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Original Research

Does chronic nicotine consumption influence visual backward masking in schizophrenia and schizotypy?

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ABSTRACT

Nicotine consumption is higher for people within the schizophrenia spectrum compared to controls. This observation supports the self-medication hypothesis, that nicotine relieves symptoms in, for example, schizophrenia patients. We tested whether performance in an endophenotype of schizophrenia (visual backward masking, VBM) is modulated by nicotine consumption in i) smoking and non-smoking schizophrenia patients, their first-degree relatives, and age-matched controls, ii) non-smoking and smoking university students, and iii) non-smoking, early and late onset nicotine smokers. Overall, our results confirmed that VBM deficits are an endophenotype of schizophrenia, i.e., deficits were highest in patients, followed by their relatives, students scoring high in Cognitive Disorganisation, and controls. Moreover, we found i) beneficial effects of chronic nicotine consumption on VBM performance, in particular with increasing age, and ii) little impact of clinical status alone or in interaction with nicotine consumption on VBM performance. Given the younger age of undergraduate students (up to 30 years) versus controls and patients (up to 66 years), we propose that age-dependent VBM deficits emerge when schizotypy effects are targeted in populations of a larger age range, but that nicotine consumption might counteract these deficits (supporting the self-medication hypothesis).

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1. Introduction

Schizophrenia is characterized by multiple deficits including hallucinations and higher cognitive functions (e.g. memory, language: Fatouros-Bergman et al., 2014; Park & Gooding, 2014; Silverstein et al., 1998). In addition, patients have sensory deficits, such as reduced P50 suppression and contrast sensitivity (Green et al., 2004; Keefe & Harvey, 2012; Silverstein & Keane, 2011). Sensory deficits are of particular interest, because they might cause deficient higher cognitive functions (Mayer et al., 2012). Moreover, sensory deficits reflect vulnerability for the disease, i.e., they are endophenotypes of schizophrenia (Braff et al., 2007; Chkonia et al., 2010; Quednow et al., 2011). Another evidence for an endophenotype is the fact that sensory deficits are not restricted to patients but are also evident, though in milder forms, in relatives of patients (Clementz et al., 2014) and healthy individuals scoring high on schizotypy (Cadenhead et al., 2014; Koychev et al., 2010; Raine et al., 1992). Schizotypy is a personality trait with symptoms similar to the ones of patients with schizophrenia (Claridge, 1997; Kwapil & Barrantes-Vidal, 2014; Gross, et al., 2014).

Interestingly, controls consume nicotine less frequently and heavily than patients with schizophrenia (De Leon & Diaz, 2005; Leonard et al., 2007), their relatives, and individuals scoring high in schizotypy (Esterberg et al., 2007). This elevated nicotine consumption might be a form of self-medication, compensating for the dysfunctions associated with the disease (Evans & Drobes, 2009; Hahn et al., 2013; Kumari & Postma, 2005; Leonard et al., 2007). First, acute nicotine administration improved attentional functioning in patients (Kumari et al., 2001). Second, smoking nicotine *acutely* reduced auditory gating deficits in patients but not controls (Adler et al., 1993; Song et al., 2014). Third, high scoring schizotypes, who were chronic smokers, had stronger auditory gating (increased P50 response) compared to non-smokers (Wan et al., 2007). Fourth, in smooth-pursuit eye movements, chronic smoking was associated with superior performance in patients but not in controls (Klein & Andresen, 1991; Myers et al., 2004; Olincy et al., 1998; Petrovsky et al., 2013b; Smith et al., 2002).

In this line, sensory gating deficits in schizophrenia are associated with genes related to the nicotinic cholinergic receptors (Bridgman et al., 2014; De Luca et al., 2004; Freedman et al., 2008; Leonard et al., 2007; Petrovsky et al., 2013a), particularly, to the receptor alpha 7

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subunit (CHRNA7; De Luca et al., 2004; Leonard et al., 2007). Another recent study showed that a single nucleotide polymorphism (SNP) in the alpha 7 subunit gene correlated with both the diagnosis of schizophrenia and impaired performance in visual backward masking (VBM; Bakanidze et al., 2013).

In this VBM paradigm, a vernier stimulus (i.e., two vertical lines that are offset horizontally) is presented on the computer screen. Participants indicate whether the offset of the lower line is to the right or left of the upper line. A subsequent grating mask impairs vernier offset discrimination. This VBM paradigm shows the main characteristics of an endophenotype of schizophrenia (Chkonia et al., 2010; Herzog et al., 2013). VBM deficits were much stronger in patients with schizophrenia than controls (Herzog et al., 2004). First-degree relatives of patients with schizophrenia were impaired with performance levels in between the performance levels of controls and patients. Cappe et al. (2012) found VBM impairments in healthy students scoring high as compared to low in Cognitive Disorganisation, one of the three commonly reported schizotypy dimensions. There were no correlations of VBM deficits with the positive and negative schizotypy dimensions.

VBM deficits can be linked to the physiology of the nicotinic system (Herzog et al., 2013). In the macaque brain, the nicotinic cholinergic system projects to layer IV of the primary visual cortex, the first cortical stage of retinal projections (Disney et al., 2007). The cholinergic modulation enhances target-relevant information (e.g., Deco & Thiele, 2009). In humans, visual contrast detection performance of grating stimuli was superior when healthy individuals were exposed to nicotine as compared to a placebo (Smith & Baker-Short, 1993). A weaker cholinergic system in schizophrenia patients may impede the enhancement of briefly presented stimuli as they are used in VBM (Herzog et al., 2013). Hence, nicotine consumption may compensate for sensory impairments, supporting the self-medication hypothesis (Evans & Drobes, 2009; Green, 2006).

The attenuation of the cholinergic activity may be directly caused by the schizophrenia disease or by the antipsychotic medication (e.g. clozapine, olanzapine). Schizophrenia patients have an over production of neurotransmitters and antipsychotic medication compensates this over production by blocking the receptors (Carlsson et al., 1999; Manzella et al., 2015).

In the current study, we had two main goals. First, we investigated whether VBM deficits are more pronounced in individuals pertaining to the schizophrenia spectrum compared to controls. Second, for individuals pertaining to the spectrum, we investigated whether VBM deficits are more evident in non-smokers than smokers (supporting the self-medication hypothesis). We tested VBM performance in three studies, in i) non-smoking and smoking schizophrenia patients, their first degree relatives, and age-matched controls, ii) non-smoking and smoking university students, and iii) another sample of non-smoking and smoking university students with half of them having started nicotine consumption before the age of 16 years (Khuder et al., 1999; Reidpath et al., 2013). Early-onset drug consumption might be indicative of a stronger proneness for a schizophrenia spectrum disorder (De Leon, 1996; Green, 2006). VBM performance of our university students was assessed as a function of their self-reported schizotypy scores (see also Cappe et al., 2012). According to the previous literature, we expected VBM deficits to be most pronounced in patients with schizophrenia and healthy individuals scoring high in Cognitive Disorganisation. We expected that these VBM deficits would be less pronounced in smokers, probably even least pronounced in early smokers.

2. Methods

2.1. Participants

All participants had normal or corrected-to-normal vision, with scores above 0.8 for at least one eye, as determined by the Freiburg Visual Acuity Test (Bach, 2007). All participants gave written informed consent after having received comprehensive study information.

Table 1
Demographic, clinical and questionnaire data of participants in the three studies.

First study	Schizophrenia Patients (N = 120)		Relatives (N = 113)		Controls (N = 91)	
	Mean	Sd	Mean	Sd	Mean	Sd
Female (n)	26		61		35	
Age	34.97	8.309	34.38	11.66	34.87	8.85
Age range	18–60		16–66		19–55	
Education	12.92	2.55	14.19	3.82	15.33	2.68
SANS	11.4	5.39				
SAPS	10.23	3.56				
CPZ	607.63	421.71				
VD	60.67	71.01	29.29	20.47	23.08	9.5
Smokers (n)	87/120		54/113		41/91	

Second study: University Students (N = 80)			Non-Smokers (N = 40)				Smokers (N = 40)			
	Mean	Sd		Mean	Sd	Median		Mean	Sd	Median
Female (n)	69		CogDis	4.5	2.69	4	CogDis	5.1	2.53	5
Age	21.2	2.21	UnEx	3.15	2.76	3	UnEx	3.45	2.86	3
Age range	18–30		IntAn	1.8	1.77	1	IntAn	1.85	1.52	2
Education	University		Impnon	2.77	2.43	2	Impnon	3.27	1.93	3
VD	10.62	2.9								
Smokers (n)	40/80									

Third study: University Students (N = 66)				Non-Smokers (N = 26)				Early-Smokers (N = 20)				Late-Smokers (N = 20)			
	Mean	Sd			Mean	Sd	Median		Mean	Sd	Median		Mean	Sd	Median
Female (n)	34			CogDis	4.077	2.99	4	CogDis	4.2	2.74	4	CogDis	5.45	2.35	5
Age	22.3		2.5	UnEx	2.8	2	3	UnEx	3.15	2.43	3	UnEx	2.5	1.93	2
Age range	18–29			IntAn	1.42	1.1	1	IntAn	1.5	1.53	1.5	IntAn	2.4	2.08	2
Education	University			FagTot				FagTot	2.75	2.55	2	FagTot	2.25	2.02	2
VD	10.3		1.72												
Smokers (n)	40/66	Early:20	Late:20												

Abbreviations: Scale for the Assessment of Positive Symptoms (SAPS), Scale for the Assessment of Negative Symptoms (SANS), Chlorpromazine (CPZ) equivalent, Vernier Duration (VD), Cognitive Disorganisation (CogDis), Unusual Experiences (UnEx), Introvertive Anhedonia (IntAn), Impulsive Nonconformity (Impnon), FagerströmTotal score (FagTot).

For the first study (Table 1), we recruited schizophrenia patients from the Tbilisi Mental Health Hospital or the psychosocial rehabilitation centre. Control participants were recruited from the general population. We contacted relatives once patients had agreed to participate. We excluded participants who reported drug or alcohol abuse or any mental illnesses. An experienced psychiatrist gave the final diagnosis of schizophrenia. The diagnosis was based on i) an interview based on the SCID (DSM-IV criteria), ii) the scales for the assessment of negative and positive symptoms (SANS and SAPS; Andreasen, 1984a, 1984b), and iii) information from clinician–patient interactions. The Georgian National Council on Bioethics in Tiblisi had approved the study.

For the second study, we tested 80 students (69 females, Table 1) from the University of Lausanne or from the Swiss Federal Institute of Technology in Lausanne (EPFL). According to self-report, 40 were non-smokers (32 females). None of these participants reported a history of neurological or psychiatric illness.

For the third study, we tested 66 university students (34 females, Table 1). Participants were pre-selected according to whether they were non-smokers (14 women, 12 men), early smokers (10 women, 10 men) or late smokers (10 women, 10 men). Early and late smokers were divided according to their age of smoking onset (late smokers started smoking after 15 years of age; Khuder et al., 1999; Reidpath et al., 2013).

2.2. VBM stimuli and apparatus

The VBM protocol was similar to the ones used before (e.g. Herzog et al., 2004; Cappe et al., 2012). Participants sat in a dimly illuminated room at a distance of 5 m from the computer screen. We presented vernier stimuli consisting of two white horizontal bars of 10' (arc min) slightly offset in the horizontal direction. The stimuli were presented on a black background and the offset direction was chosen randomly. The lower line of the vernier was either offset to the left or right relative to the upper line. Participants indicated by button presses whether the offset of the lower line was to the left (left button presses with the left hand) or right (right button presses with the right hand). Errors were indicated by an auditory signal. For each subject, we determined the time that the vernier had to stay on the screen in order to reach 75% correct responses based on a staircase procedure (see Herzog et al., 2004). This time is called the vernier duration (VD). We used this individual VD in the next experimental step, where we presented the vernier with an offset of 1.15'. A blank screen (inter-stimulus interval (ISI)) and a mask grating followed the vernier. The grating comprised either 25 verniers or 5 verniers. Verniers had no offset. Using the adaptive Parametric Estimation by Sequential Testing (PEST) procedure (Taylor, 1967), we determined the ISI, for which participants reached 75% correct

Table 2
Means and standard deviations for performances in the VBM task.

First Study

	Schizophrenia		Relatives		Controls	
	Smo (N = 87)	N-Smo (N = 33)	Smo (N = 54)	N-Smo (N = 59)	Smo (N = 41)	N-Smo (N = 50)
BM 25 (+/-)	143.34 (±13.9)	150 (±15.25)	49.98 (±6.53)	74.42 (±7.8)	30.42 (±3.32)	40.25 (±3.8)
BM 5 (+/-)	221.83 (±13.99)	236.9 (±19.27)	121.12 (±9.3)	159.69 (±10.2)	100.6 (±5.33)	116.68 (±7.35)

Second Study

	CogDis				UnEx				IntAn			
	High		Low		High		Low		High		Low	
	Smo (N = 26)	N-Smo (N = 18)	Smo (N = 14)	N-Smo (N = 22)	Smo (N = 20)	N-Smos (N = 21)	Smo (N = 20)	N-Smo (N = 19)	Smo (N = 32)	N-Smos (N = 30)	Smo (N = 8)	N-Smo (N = 10)
BM 25 (SD+/-)	28.9 (±2.78)	26.43 (±3.4)	21.47 (±3.03)	25.69 (±2.63)	25.74 (±3.31)	25.45 (±3.27)	26.96 (±2.83)	26.66 (±2.57)	25.36 (±2.25)	23.85 (±2.14)	30.28 (±6.04)	32.54 (±4.92)
BM 5 (SD+/-)	75.98 (±5)	62.07 (±4.8)	53.81 (±6.38)	66.13 (±4.44)	71.14 (±6.19)	59.1 (±3.82)	65.3 (±5.88)	70.05 (±5.14)	67.4 (±4.9)	57.86 (±3.15)	71.48 (±8.68)	83.6 (±5.5)

Third study

	Controls		Early smokers		Late Smokers	
	CogDis		CogDis		CogDis	
	High (N = 11)	Low (N = 15)	High (N = 7)	Low (N = 13)	High (N = 12)	Low (N = 8)
BM 25 (SD+/-)	29.62 (±4.54)	24.18 (±2.76)	30.93 (±5.51)	25.99 (±3.52)	26.36 (±5.2)	21.92 (±4.4)
BM 5 (SD+/-)	55.91 (±5.56)	60.63 (±5.53)	56.53 (±7.31)	63.34 (±4.7)	59.9 (±7.43)	64.22 (±6.35)
	UnEx		UnEx		UnEx	
	High (N = 14)	Low (N = 12)	High (N = 12)	Low (N = 8)	High (N = 8)	Low (N = 12)
BM 25 (SD+/-)	29.83 (±3.7)	22.57 (±3.1)	25.54 (±3.8)	31 (±4.77)	25.18 (±5.7)	24.18 (±4.66)
BM 5 (SD+/-)	62.43 (±6.2)	54.21 (±4.4)	60 (±4.6)	62.5 (±7.4)	64.52 (±8.25)	59.71 (±6.58)
	IntAn		IntAn		IntAn	
	High (N = 13)	Low (N = 13)	High (N = 10)	Low (N = 10)	High (N = 11)	Low (N = 9)
BM 25 (SD+/-)	27.11 (±3.81)	25.86 (±3.38)	28.4 (±4.56)	27.04 (±4)	23.76 (±4.92)	25.58 (±5.3)
BM 5 (SD+/-)	58.55 (±6.1)	58.72 (±5.2)	57.04 (±5.82)	64.87 (±5.32)	62.44 (±8.11)	60.64 (±5.7)

Data are given separately for the BM25 and BM5, the smoking groups and "symptom" groups (clinical status in 1st study, schizotypy subscales in 2nd and 3rd study).

responses. We plot data as the Stimulus Onset Asynchrony (SOA), which is VD plus ISI (see Table 2).

2.3. Self-report questionnaires used in studies 2 and 3

In studies 2 and 3, students filled in the validated French version (Sierro et al., in press) of a standardised self-report schizotypy questionnaire (Mason et al., 2005). In study 3, participants additionally filled-in a standardised nicotine consumption scale (Heatherton et al., 1991).

2.3.1. Self-report schizotypy questionnaire — short O-Life

The 43-item true–false, short O-LIFE (Mason et al., 2005) measures schizotypy along 4 dimensions comprising positive schizotypy (Unusual Experiences, UnEx, e.g., "Are your thoughts sometimes so strong that you can almost hear them?"), negative schizotypy (Introvertive Anhedonia, IntAn, e.g., "Do you prefer watching television to going out with people?"), Cognitive Disorganisation (CogDis, e.g., "Are you easily confused if too much happens at the same time?") and Impulsive Nonconformity (ImpNon, e.g., "Do you at times have an urge to do something harmful or shocking?). Impnon does not constitute a classical schizotypy dimension, and measures impulsive, anti-social, and eccentric behaviours. Positive answers (for reverse coded items, negative answers) weight one point. For each dimension, we computed scores by summing the points, so that higher scores denote higher schizotypy. Information on the French translation including normative values for student samples can be found in Sierro et al. (in press).

2.3.2. Self-report questionnaire — Fagerström Test of Nicotine Dependence (FTND)

The FTND tests for the level of nicotine dependence (Heatherton et al., 1991). Participants have to judge their smoking behaviour according to six questions, such as: "How soon after waking do you smoke your first cigarette?", "Do you find it difficult not to smoke in forbidden places?", "Which cigarette would you hate to give up?", "How many cigarettes do you smoke per day?". In the case of questions requiring yes–no responses, yes responses are scored as 1, and no responses are scored as 0. For the remaining questions, scores are determined through responses on a 4-point Likert scale (scores range from 0 to 3). An overall sum score of 10 indicates highest nicotine dependence and a score of zero lowest nicotine dependence (Heatherton et al., 1991).

2.4. Data analysis

For study 1, we calculated a $3 \times 2 \times 2$ repeated measures ANOVA with Group (patients, relatives and controls) and Smoking Habit (smokers, non-smokers) as between-subject factors and Task (BM25, BM5) as within-subject factor on mean SOAs.

For studies 2 and 3, we first determined separate high and low schizotypy groups according to a median-split for each O-Life subscale score (see Table 1, see also Cappe et al., 2012). For study 2, we calculated 3 separate $2 \times 2 \times 2$ repeated measures ANOVAs with Group (high, low schizotypy group) and Smoking Habit (smokers, non-smokers) as between-subject factors and Task (BM25, BM5) as within-subject factor on mean SOAs for UnEx, IntAn and CogDis groups, separately. For study 3, we performed analogue ANOVAs to the ones in study 2, but instead of two smoking groups, we added three Smoking Groups (non-smokers, early smokers, late smokers) as between-subject factor. Please note that for schizotypy, a participant can be part of the high group in one dimension and in the low group in another dimension (see also Cappe et al., 2012).

We performed Pearson's correlations between SOAs in the VBM (separately for BM25 and BM5 SOAs) and age, symptom scores, schizotypy scores and FTND scores, respectively.

Kolmogorov–Smirnov tests revealed normal distribution for questionnaire scores and behavioural measures. All p-values were two-tailed, the α-level was set at 0.05 and all post-hoc tests were Tukey tests.

3. Results

3.1. Study 1: testing patients with schizophrenia, relatives and controls

The ANOVA showed a significant main effect of Group, $F(2, 318) = 54.34$, $p < 0.001$, Smoking Habit, $F(1, 318) = 3.95$, $p = 0.047$ (smokers < non-smokers), and Task, $F(1,318) = 424,75$, $p < 0.001$ (BM25 < BM5; Table 2). Post-hoc tests showed that schizophrenia patients had higher SOAs than their relatives ($p < 0.001$) and controls ($p < 0.001$). SOAs were higher in relatives than controls ($p = 0.02$; Fig. 1). There were no significant 2-way and 3-way interactions (all p values > 0.2).

3.2. Study 2: VBM performance as a function of schizotypy in smokers and non-smokers

To test whether the O-LIFE subscale scores differed between smoking groups, we conducted separate ANOVAs on these scale scores with Smoking Groups as between-subject factor. The ANOVAs were not significant for CogDis scores, $F(1,79) = 3.3$, $p = 0.08$, UnEx scores, $F(1,79) = 0.49$, $p = 0.86$, and IntAn scores, $F(1,79) = 0.28$, $p = 0.6$.

The ANOVA on CogDis groups showed a significant main effect of Task, $F(1, 76) = 298.13$, $p < 0.001$ (BM25 < BM5). We replicated the main effect of CogDis groups (Cappe et al., 2012) on a one-tailed level, $F(1, 76) = 3.23$, $p = 0.038$ (high > low). The main effect of smoking groups was not significant, $F(1, 76) = 0.01$, $p = 0.99$. There were no significant 2-way or 3-way interactions (all p values > 0.2).

The ANOVA on UnEx groups showed again the significant main effect of Task, $F(1, 76) = 327.76$, $p < 0.001$ (BM25 < BM5). Neither the main effect of smoking groups, $F(1, 76) = 0.28$, $p = 0.6$, nor the one on UnEx groups, $F(1, 76) = 0.25$, $p = 0.61$, was significant. There were no significant 2-way or 3-way interactions (p values >0.45).

The ANOVA on IntAn groups showed again the significant main effect of Task, $F(1, 76) = 254.81$, $p < 0.001$ (BM25 < BM5). There was a significant main effect of IntAn groups, $F(1,76) = 6.51$, $p = 0.013$ (high < low). The main effect of smoking groups was not significant, $F(1,76) = 0.039$, $p = 0.84$. There were no significant 2-way and 3-way interactions (all p values >0.12).

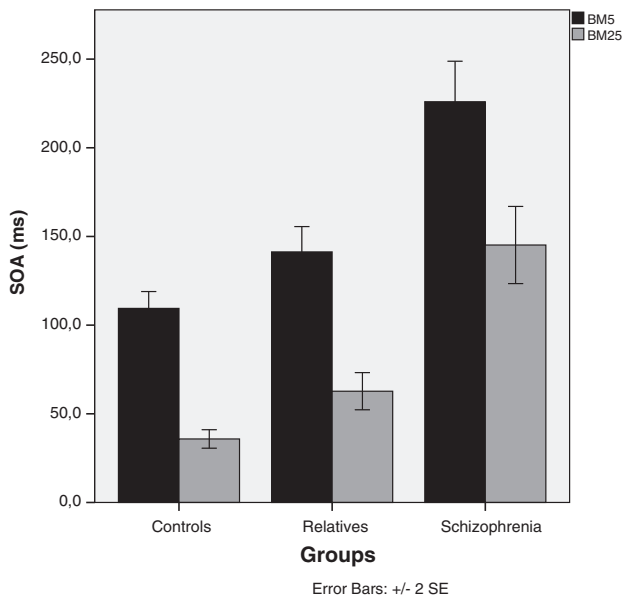

Fig. 1. Mean SOAs for the different grating conditions as a function of group. Vertical bars denote 2 SE of the mean. Results showed significant main effects of Group and Task (but no significant interaction).

Table 3
Pearson's correlations between participants' age, VBM performance (BM25, BM5), symptoms (study 1), O-LIFE scores (studies 2 and 3) and Fagerström scores (study 3).

First Study			BM25	BM5	SANS	SAPS	Second Study		BM25	BM5	CogDis	UnEx	IntAn	Third Study			BM25	BM5	CogDis	UnEx	IntAn	FagTot
N-smo	Controls	Age	0.32*	0.41**	–	–	N-smo	Age	−0.03	0.13	−0.21	−0.58	0.01	N-smo		Age	0.08	−0.20	−0.34	−0.26	−0.51**	
		BM25	–	0.72**	–	–		BM25	–	0.47**	0.03	−0.05	−0.29			BM25	–	0.45*	0.22	0.29	0.05	
		BM5		–	–	–		BM5		–	−0.10	−0.27	0.55**			BM5		–	−0.12	0.21	0.33	
		SANS			–	–		CogDis			–	0.16	0.17			CogDis			–	0.64**	0.36	
		SAPS			–	–		UnExp				–	0.26			UnEx				–	0.35	
								IntAn					–			IntAn					–	
	Relatives	Age	0.51**	0.39**	–	–										FagTot						
		BM25	–	0.72**	–	–																
		BM5		–	–	–	Smo	Age	0.03	0.20	0.60	−0.62	0.23									
		SANS			–	–		BM25	–	0.60**	0.27	−0.05	−0.15	Smo	Early	Age	−0.11	0.09	0.40	0.03	0.33	0.51*
		SAPS			–	–		BM5		–	0.40*	0.11	−0.06			BM25	–	0.62**	0.18	−0.21	0.05	0.00
								CogDis			–	0.00	−0.11			BM5		–	−0.19	−0.07	−0.23	0.14
	Schizophrenia	Age	0.06	0.06	−0.12	−0.12		UnExp				–	0.00			CogDis			–	0.17	0.52*	0.20
		BM25	–	0.70**	−0.14	0.28		IntAn					–			UnEx				–	−0.20	0.53*
		BM5		–	−0.08	0.40*										IntAn					–	0.10
		SANS			–	0.21										FagTot						–
		SAPS				–																
Smo	Controls	Age	0.35*	0.23	–	–									Late	Age	−0.30	−0.21	0.01	0.08	−0.02	0.34
		BM25	–	0.52**	–	–										BM25	–	0.77**	0.14	0.03	−0.06	−0.02
		BM5		–	–	–										BM5		–	−0.10	0.11	0.04	0.00
		SANS			–	–										CogDis			–	0.04	0.08	−0.31
		SAPS			–	–										UnEx				–	0.12	0.10
																IntAn					–	−0.24
	Relatives	Age	0.16	0.21	–	–										FagTot						–
		BM25	–	0.78**	–	–																
		BM5		–	–	–																
		SANS			–	–																
		SAPS			–	–																
	Schizophrenia	Age	−0.01	0.02	0.07	0.21																
		BM25	–	0.73**	0.28**	0.12																
		BM5		–	0.42**	0.20																
		SANS			–	0.12																
		SAPS				–																

Significant results are marked by asterisks.
Abbreviations: Smoking (Smo), Non-smoking (N-Smo).
* $p \leq 0.05$.
** $p \leq 0.01$.

3.3. Study 3: VBM performance as a function of schizotypy in non-smokers, late and early smokers

To test whether the O-LIFE subscale scores differed between smoking groups, we conducted separate ANOVAs on these scale scores with Smoking Groups as between-subject factor. The ANOVAs were not significant for CogDis scores, $F(2,63) = 1.63$, $p = 0.2$, UnEx scores, $F(2,63) = 2.48$, $p = 0.09$, and IntAn scores, $F(2,63) = 0.47$, $p = 0.62$.

The ANOVA on CogDis groups showed a main effect of Task, $F(1,60) = 289.11$, $p < 0.0001$ (BM25 < BM5). There were no significant main effects of Smoking Groups, $F(2, 60) = 0.017$, $p = 0.94$, or CogDis groups, $F(1, 60) = 0.002$, $p = 0.96$. We found an interaction between Task and CogDis groups, $F(1,60) = 6.7$, $p = 0.012$. Yet, post-hoc comparisons revealed faster performance in the BM25 than BM5 condition for both the high CogDis group ($p < 0.0001$) and low CogDis group ($p < 0.0001$). Moreover, the two CogDis groups performed comparably on both the BM25 condition ($p = 0.21$) and BM5 condition ($p = 0.33$).

The ANOVA on UnEx groups showed again the main effect of Task, $F(1,60) = 276.97$, $p < 0.0001$. There were no significant main effects of Smoking Groups, $F(2, 60) = 0.86$, $p = 0.86$, and UnEx groups, $F(1,60) = 0.32$, $p = 0.97$, and no significant 2-way and 3-way interactions (all p values > 0.53).

The ANOVA on IntAn groups showed again the main effect of Task, $F(1, 60) = 290.04$, $p < 0.001$. There were no significant main effects of Smoking Groups, $F(2, 60) = 0.074$, $p = 0.93$, and IntAn groups, $F(1, 60) = 0.054$, $p = 0.82$, and no significant 2-way interactions and 3-way interaction (all p values >0.45).

3.4. Correlations in the three studies

Pearson correlation coefficients can be found in Table 3. Across all studies and groups, higher SOA values in BM25 correlated with higher SOA values in BM5. For the first study, higher age correlated with higher BM25 and BM5 values in most non-smoking groups (controls and relatives, but not patients). The significant correlation in the smoking groups was found only in controls for BM25. In smoking patients, higher SANS scores correlated with higher BM25 and BM5 values. In non-smoking patients, higher SAPS scores correlated with higher BM5 values.

For the second study, higher IntAn scores correlated with higher BM5 values in non-smokers. In smokers, higher CogDis scores correlated with higher BM5 values.

For the third study, higher age correlated with higher IntAn scores in non-smoking participants. Also, higher UnEx scores correlated with higher CogDis scores. In early smokers, higher age correlated with higher Fagerström scores and higher UnEx scores. In addition, higher IntAn scores correlated with higher CogDis scores. In late smokers, no significant correlations were observed.

4. Discussion

Sensory deficits are common within the schizophrenia spectrum (Cadenhead et al., 2014; Koychev et al., 2010; Silverstein & Keane, 2011) and are often endophenotypes of schizophrenia (Braff et al., 2007; Chkonia et al., 2010; Quednow et al., 2011). Sensory deficits may be reduced by nicotine consumption (Kumari et al., 2001; Leonard et al., 2007). Better sensory functioning was reported for participants with chronic nicotine consumption (Olincy et al., 1998; Petrovsky et al., 2013b; Wan et al., 2007) or acute nicotine consumption (Adler et al., 1993; Kumari et al., 2001). Here, we tested whether VBM performance, an endophenotype for schizophrenia (Chkonia et al., 2010), differs in people within the schizophrenia spectrum depending on their nicotine consumption.

First, our results support the notion that VBM deficits are an endophenotype for schizophrenia (Chkonia et al., 2010) because VBM deficits were highest in patients, followed by their relatives and finally controls (see Table 2). Second, we found higher SOAs in the high as compared to the low CogDis student group in study 2, replicating previous results (see Cappe et al., 2012). However, we could not replicate the results in study 3. One reason for the replication failure may be that effect size is small and hence, even large sample sizes of participants do not always lead to significant results (Francis, 2012). Third, only in study 1, smokers had lower SOAs (superior performance) than non-smokers, independent of illness status. However, we did not find this result in studies 2 and 3. Fourth, age correlated negatively with VBM performance, mainly in non-smoking controls and relatives in study 1 (age range up to 66 years, while age range in the student populations was up to 30 years).

Our findings can be explained in at least three ways. First, nicotine may not affect VBM performance. This explanation, however, is unlikely. As mentioned before, previous studies found significant differences in other visual tasks such as smooth-pursuit eye movements or contrast sensitivity. There is no reason to assume that chronic nicotine effects are only relevant to these visual functions. Second, effects of nicotine are often short term and are followed by fast adaptation of nicotinic receptors (Adler et al., 1998; Dome et al., 2010; Girod & Role, 2001). Adler et al. (1993) found transient effects of nicotine consumption on P50 gating. However, the beneficial effects of smoking disappeared within 30 min after nicotine intake. Thus, only acute nicotine effects might impact VBM performance. A way to test this hypothesis is to administrate nicotine via a transdermal patch to non-smoking patients and determine VBM performance. Administration of nicotine with a transdermal patch improved attention in healthy non-smoking participants (Levin et al., 1998).

Third, our student samples had a lower nicotine dependence compared to other studies (Brinkmeyer et al., 2011; Rissling et al., 2007). For example, Brinkmeyer et al. (2011) found a difference on the P50 gating between heavy and light smokers as well as controls. Participants had much higher Fagerström score than in our study (5.64 vs. 2.75, respectively; we cannot compare study 3 with studies 1 and 2 since the Fagerström test was not applied in studies 1 and 2). Therefore, performance on the VBM might improve with a higher nicotine dependence (see also Herzig et al., 2010). Our third study showed that nicotine dependence increases with age. Also, study one showed that performance on the VBM task decreases with age (see also Kunchulia et al., 2014). Hence, the difference of study 1 compared to studies 2 and 3 may also be explained by the larger number of older participants in study 1.

In conclusion, there seem to be positive but very small effects of nicotine consumption on backward masking performance.

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