Olfactory threshold selectively predicts positive psychometric schizotypy

Naina Mathur, Christopher Dawes, Paula M. Moran *

School of Psychology, University of Nottingham, Nottingham NG72RD, UK

ABSTRACT

Olfactory impairment might be useful as a non-invasive pre-morbid biological marker of psychosis. People with schizophrenia show consistent impairments, but an association between olfaction and schizotypy in non-clinical populations is inconclusive and has been somewhat controversial. This is important as impairment in patients may be artefacts of antipsychotic medication. Meta-analyses indicate small effect sizes in non-clinical populations, suggesting prior negative studies may have been underpowered to demonstrate them.

We measured olfaction and psychometrically-defined schizotypy in a sample of 739 non-clinical volunteers [mean age 23.1]. Subsets reported whether they had a history of mental illness in the family or smoked. We used (sniffin' sticks) to measure threshold detection, discrimination and identification of odours. O-LIFE was used to measure schizotypy.

Lower olfactory-threshold selectively predicted higher scores on the positive dimension, unusual experiences. This association was most evident in sub-groups reporting history of mental illness in the family and/or smoking. There was a weak trend for an association between identification and introvertive anhedonia and discrimination and cognitive disorganisation in those with a history of mental illness in the family.

These data support the idea that olfaction merits further investigation as a biomarker for psychosis and that olfactory-threshold detection in particular has potential to selectively predict unusual experiences. Variability in previous studies may have been exacerbated by including different proportions of participants with history of mental illness in the family and/or smoking. We propose that non-clinical participants be stratified by these factors in future studies of olfaction and potentially any study that measures psychometric schizotypy.

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1. Introduction

A number of studies have found that people with psychosis and schizophrenia have abnormal olfactory abilities, with most, but not all, finding impairment (Bradley, 1984; Brewer et al., 1996; Corcoran et al., 2005; Good and Sullivan, 2015; Kamath et al., 2018; Moberg et al., 2014; Robabeh et al., 2015). Olfaction is established early in embryonic development, being fully functional by approximately week 24 of gestation. The neural circuitry underlying olfaction comprises regions implicated in schizophrenia including subregions of the frontal cortex, the amygdala, hippocampus and the parahippocampal gyrus (Gottfried and Zald, 2005; Harrison, 1999; Kamath et al., 2014; Malaspina et al., 1998; Schneider et al., 2007; Turetsky et al., 2009). For these reasons impaired olfaction is of interest as a potential bio-behavioural marker for early neurodevelopmental abnormalities that precede the onset of the symptoms of schizophrenia in adolescence and adulthood. Olfactory deficits were originally described in Parkinson's and Alzheimer's Diseases and there is recent evidence for

deficits associated with mood disorders, (Foguem et al., 2018; Naudin et al., 2014; Olofsson et al., 2016) and with 22q11 syndrome associated with psychosis (Tang et al., 2018). This suggests that the impairments may have wider bio-marker application across multiple neuropsychiatric and neurological disorders.

Olfaction can be considered to involve at least three separate sub-processes, Identification; the ability to identify or name an odour, discrimination the ability to discriminate one odour from another and Threshold; the ability to detect specific odours above background. Different studies measuring olfaction in schizophrenia and schizotypy have used different methods to measure olfaction, with only a few analysing all three aspects e.g. (Kamath et al., 2018). There is evidence for specific deficits in identification in people with schizophrenia. (Park and Schoppe, 1997) found that psychometrically defined schizotypal men, but not women, showed olfactory identification deficits. (Brewer et al., 2003) found impairment of identification in individuals identified as high risk for developing psychosis who later developed schizophrenia or schizophreniform psychosis. However, there was no evidence of lower olfactory identification scores in those classified as high risk who went on to develop other psychotic disorders. This suggests olfactory identification may have some specificity as a pre-morbid marker of transition from high risk to schizophrenia. (Kamath

and Bedwell, 2008) however failed to find group differences in olfactory identification between individuals scoring high and low in schizotypy. (Compton and Chien, 2008) also found no relationship between olfactory identification and schizotypy in first-degree relatives of those with schizophrenia. Using discrimination as the olfactory measure (Kamath et al., 2014) found that clinical risk subjects showed robust impairments in olfactory discrimination as well as identification. However, some studies have failed to find a discrimination deficit in individuals with schizotypy (Zou et al., 2015). Relatively fewer studies have investigated olfactory threshold in connection with schizotypy. Whilst Park and Schoppe (1997) failed to find a relationship between threshold and Schizotypy, one study by Mohr, Rohrenbach, Laska and Brugger (2001) found elevated detection thresholds (diminished acuity) in individuals who scored at or above the median magical ideation score compared to those who scored below.

Schizotypy is a psychometrically defined, hypothetical personality construct, linked to a developmental theory of latent susceptibility to schizophrenia (Korfine and Lenzenweger, 1995). Schizotypy is considered in terms of the dimensional or "quasi-dimensional" view that traits that correspond to various dimensions of schizophrenia are seen to varying degrees in the general population. There are significant numbers of individuals who have psychotic experiences within the general population (Linscott and van Os, 2013; van Os et al., 2009) and taxonometric studies investigating the latent class structure of schizotypy, confirm that many symptoms associated with psychosis exist on a dimension in the general population (Elahi et al., 2017; Grant et al., 2018). The dimensional or personality-based approach suggests a continuum that includes all of the population with schizophrenia at the extreme end (Claridge and Beech, 1995), (Grant et al., 2018; Rawlings et al., 2008). In support of this approach a number of studies have found that particularly positive symptoms such as hearing voices are relatively prevalent in the general population (Linscott and van Os, 2013; van Os, 2003). The "quasi-dimensional" or disease-based approach suggests that schizotypy refers to a small percentage (estimates vary between 3 and 10%) of the population who carry very specific, potentially genetic, vulnerability to schizophrenia; reviewed in (Claridge and Beech, 1995; Grant et al., 2018; Nelson et al., 2013). Studies investigating the association between olfaction and schizotypy have not consistently used one approach or the other. While there is a difference of opinion about the factor structure of schizotypy there is good agreement that it comprises at least three distinguishable factors which correspond to positive, negative and disorganised symptoms dimensions in schizophrenia (Fonseca-Pedrero et al., 2011; Nelson et al., 2013). The O-LIFE questionnaire used in the present study include scales derived from DSM description of these symptoms.

(Cohen et al., 2012) controversially suggested that olfactory deficits in schizotypy are subtle, if at all present and that they do not constitute a meaningful vulnerability marker. A subsequent meta-analysis found that olfactory deficits (which combined different measures of olfaction) are associated with small effect sizes in individuals who scored high in schizotypy (Moberg et al., 2014). Given the variability in the way both olfaction and schizotypy are defined and measured across studies, coupled with the likely lack of experimental power in the majority of studies, it is difficult to make definitive conclusions about whether individuals with high psychometrically defined schizotypy show olfactory impairments. This is an important question in the context of using olfaction as a potential biomarker for future psychosis. In this study we investigated olfactory performance across three measures of olfaction: identification, discrimination, and threshold using sniffin' sticks (Hummel et al., 2007). We measured schizotypy using the O-LIFE (Mason and Claridge, 2006; Mason et al., 1995), a scale that measures positive, negative and cognitive related symptomatology in a majority young adult population. Results suggest that olfactory threshold is a weak but selective predictor of unusual experiences but that this is moderated by whether individuals report current smoking and/or history of mental illness in the family.

2. Methods

2.1. Participants

The study was carried out under the ethical approval of the School of Psychology, University of Nottingham, Ethics Committee. A total of 739 participants (264 M /475 F, mean age 23.1, S.D. 9.28) were recruited in seven cohorts between 2012 and 2018. N numbers for each cohort were 73, 141, 126, 102, 100, 40 and 149 respectively. Mostly participants were recruited as an opportunity sample. Some students were 1st year psychology students from the University of Nottingham who were reimbursed with participation credits. Participants who had recently chewed gum (in past 3 h), or had a respiratory infection were excluded from the study ($n = 8$). There was some variability between cohorts in terms of olfactory scores, however we did not consider variability large enough to warrant normalisation [highest mean TDI score was 31.6 (2016 cohort) and the lowest 27.9 (2018 cohort)] (see supplementary information section for full scores).A short demographics questionnaire was given to all participants either prior to the study or prior to olfactory testing. This requested age, sex, and whether they were currently taking any medications and if so which ones - the wording differed slightly but not substantively between cohorts e.g. text of question ["Are you currently on any medication (including contraception)? Yes/No /Prefer not to say If so, please specify:"]. None reported taking antipsychotic medication, the most frequently reported medications were contraceptives, acne-medication/roaccutane, antidepressants and salbutamol inhalers. Some cohorts additionally completed questions whether they smoked cigarettes (Yes/No/Prefer not to say), whether they smoked cannabis (Yes/No/Prefer not to say) and whether there was a history of mental illness in their family (Yes/No/Prefer not to say). Some additional details were requested in some single cohorts (e.g. stage of menstrual cycle, education level) but as they were not collected systematically or in sufficient numbers of cohorts they are not reported.

2.2. Olfaction (Sniffin' sticks)

The Sniffin' Sticks test used is a reliable and widely used test that has been validated for European populations (Haehner et al., 2009; Hummel et al., 2007; Hummel et al., 1997). It includes threshold, discrimination and identification tests using odour dispensing felt-pens (14 cm in length, 1.3 cm inner diameter). Each pen contains 4 ml of either a liquid odour or an odour that had been dissolved in propylene glycol.

Threshold levels were assessed using n-butanol detection. The test consisted of 16 pen-triplets, those marked with higher numbers indicating a lower dilution of n-butanol (i.e.1 was the strongest and 16 was the weakest dilution with 4% n-butanol). Two of the pens dispensed propylene glycol and one the target odour (n-butanol). The discrimination test consisted of 16 pen-triplets; within each triplet 2 pens dispensed the same odour, one dispensed a different odour. The identification test consisted of 16 pens with different common odours and 16 cards naming 4 alternative odours to select from.

2.3. Schizotypy (O-LIFE)

The Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE; Mason and Claridge, 2006, (Mason and Claridge, 2006) (150 questions, YES-NO format) was used to assess participants level of schizotypy. 104 of the questions were scored, the additional questions were filler questions (score range: 0–104). The 104 scored questions measured 4 dimensions. There were 30 questions on "unusual experiences", 24 on "cognitive disorganisation"; 27 on "introvertive anhedonia" and 23 assessing "impulsive nonconformity" dimensions.

2.4. Experimental procedure

The olfaction tests were conducted in the order: threshold, discrimination, identification. To avoid confounds by visual input participants wore a blindfold during the threshold and discrimination tests. Presentation of pens was always in sets of three (green – blue – red), separated by about 20 s. Within triplets, colour-presentation was randomised. In all tests, pens were presented directly underneath both nostrils for about 2–3 s per pen. Pens were presented in intervals of approximately 3 s (allowing for a natural breath to be taken). Between the three olfaction tasks a break of approx. 5 min was taken in an attempt to avoid desensitisation. Scores from each test (threshold, discrimination, identification) were on scales of 1–16, all three tests were also combined into a composite "TDI score" (score range: 1–48). The procedure lasted approx. 30 min per participant.

The full methodological details are outlined in the supplementary online information.

Secondly, participants completed the O-LIFE questionnaire, taking approx. 25 min. The experiment (including the pre-questionnaires and O-LIFE) lasted approx.1 h excluding breaks. Each cohort then performed different neuropsychological tests which will not reported here as they were carried out only in single cohorts (e.g. emotional bias task, associative learning task). In cohorts that went on to investigate additional cognitive tests (including a break if required) experimental sessions lasted approx. 1.5-2 h.

The O-LIFE was presented on a computer and participants were required to press computer keys to indicate yes or no answers. Scores for individual scales were calculated automatically.

2.5. Statistics

Statistics were performed using SPSS [IBM Corp.Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk,NY :IBM Corp.] except for mediation analysis which used R version 3.3.1 [R Development Core Team (2016) R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna]. Regression analyses were carried out following confirmation of normality, linearity and homoscedasticity using Wilk-Shapiro, plots of residuals against fitted values and VIF scores respectively, graphs were plotted using Graphpad Prism version 7.05 [Graphpad Software Inc. 2018].

The following abbreviations were used to describe the O-LIFE scales in the reporting of results: Unusual experiences (UNEX), introvertive anhedonia (INTAN), Cognitive disorganisation (COGDIS), impulsive non-conformity (IMPNON).

3. Results

3.1. Does composite olfaction score (TDI) predict total schizotypy score?

The composite olfactory score (TDI) was entered as predictor in linear regression analysis with total schizotypy score as the outcome variable. The model was significant ($r^2 = 0.01$, $\beta = -0.31$, $T = -2.7$, $p = 0.007$), suggesting that overall olfactory score weakly predicts total schizotypy score.

3.2. Which olfactory measure best predicts total schizotypy score?

A hierarchical regression model with olfactory subscales entered in the order identification, discrimination and threshold, (order based on prior literature) as predictors and schizotypy total as the outcome variable was significant ($F_{3,728} = 3.996$, $P = 0.008$). The model predicted 1.6% of the variance with only threshold reaching individual significance ($r^2 = 0.01$, $\beta = -0.61$, $T = -3.3$, $P < 0.001$). This suggests that olfactory threshold is the most predictive olfaction measure for total schizotypy.

3.3. Which schizotypy subscales are best predicted by which olfactory measures?

A linear regression model with identification, discrimination and threshold olfactory subscales entered as predictors and UNEX as the outcome variable was significant ($F_{3,728} = 4.6$, $P < 0.005$). The overall model predicted 1.9% of the variance with only threshold reaching individual significance ($\beta = -0.25$, $T = -3.5$, $P < 0.001$).

A similar linear regression model with INTAN as the outcome variable was significant ($F_{3,728} = 2.6$, $P < 0.05$). The overall model predicted 1.1% of the variance with only identification reaching individual significance ($\beta = -0.07$, $T = -2.1$, $P < 0.05$).

Models with COGDIS and IMPNON as outcome variables were not significant. In summary olfactory threshold weakly predicts UNEX while olfactory identification weakly predicts INTAN.

3.4. Do sex, cannabis/cigarette smoking or reported presence of mental illness in the family affect schizotypy or olfaction?

Total schizotypy or UNEX were not significantly different between Males and Females (see Table 1). The subscale COGDIS was higher in females while IMPNON and INTAN were lower in females (see Table 1). Smokers had higher scores on all schizotypy measures, these were significant for schizotypy total, UNEX and IMPNON (Table 1). Cannabis smokers had higher scores only on IMPNON (Table 1). Individuals reporting a history of mental illness in the family had higher scores on all scales except IMPNON (Table 1).

In summary, report of smoking was associated with higher positive schizotypy while report of a history of mental illness was associated with higher scores on all schizotypy measures (except IMPNON). Females showed higher COGDIS while males showed higher INTAN and IMPNON. As might be expected IMPNON was higher in cannabis smokers and numerically higher in smokers (though this was not statistically significant for smokers).

None of these factors, sex, smoking, cannabis smoking or history of mental illness showed any significant independent effect on any of the olfactory scales.

3.5. Does the prediction of positive schizotypy by olfactory threshold differ between those who report and do not report a history of mental illness in the family?

In the subset of participants ($n = 126$) that reported a history of mental illness in the family a linear regression model with identification, discrimination and threshold olfactory subscales entered as predictors and UNEX as outcome variable was significant ($F_{3,122} = 3.9$, $P < 0.01$) (Fig. 1B). The overall model predicted 8.8% of the variance with threshold reaching individual significance ($\beta = -0.23$, $T = -2.6$, $P < 0.01$). In participants that report no history of mental illness in the family ($n = 320$) the overall model was not significant ($F < 1$) the model predicted 0.5% of the variance (Fig. 1A). This was also reflected when total schizotypy score was the outcome variable; the model predicted 9.2% of the variance in those reporting a history of mental illness and 0.6% in those reporting none.

To assess whether threshold and history of mental illness either independently predicted UNEX, or whether one variable may mediate the other, three further linear regression models were conducted. In the first two models, UNEX was significantly predicted by threshold ($F_{1,445} = 5.944$, $P < 0.01$, $r^2 = 0.013$) and history of mental health ($F_{1,446} = 7.536$, $P < 0.01$, $r^2 = 0.016$) in separate analyses. When adding both variables as predictors simultaneously, each continued to be significant predictors of UNEX ($F_{2,444} = 6.945$, $p = 0.001$, adjusted $R^2 = 0.025$), suggesting that both history of mental health and threshold independently predicted UNEX. Correlational analysis also supports this conclusion. There was a significant negative correlation between UNEX and threshold in those reporting history of mental illness in the

Table 1
Mean (SD) O-LIFE scores by sex, smoking, cannabis and history of mental illness in family.

	N	UNEX	Schizotypy total	COGDIS	INTAN	IMPNON
Male	263	6.46(5.1)	28.99(13.5)	9.39(5.5)	5.01(3.9)	8.1(4.3)
Female	474	6.44(5.5)	28.63(13.9)	10.83(5.6)	4.37(4.0)	6.98(3.9)
F df value		<1	<1	$F_{1,735} = 10.9$**	$F_{1,735} = 4.3$*	$F_{1,735} = 16.5$***
Non-smoker	564	6.49(5.2)	29.5(13.1)	10.6(5.4)	4.82(3.9)	7.5(3.9)
Smoker	106	7.93(6.2)	33.4(14.9)	11.58(6.2)	5.2(4.5)	8.6(4.2)
F df value		$F_{1,668} = 6.2$**	$F_{1,668} = 7.5$**	<1	$F_{1,668} = 7.0$**	<1
No cannabis	497	6.6(5.4)	29.7(13.5)	10.8(5.6)	4.9(4.0)	7.2(3.8)
Yes cannabis	92	7.3(6.4)	33.2(14.6)	11.3(5.7)	4.6((4.3)	9.9(4.3)
F df value		<1	$F_{2,589} = 2.5$ NS	<1	<1	$F_{2,589} = 17.7$****
No History	322	6.2(5.1)	27.6(12.2)	9.66(5.2)	4.3(3.6)	7.4(3.9)
Yes History	126	7.7(5.8)	34.6(15.3)	13(5.8)	5.9(5.3)	7.9(3.6)
F df value		$F_{1,446} = 7.5$*	$F_{1,446} = 25.8$****	$F_{1,446} = 34.4$****	$F_{1,446} = 13.3$****	<1

SD = standard deviation, df = degrees of freedom. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ $p < 0.0001$. UNEX = unusual experiences, COGDIS = cognitive, ****disorganisation, INTAN = introvertive anhedonia, IMPNON = impulsive non-conformity. Note 1 respondent who checked 'prefer not to say' for history of mental illness question was excluded.
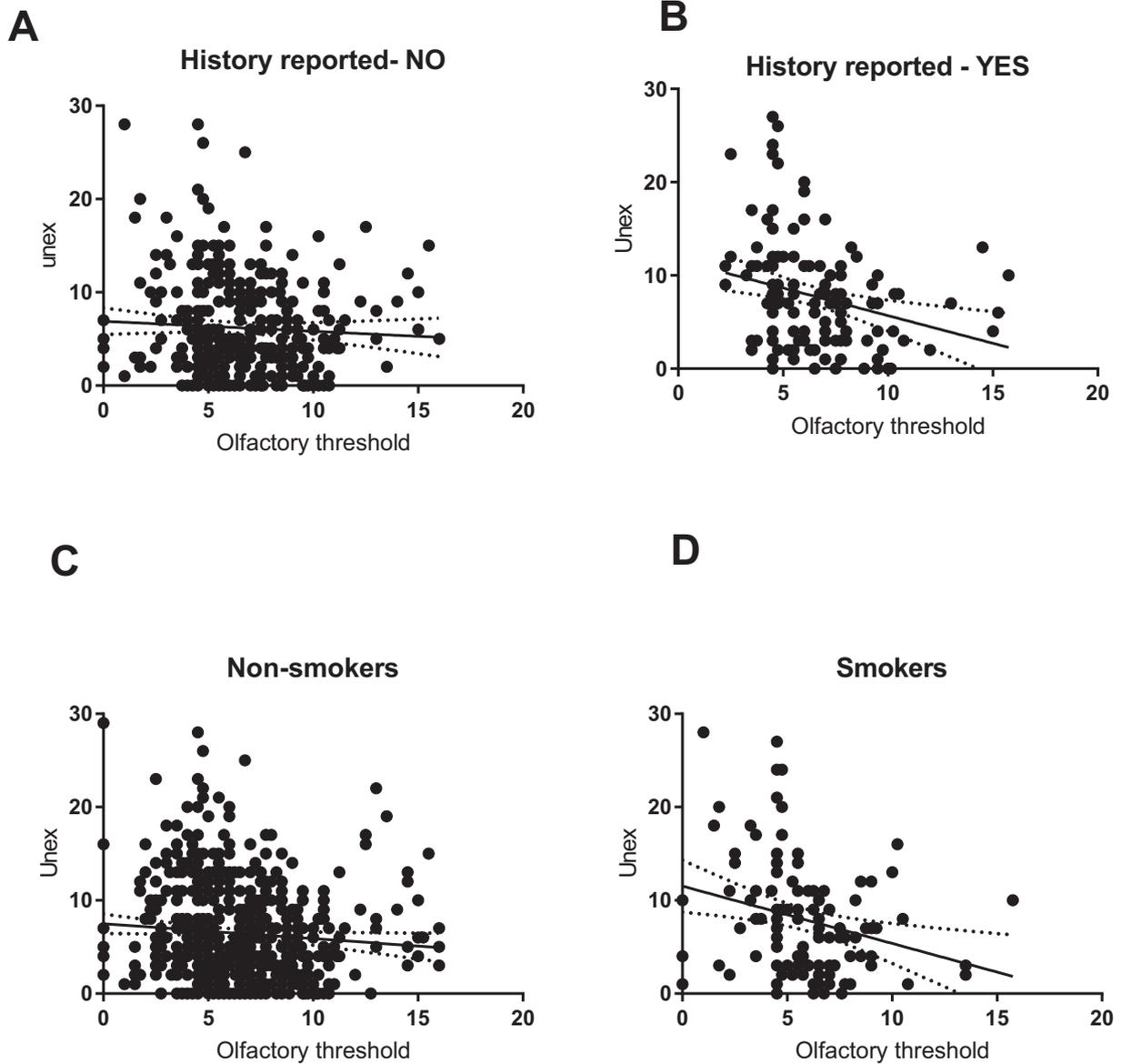

Fig. 1. Plot of regression data for olfactory threshold and UNEX in subgroups of individuals asked whether they had a history of mental illness in their family (A & B) or whether they smoked (C & D). Solid lines indicate best fit regression line, dotted lines the 95% confidence interval. Panel A indicates no significant prediction of unusual experiences by olfactory threshold in those reporting no, while panel B shows significant prediction of UNEX by olfactory threshold in those reporting yes. Panels C and D show a trend that olfactory threshold may predict UNEX better in smokers.

Table 2
Pearson's correlation O-LIFE subscales by olfactory measures.

	UNEX	INTAN	COG	IMPNON
Not asked N = 285				
Threshold	−0.16	−0.08	−0.11	−0.16
Uncorrected p	0.005	NS	NS	0.006
Identification	−0.06	−0.05	0.03	−0.11
Uncorrected p	NS	NS	NS	0.04
Discrimination	0.00	−0.07	−0.00	−0.05
Uncorrected p	NS	NS	NS	NS
No history N = 322				
Threshold	−0.05	−0.03	−0.03	−0.02
Uncorrected p	NS	NS	NS	NS
Identification	0.02	0.13	0.06	0.04
Uncorrected p	NS	0.01	NS	NS
Discrimination	0.01	−0.02	0.09	0.01
Uncorrected p	NS	NS	NS	NS
Yes history N = 126				
Threshold	−0.26*	−0.11	−0.06	−0.17
Uncorrected p	0.003	NS	NS	NS
Identification	−0.14	−0.08	−0.05	−0.02
Uncorrected p	NS	NS	NS	NS
Discrimination	−0.13	−0.09	−0.28*	−0.17
Uncorrected p	NS	NS	0.001	NS

* indicates p < 0.05 following Bonferroni correction for multiple comparisons. NS = p > 0.05. UNEX = unusual experiences, COGDIS = cognitive disorganisation, INTAN = introvertive anhedonia, IMPNON = impulsive non-conformity.

family (Table 2). A weaker correlation of similar magnitude was also seen in the group not asked the question (though this did not survive multiple comparison correction; p < 0.06 after correction). No correlation was seen in the group reporting no to history of mental illness in the family (Table 2).

3.6. Does the prediction of negative schizotypy by olfactory identification differ between those who report and do not report a history of mental illness in the family?

A regression model with identification, discrimination and threshold olfactory subscales entered as predictors and INTAN as outcome variable was not significant in either those that reported a history of mental illness in the family or those that did not (both F's < 1). A positive correlation between identification and INTAN was found only in the group that reported no history of mental illness in the family (Table 2), this did not survive correction for multiple comparisons however.

3.7. Is cognitive disorganisation predicted by olfactory discrimination in those who report history of mental illness in the family?

The overall regression model with all participants did not support prediction of cognitive disorganisation by olfactory discrimination (see 3.3). However Table 2 indicates a significant correlation in the group reporting history of mental illness. To explore this further we performed a regression model with threshold identification and discrimination as predictors and cognitive disorganisation as outcome variable in the group that reported history of mental illness. The model was significant ($F_{3,122} = 3.6$, $P < 0.01$). The overall model predicted 8.2% of the variance with discrimination reaching individual significance ($\beta = -0.27$, $T = -3.1$, $P < 0.01$).

3.8. Does olfactory threshold predict positive schizotypy in individuals scoring at or above the 75th percentile of schizotypy scores?

The previous analysis suggests that the association between positive schizotypy and olfactory threshold was predominantly seen in those reporting a history of mental illness. We also found that those reporting a history of mental illness have higher UNEX scores (Table 1). We investigated a subgroup of individuals at the 75th percentile score of 10 or higher on UNEX with a view to investigating whether the association

between threshold and UNEX was mediated by higher UNEX scores. A linear regression model with threshold olfactory subscale entered as predictor and UNEX as outcome variable was significant ($F_{1181} = 5.3$, $P < 0.05$) the model predicted 2.9% of the variance. To further explore this relationship we investigated a hierarchical regression model with threshold and history of mental illness (coded as a dummy variable) and entered as predictors and UNEX as outcome variable. The model with both threshold and history of mental illness was significant ($F_{2,445} = 6.8$, $P < 0.001$). Threshold alone predicted 1.1% of the UNEX variance and was 3% when history of mental illness was added to the model. With both threshold ($\beta = -0.11$, $T = -2.5$, $P < 0.01$) and history of mental illness ($\beta = 0.12$, $T = -2.7$, $P = 0.006$) reaching individual significance. Threshold and UNEX were also found to be negatively correlated ($r = -0.13$, $P < 0.0001$) in this group but to a lesser degree than the subgroup reporting a history of mental illness ($r = -0.26$, $P < 0.001$) (Table 2). This weaker correlation suggests that while the threshold/UNEX or threshold/schizotypytotal associations are seen in the subgroup reporting a history of mental illness, these associations may not be mediated solely by the fact that they have high UNEX scores. Thus, while reporting or not of a history of mental illness influences the association between threshold and UNEX, there is an independent albeit weak residual association between olfactory threshold and UNEX in those reporting no history.

3.9. How does smoking influence the association between reporting history of mental illness in the family, threshold and positive schizotypy?

Table 3 indicates that the correlation between olfactory threshold and UNEX differs depending on not only whether an individual reports a history of mental illness in the family (as we have deduced previously), but also by smoking. In individuals not asked about smoking or history (similar to many studies measuring psychometric schizotypy) correlations are weak, however when stratified it can be seen that both smoking and history groups show significant correlations Table 3). The non-smoking group reporting no family history clearly does not show a correlation between threshold and UNEX. The numbers per group preclude a regression analysis, however these data suggest that smoking and reporting of mental illness in the family may have independent influence on the correlation between threshold and UNEX (see also Fig. 1 A–D).

3.10. How does smoking influence the association between reporting history of mental illness in the family, identification and negative schizotypy?

Table 4 indicates that unlike the threshold-UNEX association, the correlation between olfactory identification and INTAN does not differ depending on whether an individual reports a history of mental illness in the family in non-smokers. However when stratified it can be seen that a correlation is found in smokers with no history of mental illness but not in smokers who report a history. In common with the threshold-UNEX correlation (Table 4) the non-smoking group reporting no family history clearly does not show a correlation between identification and INTAN. The numbers per group preclude a regression analysis, however these data suggest that smoking and reporting of mental illness in the family may have independent influence on the association

Table 3
Spearman's ρ correlation UNEX and threshold by smoking and report of mental illness in family.

	Non-smoker	Smoker
No history	0.01	−0.37*
	N = 283	N = 38
Yes history	−0.256*	−0.38
	N = 100	N = 26
Not asked	−0.13	−0.18
	N = 178	N = 42

* p < 0.05.

Table 4
Spearman's ρ correlation INTAN and identification by smoking and report of mental illness in family.

	Non-smoker	Smoker
No history	0.07	−0.35*
	N = 283	N = 38
Yes history	−0.10	−0.02
	N = 100	N = 26
Not asked	0.03	−0.20
	N = 178	N = 42

* p < 0.05.

between identification and INTAN. However this is dissociable from the influence of these factors on the threshold-UNEX association. While both correlations are highest in smokers the threshold-UNEX is higher in those reporting history of mental illness while the Identification-INTAN correlation is highest in those who report no history of mental illness.

4. Discussion

Olfactory threshold was found to weakly predict the positive symptom dimension UNEX, but not other schizotypy measures. This was seen in those reporting yes to the question "is there a history of mental illness in your family". This is theoretically consistent with findings of a deficit in olfactory threshold in several studies in patients with schizophrenia (Chen et al., 2018; Isseroff et al., 1987; Kamath et al., 2018; Rupp et al., 2005a; Rupp et al., 2005b; Turetsky and Moberg, 2009). A specific association with positive symptom-related dimension is also consistent with patient studies where Chen et al., (2017) found an association between olfactory threshold and positive symptoms while Kamath et al. (2018) showed that threshold for one odorant citralva was associated with clinician rated positive symptomatology. Other studies (Auster et al., 2014) have found no associations with positive symptomatology though these used composite measures of olfactory accuracy, not being sufficiently powered to analyse measures of specific subscales.

One factor suggested to affect threshold sensitivity is dryness of the nasal mucosa induced by antipsychotic drugs, which may mediate threshold deficits in patient studies (Isseroff et al., 1987). Meta-analysis has additionally identified duration of illness as a moderator of general olfactory deficits (Moberg et al., 2014), also raising the possibility that length of time on medication might affect olfaction. An association between olfactory threshold and positive symptomatology suggests that at least conceptually, this association can be demonstrated in individuals not currently taking antipsychotic medication.

Meta-analyses of patient studies have indicated that odour memory or olfactory identification showed the largest effect sizes and threshold the smallest (Cohen et al., 2012; Kamath et al., 2014; Moberg et al., 2014). It is therefore surprising that threshold was the aspect identified here. It should be noted that different studies have used different odourants for the threshold testing, we used N-butanol here which is one of the most common but several studies have used citralva or lyrol, though there has been little difference found between them in terms of demonstrating a clinical deficit in patient groups (Kamath et al., 2018; Turetsky and Moberg, 2009).

We found a weaker trend for a negative association between identification and the negative symptom scale INTAN. Identification deficits in schizophrenia patients are the most widely reported and have the largest effect sizes (Kamath and Bedwell, 2008). The correlation in this study was positive but did not survive multiple correction therefore is a trend only. This direction of effect, if not effect size, is nonetheless consistent with a number of studies in patients e.g. (Chen et al., 2018; Kamath et al., 2018). Kamath et al., (2017) reported identification deficits were associated with self-reported anhedonia and clinician rated negative symptoms. It should be noted that these prior studies additionally found discrimination deficits. We also found discrimination

predicted cognitive disorganisation, this was not seen in our full sample analysis but was evident in the group reporting history of mental illness. This is congruent with Kamath's prior findings of discrimination deficits in patients and their relatives and may suggest some selectivity of this olfactory measure for cognitive symptoms.

We found that the association between olfactory threshold and UNEX is seen in those reporting a history of mental illness in the family with a weaker trend in the group of individuals not asked the question. While there have been many clinical studies that have investigated relatives of people with schizophrenia, this factor is sometimes not considered in non-clinical population studies. Family history is a significant risk factor for most psychiatric disorders and its measurement is becoming increasingly common in large scale genetic studies and in clinical practice (Milne et al., 2009). There are many studies that have shown that risk for psychosis is higher in those reporting a family history of psychosis in both patients and non-patients (Esterberg et al., 2010; Seidman et al., 2012). We confirmed that those reporting yes to mental illness in the family have significantly higher schizotypy scores on all scales with the exception of IMPNON. As IMPNON is included as a control scale not directly related to schizophrenia symptom dimensions (Mason et al., 1995), this is consistent with theory. We have not specified mental illness therefore we might expect to have included relatives of people with other disorders such as depression, anxiety or bipolar. The closeness of the relationship was not interrogated by this general question either, therefore we might expect both first and second degree relatives to have responded yes. This could readily be included in future studies as there are a number of clinical instruments that can address this question comprehensively e.g. (Milne et al., 2009). Whether an individual might declare a history of mental illness in the family might be influenced by a number of different factors and may reflect other factors such as personality or demand characteristics. The only measure that might approximate this in the present study is IMPNON, for which we did not see a difference between those reporting, not reporting or not asked about history of mental illness, suggesting impulsive behaviour increasing probability to respond yes is unlikely to have mediated the effect.

Despite clinical studies suggesting that smoking does not affect olfactory deficits (Corcoran et al., 2005; Moberg et al., 2014), it is possible that those reporting a history of mental illness may be more likely to smoke and this could be a mediating variable. Here in agreement with other studies we found that smokers have higher schizotypy scores (Stewart et al., 2010) and this appears to be associated with the positive symptom dimension. We also found that the UNEX/olfactory threshold correlation is not seen in non-smokers who do not report a family history of mental illness but is in non-smokers that do, as well as in smokers who do not report a history of mental illness. This suggests that either smoking or history of mental illness in the family can independently influence the expression of the association between UNEX and olfactory threshold. Regression models suggest that taken independently, smoking and reporting of family history of mental illness are sufficient but not necessary for the demonstration of the association between positive schizotypy and olfactory threshold identified in this study.

When we investigated the weak identification-INTAN correlation in detail, we found that correlation was seen only in smokers with no history. This suggests that smoking or history of mental illness in the family can independently influence the association between identification and INTAN. For history of mental illness this differs qualitatively from how these factors influence the threshold-UNEX correlation. Why this would be absent in those with history of mental illness is not clear, it is unlikely to be attributable to different INTAN profiles between the groups as the groups have similar mean values and range [mean INTAN non-smoking no history group 4.2 range 0–21; mean INTAN non-smoking yes history group 4.4 range 0–19]. These scores are low compared to published norms for INTAN scores for a similar age group which average approx. 5–6 depending on sex (Mason and Claridge, 2006). Extreme low scores may indicate some other pathology or some adaptation in response to pathology. Low schizotypy scale scores

are not necessarily indicators of extreme psychological health and may instead describe absence of schizotypal deviance (Lenzenweger, 2015).

Given the predictive effects of smoking and olfaction we additionally asked the question whether they could predict reporting of history of mental illness. Using logistic regression we found that while smoking showed a predictive effect, threshold did not (this is discussed further in supplementary information).

A limitation of this study is that single-question measures of smoking and history of mental health in the family are simplistic and do not allow differentiation from ex-smokers, degree of smoking, relationship to family member, type of mental illness or demand characteristics which may limit interpretations of the data in terms of understanding mechanisms. However the simplicity of the measures also means that either or both could be readily implemented in future studies.

In summary we have established that lower olfactory threshold is weakly but significantly associated with higher unusual experiences in non-clinical participants, but that the expression of this association can be moderated by smoking and reported history of mental illness in the family. This may help to explain variable inconsistent findings in prior studies. We found weak evidence for an association between olfactory identification and negative symptom relevant scale and no evidence for an association between olfactory discrimination and schizotypal characteristics, with the exception of a weak negative correlation with cognitive disorganisation in those reporting history of mental illness. These data support prior suggestions that olfactory abnormality may prove useful as a biomarker for premorbid psychosis and suggest the threshold measure may have some selectivity for characteristics related to positive symptoms. It is suggested that future studies of olfaction and psychometrically defined schizotypy (and potentially any psychometric schizotypy study) consider stratification by smoking and history of mental illness in the family.

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Declaration of Competing Interest

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Ethical standards

Appendix A. Supplementary Information

Supplementary information to this article can be found online at https://doi.org/10.1016/j.schres.2019.05.014.

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