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Pleasant and unpleasant odor identification ability is associated with distinct dimensions of negative symptoms transdiagnostically in psychotic disorders

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ABSTRACT

Negative symptoms are among the greatest sources of functional impairment for individuals with schizophrenia, yet their mechanisms remain poorly understood. Olfactory impairment is associated with negative symptoms. The processing of pleasant olfactory stimuli is subserved by reward-related neural circuitry while unpleasant olfactory processing is subserved by emotion-related neural circuitry, suggesting that these two odor dimensions may offer a window into differential mechanisms of negative symptoms. We examined whether pleasant and unpleasant odor identification bears differential relationships with avolition and inexpressivity dimensions of negative symptoms, whether these relationships are transdiagnostic, and whether pleasant and unpleasant odor processing also relate differently to other domains of functioning in a sample of individuals diagnosed with schizophrenia ($N = 54$), other psychotic disorders ($N = 65$), and never-psychotic adults ($N = 160$). Hierarchical regressions showed that pleasant odor identification was uniquely associated with avolition, while unpleasant odor identification was uniquely associated with inexpressivity. These relationships were largely transdiagnostic across groups. Additionally, pleasant and unpleasant odor identification displayed signs of specificity with other functional and cognitive measures. These results align with past work suggesting dissociable pathomechanisms of negative symptoms and provide a potential avenue for future work using valence-specific olfactory dysfunction as a semi-objective and low-cost marker for understanding and predicting the severity of specific negative symptom profiles.

1. Introduction

Olfactory functioning has shown notable utility as a diagnostic and prognostic marker across psychiatric and neurodegenerative conditions (Atanasova et al., 2008; Devanand et al., 2000; Schecklmann et al., 2013). In schizophrenia, olfaction is the sensory modality most closely aligned in its neuroanatomical substrates with cognitive and emotional disturbances characteristic of the disorder (Turetsky et al., 2009). Thus, it has been hypothesized that olfactory impairments observed in schizophrenia may constitute a readily-measurable phenotype that offers a window into neural dysfunctions underlying such symptoms (Turetsky et al., 2009). Olfactory impairments are frequently associated with the common deficits in motivational and affective capacities known as negative symptoms (Brewer et al., 2001; Ishizuka et al., 2010; Kamath et al., 2018a, 2018b; Kamath et al., 2013a, 2013b; Lui et al., 2020; Zou et al., 2018) and as such may help shed light on these symptoms' mechanisms. Different neural processes underlie pleasant versus unpleasant odor identification (Mohanty and Gottfried, 2013). Negative symptoms are similarly thought to comprise two factors with distinct pathomechanisms underlying avolition and inexpressivity (Blanchard and Cohen, 2006; Kotov et al., 2016; Kring et al., 2013; Messinger et al., 2011; Strauss et al., 2013). A growing body of past work implies the possibility of overlapping mechanisms between specific odor valence identification and negative symptom subdimensions. However, few

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studies have directly assessed this, nor has extant work focused on identifying unique clinical relationships as a function of olfactory valence. Such an examination can highlight the utility of olfactory identification as a marker of specific clinical characteristics and provide clues into the shared and unique mechanisms of negative symptom dimensions.

Compared to other sensory modalities, olfaction is unique in that valence (pleasant vs unpleasant) forms the principal dimension that explains olfactory perception (Yeshurun and Sobel, 2010). Valence is a primary factor in explaining variance in neural activity and behavior across a range of species from mice to humans (Haddad et al., 2008; Mandairon et al., 2009). Indeed, pleasant and unpleasant odorants elicit different behavioral and autonomic responses, with unpleasant odors being associated with increased heart rate response and faster response times compared to pleasant odors (Bensafi et al., 2002a, 2002b). They are additionally processed via dissociable neural substrates (Gottfried et al., 2002; Grabenhorst et al., 2007; Masago et al., 2001; Mohanty and Gottfried, 2013; Pause and Krauel, 2000; Rolls et al., 2003; Royet et al., 2000; Zald and Pardo, 1997). While some researchers have argued that valence is so critical to olfaction that it precedes odor identification, others have demonstrated that identification occurs even earlier (Olofsson et al., 2012). Pleasant odor perception preferentially relies on orbitofrontal and frontostriatal regions (Bensafi et al., 2012; Rolls et al., 2003), while unpleasant odor perception involves increased activity in amygdala, insula, and sensory cortices (Gottfried et al., 2002; Katata et al., 2009; Royet et al., 2003; Zald and Pardo, 1997). Some studies have shown an even more fine-tuned discrimination, with pleasant odors increasing activation in posterior medial orbitofrontal cortex, and unpleasant odors increasing activation in the lateral orbitofrontal cortex (Gottfried et al., 2002; Grabenhorst et al., 2007; Rolls et al., 2003). Overall, research in basic olfaction establishes valence as a primary dimension for odor perception and shows differential brain correlates for perception of pleasant and unpleasant odors.

Olfactory dysfunction is common in schizophrenia spectrum disorders (for review see Moberg et al., 2014), and differential brain correlates of pleasant and unpleasant odor perception may map onto similar dissociable neural markers of negative symptom subdomains. Factor analyses of negative symptoms have identified two replicable subdimensions. *Avolition* (sometimes referred to as "*motivation and pleasure* impairments/deficits") is characterized by apathy, asociality and anhedonia. *Inexpressivity* (sometimes referred to as "*diminished expression*") is characterized by blunted affective expression and alogia (Blanchard and Cohen, 2006; Kaiser et al., 2017; Kotov et al., 2016; Kring et al., 2013; Messinger et al., 2011; Strauss et al., 2013). These dimensions are stable over the course of the illness, and moderately correlated ($r = 0.47$–0.56; Kotov et al., 2016). While other factor models of negative symptoms are also possible (e.g., Strauss et al., 2018); such alternatives were tested comprehensively in the present cohort by Kotov et al. (2016), who found that two dimensions of negative symptoms are more reliable and valid than alternatives.

Past work investigating the pathomechanisms of negative symptom subdomains reported that avolition is associated with impaired reward processing (Der-Avakian and Markou, 2012; Strauss et al., 2016) and altered activity in frontostriatal brain regions (Barch and Dowd, 2010; Der-Avakian and Markou, 2012; Dowd and Barch, 2012; Segarra et al., 2016; Suk Lee et al., 2015). Mechanistic accounts of inexpressivity suggest that it is associated with emotion processing impairments (Gur et al., 2006) and altered activity in regions including amygdala, inferior and middle frontal gyrus, and visual sensory cortices (Anticevic et al., 2012; Fahim et al., 2005; Gur et al., 2007; Lee et al., 2014; Lepage et al., 2011; Li et al., 2010; Rahm et al., 2015). These distinct neurological pathways suggest the possibility that mechanisms of pleasant odor processing may specifically overlap with those of the avolition dimension of negative symptoms, while those of unpleasant odor processing may specifically overlap with inexpressivity. Only two studies to date have directly examined this question: in a small sample of patients with schizophrenia ($N = 41$), Strauss et al. (2010) found positive associations between negative symptom dimensions and both pleasant and unpleasant odors. Conversely, in another small sample of patients with schizophrenia ($N = 39$) and controls ($N = 21$ controls), Strauss et al. (2015) found no relationships between negative symptom domains and identification of pleasant or unpleasant odors. Together, these studies provided equivocal evidence regarding the present hypothesis due to low sample sizes as well as the absence of direct comparisons of unique predictive power for pleasant vs unpleasant odor identification accuracy.

Olfactory dysfunction is also present in psychotic disorders outside the schizophrenia-spectrum, though such deficits may be less pronounced (Brewer et al., 2003; Cumming et al., 2011; Kamath et al., 2018a; Kamath et al., 2018b). Notably, negative symptoms are also present widely in psychotic disorders other than schizophrenia (e.g. Fennig et al., 1996) and are detectable at subclinical levels in the general population (Stefanis et al., 2002). While reliable mean differences in these symptom dimensions exist between groups, such that schizophrenia tends to present with greater negative symptoms than other psychotic disorders (Fennig et al., 1996), their distributions are notably overlapping, and it may be the case that the hypothesized *relationships* of olfactory dimensions with negative symptoms may be transdiagnostic across psychotic disorders. This dimensional hypothesis is in line with theoretical frameworks that take a non-categorical approach to investigating clinical constructs that extend from normalcy to pathology and cut across traditional diagnostic boundaries (Insel et al., 2010; Kotov et al., 2017a, 2017b; Kotov et al., 2022; Michelini et al., 2021).

Finally, there is reason to believe that olfactory impairment is associated with specific functional domains, specifically social and verbal functioning, in psychotic disorders. Evolutionarily, olfaction is linked with social functioning due to its role in mating, parenting, affiliation, and prey-predator relationships in mammals (Barton, 2006). The social importance of olfaction is apparent in infancy: babies as young as two weeks orient towards familiar perfumes (Schleidt and Genzel, 1990) and can identify their mothers via smell (Porter and Winberg, 1999; Schaal et al., 1995). In adults, olfactory processing aids in social action preparation (Aglioti and Pazzaglia, 2011), and social odors are processed differently for friends versus strangers (Lundström et al., 2008). Deficits in human reproductive social behavior are associated with congenital anosmia, but not with other congenital sensory impairments such as blindness, deafness, or mutism (Naftolin et al., 1971). Olfactory functioning is also linked with language, as evidenced by research showing humans are unusually poor at identifying verbal labels of odors, despite having superior ability to discriminate and detect them (Olofsson et al., 2014; Yeshurun and Sobel, 2010). Evolutionary scientists have noted that the relative difficulty most people exhibit in identifying odors is likely attributable to a mismatch in the development of olfactory and verbal abilities, with language being more recently acquired (Arbib, 2005; Cain, 1979; Cain et al., 1998; Herz, 2005; Larsson, 2002; Lawless and Engen, 1977; Stevenson et al., 2007). Evidence suggests that a complex multi-system process is implicated in odor identification, in which difficulty arises due to signal fidelity loss between low-level object perception and semantic/verbal integration (Olofsson and Gottfried, 2015). While studies have suggested olfactory dysfunction in psychosis may relate to deficits both in social (Cumming et al., 2011; Malaspina and Coleman, 2003) and verbal functioning (Chen et al., 2019; Corcoran et al., 2005), no study has examined whether such effects are specific to certain odor valences, nor whether these relationships exist over and above relationships with negative symptoms, which also bear close relationships to social and verbal functioning (Hunter and Barry, 2012; Marder and Galderisi, 2017).

The present study examines the specificity of relationships between olfactory identification dimensions and negative symptom dimensions as well as measures of social and verbal functioning. We conducted assessments of pleasant and unpleasant odor identification, avolition and inexpressivity dimensions of negative symptoms, as well as linguistic

and social functioning across a large sample of individuals with schizophrenia spectrum and other psychotic disorders, and never-psychotic adults. We focused on odor identification because it has been shown to be key for valence decoding (Olofsson et al., 2012). We hypothesized that 1) avolition would be associated with less accurate pleasant odor identification, 2) inexpressivity would be associated with less accurate unpleasant odor identification, and 3) these associations would be transdiagnostic. We additionally assessed whether such relationships remained when controlling for antipsychotic medication, time since illness onset, and smoking, all of which are associated with olfactory impairment (Moberg et al., 2014). Finally, as an exploratory aim of the study, we attempted to elucidate whether olfaction explains social and verbal functioning over and above negative symptoms.

2. Material and methods

2.1. Sample

Participants were drawn from the 25-year follow-up of the Suffolk County Mental Health Project (SCMHP; Bromet et al., 1992, 2011; Kotov et al., 2017a, 2017b), a longitudinal epidemiologic study of psychosis which has followed patients beginning at first admission. Eligibility and recruitment details are available in supplemental materials. The present sample includes 119 cases with schizophrenia-spectrum disorders (SZ; $N = 54$; breakdown: Schizophrenia; $n = 38$, Schizoaffective Disorder; $n = 15$) and other psychotic disorders (OP; $N = 65$; breakdown: Bipolar Disorder; $n = 41$, Major Depression; $n = 9$; drug-induced; $n = 5$; other; $n = 10$). Data were also collected from 160 comparison participants who had never been psychotic (NP) as determined by a diagnostic interview and matched to cases on age, gender, race, and zip code. See supplemental materials for differences between participants who did and did not complete olfaction measures. Informed consent was obtained prior to study participation, and all procedures were approved by the Committees on Research Involving Human Subjects at Stony Brook University.

2.2. Measures

2.2.1. Diagnoses

Analyses used the last available diagnosis for each participant. Diagnoses were made by consensus of study psychiatrists at the 6-month, 24-month, 10-year, and 20-year follow-ups using all available information, including medical records, significant other interviews, and diagnostic interviews (including the Structured Clinical Interview for DSM (First and Gibbon, 2004)). The diagnostic process is outlined in Bromet et al. (2011).

2.2.2. Covariates

Socio-economic status (SES) was measured using the Hollingshead rating (Hollingshead, 1975), based on the occupation of the primary breadwinner in a participant's household; scale values range from 1 ("large business owner/major professional/executive") to 8 ("not working"). The most recent available assessment of SES was conducted at the 20-year follow-up assessment for NP, while for cases this measure was collected at the baseline visit. Smoking status was coded as two binary variables, indicating respectively whether a participant was a current smoker vs not and was a past smoker vs not (Kotov et al., 2010). Preadmission cognitive ability was assessed by collecting data from participants' school records (Jonas et al., 2022). Where IQ scores were not available, academic achievement scores, translated to the IQ metric, were used. Antipsychotic medication was coded dichotomously as present vs absent during the month leading up to the 25-year interview. Time since illness onset was calculated as the number of years between first clear psychotic symptom and 25-year follow-up (Jonas et al., 2020).

2.2.3. Symptoms variables

Symptoms were assessed using the Scale for Assessment of Positive Symptoms (SAPS; Andreasen, 1984) and Scale for the Assessment of Negative Symptoms (SANS; Andreasen and Grove, 1986). These measures were administered as part of a data collection session which included a battery of clinical interviews, assessing numerous illness-related dimensions. Negative symptoms were scored as two subscales: avolition and inexpressivity. See Kotov et al. (Kotov et al., 2016) for further details on the derivation and characteristics of these scales. Our sample had good reliability for both avolition (Cronbach's $\alpha = 0.82$) and inexpressivity (Cronbach's $\alpha = 0.86$).

2.2.4. Olfaction

Smell identification was assessed using the "Sniffin' Sticks" battery (Hummel et al., 1997, 2007). Participants were presented with a total of 16 odors birhinally via a pen-shaped stimulus object and asked to identify the scent from a list of 4 options. Each item was designated as pleasant or unpleasant based on hedonics ratings from the validation sample published by Hummel et al. (1997), which included a total of ten odors categorized as "pleasant" (hedonic rating > 0) and six as "unpleasant" (hedonic rating < 0). Number of items correct were summed to form pleasant and unpleasant accuracy subscales. Only participants with 2 or fewer missing items for the pleasant subscale and 1 or no missing items for the unpleasant subscale were included in the analyses. Scores were prorated, so that all scores were on a range of 0–10 and 0–6 respectively. Of note, other methods of computing pleasant and unpleasant accuracy subscales exist (e.g. Walsh-Messinger et al., 2018); we report results of the present analyses using one such alternate method in supplemental materials, finding that main results are robust to scoring method alterations.

2.2.5. Social and verbal functioning

Social functioning was assessed using the Quality of Life interview (Heinrichs et al., 1984) and creating a composite variable by summing 3 ratings that comprised social activity, social sexual relationships, and relationships with friends (Velthorst et al., 2017). This interview was administered as part of the battery of clinical interviews, which included symptom ratings as well as other illness-related measures. Verbal functioning was assessed using the Controlled Oral Word Association Test (COWAT; FAS version) (Benton, 1967), a measure of spontaneous verbal fluency. This more specific ability was chosen to represent verbal functioning, as it is thought to play an important role in the production of verbal labels for odors (Oleszkiewicz et al., 2016; Olofsson and Gottfried, 2015). The COWAT was administered as part of a larger battery of neurocognitive measures. For comparison, we also include a second measure of verbal functioning (the vocabulary subtest from WAIS-III; Wechsler, 1997) in supplemental materials.

2.3. Analyses

Statistical analyses were performed using IBM SPSS Statistics version 27. Data visualizations were created using the ggplot2 package (Wickham, 2016) of the R programming environment (R Core Team, 2020).

We examined group (SZ, OP, and NP) differences for all variables using one-way analysis of variance (ANOVA) or chi-square goodness of fit tests. Tukey HSD post-hoc tests were employed to assess pairwise differences between groups. Next, we examined associations of pleasant and unpleasant odor identification with avolition and inexpressivity symptom dimensions. To assess specificity, robustness to covariates, and transdiagnosticity of these associations, we conducted two separate sets of hierarchical linear regressions, with avolition or inexpressivity as the dependent variable. In these regressions, independent variables were entered in the following order: (a) pleasant and unpleasant odor identification, (b) age, gender, and smoking status (c) case status (SZ and OP vs NP) and antipsychotic medication, and (d) the interaction between pleasant/unpleasant odor identification and case status. We repeated

these models in cases only with diagnosis (SZ vs OP) in place of case status for step (c), to test whether associations were consistent across diagnoses.

Next, we conducted two hierarchical regressions to examine the relationships between olfactory identification and social and verbal functioning. Social or verbal functioning were entered as dependent variable, and independent variables were entered in the following order: (a) pleasant and unpleasant odor identification, (b) age, gender, and smoking status, (c) case status (cases vs NP) and antipsychotic medication, and (d) negative symptoms.

Finally, we conducted two exploratory and robustness checks of the results. As an exploration of the specificity of effects, we conducted several regression models including positive symptoms in addition to or in place of negative symptoms. Results of these analyses can be viewed in supplemental Table S6. Second, as we did not directly measure anosmia in our sample, we conducted a robustness check of results by computing a threshold based on past work (Kobal et al., 2000) for possible anosmia and excluded and reran analyses excluding the subsample outside this cutoff.

3. Results

3.1. Sample characteristics

Table 1 reports descriptive characteristics. Zero-order correlations of all study variables are displayed in supplemental Table S2. The three groups (SZ, OP and NP) differed in age (difference < 5 years) and smoking status (rates two- to three-fold higher in cases).

3.2. Odor identification performance for different groups

Mean accuracy for each group is displayed in Fig. 1. ANOVA results showed an effect of group on identification of both pleasant and unpleasant odors (see Table 1). A linear trend analysis indicated a significant effect for both identification of pleasant ($F = 17.29$, $p < .01$) and unpleasant ($F = 7.74$, $p < .01$) odors. Post-hoc tests showed that, compared to NP, both diagnostic groups showed worse identification of pleasant (SZ: Cohen's $d = 0.64$; OP: Cohen's $d = 0.38$) and unpleasant (SZ: Cohen's $d = 0.43$; OP: Cohen's $d = 0.41$) odors. However, SZ and OP did not differ from one another (both $ps > 0.32$). These results remained the same when controlling for age, gender, smoking and medication status.

3.3. Relationship between odor identification and negative symptom dimensions

In the linear regression model predicting avolition (Table 2a), worse pleasant (but not unpleasant) odor identification was a significant predictor, a pattern which remained when controlling for demographic factors, smoking status, antipsychotic medication status, and case status. The interaction between case status and pleasant odor identification was not significant ($\Delta R^2 = 0.001$, $p = .49$). In the model predicting inexpressivity (Table 2b), worse unpleasant (but not pleasant) odor identification was a significant predictor, and this relationship similarly held even when controlling for demographic, smoking, antipsychotic and case status variables. The interaction between case status and unpleasant odor identification was not significant ($\Delta R^2 = 0.009$, $p = .08$). All variables in all models displayed acceptable levels of collinearity (VIFs<2.0). Fig. 2 displays partial associations between odor identification and negative symptoms.

3.4. Transdiagnosticity of odor identification-symptom relationships across psychotic disorders

When we observed a *non-significant* increment in variance explained (R^2) by the interaction term in step (d), we interpreted this as evidence that a *relationship* between odor identification and negative symptoms did not differ based on diagnostic group (SZ vs OP (Sheffield et al., 2017)).

In analysis of cases only, the interaction of pleasant odor identification with diagnostic group did not account for unique variance in avolition ($\Delta R^2 = 0.011$, $p = .229$). In contrast, the interaction of

Table 1
Descriptive characteristics of the sample.

	SZ ($n = 54$)		OP ($n = 65$)		NP (n = 160)			
	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range	*F* test	SZ-OP Post Hoc
Age (years)	51.94 (7.67)	42–71	52.22 (9.02)	40–76	56.75 (9.00)	40–76	$p < .001$	$p = .985$
SES	4.37 (1.98)	1–8	4.03 (1.84)	1–8	4.14 (1.74)	1–8	$p = .588$	$p = .568$
Social Functioning	6.84 (4.33)	1–16	10.59 (4.08)	2–17	12,79 (3.81)	3–17	$p < .001$	$p < .001$
Verbal Functioning	28.52 (11.64)	6–50	37.11 (15.63)	7–78	41.77 (13.54)	14–82	$p < .001$	$p = .002$
Premorbid IQ	97.0 (16.75)	64–128	102.60 (16.34)	62–131	–	–	–	$p = .236$
Inexpressivity	9.25 (9.96)	0–33	4.62 (6.03)	0–24	1.75 (3.21)	0–18	$p < .001$	$p < .001$
Avolition	17.0 (8.07)	1–32.67	9.44 (7.54)	0–27	4.35 (5.10)	0–20	$p < .001$	$p < .001$
Positive Symptoms	11.12 (9.67)	0–32	5.07 (6.48)	0–26	1.46 (2.63)	0–11	$p < .001$	$p < .001$
Time Since Onset (years)	26.90 (3.30)	23–39	25.97 (4.01)	22–47	–	–	–	$p = .189$

	N (%)	N (%)	N (%)	χ^2 test	
Gender (Female)	23 (42.6)	29 (44.6)	75 (46.9)	$p = .890$	$p = .894$
Race/Ethnicity				$p < .001$	$p = .606$
Caucasian	39 (72.2)	52 (80.0)	146 (91.3)		
African-American	8 (14.8)	6 (9.2)	9 (5.6)		
Multiple/Other	5 (9.3)	6 (9.2)	0 (0.0)		
Smoking Status					
Current Smoker	24 (44.4)	21 (32.3)	22 (13.8)	$p < .001$	$p = .094$
Past Smoker	14 (28.6)	32 (50.8)	89 (56.7)	$p = .003$	$p = .018$
Remission (Remitted)	3 (5.6)	20 (31.3)	–	–	$p < .001$
Antipsychotic (Taking)	42 (77.8)	27 (41.5)	2 (0.6)	$p < .001$	$p < .001$

Note. SZ = schizophrenia-spectrum disorders, OP = other psychotic disorders, NP = never-psychotic neighbors. Inexpressivity and Avolition scores were derived from the Scale for the Assessment of Negative Symptoms (SANS; Andreasen and Grove, 1986). Positive symptoms were derived from the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984). The measure of social functioning was extracted from the Quality of Life interview (Heinrichs et al., 1984). Verbal functioning was measured by the Controlled Oral Word Association Test (Benton, 1967). Remission status defined based on definition put forward by Andreasen et al. (2005).

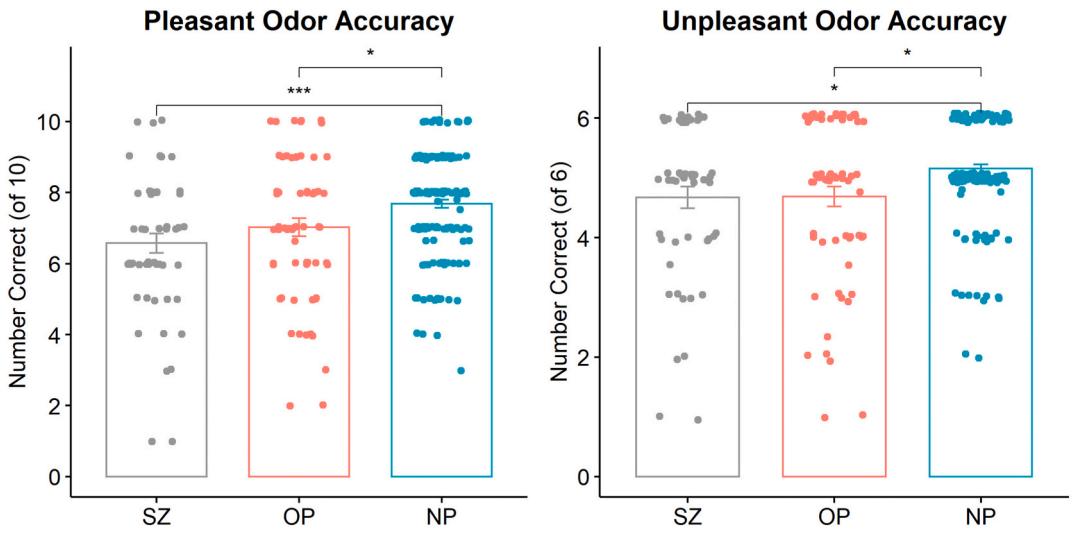

Fig. 1. Bar Graphs of Mean Number of Items Correct By Diagnosis and Olfactory Domain.
Note. SZ = schizophrenia-spectrum disorders, OP = other psychotic disorders, NP = never-psychotic neighbors. *$p < .05$; ***$p < .001$.

Table 2a
Regression of avolition on odor identification.

DV = Avolition	Step 1		Step 2		Step 3	
	$\Delta R^2 = 0.103$ ($p < .001$)		$\Delta R^2 = 0.078$ ($p < .001$)		$\Delta R^2 = 0.157$ ($p < .001$)	
	β	*p*	β	*p*	β	*p*
Pleasant Accuracy	−0.28	<0.01	−0.24	<0.01	−0.15	0.02
Unpleasant Accuracy	−0.08	0.24	−0.07	0.26	−0.03	0.60
Age			0.01	0.84	0.09	0.10
Gender			−0.05	0.35	−0.05	0.30
Current Smoking			0.30	<0.01	0.18	<0.01
Past Smoking			0.05	0.70	0.05	0.48
Antipsychotic Status					0.17	0.01
Case status					0.31	<0.01

Note. Adjusted R^2 values: Step 1 = 0.096, Step 2 = 0.162, Step 3 = 0.317. All continuous predictors are grand mean-centered. Case status indicates NP (0) vs SZ and OP combined (1).

Table 2b
Regression of inexpressivity on odor identification.

DV=Inexpressivity	Step 1		Step 2		Step 3	
	$\Delta R^2 = 0.088$ ($p < .001$)		$\Delta R^2 = 0.065$ ($p < .001$)		$\Delta R^2 = 0.088$ ($p < .001$)	
	B	*p*	B	*p*	β	*P*
Pleasant Acc.	−0.13	0.06	−0.09	0.19	−0.01	0.86
Unpleasant Acc.	−0.22	<0.01	−0.22	<0.01	−0.20	<0.01
Age			−0.10	0.10	−0.03	0.65
Gender			0.08	0.19	0.08	0.18
Current Smoking			0.21	<0.01	0.13	0.08
Past Smoking			0.01	0.87	0.02	0.80
Antipsychotic Status					0.20	<0.01
Case status					0.17	0.03

Note. Adjusted R^2 values: Step 1 = 0.080, Step 2 = 0.132, Step 3 = 0.216. All continuous predictors are grand mean-centered. Case status indicates NP (0) vs SZ and OP combined (1).

unpleasant odor identification with diagnostic group did account for unique variance in inexpressivity ($\Delta R^2 = 0.034$, $p = .045$). Examination of simple slopes revealed that this interaction resulted from a somewhat steeper slope in SZ (β = −0.34) compared to OP (β = −0.09). All variables in all models displayed acceptable levels of collinearity (VIFs<2.2).

3.5. Relationship between odor identification and social and verbal functioning

In the linear regression model with social functioning as outcome (Table 3a), worse pleasant (but not unpleasant) odor identification was a significant predictor, even when controlling in step 2 for age, gender, and smoking status. This relationship did not remain when controlling for case status, medication (step 3), and negative symptoms (step 4). In the model with verbal functioning as outcome (Table 3b), both pleasant and unpleasant odor identification were significant predictors of verbal functioning, even controlling for age, gender and smoking status (step 2) as well as case status and medication (step 3). When adding negative symptoms to the model (step 4), pleasant odors reduced to a trending relationship (β = 0.13 $p = .07$), but unpleasant odors remained significant (β = 0.14 $p = .03$). All variables in all models displayed acceptable levels of collinearity (VIFs<2.0). For analyses using the alternate measure of verbal functioning, see supplemental Table S3.

4. Discussion

This investigation examined specific relationships between olfactory identification ability for pleasant and unpleasant odors and negative symptom dimensions. Results indicated a relationship between worse pleasant odor identification and avolition when controlling for unpleasant odor identification, and a relationship between worse unpleasant odor identification and inexpressivity when controlling for pleasant odor identification. Only two studies have directly assessed differential associations between negative symptom dimensions and olfactory identification as a function of odor valence, and the present work is the first to do so while controlling for shared variance between odor valences. We additionally found specificity of pleasant odor identification as a predictor of social functioning (though this relationship did not remain when controlling for other factors), while both olfactory domains related independently to verbal functioning.

Differential relationships between olfaction and negative symptom domains in the present study support the notion that avolition and inexpressivity result from distinct circuits (Kaiser et al., 2017). Evidence suggests that avolition is associated with reward-related mechanisms (Der-Avakian and Markou, 2012; Dowd and Barch, 2012; Kirschner et al., 2016; Simon et al., 2010; Suk Lee et al., 2015), while inexpressivity is associated with emotion-processing mechanisms (Anticevic et al., 2012; Fahim et al., 2005; Gur et al., 2007; Gur et al., 2006; Kaiser et al., 2017; Lee et al., 2014; Lepage et al., 2011; Li et al., 2010; Rahm

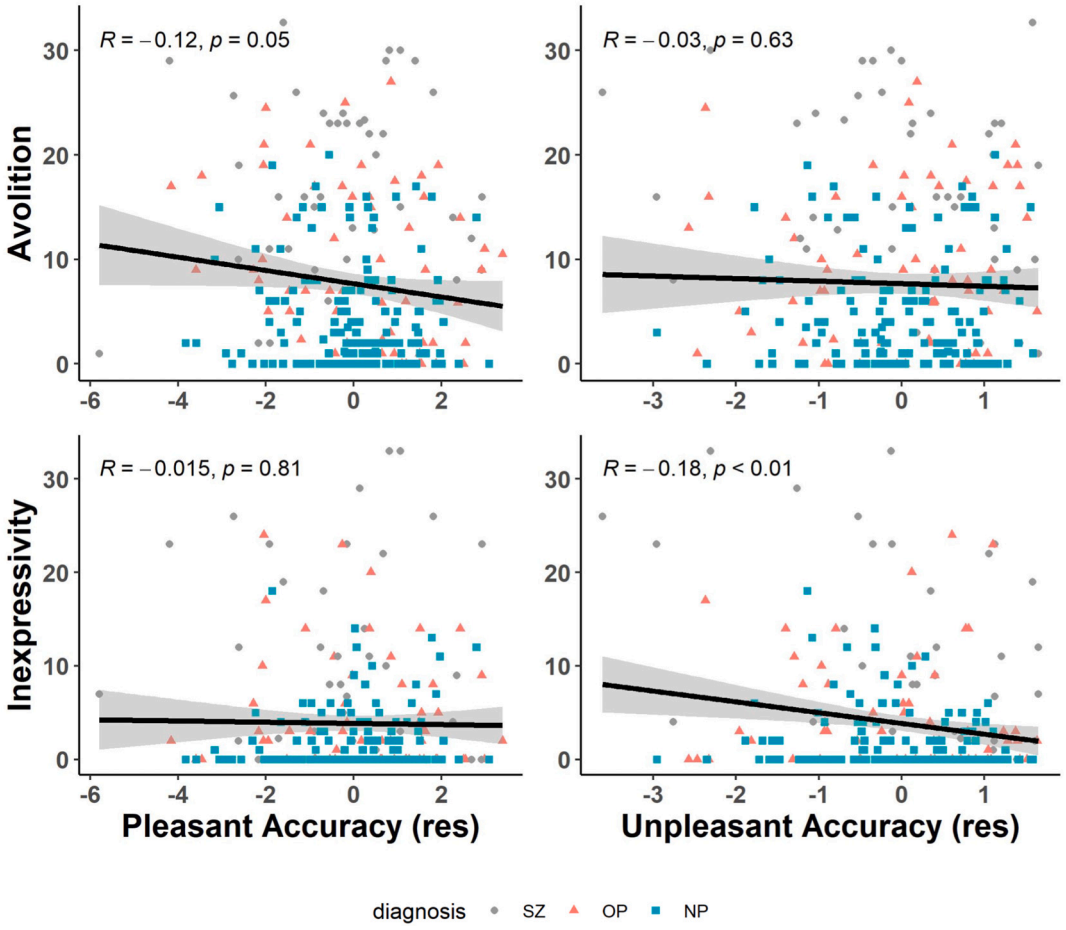

Fig. 2. Scatterplots of Associations between Olfactory Identification and Negative Symptoms.
Note. X-axis for all plots is residualized score with adjustment for opposite odor accuracy, age, gender, smoking status, case status and antipsychotic medication status. Shading indicates 95 % confidence interval of estimates. SZ = Schizophrenia-spectrum disorder, OP = Other Psychotic Disorder, NP = never-psychotic.

Table 3a
Regression of social functioning on odor identification.

DV=Social Functioning	Step 1		Step 2		Step 3		Step 4	
	$\Delta R^2 = 0.063$ ($p < .001$)		$\Delta R^2 = 0.048$ ($p = .015$)		$\Delta R^2 = 0.117$ ($p < .001$)		$\Delta R^2 = 0.423$ ($p < .001$)	
	β	*P*	β	*P*	β	*p*	β	*p*
Pleasant Acc.	0.25	<0.01	0.21	<0.01	0.11	0.13	−0.01	0.85
Unpleasant Acc.	0.00	0.99	0.00	0.97	−0.03	0.60	−0.06	0.19
Age			−0.04	0.58	−0.13	0.04	−0.07	0.09
Gender			0.01	0.84	0.02	0.75	−0.03	0.43
Current Smoking			−0.23	<0.01	−0.17	0.02	−0.06	0.23
Past Smoking			−0.08	0.29	−0.08	0.28	−0.07	0.18
Antipsychotic Status					−0.17	0.05	0.05	0.40
Case status					−0.27	<0.01	−0.05	0.34
Inexpressivity							0.01	0.78
Avolition							−0.81	<0.01

Note. Adjusted R^2 values: Step 1 = 0.056, Step 2 = 0.089, Step 3 = 0.202, Step 4 = 0.636. All continuous predictors are grand mean-centered. Case status indicates NP (0) vs SZ and OP combined (1).

et al., 2015). Due to the unique associations of pleasant and unpleasant odors with neural processing in reward- and emotion-related regions respectively (Katata et al., 2009; Rolls et al., 2003), the present findings are in line with the notion of reward and emotion system disturbances as etiological factors and thus important potential treatment targets for avolition and inexpressivity respectively. By dissociating dimensions of negative symptoms and olfactory valences, our findings expand past work that has explored relationships between negative symptoms as a unidimensional construct and found no relationship with olfactory identification (Hudry et al., 2002; Kamath et al., 2011a; Kamath et al., 2013a, 2013b). However, our findings are inconsistent with one smaller study that failed to find a relationship between anhedonia and pleasant odor identification (Kotlicka-Antczak et al., 2017), possibly because it had lower power to detect the effects and used zero-order tests only. Our findings are also inconsistent with a study which found a surprising *positive* bivariate correlation between anhedonia and unpleasant odor identification (Kamath et al., 2011b), however, this study also relied on a small sample size and zero-order tests only, and no other studies have

Table 3b
Regression of verbal functioning on odor identification.

DV=COWAT	Step 1		Step 2		Step 3		Step 4	
	$\Delta R^2 = 0.120$ ($p < .001$)		$\Delta R^2 = 0.013$ ($p = .481$)		$\Delta R^2 = 049.$ ($p = .001$)		$\Delta R^2 = 0.040$ ($p = .003$)	
	β	*p*	β	*P*	β	*p*	β	*p*
Pleasant Acc.	0.21	<0.01	0.21	<0.01	0.15	0.03	0.13	0.07
Unpleasant Acc.	0.20	<0.01	0.19	<0.01	0.17	<0.01	0.14	0.03
Age			−0.01	0.94	−0.06	0.37	−0.05	0.41
Gender			0.02	0.78	0.02	0.73	0.03	0.66
Current Smoking			−0.02	0.79	0.04	0.64	0.08	0.32
Past Smoking			0.10	0.19	0.09	0.22	0.10	0.17
Antipsychotic status					−0.19	0.02	−0.13	0.10
Case status					−0.08	0.32	−0.02	0.83
Inexpressivity							−0.14	0.06
Avolition							−0.13	0.11

Note. Adjusted R^2 values: Step 1 = 0.113, Step 2 = 0.111, Step 3 = 0.155, Step 4 = 0.189. All continuous predictors are grand mean-centered. Case status indicates NP (0) vs SZ and OP combined (1).

supported the existence of such a relationship.

We furthermore found that these relationships did not differ between cases and neighbors or across psychotic disorders (the one exception being a marginally-significant value for one of the tested group interactions). These findings are largely in line with dimensional views of psychiatric illness such as those outlined by the Research Domain Criteria (Insel et al., 2010). Such a dimensional lens applied to the present results suggests that the mechanisms underlying olfaction-symptom relationships are not functions of psychotic illness per se, but rather operate at varying levels of severity in individuals with different psychotic disorders as well as non-psychotic individuals. Though a few past studies have examined olfaction as a clinical marker in diverse psychotic disorders, none to our knowledge have explicitly tested transdiagnositicity of relationships. Thus, our findings make the preliminary suggestion that pleasant and unpleasant olfactory impairments may have broad applicability as markers for avolition and inexpressivity across populations, and future work should attempt to replicate this in varied clinical and non-clinical samples.

Our findings expand past suggestions of close associations between olfaction and social functioning in psychosis (Cumming et al., 2011; de Nijs et al., 2018; Malaspina and Coleman, 2003). Malaspina and Coleman (2003) postulated that olfactory deficits in schizophrenia are related to social dysfunction due to the link between olfaction and social affiliative drive in most mammals. They further reported that the relationship between negative symptoms and olfaction was largely explained by social functioning. The present findings imply specificity of this relationship to pleasant odor processing, possibly as a result of a shared reliance of social function and pleasant odor processing on reward circuits. This is supported by the finding that the relationship did not remain when controlling for avolition, which suggests specificity of the findings of Malaspina and Coleman (2003) to the avolition dimension of negative symptoms. We again emphasize that this finding should be regarded as tentative, as the relationship was not robust to some covariates.

In contrast, both pleasant and unpleasant odor identification were associated with verbal functioning, indicating domain generality of olfaction as a marker of verbal ability, and suggesting multiple mechanisms may underlie language deficits in psychotic disorders. Unlike social functioning, relationships with verbal functioning were not fully explained by negative symptoms, which have been linked in past work to aberrations in speech and paralinguistic behavior (Messinger et al., 2011), as well as deficits in other measures of verbal ability (Alpert et al., 2000; Kaiser, 2015). Language deficits in schizophrenia have early onset (Blanchard et al., 2010; Reichenberg et al., 2010), are persistent (Reichenberg et al., 2010), and have large effect sizes (Fioravanti et al., 2012), making them an important area for intervention (García-Mieres et al., 2020). The finding of independent relationships for performance on both odor types with verbal functioning may suggest heterogeneity of mechanisms accounting for language deficits and thus multiple possible routes for remediation.

4.1. Limitations & future directions

Our conclusions are tentative due to a number of limiting factors of the present investigation. First, while as we noted, evidence is growing in support of the hypothesis that pleasant and unpleasant olfactory function rely on reward- and emotion-related neural regions respectively, the overlap is not perfect, and some work focusing on other domains of olfaction (e.g. hedonic judgment) has shown a less straightforward mapping (Zou et al., 2016), with some circuit components shared between valences. Secondly, we did not measure individual perceptions of odor hedonics in this study, opting rather to rely on normative sample ratings of odor valence. This is a limitation due to the inherently subjective nature of valence, and its influence by culture and other individual-difference factors. Thirdly, due to the large epidemiologic nature of our dataset, it was not logistically feasible to measure all variables potentially relevant to olfactory functioning; thus it is a limitation that we are not able to identify or control for possible effects of factors such as sinonasal conditions (e.g. recurrent sinus infections or deviated septum), common cold or flu-like symptoms, recurrent allergies, or history of nasal/sinus surgery.

The present findings suggest a number of important future directions. *First*, these effects would benefit from more granular investigation. For example, inexpressivity may reflect aberrations in a number of areas of affective function; past work has noted that emotion processing can be parsed into at least 3 dimensions (expression, experience, and physiology (Kring and Moran, 2008)). *Second*, the present results implicate reward and affective processes in the etiology of negative symptoms; future work should assess whether corresponding neural activation is observed in the context of olfactory processing in individuals with avolition and inexpressivity. Regions of interest to examine could include the mesolimbic social/reward pathway (O'Connell and Hofmann, 2011) and amygdala, while electrophysiological indices may include the reward positivity (Proudfit, 2015) and late positive potential (Hajcak et al., 2012). While preliminary past work has begun to assess some such correlates (e.g. Crespo-Facorro et al., 2001; Pause et al., 2008; Plailly et al., 2006; Schneider et al., 2007), studies have not been statistically powered to identify the fine-grained relationships between symptom and olfactory sub-domains that our data suggest. *Third,* olfactory abilities decline with age as well as with longer duration of psychotic illness (Moberg et al., 2014); future work might test whether olfaction is associated with worsening symptoms during aging longitudinally. *Fourth,* recent work has suggested three distinct stages of olfactory processing including object perception, lexical–semantic integration, and verbalization (Olofsson and Gottfried, 2015); olfactory dysfunction in schizophrenia may occur at any one of

these stages, and the stage at which dysfunction occurs may differ between negative-symptom-odor-valence pairs. *Fifth,* longitudinal studies should examine the predictive power of olfactory identification by valence for symptom course. Demonstration of such predictive utility would further support the use of olfaction as a method to identify specific preferential clinical targets. Promising past work has again shown preliminary utility in using olfaction as a longitudinal predictor, for example showing that pleasant (but not unpleasant) odor identification impairment is associated with increased odds of conversion to psychosis in an at-risk sample (Kotlicka-Antczak et al., 2017), and that poor olfactory identification performance generally predicts longitudinal persistence of negative symptoms measured univariately (Good et al., 2006). Our findings suggest that better-powered samples and a more fine-grained assessment of symptoms may enable greater predictive utility in the clinical domains assessed in this past work.

In sum, the present work suggests that valence-specific olfactory function may be a marker of avolition and inexpressivity, expanding a growing literature reporting differential correlates of negative symptom dimensions. Critically, though negative symptoms are a major source of functional impairment (Galderisi et al., 2014; Harvey and Strassnig, 2012), effective treatments are lacking (e.g. Aleman et al., 2017; Fusar-Poli et al., 2015). To advance treatment development, it is essential to understand the pathophysiology of negative symptoms, and to continue to take a fine-grained approach to their dissociable aspects (Aleman et al., 2017; Galderisi et al., 2018; Strauss and Cohen, 2017). The present findings represent a novel step in this direction. Further work is needed to confirm the utility of olfactory identification of pleasant and unpleasant odors for understanding the etiology, assessment, and treatment of negative symptoms.

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Declaration of competing interest

All authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2022.08.011.

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