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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).

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).