject must press a button to signal the onset of the odorant perception
Odour "sniffing"	Subjects are given instructions to inhale the odorant during presentation
Olfactory intensity	Rating the odorant as to its perceived strength. Can be done by a button press (Is the odour "strong"?)
	Intensity may be assessed by ratings of odorants (*e.g.*, VAS) outside of the scanner and presenting odours that have been rated on opposite ends of the continuum (very strong *vs* very weak)
Olfactory familiarity	Recollect prior exposure without the exact autobiographical context and also without naming. Button press if odour is "familiar"
Olfactory hedonics (valence)	The determination of pleasantness of the odorant.
	Button press to rate whether an odorant is pleasant
	Pleasant/Unpleasant odorant rated (*e.g.*, VAS) outside of the scanner and presenting odours that have been rated on opposite ends of the continuum (very unpleasant to very pleasant)
Olfactory identification	Correct identification- those items that are correctly labeled *vs* those for which label is incorrect
	Olfactory identification test score used to capture most impaired, compared with normal sense of smell
	Forced choice odour naming during scanning

the primary dimension by which humans characterize odorants is according to the odour's pleasantness, and particularly when odorants are difficult to name[51]. Researchers have capitalized on this aspect of olfactory processing in imaging studies; but unfortunately, mixed findings have resulted. The data is clear on one point: pleasant and unpleasant odorants invoke activation in similar neural networks, (primary and secondary cortices). However, intensities and degree of engagement may differ and some unique brain regions may also be invoked[52], particularly for unpleasant/aversive odorants. Both pleasant and unpleasant odorants activate the bilateral piriform/amygdala[45,53,54] but see also[55], right[49] and bilateral insula[45,56], and orbitofrontal cortex[49,53,54,57,58]. Most contrasts between pleasant (P) and unpleasant (UP) odorants have shown a greater degree of activation in the UP-P subtraction, rather than the other way around (P-UP). To this end, aversive or unpleasant odorants appear to further engage orbitofrontal cortex[54] - but only when subjects are engaged in a hedonic estimation task, and the activation seems to be concentrated in the lateral aspect rather than medial subdivisions[58]. Moreover, the left insula[45,52], but see also[56] who showed insular activity predominantly during pleasant odour stimulation), the anterior cingulate[45,52,58], brainstem/hypothalamus[52], and piriform/amygdala[45] activation has been noted after unpleasant odor presentation over and above that demonstrated during pleasant odorant stimulation.

Odour familiarity: Determining whether an odour is familiar requires an implicit set of memory processes; the perceptual input needs to be compared with semantic odour associations[59]. The smeller must recollect prior exposure without the exact autobiographical context and also without naming. Only few studies have examined this aspect of olfactory processing. In 1999, Royet *et al*[60] examined, among other aspects of olfactory processing, odour familiarity in healthy subjects. In this study, they demonstrated right orbitofrontal cortex activation during odour familiarity ratings, suggesting a lateralization of secondary olfactory cortical function. In a later study by this same group, Royet *et al*[57] noted a larger network of olfactory brain regions associated with odour familiarity. Bilateral orbitofrontal cortex (OFC), anterior cingulate along with left superior and right middle frontal gyri were all active during a PET scan during which an odour familiarity task was compared to control activation (presentation of odorless air). When compared with odour detection, left superior and left inferior frontal gyri engagement was noted, suggesting a hierarchical process, with odour familiarity ratings at higher levels of processing. This group suggested that the lateral frontal activation may represent accessing stored representations.

Odour intensity: A further dimension of odour processing is that of rating odour intensity. Odour pleasantness ratings change as a function of an odour's perceived intensity. For example, the rose-like odorant (phenyl ethanol) tends to be perceived as pleasant at lower concentrations, but less pleasant at higher concentrations[61]. In many studies assessing olfactory hedonics, the intensity of presented odorants was not controlled. In order to dissociate intensity and valence, Anderson *et al*[54] focused on the amygdala and the orbitofrontal cortex. The amygdala has been reliably shown to activate during presentation of aversive stimuli[62]. The orbitofrontal cortex, as mentioned previously, appears to be invoked in higher order processing of olfactory stimuli. By presenting two different odorants at two different concentrations (high intensity-unpleasant, high intensity-pleasant, low intensity-unpleasant, low intensity-pleasant), Anderson *et al*[54] noted that that the orbitofrontal cortex engaged in relation to the valence of the odorant while the amygdala was preferentially engaged according to the intensity of the odorant. No ratings were performed during the scan; rather, subjects were only

instructed to "sniff" for the duration of a presented message and respond if an odour was detected. A more recent study lent some further explanation to this unexpected finding. Winston *et al*[63] replicated the Anderson *et al*[54] study, but included both high- and low-intensity neutral odours for comparison. In this study, the amygdala was engaged predominantly with both the pleasant and unpleasant high-intensity odors, but not the high intensity neutral odour (nor any of the low intensity odours either). A more parsimonious explanation was suggested by these researchers in that the amygdala is engaged when odours are encountered that may be relevant for survival. High intensity pleasant or unpleasant odours are more likely to be behaviorally salient than are neutral odours (or low intensity odours along the hedonic spectrum).

Olfactory identification: Odor naming, particularly when potential exemplars are not provided, is a difficult task for humans[64,65]. By providing a multiple-choice format, such as the University of Pennsylvania Smell Identification Test (UPSIT), performance is improved significantly[61].

In a recent study, Kjelvik *et al*[47] examined whether there were any differences in activation patterns when individuals were successful in naming odorants *vs* when they incorrectly named the odours. Odorants were presented to subjects (only women) during an FMRI scan. Post scanning, subjects were presented with these same odours and were instructed to spontaneously name them (no exemplars provided). Brain activation patterns differed between correctly identified odours *vs* those not correctly identified in left entorhinal cortex, bilateral temporal poles, orbitofrontal cortex (right moreso than left), right thalamus and left insula. Other, non-olfactory areas (*e.g.*, putamen, primary visual and auditory cortices, premotor cortex, SII and cerebellum, inferior frontal, and fusiform area) were also activated more during identified *vs* non-identified odours. When specifically examining the medial temporal regions, left entorhinal cortex, and bilateral posterior parahippocampal gyri were engaged. The data suggested that the entorhinal cortex and the hippocampus are more attuned to identifying odours.

Sex differences: Many of the studies mentioned above (*e.g.*,[47,55]) examined only female subjects as women reliably outperform men on olfactory detection, memory and identification tasks[66-68]. Three different research groups have examined whether this female olfactory superiority translates into enhanced brain activity. In an early FMRI study, Yousem *et al*[69] noted that female brains had significantly more active voxels in the perisylvian and inferior frontal regions during odour presentation. Levy *et al*[53], using a ratio of pixel activated to the number of pixels in a region, also showed sex differences; However, their findings were in the opposite direction (males > females). In contrast, Bengtsson *et al*[70] were unable to detect

any male/female differences in brain activation during passive perception of odours. This group suggested that males and females engage similar networks during low level processing of olfactory stimuli. However, due to methodological inconsistencies, the intensity of activation was not examined in this PET study, making comparisons with other papers data difficult. In contrast, Royet *et al*[45] found that women activated the left orbitofrontal cortex over and above what was noted in male brains. The differences again may prove to be related to methodological differences, or rather due to the processing demands placed on the subjects during olfactory scanning (for part of the study, subjects in the Royet *et al*[45], study were asked to make an hedonic judgment regarding the odours presented while Bengtsson *et al*[70] were examining olfactory processing during passive administration). Nevertheless, these data taken as a whole, suggest that sex differences should be taken into account when examining olfactory brain activations.

Age
As the ability to perceive odours deteriorates with age, do functional alterations in brain regions associated with the sense of smell also accompany these changes? A study published by Wang *et al*[71] noted that there were significant differences in the processing of olfactory stimuli when comparing young and older subjects. Although for both groups, the same regions were activated by odorants, lower cluster volumes and intensities were noted in the aged group when compared to the younger group. This finding suggests that age should be taken into consideration when examining neural activation to olfactory stimuli (Table 2).

NEURAL SUBSTRATES OF OLFACTORY PROCESSING DEFICITS IN PATIENTS WITH PSYCHOTIC DISORDERS

Although many studies exist demonstrating olfactory deficits in patients with psychotic disorders, only few neuroimaging investigations have been published to date examining the relationship of olfactory deficits to neural abnormalities.

Passive odour administration
Odour activation patterns are similar between patients with psychotic disorders and control subjects during passive odour administration[25]. However, there are some differences regarding the intensity or cluster volume in these regions between patients and control subjects. Plailly *et al*[25] examined olfactory detection (passive odour administration), hedonics and familiarity using PET. A moderately sized sample of patients with schizophrenia and healthy controls were presented with odours during the scan and were instructed to press a button when they detected an odour (for the detection condition), if the odour was pleasant (for

Table 2 Olfactory studies

Ref.	Authors	Year	Modality	Subject group(s)	Finding
	Passive smelling				
[46]	Zatorre *et al*	1992	PET	Healthy subjects	Piri (B) and OFC (RH)
[53]	Levy *et al*	1997	FMRI	Healthy subjects	P and UP: piri, amyg, hippocam, cing and post inf front cortex (laterality not specified)
[43]	Sobel *et al*	1998	FMRI	Healthy subjects	Passive smelling, lat OFC; Sniffing-piri (B) and post OFC (B)
[48]	Savic *et al*	2000	PET	Healthy subjects	OFC (RH), amyg/piri (RH), thal (RH), insula (LH), ant cing
[49]	Gottfried *et al*	2002	FMRI	Healthy subjects	P and UP: Amyg (B), post OFC (B), post piri (B), insula (RH)
[45]	Royet *et al*	2003	FMRI	Healthy subjects	UP and P odorants-piri/amyg, hypothal, sup temp, insula and OFC, ant cing
[44]	Kareken *et al*	2004	PET	Healthy subjects	Piri (B), amyg (B), insula (B); sniffing lateral OFC (B)
[47]	Kjelvik *et al*	2012	FMRI	Healthy subjects	Piri (B), amyg (B), OFC (B) and thal (B) cing (RH), insula (LH)
[25]	Plailly *et al*	2006	PET	Psychosis patients	HC > SZ Piri (LH) and inf front (LH)
					SZ > HC insula (RH)
	Good *et al*	Under review	FMRI	Psychosis patients	HC > SZ thal (RH), caud (B), ant cing, OFC (B only midly greater), mid temp gyrus (B)
	Hedonics (Valence)				
[55]	Zald *et al*	1997	PET	Healthy subjects	Aversive odorant- amyg and OFC; less aversive- only OFC (LH)
[56]	Fulbright *et al*	1998	FMRI	Healthy subjects	Pleasant- BA 46/9 (RH), 32 (LH), 8 (B) 6 (RH) and insula (B); Unpleasant- 46/9 (RH), 32 (LH), 6 (B), insula (RH)
[57]	Royet *et al*	2000	PET	Healthy subjects	Hedonic judgement- ant cing, OFC (LH), sup front (LH), midd front gyrus (LH), inf midd temporal (LH)
[49]	Gottfried *et al*	2002	FMRI	Healthy subjects	UP: insula (RH), lat hypothal (LH), amyg (RH), post OFC (L); P: piri (RH), insula (RH), post OFC (RH)
[45]	Royet *et al*	2003	FMRI	Healthy subjects	Hedonic valence -UP > P: piri (LH), amyg (LH); P > U: cing (LH)
[58]	Rolls *et al*	2003	FMRI	Healthy subjects	P: med OFC; ant cing
[54]	Anderson *et al*	2003	FMRI	Healthy subjects	
[72]	Crespo-Facorro *et al*	2001	PET	Psychosis patients	HC > SZ P *vs* UP: insula (LH), para hipp (LH), sup temp gyrus (LH), accumbens (RH), lingual gyrus (B), cb. vermis (LH)
					SZ > HC Med OFC (B), DLPFC (B), med front (LH), lat front (RH), lat front (LH), front operculum (LH), parahipp (RH), post cing (LH)
[25]	Plailly *et al*	2006	PET	Psychosis patients	HC > SZ Insula (LH) and Inf front (LH)
[27]	Schneider *et al*	2007	FMRI	Psychosis patients	HC > SZ UP: Midd temp gyrus (RH) Midd front gyrus (RH) Insula; P: thal (L)
					SZ > HC UP: Midd front (RH) ant cing (RH)
	Intensity				
[54]	Anderson *et al*	2003	FMRI	Healthy subjects	Amyg (B)
[63]	Winsto *et al*	2005	FMRI	Healthy subjects	Amyg, (but only at the extremes of valence), OFC and piri
	Familiarity				
[60]	Royet *et al*	1999	PET	Healthy subjects	Med frontal (RH), inf front (LH), sup front(LH) cingulate (B)
[57]	Royet *et al*	2000	PET	Healthy subjects	OFC (B), ant cing, sup front (LH) midd front (RH)
[25]	Plailly *et al*	2006	PET	Psychosis patients	HC > SZ piri (LH), sup temp gyrus(LH), gyrus rectus(RH), OFC (LH), inf OFC (LH)
	Identification				
[47]	Kjelvik *et al*	2012	FMRI	Healthy subjects	Correctly identified entorhinal cortex (LH), Hippocam (RH), parahippocam gyrus (B), OFC and piriform cortices
					Incorrectly identified: OFC and piri cortices
[73]	Clark *et al*	1991	PET	Psychosis patients	HC > SZ front (B) parietal (B); Norm > Micro thal (RH) and basal ganglia
[33]	Malaspina *et al*	1998	SPECT	Psychosis patients	HC > SZ inf. Front (RH), sup temp (RH) supramarg/angular gyrus (RH)
					HC (but not SZ) hippocam(B), fusiform(RH)
	Genetic Trait				
[27]	Schneider *et al*	2007	FMRI	Psychosis patients	HC > FDR UP: mid front gyrus(RH)
					FDR > HC P: ant cing(LH)

FMRI: Functional magnetic resonance imaging; PET: Positron emission tomography; SPECT: Single photon emission computed tomography; HC: Healthy controls; SZ: Schizophrenia patients; FDR: First-degree relatives; UP: Unpleasant; P: Pleasant; B: Bilateral; LH: Left hemisphere; RH: Right hemisphere; ant: Anterior; post: Posterior; lat: LAteral; inf: Interior; sup: Superior; midd: Middle; temp: Temporal; front: Frontal; Amyg: Amygdala; piri: Piriform cortex; hippocam: Hippocampus; OFC: Orbitofrontal cortex; ant cing: Anterior cingulate; thal: Thalamus; hypothal: Hypothalamus; parahippocam: Parahippocampal; DLPFC: Dorsolateral prefrontal cortex.

the hedonic condition) and if it was familiar (for the familiarity condition). For the detection condition, this group noted that the piriform cortex and the orbitofrontal cortex (inferior frontal) were activated in both groups. However, small clusters remained in these two regions when a subtraction analysis (HC-SZ) was performed. So, although both primary and secondary cortices were activated in both groups,

patients with psychotic disorders appeared to show less robust activity in these two regions. Our group has recently examined passive odour administration in a group of patients with non-affective psychosis (Good *et al*, under review). We noted that patients and controls had similar activation patterns in amygdala, OFC and left thalamus, but the subtraction analysis (HC-SZ) showed slightly greater activation in OFC and
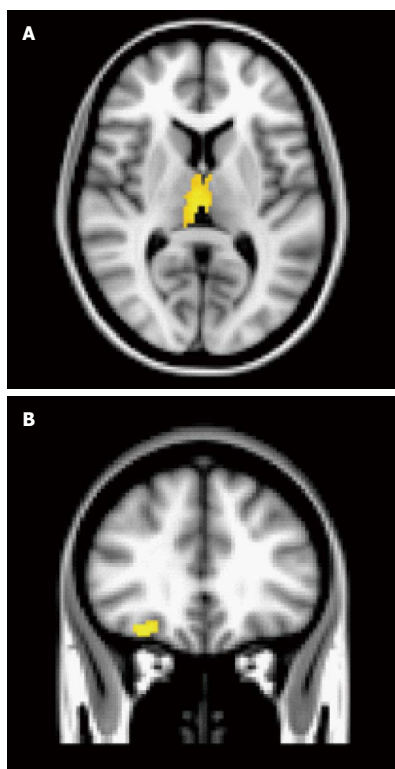
Figure 1 Neural activation for passive smelling in controls-patients. For both locations (thalamus and right orbitofrontal), controls showed significant activation relative to psychosis patients that was unrelated to sex. A: Thalamus; B: Right orbitofrontal. From Good *et al* (under review).

left thalamus. In contrast, controls, but not patients, activated right thalamus, caudate (bilateral), cingulate, middle temporal gyrus and frontal pole (Figure 1).

Hedonic processing

In contrast to passive odour administration, other aspects of olfactory processing appear to engage different brain regions between patients and control subjects. As previously mentioned, rating the pleasantness of odorants is an automatic process and may have survival significance, particularly if the odour is intense. As described above, in patients with psychotic disorders, their ability to rate odour pleasantness may be abnormal. In imaging studies, significant patient/control differences have emerged and show some contrasting findings. For instance, in the PET study published by Crespo-Facorro *et al*[72], patients were impaired on rating the pleasantness of pleasant odours, but no differences were noted between patients and control in neural processing of these same odours. In contrast, patients did not differ from control subjects on ratings of unpleasant odours; however, neural activation did differ. Control subjects engaged the left anterior insula, left parahippocampal gyrus, left superior temporal gyrus, lingual gyrus (bilateral) and left cerebellar vermis along with right accumbens when contrasted with unpleasant *vs* pleasant odorants, while patients did not. Interestingly, patients demonstrated higher metabolic rates in other brain regions relative

to the controls, suggesting that patients invoked compensatory structures during processing. These regions included a number of right hemisphere regions (dorsolateral, lateral and parahippocampal gyrus) and left hemisphere activations (dorsolateral, medial and lateral frontal along with posterior cingulate). In a more recent PET study[25], where both positively and negatively valenced odorants were compared together, greater regional cerebral blood flow (rCBF) was noted in the left insula and left inferior orbitofrontal regions in control subjects relative to patients (Figure 2).

In an FMRI study, hypoactivity of right middle temporal and right middle frontal (BA 46) cortices in patients with psychotic disorders relative to controls during the presentation of a negatively valenced odorant; a relative hyperactivity was also seen in the middle frontal gyrus (in BA 9) and right anterior cingulate in patients. During presentation with a pleasant odorant, left thalamic hypoactivation was noted in patients relative to controls. In the presentation of both types of odorants, insular hypoactivation just missed statistical significance. Unfortunately, unpleasant and pleasant odours were never compared to each other in this study[27].

Taken together, despite different methodology and analytic techniques, the data presented suggest that dysfunction in secondary olfactory cortices and perhaps the insula may account for the olfactory hedonics dysfunction in patients with psychotic disorders. As no group noted differences in amygdala and piriform cortex activations suggest that primary olfactory cortices may be normally activated in these patients.

Odour intensity

The neural underpinnings of processing odour intensity have not been contrasted between patients and control subjects. But as mentioned previously, no differences between these two groups have been noted on odour intensity ratings. Nevertheless, future research should examine this dimension of olfactory processing.

Odour familiarity

Determining whether an odorant has been experienced before appears to further engage frontal brain regions (see above). When patients with psychotic disorders were compared with control subjects on a familiarity task, hypoactivity of piriform cortex, orbitofrontal and superior temporal gyrus (all on the left) was observed[25]. This study also noted that patients rated odours as less familiar than did healthy controls. It was suggested that impaired familiarity ratings may be accounted for by temporolimbic/orbitofrontal dysfunction.

Odour identification deficits

The neural underpinnings of olfactory identification have not been adequately examined in patients with psychotic disorders, despite the fact that olfactory identification deficits are the most robust finding in this patient group. Malaspina *et al*[33] were the first
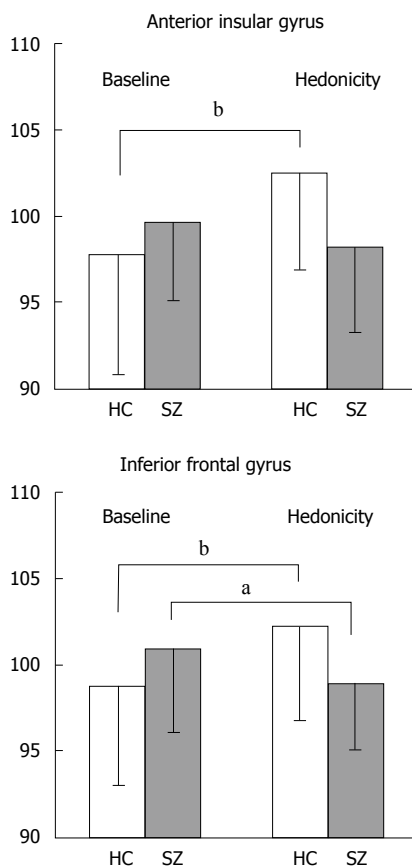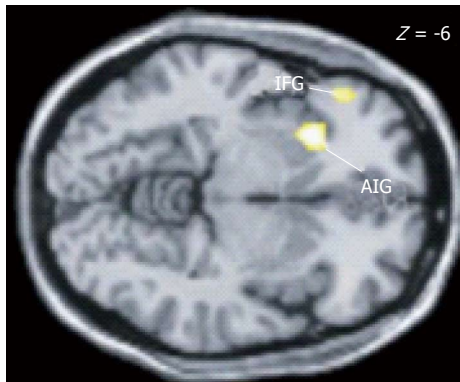
Figure 2 **Figure showing difference between hedonic processing and baseline (air) for patients with psychotic disorders and control subjects.** Differences in activation were noted between patients and control subjects in anterior insula and inferior frontal gyrus. Controls had enhanced activation in both sites for the hedonicity condition (relative to baseline) while for the anterior insula, patients showed no increase and for inferior frontal regions patients saw a statistically significant decrease in regional cerebral blood flow (H-B). Reprinted with permission from Plailly *et al*[25]. [a]$P < 0.05$, [b]$P < 0.001$.

to examine olfactory identification using SPECT. In this study, a small sample of patients with psychotic disorders and controls were scanned while engaging in a forced-choice odour identification test and a comparator picture matching test. Differences in rCBF between the two tasks included hypometabolism in patients in inferior frontal, superior temporal and supramarginal/angular gyri (on the right). Controls, but not patients engaged right fusiform gyrus and bilateral hippocampi during the odour activation task

relative to the control task. The right-sided deficits are consistent with lesion data showing more severe deficits in odour identification after rights than left sided lesions. However, the data is not entirely consistent with the majority of neuropathological studies of schizophrenia showing a predominance of left sided structural abnormalities. Moreover, there was no examination of the differences in odour activation according to the correctness of identification of the odorants.

As it appears that only a proportion of patients demonstrate abnormalities on olfactory identification testing, dividing the groups of patients into those who are impaired *vs* those who have normal olfactory function, may have merit. Clark *et al*[73] examined glucose metabolism in three groups of subjects: a group of patients with olfactory agnosia (impaired olfactory identification ability and normal olfactory detection), a group of patients with normal sense of smell (normosmic) and healthy controls (age matched). PET scanning occurred in the absence of any olfactory stimulation (resting state). In all brain regions, the agnosia patient group had the lowest metabolic rates compared to the other two groups, followed by the normosmic patients and then controls. Controls had higher rCBF than both patient groups in bilateral frontal and parietal regions. The two patient groups differed from each other on right thalamus and basal ganglia metabolism (olfactory agnosia group lower than normal olfactory group). The results of this study are consistent with earlier reports of structural and functional abnormalities in thalamic and basal ganglia. As no olfactory task was presented, these data suggest an underlying hypofunction in regions of the brain that subserve olfactory processing, rather than a processing abnormality. Nevertheless, the heterogeneity of schizophrenia should be taken into account, or at least acknowledged, when examining the neural underpinnings of olfactory function in patients with psychotic disorders. Further investigation is required.

Genetic trait
Not only do patients with psychotic disorders exhibit abnormalities in olfactory processing, but their unaffected first-degree relatives also demonstrate mildly abnormal brain activation patterns when contrasted to non-related controls[27]. When presented with an unpleasant odour, patients' unaffected brothers demonstrated reduced frontal activation (relative to the healthy control group) and increased activation in anterior cingulate, but during the presentation of a pleasant odorant, no differences were noted. This group suggested that hypofrontality may be a genetic trait that is expressed to a lesser degree in the non-affected brothers.

Age
Despite age being considered an important factor to consider in olfactory neuroimaging research[71], to date, no studies have examined the difference in olfactory neural processing between young and older patients

with psychotic disorders. In all studies presented in this literature review, the age of the patients and that of control subject have been well matched and also relatively young (Mean ages < 35 years). Further research may be informative in this regard.

LIMITATIONS

While many olfactory neuroimaging studies of healthy subjects have recruited and assessed only female subjects, the data on patients with psychotic disorders has been strongly biased towards male patient data. Therefore, what is thought of as "normal" may be only normal for women and the comparison with male patients with psychotic disorders may not be appropriate. For example, only male patients were examined in the studies published by Schneider *et al*[27], Clark *et al*[73], and Plailly *et al*[25] and investigations by Crespo-Facorro *et al*[72] and Malaspina *et al*[33] contained samples that were predominantly male. Only Turetsky *et al*[20] (not described) and Good *et al* (under review) examined almost equal numbers of males and female subjects. The data on sex differences in olfactory processing is not fully developed; however, in patients with psychotic disorders, the overwhelming number of sex differences is a very important aspect of the disorder and is likely overlooked in neuroimaging studies of this population.

Not all patients with psychotic disorder are impaired on olfactory testing. Some of the data provided herein suggest that may be subgroups within the heterogenous diagnostic category "schizophrenia". Not only are there potential differences in brain activation, but there are within diagnostic group differences in symptomatology and outcome[8,9]. Further investigations are needed to tease out the differences within schizophrenia.

A further limitation on the data that were presented is that patients and controls differ on many variables that are related to brain activation patterns. Most patients are medicated with antipsychotic medications. Very few studies were upfront about how much this variable may have affected their results. Clark *et al*[73] showed hypoactivation in almost all brain regions across the three groups examined (olfactory agnosia-patient, normal sense of smell-patient, healthy controls), but pointed out that cerebellar metabolism did not differ among the groups. They argued that this evidence suggested that state variables may not be responsible. Moreover, since the two patient groups differed in metabolism in specific olfactory brain regions also argues against antipsychotic medication being a causative factor. No imaging studies have examined antipsychotic naïve or withdrawn patients. The effects of antipsychotic medications on neuroimaging outcomes continue to be unknown. Moreover, patients with psychotic disorders are also more likely to be heavy consumers of tobacco and caffeine. Both of these substances are found to impact on activation patterns. Very few studies have controlled for smoking status (and pack-years) and none have examined caffeine use (particularly prior to scanning). These two variables should be examined more closely to uncover any effects on resultant activation maps between patients and controls. Finally, examining the effects of age in this population may be worthwhile and may provide further insights into changes in brain activity in olfactory regions with aging.

Finally the unique and varied protocols used make for a more challenging task to understand the contribution to olfactory dysfunction in patients with psychotic disorders. Whether resting state activation abnormalities are similar to that noted when patients are engaged in different olfactory tasks (*e.g.*, hedonic ratings *vs* passive presentation of pleasant and unpleasant odorants; PET *vs* FMRI *vs* SPECT) is unknown. Further, more extensive research is needed to parse out the effects of each type of odour presentation/protocol.

CONCLUSION

Psychosis is linked to observable olfactory deficits in many different olfactory domains. Olfactory identification deficits tends to be most commonly reported, likely because of the availability of standardized tests. Olfactory familiarity and memory are also robustly affected in this disorder. Olfactory intensity ratings are not noticeably impaired in these patients. Olfactory hedonics and detection threshold, however, are more troublesome as the methods by which researchers have examined these domains differ markedly. It is not surprising, therefore, that conflicting results have been published. Nevertheless, the noted deficits do not appear to be state-related and may be predictive of poorer outcome.

Olfactory pathways are overlapping with areas of the brain that are found to be abnormal in schizophrenia/psychosis an assessing this sense may provide a good indicator of the integrity of different brain regions. Adding in neuroimaging techniques, we may be better able to disentangle the varied neurobiological substrates of olfactory deficits. Moreover, olfactory assessment, along with neuroimaging methods may provide a way to further our understanding of the heterogeneity of psychotic disorders

The differing methodologies employed by neuroimaging studies hampers the ability to make firm conclusions about which brain regions are impaired in patients with psychotic disorders, particularly when presented with olfactory processing demands. Hypoactivation of various brain regions is a robust finding when patients with psychotic disorders are compared with healthy, age-matched controls. What regions are hyper/hypofunctional when faced with olfactory stimuli and cognitive assessment of these inputs is still under examination. One thing is clear: patients activate the same regions as controls when faced with olfactory processing demands.

However, the degree of activation may be reduced in patients with psychotic disorders. Furthermore, if compensatory regions are invoked in patients above and beyond control subject activation, this finding requires replication as it has only been examined in one study[72]. One interesting finding emerged, however. In olfactory imaging studies of healthy controls, particularly when subjects are presented with unpleasant odorants, the amygdala is typically engaged. In neuroimaging studies examining odorant processing in patients with psychotic disorders, the amygdala was not once identified as being abnormal. Piriform cortex, as well, was not noted to be abnormally activated in patients during hedonic processing. Secondary olfactory cortex (orbitofrontal cortex, thalamus and insula), on the other hand, was noted to be abnormally activated in the neuroimaging studies examined. The lack of amygdala abnormalities may have been as a result of an inability to discern the amygdala from piriform cortex. However, masking templates for use in neuroimaging research have reliably delineated this region. Moreover, given that piriform cortices have been noted to habituate more quickly than other brain regions, this fact may be responsible for the lack of abnormalities in piriform/amygdala activation (*i.e.*, no activity may be as a result of neurobiological constraints rather than a lack of difference between groups). However, given that this review encompassed data collection using many different imaging modalities and unique protocols (some with odor presentations in the range of 2 s), this explanation is unlikely. This interesting avenue of research will undoubtedly grow and provide more insights as imaging techniques continue to improve.

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