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Drugs, schizotypy and cognition: Cognitive attenuations seem more consistently associated with substance use than schizotypal symptoms

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Résumé

La psychose est une maladie invalidant, préjudiciable à l'individu et à la société. Depuis que la détection précoce de la maladie est associée à une évolution plus bénigne, les facteurs de détection précoce de la psychose font l'objet l'investigation. Dans la présente thèse, nous nous concentrerons sur deux facteurs de risque potentiels, à savoir la schizotypie et l'usage de drogue. Le concept de schizotypie, initialement développé par Meehl (1962), comprend le fait que les symptômes de la schizophrénie se trouvent sur un spectre, et que leur sévérité va croissante de l'individu le moins touché de la population générale jusque aux patients schizophrènes les plus atteints. Sur ce spectre des troubles schizophréniques, on trouve souvent des troubles cognitifs, par exemple la diminution de l'asymétrie hémisphérique ou des fonctions du lobe frontal. Le deuxième facteur de risque (usage de drogues), affecte les mêmes fonctions cognitives. En outre, la consommation de drogues est élevée dans la schizophrénie et chez les individus ayant des scores élevés sur les échelles mesurant la schizotypie. Par conséquent, nous avons décidé d'investiguer si des atténuations cognitives, précédemment attribuées à des symptômes schizotypiques, pourraient avoir été associées à un usage de substances élevé dans cette population. Pour tester cette idée, nous avons évalué l'usage de différentes drogues (nicotine, cannabis, méphédrone, dépendance à une substance en général), mesuré des symptômes de schizotypie (O-LIFE), et mesuré soit l'asymétrie hémisphérique de la fonction (dominance de l'hémisphère gauche pour le langage, et la domination du droit pour le traitement des informations faciales), soit le fonctionnement du lobe frontal (tels que la flexibilité cognitive, la mémoire de travail, la mémoire verbale à court terme, l'apprentissage verbal et de la fluidité verbale). Les résultats de toutes ces études suggèrent que c'est surtout l'usage de drogues et non la schizotypie qui prédit le fonctionnement cognitif. Ainsi, les atténuations cognitives précédemment attribuées aux dimensions de schizotypie sont susceptibles d'être associées à une utilisation accrue de drogues. Les études futures devraient étendre la liste des facteurs de risque potentiels (par exemple la dépression et le QI) et obtenir un aperçu plus général des prédicteurs les plus fiables des profils désavantageux.

Abstract

Psychosis is a debilitating disease, causing harm to the individual and society. Since early detection of the disease is associated with a more benign course, factors are warranted that enable the early detection of psychosis. In the present thesis we will be focusing on two potential risk factors, namely schizotypy and drug use. The schizotypy concept, originally developed by Meehl (1962), states that schizophrenia symptoms exist on a spectrum, with symptoms ranging from the most severe in patients with schizophrenia to the least affected individual in the general population. Along the schizophrenia spectrum cognitive impairments are commonly found, for instance reduced hemispheric asymmetry or frontal lobe functions. The second risk factor (drug use), affects similar cognitive functions as those attenuated along the schizophrenia spectrum, and drug use is elevated in schizophrenia and people scoring high on schizotypy. Therefore, we set out to investigate whether cognitive attenuations formerly allocated to schizotypal symptoms could have been influenced by elevated substance use in this population. To test this idea, we assessed various drugs (nicotine, cannabis, mephedrone, general substance dependence) and schizotypy symptoms (O-LIFE), and measured either hemispheric asymmetry of function (left hemisphere dominance for language, and right hemisphere dominance for facial processing) or functions largely relying on the frontal lobes (such as cognitive flexibility, working memory, verbal short-term memory, verbal learning and verbal fluency). Results of all studies suggest that it is mostly drugs, and not schizotypy in general that predict cognitive functioning. Therefore, cognitive attenuations subscribed to schizotypy dimensions are likely to have been affected by enhanced drug use. Future studies should extend the list of potential risk factors (e.g. depression and IQ) to acquire a comprehensive overview of the most reliable predictors of disadvantageous cognitive profiles.

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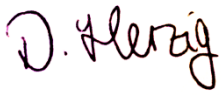
Furthermore, the author would like to thank the individual co-authors of the papers presented in this dissertation for their input (Prof. Christine Mohr, Rowan Brooks, Julia Tracy, Prof. David Nutt, Prof. Marcus Munafo), the participants who agreed to participate in my study, as well as the jury members who agreed to evaluate my work.

A very special thanks goes out to all my family members and friends who have supported me throughout this endeavor, especially those who helped by `not being there´. This particularly concerns my parents Werner and Ingeborg Herzig, as well as some of my best friends, e.g. Dr. Angeliki Theodoridou, Regina Löhndorf, Kim Dauber, Sanja Koletic and many others (unfortunately I do not have the space to thank all of them individually here). Not insisting on taking up someone´s time at peak-times of their dissertation is very difficult if that person is missed very much. The fact that they never made me feel guilty for abandoning them for long periods of time –yet always answered when I called for help- just shows how great and amazing these people truly are, and how lucky I am to have them in my life.

To conclude: Without all of the above mentioned people this work would have not been possible, and therefore this dissertation is theirs just as much as it is mine.

Declaration

I declare that the work in this dissertation was carried out in accordance with the requirements of the University's Regulations and Code of Practice for Research Degree Programs and that it has not been submitted for any other academic award. Except where indicated by specific reference in the text, the work is the candidates own work. Work done in collaboration with, or with the assistance of, others, is indicated as such. Any views expressed in the dissertation are those of the author.



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Date

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I. General introduction

A. Synopsis

Psychosis is a mental condition that haunts societies, families and individuals alike. Lifetime prevalence of any psychotic disorder (e.g. schizophrenia) varies considerably depending on the diagnostic criteria employed, however it most commonly lies between 1-3% in the general population (Perala et al., 2007; van Os & Kapur, 2009). Suffering from schizophrenia and psychotic disorders can have serious implications for the individual, e.g. the inability to manage and maintain occupational functions (Salize et al., 2009) and/or social interactions (see J. M. Ernst & Cacioppo, 1999 for overview). Additionally, these debilitating illnesses can inflict high social costs to relatives or friends of those affected, but also to society as a whole (Patel et al., 2006). Importantly, detecting individuals at an early stage of the disease seems to result in better outcomes for the patient, including a milder form of the illness as well as shorter duration (Bird et al., 2010; Larsen et al., 2011; M. Marshall & Rathbone, 2006). Therefore, risk factors that enable screening of at-risk individuals are warranted.

One potential risk factor relates to certain personality traits reminiscent of those seen in psychosis (e.g. schizotypy). As will be outlined in more detail below, the schizotypy concept is based on the idea that schizophrenia symptoms exist on a spectrum, with most severe symptoms encountered in patients, and mildest symptoms being present in healthy individuals from the general population. In the past decade the schizotypy concept has become increasingly popular to infer about the etiology of schizophrenia (van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009). One of the reasons for this increased interest in the schizotypy concept is certainly that schizotypal individuals are commonly not medicated, and do not suffer from other secondary

illness-related consequences such as frequent hospitalizations (Claridge, 1988; McGorry, Yung, & Phillips, 2003). Support for the spectrum idea of schizophrenia symptoms comes from observations that schizotypal individuals yield for instance similar -though quantitatively milder- cognitive impairments than psychotic patients, e.g. in frontal lobe functioning (Giraldez, Caro, Rodrigo, Pineiro, & Gonzalez, 1999; M.-S. Kim, Oh, Hong, & Choi, 2011; Park & McTigue, 1997; Pflueger, Gschwandtner, Stieglitz, & Riecher-Rössler, 2007; Simon et al., 2007) and hemispheric asymmetry (Broks, 1984; Brugger, Gamma, Muri, Schafer, & Taylor, 1993; Løberg et al., 2006; Mason & Claridge, 1999; Mohr, Krummenacher, et al., 2005; Suzuki & Usher, 2009).

Another risk factor relevant to the present doctoral thesis is drug use. A generally elevated drug use has been observed in both psychotic patients (Barkus & Murray, 2010; Schimmelmann et al., 2011) and schizotypal populations (Barkus & Murray, 2010; Fumero, Santamaria, & Navarrete, 2009) when compared to their respective controls. This enhanced drug use along the schizophrenia spectrum could be problematic if one considers the above mentioned cognitive functions to be sensitive to changes in schizotypal symptoms. It is well known that cognitive functioning is affected by drug use (Fernández-Serrano, Pérez-García, & Verdejo-García, 2011), and therefore the elevated drug use along the schizophrenia spectrum could be problematic for the interpretation of cognitive attenuations in schizotypal populations in previous studies. In other words, with this overlap in cognitive functions affected in schizotypy and chronic drug use it is unclear if certain links between schizotypal symptoms and cognition could at least partially be explained by the enhanced drug use. Elucidating the relationship between schizotypal symptoms and drug use on a psychotic-like cognitive profile in healthy individuals was therefore the main aim of this PhD-project. We will begin by giving a brief overview over the categorical and dimensional models of psychosis, then

review the evidence for cognitive impairments sensitive to illness-related changes, and afterwards show that drug use equally relates to schizotypal symptoms and cognitive impairments. Finally, we will give a brief summary of the empirical studies that form the present doctoral thesis, before we present them in detail in article format.

1. Categorical model

Schizophrenia is diagnosed if someone expresses a certain amount of symptoms for a certain period of time. These symptoms can be clustered into several symptom dimensions, e.g. the positive dimension, encompassing psychotic symptoms (characterized by delusions and hallucinations), and the negative dimension, with alterations in drive and volition (lack of motivation, reduction in spontaneous speech, and social withdrawal). Additionally, thought disorder or cognitive disorganization has been identified as a separate symptom cluster (Liddle, 1987), linked to alterations in cognition (difficulties in memory, attention, and executive functioning) and affective dysregulation as also seen in depressive and manic (bipolar) symptoms (van Os & Kapur, 2009).

Kraepelin described the illness at the turn of the last century, and coined it ´dementia praecox´, to stress his observations of slow mental deterioration beginning in early adulthood (Deelman, Eling, de Haan, Jennekens-Schinkel, & van Zomeren, 2003; Kraepelin, 1899, 1919). Around the same time, Bleuler (1911) introduced the term schizophrenia. The US-based Diagnostic and Statistical Manual of Mental Disorders (DSM), currently in its 4th, revised edition [DSM-IV-R (APA, 2000)], is one of the most widely used tools to diagnose schizophrenia. Based on the classical psychiatric view, schizophrenia and psychotic symptoms are viewed as markers of an illness, and therefore regarded as qualitatively different from the healthy mental profile. However, as will be outlined in detail below, strong evidence exists for a dimensional view on

schizophrenia symptoms, and the American Psychiatric Association (APA) is currently debating whether or not to include a psychosis risk syndrome in the revised DSM-V version, to be published in 2013 (Corcoran, First, & Cornblatt, 2010; B. Nelson & Yung, 2011; Ruhrmann, Schultze-Lutter, & Klosterkötter, 2010). Therefore, we will revise the most prominent dimensional models (quasi-, totally and fully dimensional) for schizophrenia in the following.

2. Dimensional models

Bleuler (1911), coming from the medical tradition (see also Figure 1), noted that healthy relatives of patients with schizophrenia were exhibiting qualitatively similar, though quantitatively milder, symptoms than their relatives suffering from the illness, and this raised doubts about a strictly categorical view of the disorder. In the personality tradition Pavlov and Kretschmer observed that psychotic states could represent normal personality variation (von Zerssen, 2002). Pavlov noted that the ability of the central nervous system to tolerate strong stimulation was reflected in natural personality variations (distinguishing of ‘nervous types’, see Figure 1; Pavlov, 1928). Around the same time Kretschmer (1921) observed personality traits like ‘schizothymia’ as closely resembling traits as those described in ‘dementia praecox’ by Kraepelin (1919), and schizoid traits as seen in patients with schizophrenia described by Bleuler (1911), see Figure 1.

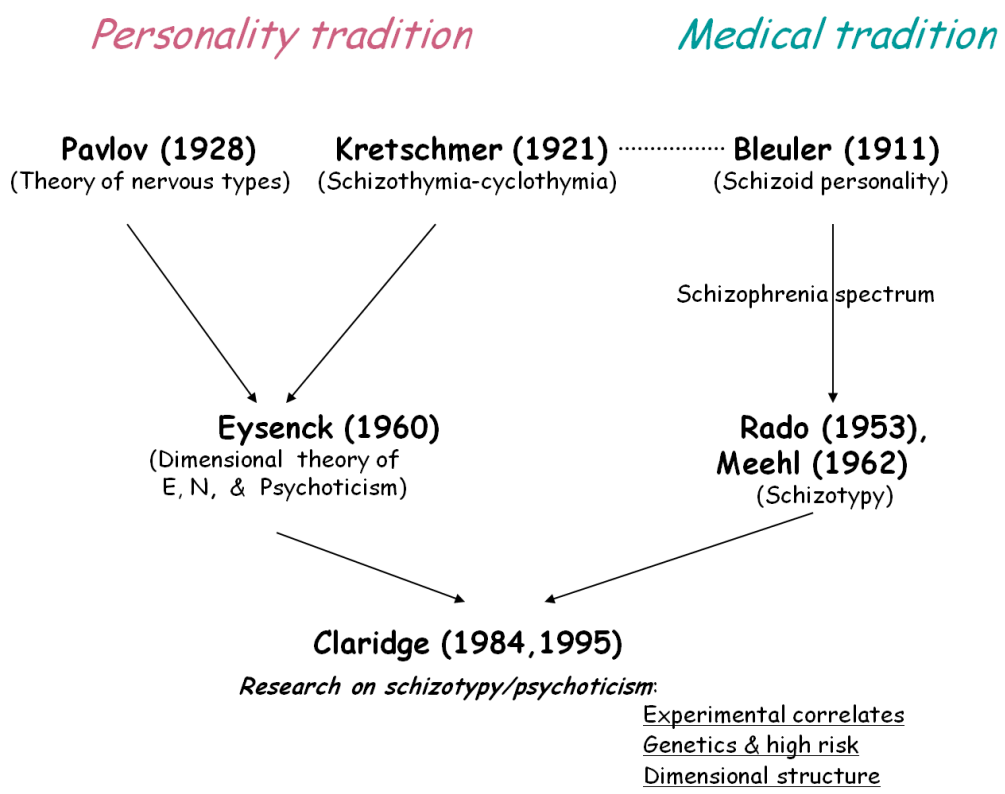

Figure 1. Historical overview of the development of the schizotypy concept and research (figure provided by Gordon Claridge, on request).

In fact, nowadays there is a wealth of evidence suggesting that unaffected relatives of patients with schizophrenia show psychotic-like traits themselves (Baron, 1985; Lenzenweger & Loranger, 1989; Parnas & Jorgensen, 1989; see also van Os, et al., 2009 for overview). All these observations led several psychiatrist and researchers to develop more dimensional/taxometric models of the schizophrenia spectrum disorders, rather than the conservative taxonic, or qualitative approach most diagnostic manuals, e.g. the DSM, are based on. Bleuler distinguished symptom dimensions ranging from patients to relatives, but also from patients before and after illness onset. Yet, it took another 50 years, until the concept of schizotypy, a trait disposition to psychosis, was developed (Meehl, 1962; Rado, 1953). This marked the official development of quasi-dimensional models of schizophrenia symptoms (see also Figure 2). Here, schizotypy is a trait disposition that increases vulnerability for schizophrenia in interaction with other

factors (e.g. social learning, or other genetic components), e.g. environmental influences in individuals with a predisposition to schizophrenia (schizotaxia). The symptoms exist on a disease-based spectrum, with increasing symptoms representing more severe schizophrenia symptoms. However, not all individuals with a predisposition to psychosis necessarily develop a psychotic disorder according to the quasi-dimensional model, and benign environmental influences could have protective effects (see also Lenzenweger, Maher, & Manschreck, 2005 for overview).

Around the same time Eysenck (1960) developed his totally dimensional approach to the schizophrenia spectrum. He continued developing the concept of 'psychoticism', by regarding patients with schizophrenia as simply occupying the extreme end of a schizophrenia spectrum (M. J. Green, Boyle, & Raine, 2008). The term 'psychoticism' referred to psychotic-like personality features in the healthy population as lying on a dimension, predisposing to the development of psychosis if certain disadvantageous environmental influences are met (Heath & Martin, 1990). Symptoms included recklessness, disregard for common sense, and inappropriate emotional expression. Eysenck's work influenced other researchers to develop the fully dimensional concept of schizotypy (Claridge & Hewitt, 1987; Eckblad & Chapman, 1983; Grove, 1982; Hewitt & Claridge, 1989; Kendler, Lieberman, & Walsh, 1989; Raine, 1987). The fully-dimensional approach as developed by Claridge sees schizotypal symptoms as part of normal behaviour and experiences. These can be broken down into similar symptom clusters as seen in schizophrenia, namely positive, negative and disorganized symptoms (Liddle, 1987). These symptoms can also be linked to positive characteristics, such as enhanced creativity and/or spiritual experiences (Batey & Furnham, 2008; Claridge & Blakey, 2009; Schofield & Claridge, 2007, see also Figure 2). The dimensional view deviates from quasi-dimensional models in the sense that the latter have the disease

model at their reference point. This means that they assume that the expression of dimensionality of schizophrenia varies only according to the degree of illness-related symptoms (Claridge, 1994), see also Figure 2.

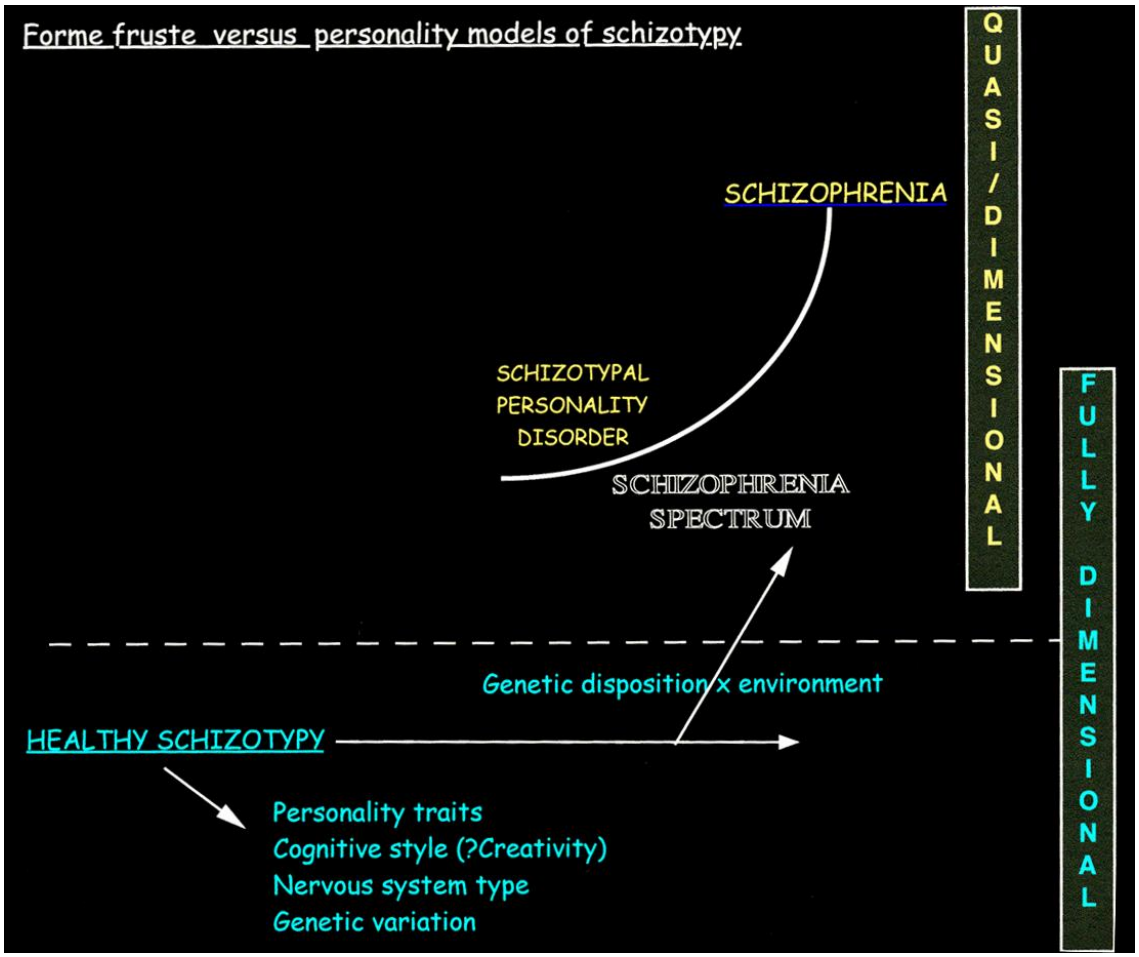

Figure 2. Comparison of quasi-dimensional (disease-based) and fully dimensional (personality-based) continuity models of schizotypy and schizophrenia [figure provided by Claridge (1994) on request]. The fully dimensional model (turquoise) assumes schizophrenia symptoms to vary naturally in the healthy general population as personality traits (below the striped line). Progression to disease (above the striped line) may occur when environmental and genetic influences exert disadvantageous influences. The quasi-dimensional model (yellow) assumes dimensionality of schizophrenia only with the severity of illness-related symptoms, ranging from comparatively mildest (schizotypal personality disorder) to most severe (schizophrenia) symptoms.

The fully dimensional models, however, base their predictions on personality traits that deviate naturally in the general population, and therefore represent healthy diversity (Claridge, 1994). They also assume a certain discontinuity of function (e.g. due to

genetic predisposition or environmental influences, see also Figure 2) as marker of disorder-related processes, which represents the main difference between the fully-dimensional model and the totally dimensional model (M. J. Green, et al., 2008).

3. Assessment tools of psychosis proneness

Psychosis-proneness and its' correlates can be measured by 1) preselecting at risk populations, or 2) by assessing schizotypal personality traits in the general population with questionnaires.

Regarding the first point, high risk populations for the development of schizophrenia are typically defined in two ways (please see also: Myles-Worsley et al., 2007; Smieskova et al., 2010): a) Either by genetic predisposition to the disease, or b) clinical high-risk subjects. With regards to a): genetic predisposition can either be investigated with monozygotic and dizygotic twins discordant for schizophrenia, or subjects with at least two first- or second-degree relatives of patients affected with psychosis [e.g. the New York High Risk Project, NYHRP (Erlenmeyer-Kimling et al., 1997), the Edinburgh High Risk Study (Johnstone, Ebmeier, Miller, Owens, & Lawrie, 2005)]. With regards to b): studies can be conducted in ultra-high risk subjects, those with an at-risk mental state, as well as subjects presenting basic symptoms such as thought and perception disturbances [e.g., the Personal Assistance and Crisis Evaluation or PACE Clinic in Melbourne Australia, (McGorry, Edwards, Mihalopoulos, Harrigan, & Jackson, 1996; McGorry, et al., 2003), the Recognition and Prevention or RAP Program at Zucker Hillside Hospital in New York, (Cornblatt et al., 2003), the Center for the Assessment and Prevention of Prodromal States or CAPPS at UCLA, (Niendam et al., 2006), and the prospective Zurich Cohort Study (Rössler, Hengartner, et al., 2011; Rössler, Vetter, et al., 2011), and also Smieskova et al. (2010) for overview].

Apart from preselecting at-risk populations to investigate psychosis-proneness, schizotypal traits can also be assessed. Typically, schizotypal personality traits reflect symptom dimensions that are reminiscent of schizophrenia symptoms, however in a milder, non-clinical form in the general, healthy population. Therefore, they can aid in understanding the etiology of schizophrenia. This is particularly the case since healthy schizotypal individuals from the general population are not affected by factors associated with the chronic forms of schizophrenia, e.g. medication, the lack of motivation, or hospitalization to name just a few (McGorry, et al., 2003; Sellen, Oaksford, & Gray, 2005). Typically, these schizotypal personality traits are assessed using self-report questionnaires (L. J. Chapman, Chapman, Kwapil, Eckblad, & Zinser, 1994; L. J. Chapman, Chapman, & Raulin, 1976; L. J. Chapman, Chapman, & Raulin, 1978; Claridge & Broks, 1984; Eckblad & Chapman, 1983; Eckblad, Chapman, Chapman, & Mishlove, 1982; Edell, 1995; Eysenck & Eysenck, 1975; Launay & Slade, 1981; Mason, Claridge, & Jackson, 1995; Mason, Linney, & Claridge, 2005; Peters, Joseph, Day, & Garety, 2004; Raine, 1991; Raine & Benishay, 1995; Rawlings & MacFarlane, 1994; Winterstein et al., 2011). People can respond either with ‘yes/no’, ´true/false´, or on a Likert-scale. Generally, higher scores indicate higher schizotypy.

Most schizotypy scales have been developed in the USA and the UK (see Table 1 below). The schizotypal personality questionnaire (SPQ), a widely used schizotypy assessment tool in the USA, has been developed to assess illness-based DSM-criteria of the American Psychiatric Association [e.g.(Raine, 1991; Raine & Benishay, 1995)]. UK-based questionnaires almost exclusively represent the dimensional view in line with the personality research tradition (Eysenck & Eysenck, 1975; Launay & Slade, 1981; Mason, et al., 1995; Mason, et al., 2005; Peters, et al., 2004; see also Figure 1). The

most recently validated questionnaires in UK-samples are the original and short version of the O-LIFE, and Peter´s Delusional Inventory (see Table 1).

Table 1. *Overview of schizotypy assessment tools and the location of their development, sorted by year.*

Scale	Author	Year	Location
Eysencks Personality Questionnaire	Eysenck & Eysenck	1975	UK
Chapman Scales: Physical Anhedonia	Chapman, Chapman, & Raulin	1976	USA
Chapman Scales: Perceptual Abberation Scale	Chapman, Chapman, & Raulin	1978	USA
Hallucinatory predisposition	Launay & Slade	1981	UK
Chapman Scales: Revised Social Anhedonia Scales	Eckblad, Chapman, Chapman, & Mishlove	1982	USA
Chapman Scales: Magical Ideation Scale	Eckblad & Chapman	1983	USA
Schizotypy Traits Questionnaire	Claridge & Broks	1984	UK
The structured interview for schizotypy	Kendler, Lieberman, & Walsh	1989	USA
Schizotypal Personality Questionnaire	Raine	1991	USA
Multidimensional Schizotypal Traits Questionnaire	Rawlings & MacFarlane	1994	AUS
Oxford and Liverpool Inventory for Feelings and Experiences	Mason, Claridge, & Jackson	1995	UK
Schizotypal Personality Questionnaire – Brief	Raine & Benishay	1995	USA
Chapman Scales: Wisconsin Psychosis-Proneness Scales	Edell	1995	USA
Peters Delusional Inventory	Peters, Joseph, Day, & Garety	2004	UK
Oxford and Liverpool Inventory for Feelings and Experiences - Short version	Mason, Linney, & Claridge	2005	UK
Chapman Scales: Wisconsin Psychosis-Proneness Scales - Short version	Winterstein et al.	2011	USA

Whereas Peter´s Delusional Inventory is focusing on delusion proneness only, the O-LIFE is assessing a more encompassing range of symptom dimensions as found in patients with schizophrenia (Liddle, 1987; Vollema & Hoijtink, 2000). These symptom dimensions incorporate positive schizotypy (e.g. cognitive-perceptual distortions, unusual experiences, magical thinking, paranoia etc.), negative schizotypy (e.g. social/physical anhedonia) and disorganized symptoms (e.g. odd speech and behaviour, difficulties with decision-making and/or attention, etc.). Additionally, the O-LIFE (Mason, et al., 1995; Mason, et al., 2005) implicates a fourth factor, impulsive non-conformity, which relates to impulsive and disinhibited behaviours. Due to its´ highly adequate internal consistency (Mason, et al., 1995), and high test-retest reliability (Burch, Steel, & Hemsley, 1998), the O-LIFE is a schizotypy assessment tool that is widely used in (but not limited to) UK-based studies.

B. Cognitive impairments and their relationship to the schizophrenia spectrum

The questionnaires assessing schizotypal symptoms tap into cognitive and perceptual biases, reflected in the similarities along the schizophrenia spectrum with regards to cognitive attenuations. We will therefore continue by elucidating cognitive impairments that are comparable along the dimension of schizophrenia, and hence relevant to the present thesis. We will review the evidence in patients with schizophrenia, high risk populations (e.g. relatives of patients with schizophrenia), and psychometrically defined schizotypy (e.g. via preselection of high versus low schizotypal individuals based on median-splits, or considering only those deviating 2xSD from the mean) for a selection

of cognitive domains discussed as potentially sensitive to pathological changes, e.g. frontal lobe functioning and hemispheric asymmetry.

1. Frontal lobe functioning

The frontal lobes entail a large proportion of the human brain (see Figure 3). Due to the vastness of the area, it is not surprising that the frontal lobes are associated with a large amount of cognitive functions, which usually correspond to either motor (see Figure 3, area 4), premotor (see Figure 3 area 6), prefrontal (see Figure 3 area anterior to area 6 and 44) and limbic regions of the frontal lobes (see Vanderploeg, 2000 for overview). The prefrontal areas are further divided into the dorsolateral (see Figure 3, areas 9, 10, 45, 46), orbitofrontal (see Figure 3, area 11, 12, 47) and medial (see Figure 3, medial portion of area 6, plus area 8 and 9) frontal lobe. The limbic area encompasses the frontal paralimbic regions together with the cingulate gyrus (see Figure 3, area 24 and 26). The associated functions range from motor functioning, language expression, olfaction, and/or eye-hand coordination to executive functions which are usually involved with the higher aspects of executing and managing behaviour (see Vanderploeg, 2000 for overview).

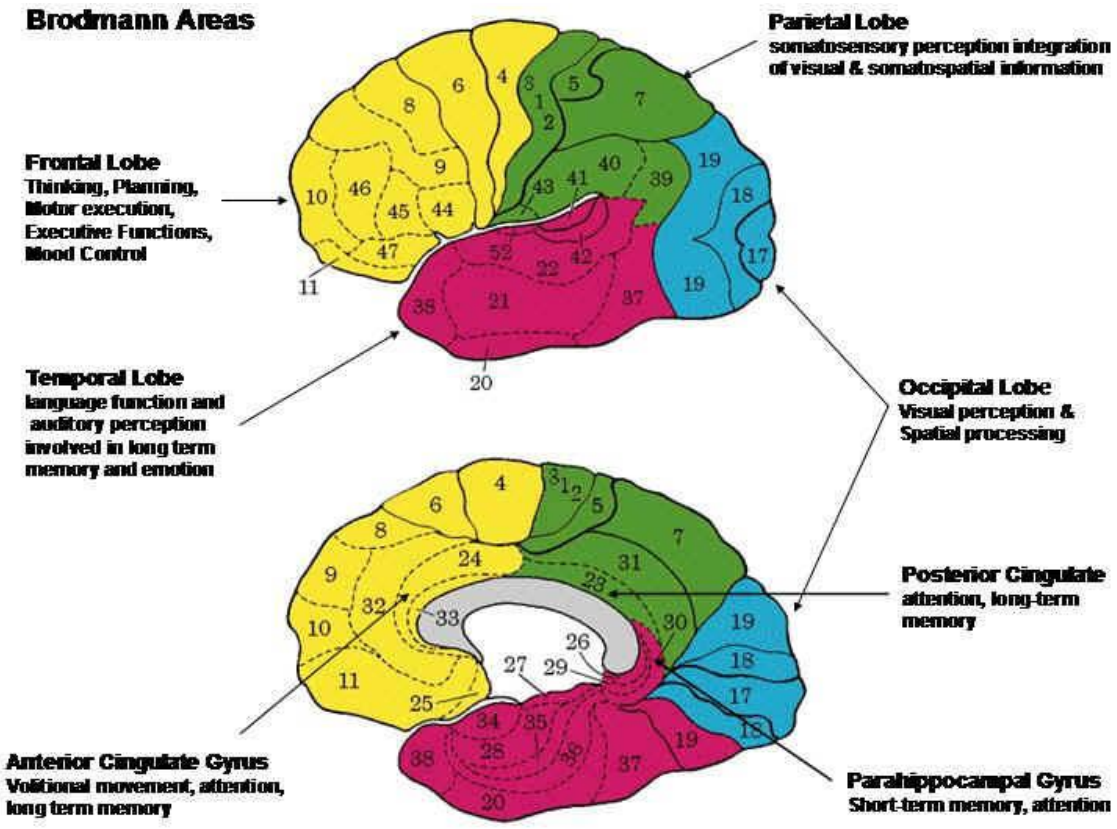

Figure 3. *Brain areas (in different colours) and associated functions. The numbers correspond to the Brodman areas (*Motor cortex= Area 4; premotor cortex= Area 6; prefrontal cortex= Area 6, 8, 9, 10, 11, 12, 45, 46, 47). *This figure was provided by Dr. Robert Thatcher (http://www.appliedneuroscience.com/NeuroGuide.htm) on request (see approval in Appendix).*

Executive functions encompass for instance short-term and working memory, cognitive flexibility, planning, problem solving, abstract reasoning, organization, initiation, self-monitoring, error detection and correction, control functions, self-awareness and reflection (see Chan, Shum, Toulopoulou, & Chen, 2008 for overview; Damasio, 1995; Grafman & Litvan, 1999; Stuss, Shallice, Alexander, & Picton, 1995; see Vanderploeg, 2000 for overview). In the laboratory, these cognitive impairments can be measured with specific tasks sensitive to modulations in these particular key functions of the frontal lobes, e.g. cognitive flexibility (Reitan, 1955; Tombaugh, 2004), verbal fluency (Bechtoldt, Benton, & Fogel, 1962; see Jurado & Rosselli, 2007 for overview), verbal

learning (e.g. Badcock, Dragović, Dawson, & Jones, 2011; Delis, Kramer, Kaplan, & Ober, 1987; Delis, Kramer, Kaplan, & Ober, 2000; Spreen & Strauss, 1998), and working memory (Barch, 2005; Owen, McMillan, Laird, & Bullmore, 2005; Schoofs, Preuß, & Wolf, 2008).

For instance, cognitive flexibility and set shifting is frequently measured with the trail making task (Reitan, 1955; Tombaugh, 2004). The Trail making task consists of two parts. In the Trail making test A, participants have to draw a line from numbered circles in chronological order (1 to 25), as fast as possible. On Trail making task B participants are presented with circles containing numbers and letters, and are instructed to draw a line in chronological order from 1 to 13, and A to L, but to switch back and forth between numbers and letters, resulting in constant switching of strategies. The reaction time of both tasks are recorded, and an index subtracting RT's of Trail making task A from RT's of Trail making task B results in an estimate of cognitive flexibility (Lezak, 1995) adjusted for individual differences in motor functioning and visual search strategies (Reitan & Wolfson, 1985). Additionally, working memory can be assessed with the n-back task (Barch, 2005; Owen, et al., 2005; Schoofs, et al., 2008), where participants see a string of items sequentially on the screen. Individuals have to indicate whether the current item n is the same as a previous item (for instance in trial n-2). Since individuals are required to continuously compare the current information with previous information, they have to use their working memory to update stored information (the item that was presented n trials back) and compare this with new information (current item on the screen) at each moment in time. Other memory tasks measure verbal learning, e.g. the Rey's auditory verbal learning test (e.g. Badcock, et al., 2011; Spreen & Strauss, 1998) or California verbal learning test (Delis, et al., 1987; Delis, et al., 2000). Here participants are asked to recall lists of words presented to them

over repetitive trials. Additionally, verbal memory is measured with story recall tasks (Bowden, Carstairs, & Shores, 1999; Ivison, 1993; Wechsler, 1987), e.g. by reading a short story (similar to short newspaper stories) to participants, which they are asked to reproduce in as much detail as possible. Verbal production can be measured with the verbal fluency test or COWAT (Bechtoldt, Benton, et al., 1962; see Jurado & Rosselli, 2007 for overview), where participants are asked to produce as many words as they can think of within a minute that either start with a particularly given letter (e.g. F), or belong to a certain category (e.g. animals).

Whereas healthy people use their frontal lobes efficiently to perform the above mentioned tasks, hypofrontality has been reported in patients with schizophrenia from imaging studies (see Hill et al., 2004 for overview; Ingvar & Franzen, 1974; Ragland, Yoon, Minzenberg, & Carter, 2007; Weinberger & Berman, 1988), and neuropsychological tasks similar to those mentioned above (see Dibben, Rice, Laws, & McKenna, 2009 for meta-analysis; M. F. Green, 2006). Taken together, the findings support the view that frontal lobe functioning is sensitive to pathological changes associated with schizophrenia. We will elaborate on this idea by reviewing cognitive impairments along the schizophrenia spectrum that relate to frontal lobe functioning.

Schizophrenia

Cognitive impairments are one of the major concerns among patients with schizophrenia (M. F. Green, Kern, Braff, & Mintz, 2000), especially since frontal lobe functions are crucial for everyday functioning, e.g. the ability to maintain occupational/educational functioning, to function independently at home, or to develop and maintain appropriate interpersonal relations (Goel, Grafman, Tajik, Gana, & Danto, 1997; M. F. Green, 1996; M. F. Green, et al., 2000). Specific frontal lobe functions

affected in this population in comparison to healthy controls are e.g. verbal short-term and working memory (Barch, 2005; Simon, et al., 2007), verbal fluency and cognitive flexibility (Dickinson, Ramsey, & Gold, 2007; Palmer, Dawes, & Heaton, 2009; Rajji, Ismail, & Mulsant, 2009). Therefore, impairments in frontal lobe functioning have been discussed as a risk marker in schizophrenia (Buchsbaum et al., 2002; Weickert et al., 2000; Weinberger & Berman, 1988), and seem to be crucial to the psychopathology of the disease (Elvevag & Goldberg, 2000; Weinberger, Aloia, Goldberg, & Berman, 1994). Additionally, this marker seems to be evident particularly for negative and disorganization symptom clusters (see Dibben, et al., 2009 for overview). As will be shown in the subsequent paragraph, these cognitive impairments are also present in individuals along the schizophrenia spectrum. For instance, high risk groups (e.g. relatives of patients with schizophrenia, or those showing prodromal symptoms) and healthy psychometrically defined schizotypes.

High risk populations

Relatives of patients with schizophrenia and those at high risk for developing psychosis and/or schizophrenia show similar cognitive impairments as those seen in schizophrenia/psychosis patients. For instance, relatives as compared to controls show reduced performance in verbal fluency (Bhojraj et al., 2009; Franke, Maier, Hardt, & Hain, 1993; Krabbendam, Myin-Germeys, Hanssen, & van Os, 2005; Meijer et al., 2011; Pukrop & Klosterkötter, 2010), working memory (Pflueger, et al., 2007; Pukrop & Klosterkötter, 2010), verbal learning and memory (Pukrop & Klosterkötter, 2010; Trandafir, Méary, Schürhoff, Leboyer, & Szöke, 2006) and cognitive flexibility (Klemm, Schmidt, Knappe, & Blanz, 2006; Pukrop & Klosterkötter, 2010). Some researchers even report a reduced global neurocognitive performance (Eastvold, Heaton, & Cadenhead, 2007). Comparatively reduced performance has also been reported from

clinically defined prodromal individuals, e.g. for verbal fluency (H. S. Kim et al., 2011; Magaud et al., 2010; Meijer, et al., 2011; Pukrop & Klosterkötter, 2010), verbal learning and memory (H. S. Kim, et al., 2011; Niendam, et al., 2006; Pukrop & Klosterkötter, 2010), cognitive flexibility (Pukrop & Klosterkötter, 2010) and working memory (Jahshan, Heaton, Golshan, & Cadenhead, 2010; H. S. Kim, et al., 2011). Finally, relative reduced performance has been observed in schizotypal personality disorder, again for verbal fluency (Voglmaier et al., 2000), cognitive flexibility (Diforio, Walker, & Kestler, 2000; Trestman et al., 1995), working memory (Mitropoulou et al., 2002), and verbal memory / learning (Voglmaier, et al., 2000).

Schizotypy

To provide a comprehensive overview of studies investigating whether cognitive attenuations extend from schizophrenia to high-risk samples to psychometrically defined schizotypy, we searched PubMed, Web of Science and ScienceDirect for relevant literature combining keywords representing the schizophrenia spectrum (including schizotypy, psychosis-proneness, O-LIFE, SPQ, high-risk, schizophrenia spectrum and schizophrenia dimension etc.) and cognitive functioning (including cognition, frontal lobe functioning, executive functioning, neuropsychology, cognitive flexibility, verbal memory, working memory, verbal fluency, laterality, hemispheric asymmetry etc.). Detailed results are presented in the Appendix (Table 30). To summarise, similar cognitive functions to those seen affected in patients with schizophrenia and high risk populations are reduced in schizotypal populations. For instance, studies report reductions in cognitive flexibility (e.g. Laws, Kondel, Clarke, & Nillo, 2011; Suhr, 1997), verbal fluency (e.g. Giraldez, et al., 1999; Koychev et al., 2011), verbal learning and memory (e.g. Burch, Hemsley, Corr, & Gwyer, 2006; Kaczorowski, Barrantes-Vidal, & Kwapil, 2009) as well as working memory (e.g.

Koychev, et al., 2011; Park & McTigue, 1997; see Table 30 in Appendix for overview). To note: the amount of findings will likely exceed the amount of studies, as several studies reported more than one finding on the link between schizotypy and cognition (see Table 30 in Appendix). Additionally, the direction of effect (increase, decrease or equal performance) is related to Table 30, and does not necessarily represent within-subjects effects.

2. Hemispheric asymmetry

The human brain is naturally divided into two hemispheres, communicating via the corpus callosum (see Figure 4). These two hemispheres show asymmetries in various domains in healthy individuals, be it anatomically, neurochemically or functionally (see Hugdahl & Westerhausen, 2010 for overview). For instance, the left hemisphere is usually dominant for language processing, and the right for face processing (see also Figure 4). It is suggested that it is this functional segregation that has enabled human beings to develop and communicate via language (Cooper, 2006). However, this human hemispheric specialization may also predispose individuals to develop psychosis, the latter being firstly associated with changes in brain regions seen as uniquely human (Crow, 2000; Southard, 1915) and secondly characterized by a reduction in the usual patterns of hemispheric asymmetry (Angrilli et al., 2009; Crow, 2000, 2008; Shagass, Roemer, Straumanis, & Amadeo, 1978). Therefore, the development of high-level language abilities via hemispheric specialization may coincide with –or at least partially explain- the development of psychosis (Crow, 1997, 2000, 2008; Ketteler & Ketteler, 2010). We will outline this argument in the following sections by looking at attenuations of hemispheric asymmetry along the schizophrenia spectrum.

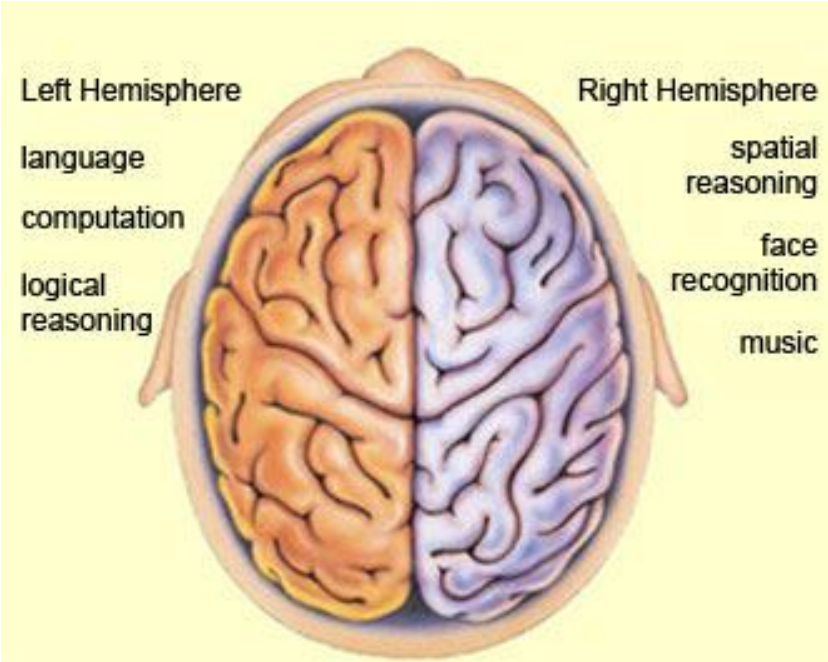

Figure 4. *The functional hemispheric segregation in right handed individuals. The two hemispheres communicate with each other via the corpus callosum. Among other functions, the left hemisphere is usually dominant over the right for language processing, and the right is usually dominant over the left for face processing. This figure was provided by Bruno Dubuc (http://thebrain.mcgill.ca; see approval in Appendix).*

Schizophrenia

In Crow's view, hemispheric asymmetry is necessary for healthy brain functioning. However, the development of language and the accompanying hemispheric specialization may have enabled the occurrence of psychotic disorders such as schizophrenia in the first place, as the core symptoms of schizophrenia (hallucinations and delusions) may derive from a failure to develop the typical cerebral dominance for language in the left hemisphere. According to Crow (1998, 2000) the lateralization of language occurred via information transmission constraints on the corpus callosum, a brain structure connecting both hemispheres. In most healthy individuals, certain components relating to speech output (e.g. the phonological output sequence) lateralized to the dominant left hemisphere, whereas other associated components relating to concept formation and thoughts were partially lateralized to the right hemisphere.

Whereas in healthy subjects this asymmetry may enable them to distinguish between internal and external speech due to time constraints of inter-hemispheric transmission, in hallucinations and delusions this mechanism would be missing due to a reduction in hemispheric asymmetry (Crow, 2000). Therefore, internal speech signals may be perceived as external by the hallucinating individual. Empirical evidence supports this theory, as atypical hemispheric asymmetry is frequently found in patients with schizophrenia (see Mitchell & Crow, 2005 for overview). For instance, during verb generation and semantic decision tasks patients with schizophrenia show a reduced left hemisphere activation as compared to healthy controls (Bleich-Cohen, Hendler, Kotler, & Strous, 2009; Sommer, Ramsey, & Kahn, 2001). These effects seem to be independent of general auditory processing (music listening; Bleich-Cohen, et al., 2009), or medication (van Veelen et al., 2011; Weiss et al., 2006). Additionally, patients with schizophrenia show a reduction in the typical right hemisphere dominance for face processing when compared to controls, as is evident from studies on chimeric faces (Kucharska-Pietura, David, Dropko, & Klimkowski, 2002; Phillips & David, 1997). Since this reduction in right hemisphere bias does not seem to be correlated with general face processing deficits (Kucharska-Pietura, et al., 2002), one can conclude that there is a specific deficit in right hemisphere processing of facial information in patients. Taken together, atypical asymmetry of the two hemispheres may reflect illness-related processes (Crow, 2000; Noguchi, Hori, & Kunugi, 2008).

High risk populations

In relatives of patients with schizophrenia similar reductions in language dominance have been observed. FMRI studies showed that relatives of patients with schizophrenia show a more bilateral activation as compared to the typical left hemisphere activation pattern seen in healthy controls when performing a lexical decision task (Li, Branch,

Bertisch, et al., 2007), and during reading, verbal comprehension and vocabulary tasks (Li, Branch, Ardekani, et al., 2007). Additionally, an abnormal lateralization pattern in schizotypal personality disorder is also partially supported (Voglmaier et al., 2009). Therefore, in high risk subjects, comparable cognitive impairments and potentially structural attenuations are seen when compared to healthy controls.

Schizotypy

To provide a comprehensive overview of studies investigating whether attenuations in hemispheric asymmetry extend from schizophrenia to high-risk samples to psychometrically defined schizotypy, we did the same literature review as outlined in section I. B. 1. c., combining keywords representing the schizophrenia spectrum (including schizotypy, psychosis-proneness, O-LIFE, SPQ, high-risk, schizophrenia spectrum and schizophrenia dimension etc.) and hemispheric asymmetry (including hemispheric asymmetry, laterality, hemispheres, lexical decision, facial decision, word bias, face bias etc.). The results are presented in the Appendix (Table 30), and in Figure 5. In summary, as a function of schizotypy (either by comparing high versus low schizotypes, or by correlating schizotypy scores with the outcome measures) decreases in hemispheric asymmetry were reported 12 times, suggesting similar attenuations of laterality patterns along the schizophrenia spectrum. To note: as with reports on frontal lobe functioning, the amount of findings will likely exceed the amount of studies, as several experiments reported more than one finding on the link between schizotypy and cognition (see Table 30 in Appendix). Additionally, the direction of effect (increase, decrease or equal performance) is related to Table 30, and does not necessarily represent within-subjects effects.

3. Heterogeneity of cognitive attenuations in schizotypy

Generally, similar functions are affected along the schizophrenia spectrum, and functions affected in patients extend to reduced performance in these functions in schizotypes (Asai, Sugimori, & Tanno, 2009; Mason & Claridge, 1999).

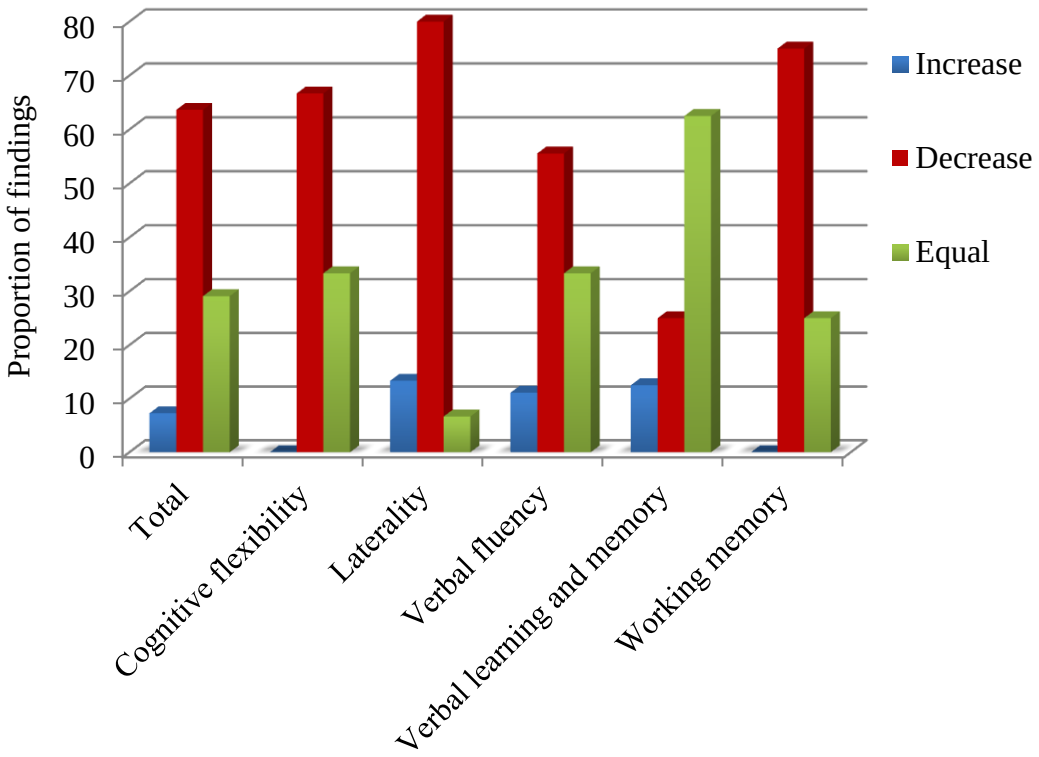

Figure 5. *Proportion of findings on the effect of psychometrically defined schizotypy on cognitive functioning, split by cognitive task and performance, e.g. relative impaired, enhanced or equal performance as a function of schizotypy (e.g. by comparing high versus low schizotypes, or by correlating schizotypy symptoms with the outcome measures).*

However, this similarity between schizophrenia and schizotypy is only evident at the first glance. When considering other studies including these tasks in psychometrically defined schizotypy, it appears that, while the vast majority of all experimental findings (Figure 5) suggest an overall reduced cognitive performance relating to schizotypy (see

also Appendix Table 30), there is a substantial amount of heterogeneity of results (Giraldez, et al., 1999; Laws, Patel, & Tyson, 2008; Liouta, Smith, & Mohr, 2008; Park & McTigue, 1997; Spitznagel & Suhr, 2002), depending on the measures used.

For instance, for frontal lobe functioning an equal amount of findings suggest no effect of schizotypy, or reduced performance in frontal lobe measures overall as a function of schizotypy (see Figure 5, and Appendix Table 30). When looking at the specific cognitive functions, cognitive flexibility, verbal fluency, working memory and laterality seem most consistently affected by schizotypy, whereas for verbal learning and memory the majority of reports suggest no effect of schizotypy.

In the following we will outline one major reason that might explain this heterogeneity, namely drug use.

C. Schizophrenia spectrum and drugs

The rationale to focus on drug use to explain heterogeneity in cognitive attenuations in schizotypes comes from a wealth of studies that suggest a link between drug use and psychotic (-like) thinking, e.g. enhanced drug use along the schizophrenia spectrum (see below, and Figure 6). As can be seen in Figure 6, using the keywords psychosis, as well as psychosis and drug use, we find an increasing amount of studies investigating these variables between 1993 and 2011.

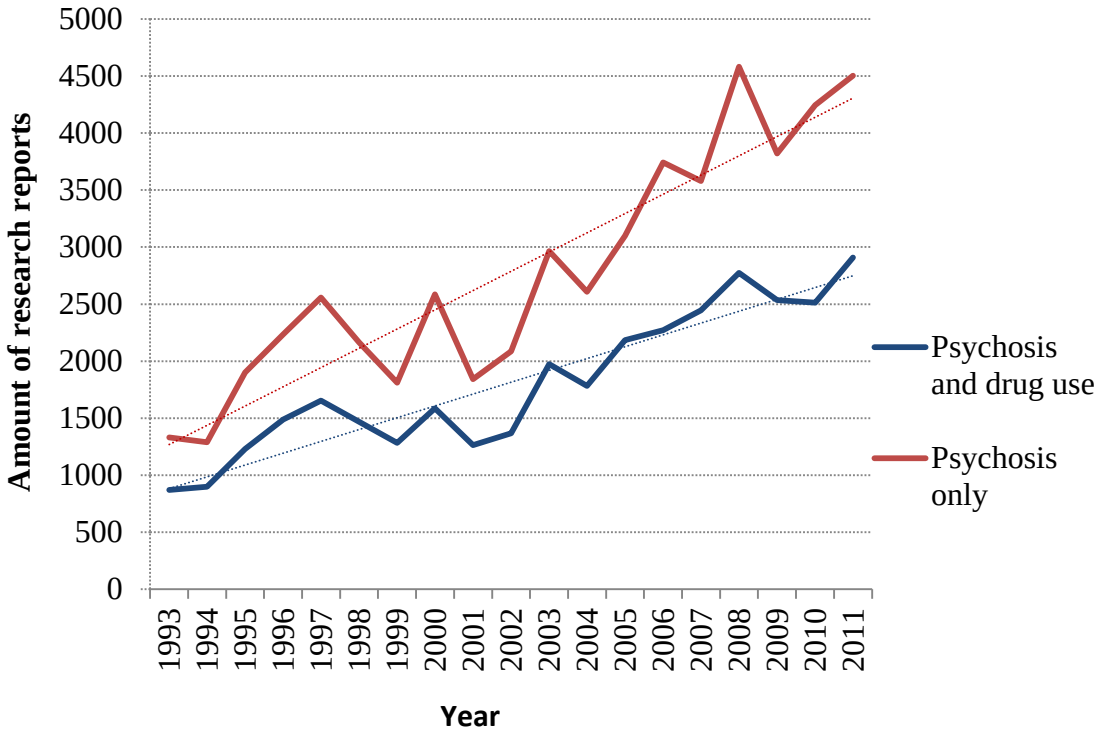

Figure 6. Amount of research articles published on ScienceDirect, using the keywords ´drug use and psychosis´, and ´psychosis only´ as search terms.

1. Drug use and schizophrenia spectrum

For years, it has been reported that patients with schizophrenia consume more drugs than healthy people, but also more than patients suffering from other mental illnesses (please see details below, and in the following sections). These drugs concern drugs currently considered legal and illegal. When controls are not simply treated like a homogenous population, but are accounted for according to their schizotypy levels, we find again support for the schizophrenia spectrum. This is because a higher incidence of drug use is reported for substances such as i) tobacco in schizotypy (Esterberg, Goulding, McClure-Tone, & Compton, 2009) and patients with schizophrenia (de Leon, Diaz, Rogers, Browne, & Dinsmore, 2002), and ii) cannabis in schizotypy (Barkus, Stirling, Hopkins, & Lewis, 2006; Skosnik, Spatz-Glenn, & Park, 2001; J. H. Williams, Wellman, & Rawlins, 1996) and schizophrenia (Archie et al., 2007; Barnes, Mutsatsa, Hutton, Watt, & Joyce, 2006). Additionally, higher rates of amphetamine use have been

reported in both schizophrenia and schizotypal populations (see Barkus & Murray, 2010 for overview). We will try to elucidate this in the following paragraphs, separating between some of the most popular drugs along the schizophrenia spectrum as mentioned above [nicotine, cannabis, and (meth)amphetamines].

Nicotine and schizophrenia spectrum

About 25% of the general population smoke daily (Bogdanovica, Godfrey, McNeill, & Britton, 2011; see also Figure 7), while it is 62% in the case of patients with schizophrenia (de Leon & Diaz, 2005). Additionally, cigarette use is elevated in unaffected relatives of patients with schizophrenia (Lyons et al., 2002; M. J. Smith, Barch, Wolf, Mamah, & Csernansky, 2008), as well as in schizotypal individuals from the general population (Esterberg, et al., 2009; Kolliakou & Joseph, 2000; Stewart, Cohen, & Copeland, 2010; J. H. Williams et al., 1996). There is evidence that in patients nicotine is frequently used to self-medicate (see Kumari & Postma, 2005 for overview). For instance, nicotine use in this population leads to a reduction in psychiatric symptoms [(Glynn & Sussman, 1990; R. C. Smith, Singh, Infante, Khandat, & Kloos, 2002), but see (Dalack, Becks, Hill, Pomerleau, & Meador-Woodruff, 1999; A. Williams & Farrell, 2007)], or a reduction in side-effects induced by anti-psychotic medication (Anfang & Pope Jr, 1997; Goff, Henderson, & Amico, 1992; Yang, Nelson, Kamaraju, Wilson, & McEvoy, 2002). Additionally, it seems to improve illness related cognitive deficits (Sacco, Bannon, & George, 2004), but the specific relevance of nicotine to cognitive functioning will be elaborated upon later.

Whereas this suggests that nicotine may be beneficial to the adverse effects of psychotic illness and related factors, one should note that the evidence is not as clear-cut. For instance, there is also evidence opposing the self-medication hypothesis for nicotine, as

smoking patients with schizophrenia are hospitalized more often and show poorer childhood social adjustment than their non-smoking counterparts (Kelly & McCreadie, 1999). In the same study there is limited evidence that earlier onset of smoking (in female patients) is associated with earlier onset of psychotic symptoms. Additionally, smoking may predict the use of other drugs and additional mental health issues (Degenhardt & Hall, 2001).

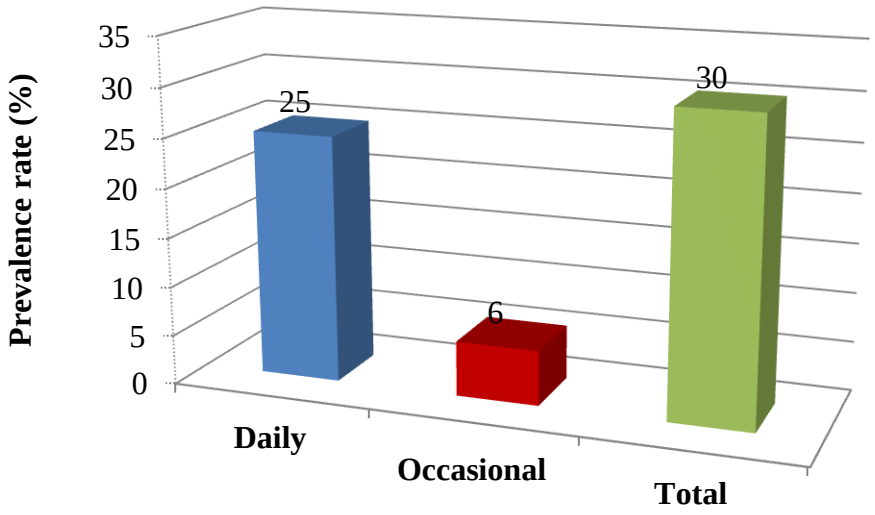

Figure 7. Prevalence rates (in %) of smoking in the general, healthy European population (age 12-75 years), split by smoking frequency [Source: Bogdanovica et al. (2011)].

Cannabis and schizophrenia spectrum

Cannabis use in the past 12 months is reported by approximately 6% of the general population (see Figure 8), whereas 29% in people diagnosed with any form of psychotic disorder have used this substance in the past 12 months (B. Green, Young, & Kavanagh, 2005). For lifetime use these rates are even higher, with a prevalence rate of 22% in the general population (see Figure 8), and 42% prevalence rate in patients with psychosis (B. Green, et al., 2005). In relatives of patients with schizophrenia, about 40% classify for cannabis abuse or dependence (M. J. Smith, et al., 2008), and individuals with

elevated psychosis proneness (schizotypy) in the general population also show a relatively elevated cannabis use (A. S. Cohen, Buckner, Najolia, & Stewart, 2011). Furthermore, the severity of schizotypal symptoms seems to relate to frequency (Barkus & Murray, 2010; Fridberg, Vollmer, O'Donnell, & Skosnik, 2011) and recency of use (Hides et al., 2009). There is nowadays also sufficient research to suggest that cannabis use relates to an increased risk for developing psychotic disorders later in life (Andreasson, Engstrom, Allebeck, & Rydberg, 1987; Fergusson et al., 2003; Hall & Degenhardt, 2000; van Os et al., 2002; Zammit, Allebeck, Andreasson, Lundberg, & Lewis, 2002). In particular, early onset of use at a young age increases the risk (Casadio, Fernandes, Murray, & Di Forti, 2011). Additionally, acute administration of THC, the psychoactive compound in cannabis, can induce psychotic symptoms in healthy individuals, and exaggerate symptoms in patients (D'Souza, 2007; D'Souza et al., 2004).

(Meth) amphetamines and schizophrenia spectrum

In the general, healthy population use of amphetamines ranges between 1% for past 12-month use, and 4% for lifetime use (European Monitoring Centre for Drugs and Drug Addiction 2011; see Figure 8). Along the schizophrenia spectrum use of (Meth) amphetamines is elevated (e.g. Barkus & Murray, 2010). Not many studies have assessed prevalence rates of general amphetamine use in patients with schizophrenia and their relatives. However, there have been reports on stimulant/hallucinogen abuse and dependence rates of around 7% in patients with schizophrenia (Cantor-Graae, Nordström, & McNeil, 2001). Additional to this, (meth-) amphetamine use is elevated in those with a schizotypal personality disorder (see Barkus & Murray, 2010 for overview), and in schizotypes from the general population (L. Wood & Barkus, 2010). These substances can induce transient psychotic(-like) symptoms in the healthy

population (see Curran, Brignell, Fletcher, Middleton, & Henry, 2002 for review; Featherstone, Kapur, & Fletcher, 2007; N. S. Gray, Pickering, & Gray, 1996). There is also evidence to suggest that its' use relates to an increased risk for developing psychosis later in life (B. D. L. Marshall & Werb, 2010; Zammit, et al., 2002). The evidence suggesting an increased risk for psychosis development with elevated ecstasy (or methamphetamine) is strong (McGuire, Cope, & Fahy, 1994; McGuire & Fahy, 1991), and earlier and longer stimulant use (such as amphetamines) predict worse symptom severity (Lichlyter, Purdon, & Tibbo, 2011).

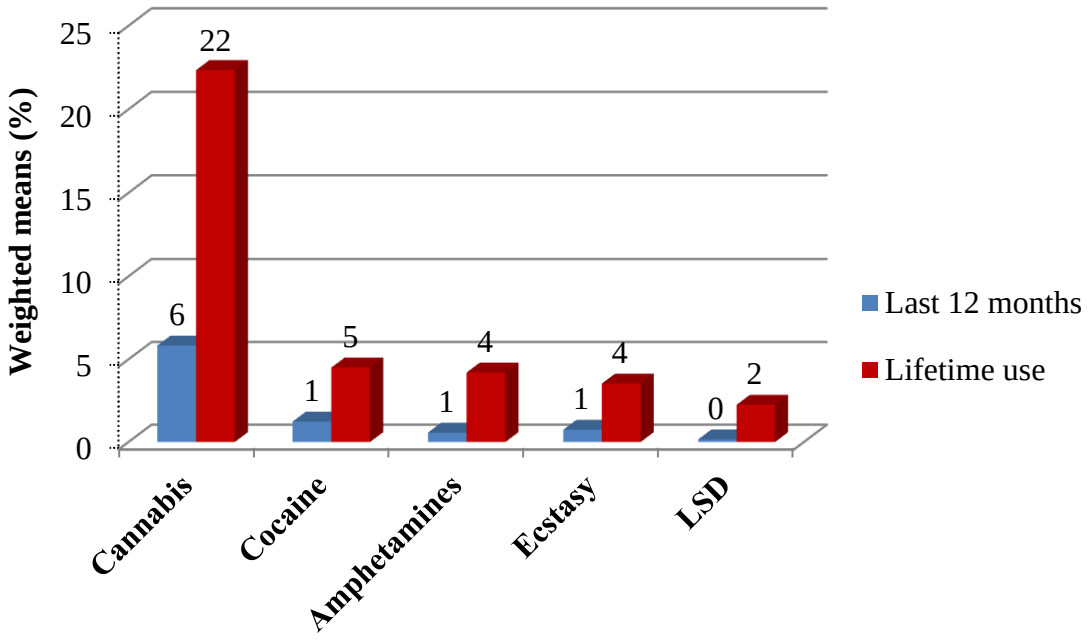

Figure 8. Prevalence rates of drug use in the past 12 months, assessed in healthy adults (age 15-64 years) from the general European population (Source: Statistical bulletin of the European Monitoring Centre for Drugs and Drug Addiction, 2011; link: http://www.emcdda.europa.eu/stats11/gps).

2. Drugs and cognition

So far, we have presented evidence for the schizophrenia spectrum by accounting for cognitive functioning and for drug use. If one goes back to Figure 5 (and Table 30 in Appendix), however, it becomes obvious that schizotypy does not always relate to

cognitive impairments. We here argued that the frequently elevated drug use along the schizophrenia spectrum may partially explain inconsistencies between studies. In other words, it may be the drug use that relates to cognitive performance. This argument is indeed not far-fetched. In tasks measuring verbal fluency, set shifting, planning, multi-tasking and interference, studies showed that polydrug users generally perform worse than non-users (Fernández-Serrano, Pérez-García, Perales, & Verdejo-García, 2010). It seems that drugs generally affect cognitive functions comparable to schizotypal symptoms, independent of the specific substances used (see Fernández-Serrano, et al., 2011 for overview). To systematically account for this argument, we will outline whether drugs of elevated use in schizotypy have also been found to impact cognition reported as relatively impaired in schizotypy.

Nicotine and cognition

(1) Frontal lobe functioning

Smokers generally seem to perform worse on a variety of cognitive tasks. For instance, relatively impaired performance has been reported for tasks measuring working memory (M. Ernst, Heishman, Spurgeon, & London, 2001; Jacobsen et al., 2005) and verbal memory, both immediate and delayed (Dunne, Macdonald, & Hartley, 1986; Jacobsen, et al., 2005). Smokers also show deficits in verbal learning during withdrawal compared to non-smokers, and these deficits are alleviated by nicotine administration (Soar, Dawkins, Begum, & Parrott, 2008). However, acute administration of nicotine seems to have beneficial effects on working memory, learning and attentional functions (see Levin, McClernon, & Rezvani, 2006 for overview). Acute nicotine consumption was also found to improve verbal memory and working memory in overnight abstinent smokers, as well as alertness (Kleykamp, Jennings, & Eissenberg, 2011).

(2) Hemispheric asymmetry

The effects of nicotine on hemispheric asymmetry are relatively sparse. However, there are indications that would suggest that functional hemispheric asymmetry might be influenced by nicotine. Studies on the acute effects of nicotine exposure on laterality report on increasing left hemisphere contribution with enhanced nicotine use (Gilbert et al., 2008; McClernon, Gilbert, & Radtke, 2003), matching findings from fMRI studies where nicotine withdrawal was related to a reduced left frontal activation during a verbal working memory task (Sweet et al., 2010). However, other studies would indicate that nicotine results in a general reduction of cerebral asymmetry (Hahn et al., 2011).

Cannabis and cognition

(3) Frontal lobe functioning

Whereas cannabis use in patients with schizophrenia seems generally associated with improved cognitive functioning (see Rabin, Zakzanis, & George, 2011 for meta-analysis), in the healthy population cannabis use seems to relate to impairments in memory and attentional functions (see Lundqvist, 2005 for overview). For instance, cannabis users show attenuations in verbal memory and learning, (Fried, Watkinson, & Gray, 2005; Sofuoglu, Sugarman, & Carroll, 2010; Solowij & Battisti, 2008; Wagner, Becker, Gouzoulis-Mayfrank, & Daumann, 2010) as compared to non-users, and heavy marijuana use is associated with small but significant impairments in memory retrieval, and verbal expression (Block & Ghoneim, 1993). Additionally, heavy cannabis use is associated with reduced function of the attentional/executive system, as indicated by decreased mental flexibility and increased perseveration and reduced learning, functions associated with the prefrontal cortex (Pope & Yurgelun-Todd, 1996). These impairments may even persist after 6 weeks of abstinence, particularly in verbal story

recall (Schwartz, Gruenewald, Klitzner, & Fedio, 1989). Moreover, these attenuations seem to worsen with increasing dose (Bolla, Brown, Eldreth, Tate, & Cadet, 2002), and elevated lifetime use (Solowij & Grenyer, 2002).

(4) Hemispheric asymmetry

The literature on functional hemispheric asymmetry and cannabis use is sparse, however fMRI studies showed an increased right prefrontal activation in cannabis users as compared to non-users when performing a task reflecting control of attention (Abdullaev, Posner, Nunnally, & Dishion, 2010), and elevated cannabis use is associated with increased left hemisphere as compared to right hemisphere hippocampal volume (Medina et al., 2007), a brain structure crucially involved in memory performance (see Battaglia, Benchenane, Sirota, Pennartz, & Wiener, 2011 for overview).

Amphetamines and cognition

(5) Frontal lobe functioning

Amphetamine use (see Fernández-Serrano, et al., 2011; Kalechstein, De La Garza, Mahoney, Fantegrossi, & Newton, 2007 for overview) negatively affects cognitive functions such as working memory (Curran & Travill, 1997), verbal fluency (Hanson & Luciana, 2004), cognitive flexibility (King, Alicata, Cloak, & Chang, 2010), and verbal learning (Gonzalez et al., 2004; Laws & Kokkalis, 2007; McCardle, Luebbers, Carter, Croft, & Stough, 2004; Parrott & Lasky, 1998). Verbal learning is even affected in non-addicted amphetamine users, suggesting that only small amounts of these substances are needed to create functional impairments (Reske, Eidt, Delis, & Paulus, 2010). This is not surprising given that chronic amphetamine use relates to cortical gray matter loss, particularly in frontal, temporal and occipital areas (Nakama et al., 2011).

(6) Hemispheric asymmetry

To our knowledge, no studies have investigated the relationship between amphetamine use and functional laterality directly. Therefore we would have to infer about the effects of these substances via other means, such as brain imaging. There is evidence that the blood flow to the Brodman area in the left hemisphere is increased as a function of quantity of MDMA use (Bauernfeind et al., 2011). Additionally, amphetamines have been shown to increase the release of certain neurotransmitters in the brain, e.g. dopamine (Steinkellner, Freissmuth, Sitte, & Montgomery, 2011). A natural dopamine receptor asymmetry in healthy participants, e.g. structures in the right frontal lobe, show elevated dopamine release during a set-shifting/cognitive flexibility task (Ko et al., 2009), which suggests that performance in this region may be affected if substances target this specific neurotransmitter such as amphetamines. More specifically, the normal asymmetry pattern that relates to healthy cognitive flexibility may be distorted with amphetamine use. This, in turn, may relate to altered hemispheric asymmetry patterns due to substance use.

D. Schizophrenia spectrum, drugs and cognition

Given the overlap between the effects of psychotic-like symptoms and drug use on cognition above, the question arises if some of the results in schizotypy research were influenced by this populations' enhanced drug use. Most studies investigating the effects of schizotypy on cognition did frequently either not report on the specific substances they controlled for (by either excluding participants consuming them, or statistically controlling for them), or they used substance dependence or abuse as an exclusion criterion (see Table 30 in Appendix). Whereas reports on drug use are relatively common in schizophrenia research, it appears relatively uncommon in schizotypy research.

Fifteen findings regarded psychometrically defined schizotypy and cognitive flexibility (see Table 30 in Appendix). Eight of them did not report assessing drug use (e.g. either by reporting on drug use characteristics of the sample, excluding participants consuming them, or statistically controlling for them), while the others employed different exclusion criteria, e.g. excluding subjects with a substance dependence or abuse history, or indicating self-reported drug (ab)use. For verbal fluency, we gathered nine findings, of which five did not report controlling or assessing drug use, and others mostly used substance abuse as an exclusion criterion. Only one study considered urine/breath tests. We also found eight findings on verbal memory and learning. Of these, five did not report controlling or assessing drug use, while the others controlled for either substance abuse, or self-reported (ab)use. Of the eight studies investigating working memory, six did not report controlling for or assessing drug use, one used self-reported cannabis and ecstasy use in the past 12 months as exclusion criterion, and one included urine/breath tests. The same we find for the 15 findings on the relationship between schizotypal symptoms and hemispheric asymmetry. Thirteen of these did not report controlling for or assessing drug use, while others controlled for self-reported drug use 24h prior to testing (see Table 30 in Appendix). It seems that studies controlling for substance use have a slightly higher rate of detecting decreases in performance as a function of schizotypy (see Figure 9). However, since most drug control measures a) used different assessments of drug use, e.g. self-report, interviews or drug tests, and b) varied in the substances they assessed, it is still unclear in which

way substance use may have influenced results.

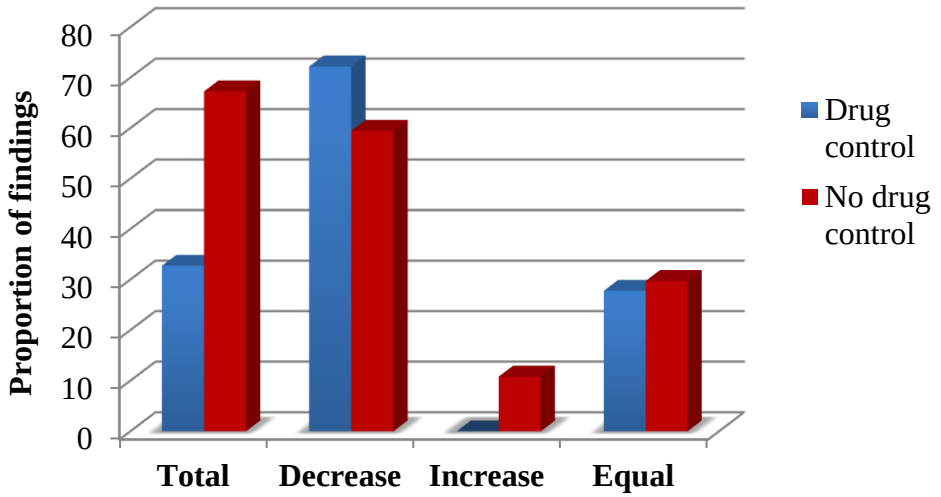

Figure 9. Proportion of findings revealing equal, relative impaired or enhanced performance as a function of schizotypy, split by control for drug use (by either reporting on drug use, excluding participants consuming drugs, or statistically controlling for drug use).

It is possible that the inconsistent findings are subject to individual differences in substance use in the samples tested. Therefore, we systematically assessed the impact of schizotypal symptoms on cognitive functions, whilst accounting for individuals' substance use.

E. Summary and conclusions

Evidence from schizotypy research challenges the conservative categorical models that view schizophrenia symptoms as indicative of illness processes, and not represented along a dimension in the general healthy population. Evidence supporting the dimensional models comes from research investigating the cognitive effects of psychometrically defined schizotypy. For instance, frontal lobe impairments are frequently reported in patients with schizophrenia, their healthy relatives and also psychometrically defined schizotypes. The same is true for a schizophrenia-typical

reduction in hemispheric asymmetry that also seems attenuated in relatives and schizotypal individuals from the general population. In the latter group, cognitive impairments do not seem to be found as consistently as in patients and their unaffected relatives, raising the question of the importance of individual differences in this population. We here suggested that one factor that may explain differences between studies is drug use. When assessing the link between psychometrically defined schizotypy and cognition, it does not seem common to control for drug use. Drugs, however, seem to exert influences on brains structures similar to the ones affected in schizophrenia and schizotypy. This observation raises the question if cognitive impairments formerly associated with schizotypy symptoms could have been (at least partially) due to elevated drug use.

F. Objectives

To test the idea that elevated drug use could (at least partially) explain cognitive attenuations formerly ascribed to schizotypal symptoms we assessed the use of a variety of drugs and the possible effect of substance consumption on the relationship between schizotypal symptoms and cognitive functioning. The substances chosen were deemed the most popular amongst the schizotypal/schizophrenia population, i.e. nicotine, cannabis, and amphetamine-like drugs. On top of this, we investigated if individual substances are more consistent predictors of cognitive attenuations than schizotypy, or if a general severity of substance use may potentially explain the controversial results in psychometric schizotypal research independent of the individual substances used.

II. Experiments

A. Overview

In short, the first study investigated nicotine dependence, the second one cannabis use, and the third study mephedrone use. In all studies (including the fourth), participants filled in the O-LIFE as a measure of schizotypal traits and performed cognitive tasks. In the fourth and final study, we did not ask for a particular drug, but wanted to investigate whether cognitive impairments are not necessarily explained by the use of particular drugs, but rather associated with general drug dependence (whether the "drug" is an actual substance, or another addiction-relevant behaviour). The fourth study was a direct consequence of the outcomes of Study 1, started before the outcomes of Studies 2 and 3 were known. Given the time-consuming efforts to find individuals with particular drug behaviours, Studies 2 - 4 were initiated and conducted in parallel. In this summary we only report on the most pertinent findings of the analyses performed, as all other results are described in detail in the four experimental chapters, i.e. in Herzig et al. (2010, see study 1), Herzig, Nutt and Mohr (under revision; see study 2), Herzig, Brooks and Mohr (submitted; see study 3), or Herzig and Mohr [(Herzig & Mohr, in press)*;* see study 4]. Please note that internal consistency was computed for the questionnaires used, and deemed acceptable (see Table 29 in Appendix). Additionally, the wording of these four experimental chapters might deviate slightly from the wording of the published or submitted articles because of consistency of word use across the dissertation and improvements suggested by the jury members.

1. Study 1: Nicotine

As previously mentioned, language dominance in the left hemisphere (LH) and visual face recognition dominance in the right hemisphere (RH) have been found to be

attenuated in schizophrenia and schizotypy. As also mentioned, in healthy individuals dopamine agonists (including nicotine) can affect hemispheric asymmetry. For instance, nicotine might enhance language functions (Gentry, Hammersley, Hale, Nuwer, & Meliska, 2000; Gilbert, et al., 2008; Knecht et al., 2004; McClernon, et al., 2003), which potentially stabilizes hemispheric asymmetry rather than attenuates it, particularly when reporting relatively elevated schizotypy (Mohr, Krummenacher, et al., 2005). Whereas this would point to an increase in left hemisphere language laterality as a function of nicotine use, other studies suggest the opposite, namely a right hemispheric shift with increasing nicotine use (M. Ernst, et al., 2001; McClernon, et al., 2003; Norton, Brown, & Howard, 1992; Rose et al., 2007). Independent of the direction of the effect, these results could indicate that reports on cognitive attenuations formerly associated with the schizophrenia spectrum - like modulations of hemispheric asymmetry of function (Broks, 1984; Brugger, et al., 1993; Mason & Claridge, 1999; Mohr, Krummenacher, et al., 2005; Suzuki & Usher, 2009) might be affected by enhanced nicotine consumption rather than personality traits associated with psychosis-vulnerability. We set out to investigate the latter hypothesis. Since studies directly measuring the effect of nicotine dependence on functional hemispheric asymmetry are sparse, we tested hemispheric asymmetry as a function of nicotine consumption and schizotypy, exploring the nature of the effect. We predicted that nicotine dependence would explain more variance than schizotypy in the laterality measures. Schizotypy scores and cognitive performance were comparable for smokers and non-smokers. Yet, increasing nicotine dependence among smokers predicted a right hemisphere shift of function in both tasks. Schizotypy, on the other hand, was mostly unrelated to hemispheric asymmetry in this study, apart from a decreased left hemisphere language bias as a function of cognitive disorganisation for one outcome variable. These findings

indicate that nicotine consumption is a more consistent predictor of shifts in hemispheric asymmetry than schizotypy, and would also indicate that the right hemisphere is linked to addictive behaviour related to nicotine dependence. Results from this study raise the question whether the right-hemisphere shift of function is nicotine-specific, if other substances may influence the relationship between cognition and schizotypy (see studies 2 and 3), or if any effect of drug use is due to addictive (compulsive, impulsive) behaviour more generally, instead of individual substances (see study 4).

2. Study 2: Cannabis

We here investigated whether cannabis use might influence the effect of schizotypy on cognition. In more detail, we investigated whether severity of cannabis use (alcohol and nicotine were used as control measures) would predict an attenuation of performance in the amount of correctly identified items in a working memory and verbal short term memory task, and reaction times in a cognitive flexibility task. Comparable to Study 1, we also investigated whether drug use would be a more consistent predictor of cognitive performance than schizotypy. Group comparisons indicated that cannabis users performed worse on a task measuring verbal short-term memory when compared to non-using controls. The regression analyses confirmed the importance of cannabis use severity for reduced verbal short-term memory performance, and alcohol dependence rates for working memory. Schizotypy did not explain any additional amount of variance in cognitive functioning (apart from impulsive non-conformity and cognitive disorganization). Generally, these findings would indicate that it is likely that drugs rather than schizotypy attenuate cognition. Additionally, we observed that it was not cannabis use severity alone, but also alcohol use severity that was related to cognitive performance. Consequently, alcohol use was again taken into account in study 3.

3. Study 3: Mephedrone / Polydrug use

Mephedrone is a derivative of cathinone, a compound found in the Khat plant (see Schifano et al., 2010 for overview). The chemical structure is similar to amphetamine, and research suggests that cathinones (like mephedrone) mimic the psychological and physiological actions of amphetamines (Kalix, 1992; Schifano, et al., 2010). However, evidence regarding the cognitive effects of mephedrone use is scarce, and research on this substance will inform about the drug's potential harms. Furthermore, even less research has been carried out on the link between mephedrone use and schizotypy, even though there seems to be evidence that mephedrone use can invoke psychotic symptoms (ACMD, 2010; James et al., 2010; Vardakou, Pistos, & Spiliopoulou, 2011). For this purpose, individuals were tested over the course of a weekend during which they planned to go "clubbing", an experience frequently associated with legal and illegal psychoactive drug use. In line with previous studies (Herzig, et al., 2010), we expected mephedrone (and / or other drug use) to exert a more consistent influence on cognition (particularly frontal lobe functioning) than schizotypy. In particular, we expected that performance after the clubbing experience should be most impaired for those who have used mephedrone (or closely related drugs) when compared to those who refrained from psychoactive drug use. This impaired functioning was expected for the cognitive measures of verbal learning, verbal fluency, and cognitive flexibility. An additional hypothesis expected mephedrone users (and those consuming related drugs) to be already relatively impaired before the clubbing experience (when having used mephedrone and related drugs) in the past, i.e. prior to the inclusion into the study. Results indicated that firstly, polydrug users scored higher on cognitive disorganization than non-using controls, and secondly the baseline performance differed prior to the actual clubbing experience between polydrug users and non-users, with the former

group performing worse to non-users on verbal recall (immediate and delayed) and verbal fluency. This performance inferiority of polydrug users was further exacerbated between the pre- and post-clubbing session (during which mephedrone was consumed). Thirdly, regression analyses (comparable to those in study 1 and study 2) showed that higher cannabis use predicted decreased immediate verbal recall performance, and elevated amphetamine use related to decreased verbal fluency pre-clubbing, whereas mephedrone use seemed unrelated to the cognitive outcome measures. Additionally, schizotypy did not predict performance on top of substance use and the control variables like premorbid IQ and depression (apart from cognitive disorganization pre-clubbing). Again, this further supports the theory that cognitive impairments previously linked to schizotypy may be associated to a significant degree with increased substance use, as is also evident from studies 1 and 2.

4. Study 4: Compensatory behaviours

It is possible that substance-based stress alleviating behaviours (= compensatory behaviours) give an estimation of general dependency of behaviour (rather than dependency on specific substances), and they may affect the influence schizotypy exerts on cognition, which is something we set out to investigate in this study (see also Herzig and Mohr, in press, or study 4). For this purpose, we again assessed hemispheric asymmetry as in study 1 to assess left and right hemisphere dominance for function, in times where students experience elevated stress (shortly before exam period). We anticipated that compensatory behaviours would predict an attenuation of performance in the lexical and facial decision task (specifically: RVF/LH bias for language, and LVF/RH bias for faces, respectively), and that schizotypy (including its four subscales unusual experiences, cognitive disorganization, introvertive anhedonia and impulse non-conformity) will not predict variance in the cognitive tasks on top of compensatory

behaviours. In line with our hypothesis, stress-relieving compensatory behaviour (substance use) was the most consistent predictor of a right hemisphere shift in language functioning. On top of this, only a few outcome measures were sensitive to schizotypal symptoms: unusual experiences predicted reduced left hemisphere language dominance in line with previous research (e.g. Kravetz, Faust, & Edelman, 1998; Nunn & Peters, 2001), whereas cognitive disorganisation contributed to a left hemisphere shift in language functioning on top of the other variables. Consequently, it is discussed that i) former reports on right hemisphere shifts in language dominance with positive schizotypy might be more consistently explained by an associated higher substance use, and ii) the findings on cognitive disorganisation contribute to published reports on inconsistent laterality – schizotypy relationships.

B. Study 1: Nicotine

Running title

Nicotine, schizotypy and hemispheric asymmetry

Reference:

Herzig, D. A., Tracy, J., Munafò, M., & Mohr, C. (2010). The influence of tobacco consumption on the relationship between schizotypy and hemispheric asymmetry. *Journal of Behavior Therapy and Experimental Psychiatry, 41*(4), 397-408.

1. Abstract

Tobacco use is positively associated with severity of symptoms along the schizophrenia spectrum. Accordingly it could be argued that neuropsychological performance, formerly thought to be associated with schizotypy, is actually influenced by drug use or an interaction of drug use and schizotypy. We tested whether habitual cigarette smokers as compared to non-smokers would show a neuropsychological profile similar to that observed along the schizophrenia spectrum and, if so, whether smoking status or nicotine dependence would be more consistent predictors of the neuropsychological profile than schizotypy. Because hemispheric dominance has been found to be attenuated along the schizophrenia spectrum, 40 right-handed male students (20 non-smokers) performed lateralised left- (lexical decisions) and right- (facial decision task) hemisphere dominant tasks. All individuals completed self-report measures of schizotypy and nicotine dependence. Schizotypy predicted laterality in addition to smoking status. While positive schizotypy (unusual experiences) was unrelated to hemispheric performance, cognitive disorganization predicted reduced left hemisphere dominant language functions. These latter findings suggest that cognitive disorganization should be regarded separately as a potentially importantly relating to thought disorganization and language processing. Additionally, increasing nicotine dependence among smokers predicted a right hemisphere shift of function in both tasks that supports the role of the right hemisphere in compulsive/impulsive behaviour.

Keywords: Smoking; Psychosis-Proneness; Hemispheric Asymmetry; Cognitive disorganization

2. Introduction

The concept of schizotypy, which was originally introduced by Meehl (1962) as a genetic diathesis-stress model for schizophrenia (see also Lenzenweger & Korfine, 1992), represents a mild and non-clinical thinking style in the general population reminiscent of the one reported from individuals with a clinical diagnosis of schizophrenia. Schizotypal symptoms in the general population are quantitatively less prominent yet qualitatively equivalent to those seen in schizophrenia (Gooding, Matts, & Rollmann, 2006; Rawlings, Williams, Haslam, & Claridge, 2008). However, while schizotypal symptoms are considered to lie at one extreme end of the schizophrenia spectrum (SSp) in the clinical population, in healthy people such symptoms are considered to express themselves in milder form along the SSp (Claridge & Broks, 1984; van Os et al., 1999). Schizotypy is typically assessed using self-report questionnaires (L. J. Chapman, et al., 1994; Mason, et al., 1995; Raine, 1991) and high scores indicate enhanced proneness to psychosis (L. J. Chapman, et al., 1994; Gooding, Tallent, & Matts, 2005). The notion that schizotypy and overt clinical psychosis are linked is also supported by observations that high-scoring, pre-selected schizotypal individuals from the general population demonstrate cognitive-attentional (Buchy, Woodward, & Liotti, 2007; Gooding, Kwapil, & Tallent, 1999; Sarkin, Dionisio, Hillix, & Granholm, 1998), sensory-motor-behavioural (Lenzenweger & Gold, 2000), physiological (Klein, Berg, Rockstroh, & Andresen, 1999; Pizzagalli et al., 2000) and neurochemical (Laruelle & Abi-Dargham, 1999; Murray, Lappin, & Di Forti, 2008) peculiarities comparable to those described in patients with schizophrenia.

Similarities between schizotypy and schizophrenia are not limited to pre-selected highly schizotypal individuals but present in randomly selected individuals from the general population (Mason & Claridge, 1999; Mohr, Bracha, & Brugger, 2003; Reed et al.,

2008; Shaw, Claridge, & Clark, 2001; Steel, Hemsley, & Pickering, 2002) that supports the notion that the SSp dimension extends across the general population. Indeed, there is an advantage in testing schizotypal individuals since basic brain mechanisms in psychosis can be studied in individuals free from confounding factors and illness-related phenomena seen in patients with schizophrenia, such as antipsychotic medication, hospitalization, or duration of illness (Claridge, Clark, & Beech, 1992; Esterberg, Jones, Compton, & Walker, 2007; Gooding, et al., 1999; Mason & Claridge, 2006).

Of particular interest to the present study is the enhanced consumption of readily available psychoactive substances as one moves along the SSp, such as i) tobacco in schizotypy (Esterberg, et al., 2009; J. H. Williams, Wellman, Allan, et al., 1996) and patients with schizophrenia (de Leon, et al., 2002), ii) cannabis in schizotypy (Barkus, et al., 2006; Skosnik, et al., 2001; J. H. Williams, Wellman, & Rawlins, 1996) and schizophrenia (Archie, et al., 2007; Barnes, et al., 2006), and iii) caffeine in schizotypy (Jones & Fernyhough, 2009) and schizophrenia (Gurpegui, Aguilar, Martinez-Ortega, Diaz, & de Leon, 2004). While some authors have suggested that dopamine-enhancing drugs such as nicotine (Montgomery, Lingford-Hughes, Egerton, Nutt, & Grasby, 2007; Murphy et al., 2002) might be involved in the development of psychosis or some aspects of it (Abi-Dargham et al., 1998; Moore et al., 2007; G. N. Smith et al., 2009), others suggest that at-risk individuals may use nicotine as means of self- medication (Adler, Hoffer, Wiser, & Freedman, 1993; Kumari & Postma, 2005; Zabala et al., 2009; Zammit et al., 2003). However, the reason for enhanced drug consumption along the SSp currently remains unexplained. Indeed, in the absence of unequivocal evidence that would fully support one or the other hypothesis (Adler, et al., 1993; G. N. Smith, et al., 2009) it could even be argued that behaviour formerly associated with the SSp might rather result from drug consumption. In line with this latter suggestion, in the current

study we focus on hemispheric asymmetry of function since language dominance in the left hemisphere (LH) and visual face recognition dominance in the right hemisphere (RH) have been found to be attenuated in schizophrenia (Bleich-Cohen, et al., 2009; Kucharska-Pietura, et al., 2002; Løberg, et al., 2006; Mitchell & Crow, 2005; Phillips & David, 1997; Sommer, et al., 2001) and schizotypy (Broks, 1984; Brugger, et al., 1993; Mason & Claridge, 1999; Mohr, Krummenacher, et al., 2005; Suzuki & Usher, 2009). While laterality studies in patients with schizophrenia frequently control for illegal drug use, this is less often the case for legal substances such as nicotine. In schizotypy research it does not seem to be common to screen for these substances; in fact, none of the above-mentioned schizotypy studies reported on controlling for either illegal or legal drug use. To lend further support to the importance of controlling for substance use in laterality research, functional hemispheric asymmetry might be affected by nicotine (Gentry, et al., 2000; McClernon, et al., 2003) as well as dopamine, which is considered to be enhanced by drugs such as nicotine (Dawe, Gerada, Russell, & Gray, 1995; Montgomery, et al., 2007; Murphy, et al., 2002). For instance, decreased hemispheric asymmetry in patients with schizophrenia seems most prevalent in the un-medicated state (Mohr, Krummenacher, et al., 2005; Purdon, Woodward, & Flor-Henry, 2001 for overviews) and cognitive impairments in first episode patients with schizophrenia were more pronounced in non-smokers as compared to nicotine smokers (Zabala, et al., 2009). In healthy individuals dopamine agonists (including nicotine) might enhance language functions (Gentry, et al., 2000; Gilbert, et al., 2008; Knecht, et al., 2004; McClernon, et al., 2003), which potentially stabilizes hemispheric asymmetry rather than attenuates it, particularly when reporting relatively elevated schizotypy (Mohr, Krummenacher, et al., 2005).

Thus the present study aims to test the conjecture that neuropsychological performance formerly associated with schizotypy might actually be explained by elevated nicotine use. If decreased hemispheric asymmetry is as a result of nicotine use rather than schizotypal symptoms, this might explain why studies on functional hemispheric asymmetry and schizotypy report findings that are heterogeneous (Liouta, et al., 2008) since the smoking status between studies might have differed. In line with this reasoning, we hypothesize that nicotine smokers as compared to non-smokers yield a reduced functional hemispheric asymmetry and might do so with increased nicotine consumption. This hypothesis does not rule out the possibility that nicotine consumption and schizotypy interact to produce reduced hemispheric asymmetry and might do so differently for separate schizotypy dimensions (Mohr, Krummenacher, et al., 2005; Mohr, Landis, Bracha, Fathi, & Brugger, 2005). We assume that any laterality: schizotypy relationship and its interaction with nicotine will be most pronounced for positive schizotypy because most studies reported on a decreased hemispheric asymmetry for positive schizotypy but less so for negative schizotypy (Liouta, et al., 2008). The limited knowledge on the influence of cognitive disorganization on hemispheric asymmetry would predict no influence on performance (Gruzelier & Richardson, 1994; Mason & Claridge, 1999). Finally, since previous studies have found more consistent findings in male as compared to mixed-sex or female study groups (Mason & Claridge, 1999; Mohr, Rohrenbach, Laska, & Brugger, 2001), the current study focused on male participants only.

3. Method

Participants

Forty male right-handed undergraduate students (20 smokers and 20 non-smokers) were recruited through public advertisement in and around the University of Bristol, and through personal contact. The smokers had a mean age (always in years, ± SD) of 22 (± 2, range 19 – 28) and the non-smokers had a mean age of 21 (± 1, range 18 – 23). The non-smokers were required never to have been regular, daily smokers or casual smokers of more than 100 cigarettes (m = 27 ± 33, range 0 – 100) in their lifetime to qualify as a non-smoker (David et al., 2005). Right-handedness was determined with the Edinburgh Handedness Inventory (Oldfield, 1971) according to previously used scoring criteria (see also Kita, de Condappa, & Mohr, 2007).

All participants were Caucasian native English speakers and had normal or corrected to normal vision. As indicated by self-report, none of the participants reported drug abuse (either recreational or psychiatric) in the past three months, or a previous history of psychiatric or neurological illness (Mohr, Landis, & Brugger, 2006). The study was approved by the local Ethics committee.

Materials

(1) Self-report questionnaires

i. The O-LIFE questionnaire

The O-LIFE questionnaire (Mason, et al., 1995) is a validated 150-item self-report questionnaire assessing schizotypy in terms of four dimensions. Positive schizotypy is assessed by 30 items pertaining to Unusual Experiences (UnEx, maximum score 30, including items such as ‘Are your thoughts sometimes so strong that you can almost hear them?’), negative schizotypy by 27 items assessing Introvertive Anhedonia (IntAn,

maximum score 27, including items such as 'Have you had very little fun from physical activities like walking, swimming or sports?'), and Cognitive Disorganization is assessed by 24 items (CogDis, maximum score 24, including items such as 'Do you find it difficult to keep interested in the same thing for a long time?'). Finally, 23 items assessing Impulsive Nonconformity (maximum score 23), which does not represent a schizotypy dimension (Mason, et al., 1995), and 40 filler items and items measuring schizotypal personality (STA) and borderline personality (STB) (Claridge & Broks, 1984), which will not be considered further. For each item, participants have to indicate whether the statement is true or false. The number of positive responses (some items are reversely formulated) is summed so that higher scores indicate higher schizotypy. Normative values can be found in Mason et al. (1995) and Mason and Claridge (2006) and the scale has shown high test-retest reliability (Burch, et al., 1998). The questionnaire also includes six lie items (taken from Eysenck's Personality questionnaire (Eysenck & Eysenck, 1975). In line with a previous study (Krumm-Merabet & Meyer, 2005), we only included participants with a lie-score ≤ 5 (mean lie score was 1 ± 1).

ii. *The Fagerström Test of Nicotine Dependency (FTND)*

The FTND is a widely used self-report questionnaire on nicotine dependence (Heatherton, Kozlowski, Frecker, & Fagerström, 1991). Participants have to rate their consumption of cigarettes for six questions (e.g.: "Do you find it difficult to refrain from smoking in places where it is forbidden?") using a yes/no response. Each response is scored between 0 – 10 on levels of nicotine dependence, with positive responses scored as 1, and negative responses scored as 0. A score of 10 indicates high nicotine dependence while a score of 0 indicates low nicotine dependence (Heatherton, et al., 1991; Japuntich, Piper, Schlam, Bolt, & Baker, 2009).

Hemi-field studies

For both hemi-field tasks participants were sat centrally at a distance of 57 cm from the computer screen (eye-screen distance). The keyboard was centrally placed in front of the participant so that the response keys were to the right and left of the body midline. Stimuli were presented using the experimental software system E-Prime (Psychology Software Tools) with a monitor display refresh rate of 60 Hz.

(2) Lateralized Lexical Decision Task (LDT)

Participants were presented with an English version of the lateralized LDT used by Mohr, Krummenacher et al. (2005). The stimulus material consisted of 24 words and 72 pronounceable non-words. The words consisted of four- and five-letter words, and were matched for neighborhood (=2), and the CELEX frequency values ranged from 7.15 to 76.20 (m = 38.07, SD = 24.47). Each word was matched with a non-word of the same length. The remaining non-words were matched to result in an additional set of non-word pairs. The word pairs were displayed in black (33 point Courier New Bold font) against a grey background on the computer screen (see Figure 10). Each letter string was presented with their centre 25 mm from central fixation (visual eccentricity: 2.5 degrees of visual angle per half-field). In each trial, we presented a fixation cross for 1000 ms before the word pair was shown for 150 ms, followed by a blank screen for 4000 ms, or until a response was given (Figure 10). Participants were instructed to indicate whether they saw a meaningful English word on the left or right, or did not see a meaningful English word at all. To do so, participants had to press the shift key ipsilateral to the word with the index finger or space bar with both thumbs if they did not see a meaningful string of letters on the screen. Per block, there were 72 trials with three 24-trial conditions (word left/non-word right, non-word left/word right, non-word/non-word). The order of the stimuli was randomized within blocks and between

participants. In addition, for the critical trials (in which a word was presented) each word stimulus appeared once in each visual field. Prior to the experimental task each participant undertook a practice block consisting of 10 trials with words not used in the experimental trial. We assessed the number of correct lexical decisions and the mean reaction times for correct lexical decisions for the left (LVF) and right (RVF) visual field separately. In the control condition, two non-words were displayed on either side of the screen (NoW).

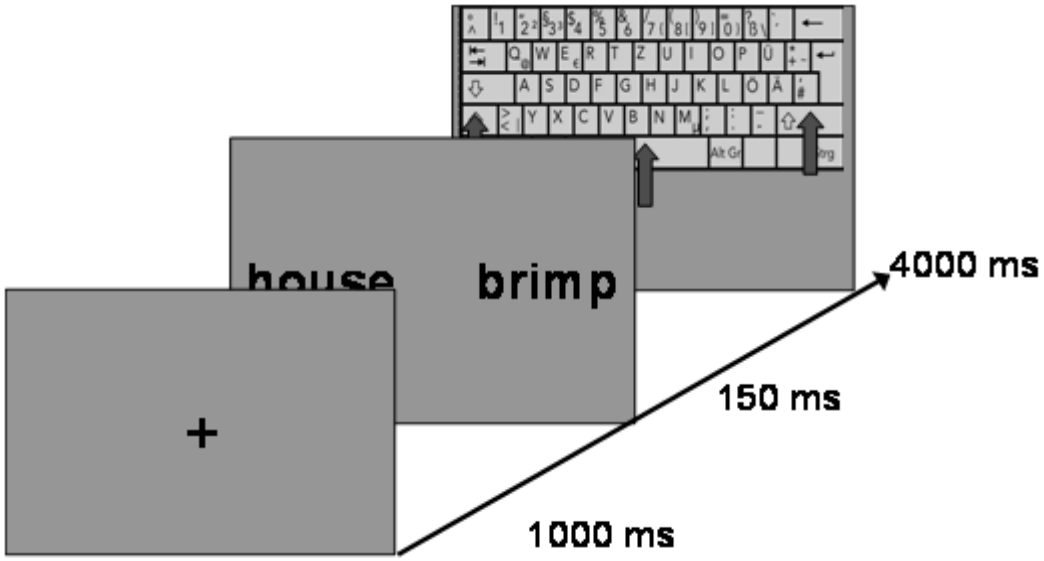

Figure 10. Example of word stimuli and procedure used in the LDT.

(3) Lateralized Facial Decision Task (FDT)

Participants were presented with facial stimuli against a grey background on the computer screen (see Figure 11). Due to the potential effect of emotional faces on laterality (Workman, Peters, & Taylor, 2000), all faces had neutral expressions and were photographed straight on so that the faces appeared as symmetrical as possible with the central plane of the face in line with the centre of the screen. The eccentricity of each face picture was ~ 4 degrees of visual angle and the pictures were 335 x 400 pixels. This

was to ensure that important facial information, such as eyes, nose and mouth, would fall in a similar visual angle as the words in the lexical decision task (~2.5 degrees). The pictures consisted of 10 male and 10 female facial images (example in Figure 11) that had been used in a previous study (Penton-Voak, Pound, Little, & Perrett, 2006). From these, 20 sexually-dimorphic composite faces were constructed (Figure 11) with an equal amount of female and male half-faces appearing in each visual field. The same 20 composite faces were also presented mirror-reversed resulting in 40 composite faces. In each trial, a black central fixation point was presented on the screen for 1000 ms followed by the stimulus that was displayed for 150 ms Following presentation of the stimulus, a blank screen was presented for a maximum of 4000 ms, or until a response was provided. In this task participants had to press the left shift key if the face appeared to be female and the right shift key if the face appeared to be male. Prior to the test trials participants were presented with a practice block of 10 trials consisting of two whole faces and eight composite faces that were not included in the experimental trials. We assessed the number and response time of facial decisions towards the left visual field (LF decisions) and right visual field (RF decisions). In the control condition, whole faces (WF) were presented (Figure 11).

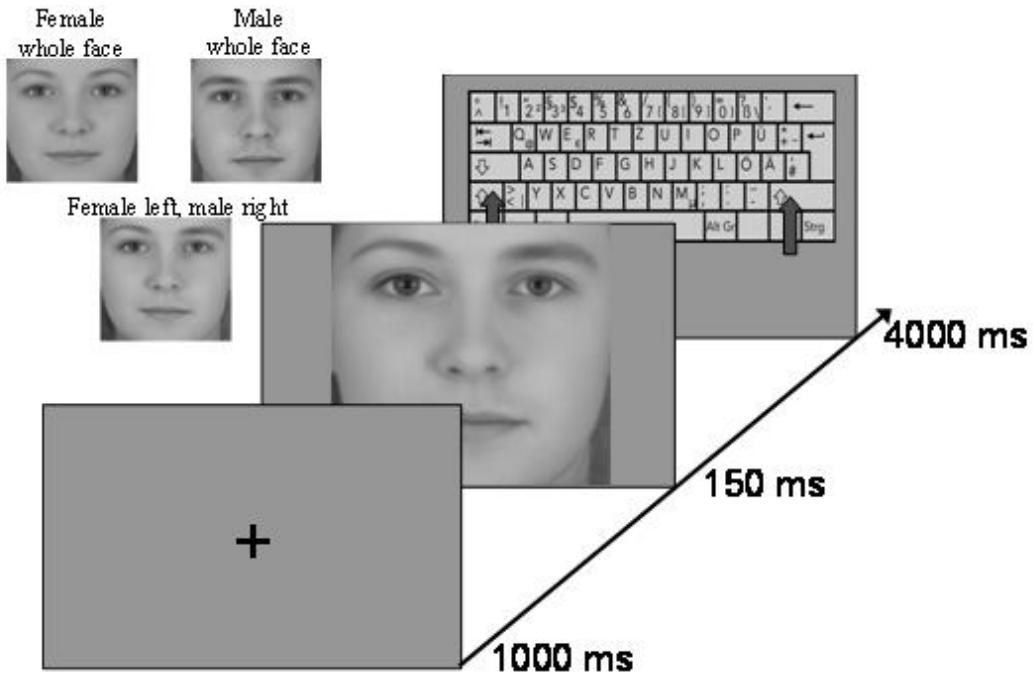

Figure 11. Example of face stimuli and procedure used in the FDT.

Data analysis

As in previous lateralized hemi-field studies (Allison, Puce, Spencer, & McCarthy, 1999; Ratcliff, Gomez, & McKoon, 2004), individual response latencies faster than 200 ms and slower than 2000 ms in both the LDT and FDT were excluded from further analysis. To test for differences in lateralized performance in smokers and non-smokers, we calculated 2 x 2 mixed sample ANOVAs with visual field (LVF/LF, RVF/RF) as the related samples factor and group (smokers vs. non-smokers) as the independent samples factor on mean reaction times (RT) of correct responses for the LDT and the FDT separately. The same ANOVA was also calculated for percent correct responses in the LDT. For the FDT, to ascertain that participants could distinguish between male and female whole faces (WF), and that the percentage of correct sex decisions (WF) was higher than the percentage of sex decisions according to the left side of the composite face (LF decisions), we performed a repeated measures ANOVA on percent correct (WF) and percent LF decisions (composite faces) as repeated measure and group as

between-subject measure. To also test whether there was a RT difference between WF and composite faces, and that LF decisions were potentially faster than those for RF decisions, we performed a repeated measures ANOVA on mean RT for sex decisions with face type (correct decisions for WF, LF decisions, RF decisions) as repeated measure and group as between-subject measure. Post-hoc tests correcting for multiple comparisons were performed using Tukey HSD tests or within subjects contrasts. Effect sizes are reported for all ANOVA-results.

We also tested whether, within each group, the tasks resulted in lateralized performance at all (Mohr, Krummenacher, et al., 2005; Mohr, et al., 2006) using conventional laterality indices (J. C. Marshall, Caplan, & Holmes, 1975). In general terms, this would mean that inferior performance is subtracted from superior performance, and that this difference is divided by its sum. Accordingly, positive values indicate an advantage of the normally dominant hemisphere (LDT: LH; FDT: RH), and negative values an advantage of the normally sub-dominant hemisphere. In order to obtain indices that would be comparable in this respect, the indices for i) accuracy in the LDT, and ii) reaction times in the FDT was *(RVF–LVF)/ (LVF+RVF)*100*, while the indices for reaction times in the LDT was *(LVF–RVF)/ (LVF+RVF)*100*. For accuracy in the FDT, we determined only percent LF decisions (as LF and RF decisions added up to 100%, including RF decisions and was deemed redundant). These indices were subjected for each group separately to one sample *t*–tests against chance level.

Finally, in order to establish an effect of schizotypy over and above smoking status or nicotine dependence on hemispheric asymmetry, we performed multiple stepwise regressions as follows. Group status and nicotine dependence scores were entered in the first step, UnEx scores, CogDis scores and IntAn scores in the second step, and the interaction between the schizotypy subscales and smoking status or FTND scores,

respectively, in the last step. Thus, three blocks of predictors were entered in nested blocks, meaning that each subsequent block contained all prior predictors and the additional predictors from the current block. Presentation of results however will only include the new predictors entered, for economy of presentation. The full model can be found in the Appendix of this dissertation (see Tables 23-24). Because all tolerance values were above .2 (Menard, 1995), and all independent variables were mean-centered, multi-collinearity between the independent variables was considered negligible. The dependent variables were i) percent index for the LDT and ii) RT-indices for the LDT and FDT separately. However, to account for a potentially different contribution of each hemisphere to decreased hemispheric asymmetry (Mohr, Krummenacher, et al., 2005; Sommer, et al., 2001), additional separate stepwise regression analyses were conducted with iii) correct word recognition in the LVF and RVF, iv) RTs for correct lexical decisions in the LVF and RVF, v) percent LF decisions and percent correct sex decisions for WF, and vi) RTs for LF decisions, RTs for RF decisions, and RTs for correct WF decisions. Kolmogorov–Smirnov tests for the smokers and non-smokers separately revealed normal distribution for all behavioural measures and questionnaire scores. All *p*-values were two-tailed and the α-level was set at .05, unless otherwise stated.

4. Results

Participants

After removal of LDT data of one participant due to erroneous usage of the three response keys, unpaired *t*-tests showed that smokers and non-smokers did not differ for age, handedness scores, UnEx scores, CogDis scores, and IntAn scores (Table 2).

Average schizotypy scores across groups were lower (UnEx: 6.15 ± 4.44, CogDis: 9.20 ± 4.68, IntAn: 4.80 ± 2.94) than those reported from a representative comparison sample (Mason & Claridge, 2006). In smokers and non-smokers, schizotypy scores were unrelated (all *p*-values > .20), apart from significant positive correlations between UnEx and CogDis scores (non-smokers: r=.62, $p < .01$; smokers: $r = 0.63$, $p < .01$)**.** FTND scores were within normal ranges (Table 2) for an unselected group of smokers (Fagerström et al., 1996), and were unrelated with schizotypy scores (all *p*-values > .20).

Table 2. *Demographic variables of the study population. Presented is age (in years), handedness scores, schizotypy scores, and Fagerström test for nicotine dependence scores for smokers (n = 20) and non-smokers (n = 20) separately. Results (t) of the unpaired t-tests (df = 37) are given together with the respective p-values (p).*

Variables	**Smoker**	**Non-Smoker**		
	Mean ± SD (range)	***Mean ± SD (range)***	***t***	***p***
Age	22.09 ± 1.92 (19 - 28)	21.59 ± 1.09 (18 - 23)	1.03	0.31
Handedness	11.08 ± 0.94 (9 - 12)	11.28 ± 0.72 (10 - 12)	-0.76	0.45
UnEx[a]	6.65 ± 5.08 (0 - 16)	5.65 ± 3.75 (0 - 14)	0.71	0.48
CogDis[b]	8.75 ± 4.93 (2 - 17)	9.65 ± 4.49 (1 - 19)	-0.60	0.55
IntAn[c]	3.95 ± 2.19 (0 - 9)	5.65 ± 3.38 (1 - 12)	-1.89	0.07
FTND[d]	1.40 ± 1.57 (0 - 5)	n/a	n/a	n/a

Note: [a] Unusual Experiences; [b] Cognitive Disorganization; [c] Introvertive Anhedonia; [d] Fagerström Test for Nicotine Dependence

Lateralized performance in smokers and non-smokers

(1) LDT

The repeated measures ANOVA on percent accuracy showed a significant main effect for visual field (F [1, 37] = 2.16, $p < .001$; *partial* $\eta^2 = .35$) with performance being superior for the RVF than LVF (Table 3). The remaining comparisons (main effect for

group: F [1, 37] = 0.46, p = .50, *partial* η^2 = .01; interaction between group and visual field: F [1, 37] = 0.67, p = .42, *partial* η^2 = .02, Table 3) were both not significant. The analogue ANOVA on mean RT revealed no significant main effects (visual field: F [1, 37] = 1.40, p = .25, *partial* η^2 = .04; smoking group: F [1, 37] = 0.80, p = .38, *partial* η^2 = .02), and no significant interaction between smoking group and visual field (F [1, 37] = 1.00, p = .33, *partial* η^2 = .03). Single t-tests against zero for the laterality indices were significant for percent accuracy, but not RT, for the whole sample (percent accuracy: t [38] = 4.65, p < .001; RT: t [38] = 0.88, p = .38, Table 3), smoker (percent accuracy: t [19] = 2.87, p = .01; RT: t [19] = 0.06, p = .95, Table 3), and non-smoker (percent accuracy: t [18] = 3.67, p < .01; RT: t [18] = 1.02, p = .32, Table 3), separately. The positive laterality indices point to a RVF advantage (and thus a LH advantage) in all instances.

(2) FDT

The repeated measures ANOVA on percentage accuracy showed a main effect for face type (WF, LF decisions) indicating that percent correct sex decisions for WF was higher than the proportion of LF decisions (F [1,38] = 222.45, p < .001, *partial* η^2 = .85, Table 3). The interaction between face type and group (F [1, 38] = 0.24, p = .63, *partial* η^2 = .01) and the main effect for group (F [1, 38] = 2.35, p = .13, *partial* η^2 = .06) were not significant. The repeated measures ANOVA on mean RT for sex decisions with face type (correct decisions for whole faces, LF decisions, RF decisions) as repeated measure (see also data analysis section) showed a significant main effect for face type (F [2,37] = 41.85, p < .001, *partial* η^2 = .52). Post-hoc within-subjects contrasts showed comparable RTs for LF and RF decisions (F [1, 38] = 2.29, p = .14, *partial* η^2 = *.06*), but faster responses for WF as compared to both LF (F [1, 38] = 48.42, p < .001, *partial* η^2 = *.56*) and RF (F [1, 38] = 62.12, p < .001, *partial* η^2 = *.62*) decisions (Table 3). The

main effect for smoking group (F [1, 38] = 0.45, p = .51, *partial* η^2 = *.01*), and the interaction were both not significant (F [2, 37] = 0.42, p = .65, *partial* η^2 = *.01*).

Table 3. *Mean (SD) lateralized task performance for the total sample (LDT[a]: n = 39, FDT[b]: n = 40), smoker (LDT: n = 20, FDT: n = 20) and non-smoker (LDT: n = 19; FDT: n = 20) separately.*

Variables		**All**		**Non-smoker**		**Smoker**	
		Mean	***SD***	***Mean***	***SD***	***Mean***	***SD***
LDT	LDT LVF[c] %[d]	54.06	19.57	51.21	19.91	56.77	19.35
	LDT RVF[e] %	69.02	12.99	68.97	12.75	69.06	13.56
	LDT NoW[f] %	43.70	20.58	48.03	21.16	39.58	19.66
	LDT index[g] %	14.01	18.81	16.95	20.15	11.22	17.50
	LDT LVF RT	680.33	182.55	714.04	198.50	648.30	164.65
	LDT RVF RT	654.83	149.30	665.98	146.05	644.23	155.34
	LDT NoW RT	936.55	209.41	945.00	229.60	928.51	193.97
	LDT index RT	1.47	10.44	2.91	12.38	0.11	8.30
FDT	FDT LF[h] %	54.38	9.72	53.00	8.54	55.75	10.81
	FDT WF[i] %	86.94	11.27	84.50	9.95	89.38	12.22
	FDT LF RT	702.04	167.42	716.64	157.29	687.45	179.84
	FDT RF[j] RT	724.13	182.22	732.36	174.59	715.91	193.73
	FDT WF RT	582.80	110.03	606.15	107.75	559.46	109.97
	FDT index RT	1.40	5.95	0.84	4.83	1.96	6.98

Note: [a] Lexical decision task; [b] Facial decision task; [c] Left visual field; [d] Percentage correct; [e] Right visual field; [f] Two non words displayed on either side of the screen; [g] Laterality index; [h] Left face decisions; [i] Whole face decisions; [j] Right face decisions

For the whole sample, a single t-test against chance level (50%) for percent LF decisions was significant (t [39] = 2.85, p < .01), but not for a single t-test against chance level (0) for the RT laterality index (t [39] = 1.49, p = .14, Table 3). Analogue t-tests for the groups separately showed no significant bias for non-smokers (percent LF

decisions: t [19] = 1.57, p = .13; RT index: t [19] = 0.78, p = .45, Table 3), but a significant LF decision bias in smokers for percent LF decisions (t [19] = 2.38, p = .03; RT index: t [19] = 1.26, p = .22, Table 3). Percent LF decisions above 50% represent a LF bias (and by inference point to a RH dominance in the FDT).

Multiple regression analyses using smoking status as a predictor variable

Hierarchical multiple regression analyses with Group (smokers, non-smokers) entered in the first block (Step 1), schizotypy subscales in the second block (Step 2) and the interaction between group and schizotypy subscales in the third block (Step 3, see also data analysis section) were conducted to evaluate the variance contributions of schizotypy as a predictor of hemispheric asymmetry on top of smoking status. Since multiple comparisons were run, we will only focus on significant R^2-changes (all other results see Table 4-7), and for economy of presentation of nested block multiple regression analyses we will present only the final block added in each model (for the full model please see Tables 23-24 in the Appendix).

(3) LDT

Results showed that group status alone (Step 1) did not significantly predict variance in any of the outcome variables. Adding schizotypy subscale scores (Step 2) improved the model for the RT index, and RVF RT (Table 4). In both cases, increasing CogDis scores predicted a decrease in the RT-index, likely resulting from a significant increase in RVF RTs (Table 4). Adding the interaction terms in the third block (Step 3) did not improve the regression model significantly (Table 4).

Table 4. *Beta-weights and ΔR² for the LDT[a] outcome variables for the whole sample accounting for smoking status.*

		Percentage correct			**RT**		
Steps regression	**Independent variables**	**LVF[f]**	**RVF[g]**	**Index[h]**	**LVF**	**RVF**	**Index**
Step 1:	Group (SM, nSM[b])	0.14	0.00	-0.15	-0.18	-0.07	-0.14
Smoking status	*ΔR²*	0.02	0.00	0.02	0.03	0.01	0.02
Step 2:	UnEx[c]	0.17	0.18	-0.07	-0.05	-0.13	0.12
Schizotypy	CogDis[d]	0.16	**-0.38**$^{+}$	-0.33	0.09	**0.55****	**-0.51***
	IntAn[e]	-0.11	0.13	0.18	-0.02	-0.12	0.13
	ΔR²	0.09	0.10	0.15	0.00	**0.23***	**0.20***
Step 3:	Group*UnEx	-0.05	0.19	0.21	-0.04	0.01	-0.05
Interaction	Group*CogDis	0.02	-0.10	-0.10	0.18	0.05	0.20
smoking status	Group*IntAn	-0.04	-0.06	-0.01	0.27	0.13	0.26
and schizotypy	*ΔR²*	0.00	0.02	0.03	0.10	0.02	0.09
	R² total	0.11	0.12	0.20	0.13	0.25	**0.31**$^{+}$
	Adjusted R² total	-0.09	-0.08	0.02	-0.06	0.08	**0.16**$^{+}$

$^{+}$ p≤.10; * significant at p≤.05; ** significant at p≤.01; *** significant at p≤.001

Note: [a] Lexical decision task; [b] SM=smoker, nSM= non-smoker; [c] Unusual experiences; [d] Cognitive disorganization; [e] Introvertive Anhedonia; [f] Left visual field; [g] Right visual field; [h] Laterality index

(4) FDT

The comparable hierarchical multiple regression analyses for the FDT (see also 2.3) showed that group status alone (Step 1) did not predict variance in any of the outcome variables (Table 5). Adding schizotypy subscale scores (Step 2) did not improve the model (Table 5). Adding the interaction terms in the third block (Step 3) improved the overall model for WF %. This improvement resulted from a significant interaction

between group and IntAn scores (Table 5). Post-hoc regressions for each group separately including only IntAn as a predictor variable revealed that increasing IntAn-scores predicted a decrease in WF% in non-smokers only (non-smokers: R^2= .47, β= -.69, p< .001; smokers: R^2= .04, β= .21, p= .37).

Table 5. *Beta-weights and ΔR^2 for the FDT[a] outcome variables for the whole sample accounting for smoking status.*

		Percentage correct		**RT**			
Steps regression	**Independent variables**	**LF[f]**	**WF[g]**	**LF**	**RF[h]**	**WF**	**Index[i]**
Step 1:	Group (SM, nSM[b])	0.14	0.22	-0.09	-0.05	-0.22	0.10
Smoking status	ΔR^2	0.02	0.05	0.01	0.00	0.05	0.01
Step 2:	UnEx[c]	-0.16	-0.20	-0.17	-0.23	-0.02	-0.24
Schizotypy	CogDis[d]	-0.06	0.18	**0.44***	**0.49***	**0.41***	0.18
	IntAn[e]	-0.30	**-0.28**$^{+}$	0.06	0.00	0.05	-0.15
	ΔR^2	0.13	0.10	0.14	0.15	0.16^{+}	0.06
Step 3:	Group*UnEx	-0.18	-0.26	0.01	0.11	0.14	0.19
Interaction	Group*CogDis	0.28	0.25	-0.11	-0.10	-0.07	-0.02
smoking status	Group*IntAn	-0.03	**0.41***	**0.44***	**0.39***	0.18	-0.04
and schizotypy	ΔR^2	0.05	**0.19***	**0.15**$^{+}$	0.13	0.04	0.03
	R^2 total	0.20	**0.33***	**0.30**$^{+}$	0.28	0.25	0.10
	Adjusted R^2 total	0.03	**0.19***	**0.15**$^{+}$	0.13	0.08	-0.10

$^{+}$p≤.10; * significant at p≤.05; ** significant at p≤.01; *** significant at p≤.001

Note: [a] Facial decision task; [b] SM=smoker, nSM= non-smoker; [c] Unusual experiences; [d] Cognitive disorganization; [e] Introvertive Anhedonia; [f] Left face decisions; [g] Whole face decisions; [h] Right face decisions; [i] Laterality index

Multiple regression analyses using nicotine dependence scores as a predictor variable

(5) LDT

The hierarchical multiple regression analysis with nicotine dependence scores (FTND) entered in the first block (Step 1), schizotypy subscales scores in the second block (Step 2) and the interaction between group and schizotypy subscales scores in the third block (Step 3, see also data analysis section) were conducted to determine the effect of schizotypy on top of nicotine dependence within smokers. Again, since multiple comparisons were run, we will only focus on the significant R^2-changes (all other results see Table 6). Results showed that FTND scores predicted 23.5% of the variance in RVF % (higher FTND scores predicted decreasing RVF %, Table 6). The addition of schizotypy subscale scores (Step 2) and the addition of the interaction terms (Step 3) did not improve the model (Table 6).

Table 6. *Beta-weights and ΔR² for the LDT[a] outcome variables for smokers only accounting for nicotine dependence.*

		Percentage correct			**RT**		
Steps regression	**Independent variables**	**LVF[f]**	**RVF[g]**	**Index[h]**	**LVF**	**RVF**	**Index**
Step 1:	FTND[b]	-0.10	**-0.48***	-0.20	0.17	0.01	0.21
Nicotine dependence	*ΔR²*	0.01	**0.23***	0.04	0.03	0.00	0.04
Step 2:	UnEx[c]	0.13	0.14	0.00	-0.08	-0.18	0.17
Schizotypy	CogDis[d]	0.21	-0.33	-0.40	0.22	**0.59**┼	**-0.53**┼
	IntAn[e]	-0.13	0.01	0.12	0.30	0.05	**0.46***
	ΔR²	0.09	0.07	0.14	0.15	0.26	0.30
Step 3:	FTND*UnEx	**-0.69***	-0.27	0.47	0.48	0.32	0.26
Interaction	FTND*CogDis	0.05	-0.23	-0.16	-0.15	-0.15	0.06
nicotine dependence	FTND*IntAn	-0.26	-0.30	0.05	0.46	0.07	0.67*
and schizotypy	*ΔR²*	0.35	0.15	0.13	0.26	0.07	**0.27**┼
	R² total	0.44	0.45	0.31	0.44	0.33	**0.61**┼
	Adjusted R² total	0.12	0.13	-0.09	0.12	-0.07	**0.38**┼

┼ p≤.10; * significant at p≤.05; ** significant at p≤.01; *** significant at p≤.001

Note: [a] Lexical decision task; [b] Fagerström Test for Nicotine Dependence; [c] Unusual experiences; [d] Cognitive disorganization; [e] Introvertive Anhedonia; [f] Left visual field; [g] Right visual field; [h] Laterality index

(6) FDT

The comparable hierarchical multiple regression analyses for the FDT (see also 2.3) showed that FTND scores explained 26% of the variance in LF % (Model 1, Table 7); increasing FTND scores predicted an increase in LF %. The addition of schizotypy subscale scores (Step 2) did not improve the model. The interaction terms showed that the interaction between FTND scores and CogDis scores explained additional variance

in WF RTs. Median-splits were performed on FTND-scores and post-hoc regressions were conducted on WF RT and CogDis scores for the high- and low-scoring FTND groups separately. Increasing CogDis scores predicted slowed responding for WF in the low-FTND group only (Low FTND: R^2= .65, β= .81, p< .01; high FTND: R^2= .07, β= -.27, p= .52).

Table 7. *Beta-weights and ΔR² for the FDT[a] outcome variables for smokers only accounting for nicotine dependence.*

		Percentage correct		**RT**			
Steps regression	**Independent variables**	**LF[f]**	**WF[g]**	**LF**	**RF[h]**	**WF**	**Index[i]**
Step 1:	FTND[b]	**0.51***	0.36	-0.04	0.11	0.08	0.21
Nicotine dependence	ΔR²	**0.26***	0.13	0.00	0.01	0.01	0.05
Step 2:	UnEx[c]	-0.09	-0.33	-0.25	-0.16	0.13	-0.01
Schizotypy	CogDis[d]	0.06	0.27	0.31	0.34	0.31	0.11
	IntAn[e]	-0.23	0.22	**0.50***	**0.41**$^{+}$	0.24	-0.14
	ΔR²	0.06	0.11	**0.34**$^{+}$	0.28	0.28	0.02
Step 3:	FTND*UnEx	-0.44	0.09	0.27	0.02	0.09	-0.45
Interaction	FTND*CogDis	0.45	0.10	**-0.60***	**-0.50**$^{+}$	**-0.72****	0.18
nicotine dependence	FTND*IntAn	0.42	-0.14	-0.06	0.22	0.24	0.49
and schizotypy	ΔR²	0.19	0.03	0.21	0.21	**0.40***	0.19
	R² total	0.51	0.27	0.55	0.51	**0.69***	0.26
	Adjusted R² total	0.22	-0.15	0.28	0.23	**0.50***	-0.17

$^{+}$ p≤.10; * significant at p≤.05; ** significant at p≤.01; *** significant at p≤.001

Note: [a] Facial decision task; [b] Fagerström Test for Nicotine Dependence; [c] Unusual experiences; [d] Cognitive disorganization; [e] Introvertive Anhedonia; [f] Left face decisions; [g] Whole face decisions; [h] Right face decisions; [i] Laterality index

5. Discussion

A varying degree of illegal and legal drug consumption along the SSp might explain heterogeneous findings when investigating the link between schizotypy and neuropsychological performance (Archie, et al., 2007; Barnes, et al., 2006; de Leon, et al., 2002; Esterberg, et al., 2009; Gurpegui, et al., 2004; Jones & Fernyhough, 2009; J. H. Williams, Wellman, Allan, et al., 1996). In particular, it could be conjectured that neuropsychological impairments formerly associated with symptom dimensions are actually the result of drug use. We therefore investigated whether a reduced hemispheric asymmetry for function (language in the LH, visual face recognition in the RH) in schizotypy might result from nicotine consumption or an interaction between schizotypy and nicotine consumption. Irrespective of schizotypy and smoking status, we replicated the commonly observed RVF over LVF advantage for lexical decisions (e.g. Bourne, 2006; Mohr, Krummenacher, et al., 2005) reflecting the LH's dominance for language processing. We also replicated the LF bias for composite faces (Butler & Harvey, 2006; Mason & Claridge, 1999; McClernon, et al., 2003) that reflects the RH dominance for visual face processing. When nicotine consumption and schizotypy were accounted for, we observed that i) nicotine consumption *per se* was unrelated to lateralized performance, ii) increasing nicotine dependence (FTND scores) seemed to predict a RH bias in both the LDT and FDT, and iii) CogDis seemed the only schizotypy dimension related to lateralized performance (increasing CogDis predicted a decreased LH language dominance and slowed responding for the sex of whole faces in individuals with low FTND scores). UnEx scores, on the other hand, were unrelated to lateralized task performance and elevated IntAn scores were related to a potentially more general visual face processing deficit.

Nicotine and lateralized performance

The finding that general smoking status was unrelated to lateralized performance is in line with previous studies showing no difference in LDT performance between a group who received a DA agonist (Levodopa) and a group who received a placebo (Mohr, Krummenacher, et al., 2005; Mohr, et al., 2006). However, studies investigating the role of nicotine on task performance more directly found that transdermal nicotine patches (slow, constant nicotine application) provided to abstinent smokers stabilized LH language functions (Gentry, et al., 2000; McClernon, et al., 2003), and smoking a nicotine cigarette (fast, acute nicotine application) impaired lexical decisions for centrally presented words (Gentry, et al., 2000). McClernon et al. (2003) additionally observed that increasing nicotine dependence was related to improved performance in both hemispheres in a language memory task; unfortunately the authors did not test a RH-dominant task. In the present study we observed that increasing nicotine dependence (FTND scores) in smokers predicted decreasing word recognition performance in the RVF and an increasing LF decision bias (irrespective of schizotypy). This RH shift in hemispheric dominance as a function of nicotine dependence would support previous electroencephalography (McClernon, et al., 2003; Norton, et al., 1992) and positron emission tomography (M. Ernst, et al., 2001; Rose, et al., 2007) studies. Also, such a RH shift might reflect a general bias towards RH functioning with increasing drug dependence since higher consumption of one drug commonly predicts higher consumption of other drugs (Degenhardt, Hall, & Lynskey, 2001; Martinez-Ortega, Jurado, Martinez-Gonzalez, & Gurpegui, 2006). In support of this possibility, the RH has been implicated in other forms of compulsive behaviours such as over-eating (Regard & Landis, 1997; Uher & Treasure, 2005), gambling (Cilia et al., 2008; Regard, Knoch, Gutling, & Landis, 2003), and violent or antisocial behaviour

(Mychack, Kramer, Boone, & Miller, 2001; Narayan et al., 2007). Given the structural and neurochemical dependence of the brain, it is not unreasonable to argue that transient short-term (Bachtold et al., 2001; Mohr, Michel, et al., 2005; Regard, Cook, Wieser, & Landis, 1994) or longer-term (Crinion & Leff, 2007; Raboyeau et al., 2008) inter-hemispheric asymmetries might be influenced by neurochemical processes (e.g. Fink et al., 2008; Hausmann & Güntürkün, 2000; Mohr, Landis, et al., 2005). Accordingly we would predict even stronger relationships between hemispheric asymmetry and nicotine (or other forms of substance and non-substance) dependence when testing hemispheric asymmetry as a function of more severe dependencies. Nicotine dependence scores were relatively low in the current sample and several of our smokers had scores of zero that are indicative of being a "light" smoker (Etter, Duc, & Perneger, 1999).

Schizotypy, nicotine and lateralized performance

While our findings on nicotine dependence were promising, those relating to schizotypy subscales did not support our predictions. Firstly, we found no relationship between UnEx scores and both hemispheric asymmetry (Kravetz, et al., 1998; Mason & Claridge, 1999) and nicotine dependence (Lopez, Maldonado, & Pueyo, 2001). A possible reason might be our relatively low UnEx and CogDis scores (Table 2) when compared to those of a normative sample (Mason & Claridge, 2006); however, our nicotine dependence (Lopez, et al., 2001; Stavem, Røgeberg, Olsen, & Boe, 2008) and schizotypy scores (Nunn & Peters, 2001; Rawlings & Goldberg, 2001; Suzuki & Usher, 2009) were comparable to previous studies. For instance, Lopez et al. (2001) reported elevated UnEx scores in smoking undergraduate psychology students compared to non-smoking ones. In the current study schizotypy scores were comparable in the two smoking groups and were unrelated to nicotine dependence scores (Esterberg, et al., 2007), although most authors report this link (Allan et al., 1995; Esterberg, et al., 2009).

Secondly, we found that increasing CogDis scores were related to a RH shift of function, i.e. a decreasing LH dominance for language and an increasing LF preference (together with slowed WF decisions). This might indicate that CogDis relates to impaired face recognition performance more generally and to impaired LH-language functions in particular. In line with our findings, a reduced LH language dominance as a function of CogDis has been reported previously (Claridge, et al., 1992; Kravetz, et al., 1998; Suzuki & Usher, 2009) although independent studies would have also predicted a similar result for UnEx scores (Brugger, et al., 1993; Kravetz, et al., 1998; Mohr, Krummenacher, et al., 2005; Pizzagalli, et al., 2000; Suzuki & Usher, 2009). Questionnaires in several of these previous studies did not distinguish between positive schizotypy and CogDis (Brugger, et al., 1993; Mohr, Krummenacher, et al., 2005) and when schizotypy dimensions were separated, both scales related to a reduced LH language dominance (Kravetz, et al., 1998; Suzuki & Usher, 2009). CogDis is frequently considered to be a distinct dimension of positive schizotypy, but it is not yet known whether it has a stronger overlap with positive or negative symptoms (Kitamura, Okazaki, Fujinawa, Takayanagi, & Kasahara, 1998; McGorry, Bell, Dudgeon, & Jackson, 1998; Spitzer, 1993; Weinstein & Graves, 2001). A stronger positive correlation between CogDis and UnEx scores than between CogDis and IntAn scores seems common (Kravetz, et al., 1998; Mason, et al., 1995; Nunn & Peters, 2001; Rawlings & Goldberg, 2001; Tsakanikos & Reed, 2003). Moreover, a stronger relationship of CogDis compared to positive schizotypy, with language "impairments" has also been reported (Johnston, Rossell, & Gleeson, 2008; S. Moritz et al., 1999; Stefanis et al., 2006). Therefore, future studies will be required to disentangle the specific or combined role of CogDis on hemispheric asymmetry.

With regards to face processing, the effect of CogDis in the present study seemed rather general than hemisphere-specific. In past studies, positive schizotypy was related to a LF bias (Leonards & Mohr, 2009; Luh & Gooding, 1999) and a decreased LF bias (Mason & Claridge, 1999). Whether this might reflect a more general pattern of face processing deficits with increasing positive schizotypy has to investigated, but the consistent direction of regression coefficients (Table 5 and 7) and other reported forms of face processing difficulties in schizotypy (Laroi, D'Argembeau, Bredart, & van der Linden, 2007) would support a more general face processing deficit with enhanced CogDis. Interestingly, the decrease in WF-processing seemed particularly relevant to individuals with low nicotine dependence who might suffer from generally slowed visual face processing abilities. If this were the case, enhanced nicotine dependence should attenuate a relationship between CogDis and face processing. Studies investigating nicotine use in relation to schizotypy subscales are few. Esterberg et al. (2007) found that smoking related to enhanced SPQ scores (Raine, 1991) in relatives of patients with schizophrenia but not in controls. Further, Esterberg et al. (2009) reported that enhanced cognitive disorganization (again SPQ) were predictive of cigarette use in a sample of healthy controls. Since increasing nicotine dependence scores in our sample were predictive of a RH-shift of function (M. Ernst, et al., 2001; McClernon, et al., 2003; Norton, et al., 1992; Rose, et al., 2007) it is possible to argue that increasing nicotine consumption might stabilize RH-functions, particularly in individuals with high CogDis scores. In order to test this prediction individuals with higher nicotine dependence would have to be tested.

The findings relating to IntAn, a negative schizotypal feature, were unexpected since negative schizotypy has previously been a largely insensitive marker for hemispheric asymmetry (see Liouta, et al., 2008; Suzuki & Usher, 2009 for recent accounts).

Performance in the LDT (none of the dependent LDT measures were related to IntAn scores), but not in the FDT, would support this notion. In our non-smoking sample, increasing IntAn scores were predictive of a decrease in WF processing. Luh and Gooding (1999) observed that participants endorsing high positive schizotypal features were left-biased for faces, but those with high social anhedonia scores lacked this LF bias, which suggests a bimodal distribution (i.e., either showing a strong LF or RF bias) (Leonards & Mohr, 2009). In two different samples, UnEx scores, but not CogDis scores, predicted a decreased LF bias for emotional composite faces (Mason & Claridge, 1999). In one of these studies, IntAn scores in women predicted a decreased LF bias. Importantly, none of the studies reported on WF performance (Luh & Gooding, 1999; Mason & Claridge, 1999) and our own findings would indicate that impaired performance in the FDT with increasing IntAn scores reflects a more general social and/or facial processing impairment in non-smokers (Haxby, Hoffman, & Gobbini, 2000; Kanwisher, McDermott, & Chun, 1997; Onitsuka et al., 2006; Pinkham, Hopfinger, Ruparel, & Penn, 2008), particularly given that non-smokers tended to score higher on IntAn as compared to smokers.

Limitations to the study

While we pre-selected participants for their right-handedness, right-handedness seems reduced in schizophrenia (Dragovic & Hammond, 2005) and schizotypy (Somers, Sommer, Boks, & Kahn, 2009) and, as such, this pre-selection might have compromised our ability to investigate a population that is truly psychosis-prone. While valid as a potential limitation of the current study, this pre-selection procedure is common practice in the study of hemispheric asymmetry in schizotypy (e.g. Mason & Claridge, 1999; Mohr, Krummenacher, et al., 2005; Suzuki & Usher, 2009) and generally in the study of hemispheric asymmetry (Bourne, 2006) since the testing of only right-handed

participants reduces the number of potential "confounds", i.e. that of a reduced hemispheric asymmetry due to handedness. However, because of the important role of reduced right-handedness to both enhanced schizotypy and reduced hemispheric asymmetry, it only seems reasonable to suggest that future studies should investigate a more representative sample that is unselected for handedness (or actually select a wider range of hand preferences (e.g. Shaw, et al., 2001; Somers, et al., 2009).

Another limitation was our control of nicotine consumption. For instance, our smoking group consisted of a group of light smokers rather than heavy smokers for whom nicotine influences on behaviour might have been more pronounced (Myers, Taylor, Moolchan, & Heishman, 2008). Some previous studies directly challenged nicotine availability by providing nicotine patches/nicotine cigarettes (Gentry, et al., 2000; McClernon, et al., 2003). Nicotine exerts differential cognitive effects depending on whether administration is acute or chronic (M. Ernst, et al., 2001; Jacobsen, et al., 2005; McClernon, et al., 2003; Rose, et al., 2007). Additionally, nicotine activates receptors in different brain regions depending on the amount of nicotine exposure (e.g. Kumari & Postma, 2005); for instance, in an EEG study higher nicotine doses seemed to result in a LH shift of EEG power (i.e., decreased LH α-power and increased RH β-power) (Norton, et al., 1992). Nicotine dependence was relatively low in our study (Esterberg, et al., 2007; Etter, et al., 1999), yet within normal ranges for an unselected group of smokers (Heatherton, et al., 1991). Future research would certainly benefit from comparing chronic and acute nicotine exposure as well as administering varying amounts of nicotine directly.

Summary

In sum, we tested whether nicotine consumption might be a better predictor of hemispheric asymmetry than schizotypy in 40 right-handed men. We were particularly interested in whether attenuated hemispheric asymmetry would be more evident as a function of smoking status and nicotine dependence than (positive) schizotypy, or its interaction. Our findings partially support this idea. Increasing nicotine dependence (but not smoking status *per se*) was related to a RH shift in hemispheric function for both a left- and right-hemisphere dominant task. These results indicate that nicotine use is relevant to the study of laterality and schizotypy, and might also be pertinent to the study of compulsive/impulsive behaviour generally. With regards to schizotypy, CogDis seemed to be a more promising schizotypal dimension than UnEx in predicting attenuated language dominance (irrespective of smoking status). IntAn seemed to relate to face processing impairments more generally, particularly in non-smokers. Given our smokers' relatively low nicotine dependence and schizotypy scores, future studies should test individuals consuming higher doses of nicotine, and control more directly how much (e.g., nicotine dosage), in which form (slow: patches, fast: inhalation) and when (time before testing) nicotine is consumed with regards to testing. Such future studies might help to further elucidate the role of drug use on links between behaviour and schizotypal symptoms as potential indicators of psychosis risk or psychosis protection. As a final note, most previous studies in the area reported on *either* a LH or RH dominant task (but not both). If we had only used the LDT, we would have found "evidence" for a reduction in LH language functions with increasing FTND scores, but no overall RH shift in function.

6. Acknowledgements

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C. Study 2: Cannabis

Running title

Cannabis, schizotypy and cognitive functioning

Reference

Herzig, D. A., Nutt, D. & Mohr, C. (submitted). Does cannabis use impair frontal lobe functioning? The role of alcohol, nicotine, and schizotypy.

1. Abstract

The prevalence of cannabis use is particularly high amongst young adults and early onset of cannabis use is associated with an earlier onset of psychotic illnesses. However, most people using cannabis will not develop psychotic disorders, so other risk factors must exist that render individuals more vulnerable to the adverse consequences of cannabis use. Two potential candidates are schizotypy and polydrug (including licit drug) use. In high schizotypes, cannabis and licit drug use is elevated, and they show similar cognitive attenuations as those suffering from psychotic illness and cannabis/polydrug use, e.g. in frontal lobe functioning. Therefore, attenuation of frontal lobe functioning may be a cognitive marker of pathology, but given the higher substance use rates amongst high schizotypes cannabis or licit drug use may have influenced previous findings along the schizophrenia spectrum. To test this idea, verbal short-term and working memory, cognitive flexibility, schizotypy and drug use were assessed in 35 pure cannabis users and 48 non-users. While pure cannabis use related to impairments in verbal short-term memory, working memory was influenced by alcohol use instead. As schizotypy seemed rather unrelated to performance in healthy controls, the results suggest that substance use, and licit drug use in particular, is an important variable to consider in future schizotypy studies. Additionally, the heterogeneity of findings for the specific cognitive tasks may reflect the difficulty of identifying consistent cognitive markers sensitive to pathological changes. Using composite scores of test batteries and including other potentially influential factors are proposed as possible solutions.

Keywords: Polydrug use, licit drug use, cognition, working memory, verbal short term memory, cognitive flexibility, schizotypy, psychosis-proneness

2. Introduction

Cannabis sativa (marijuana) is currently the most widely used non-legal substance in Europe (EMCDDA 2010 report). About 23 million Europeans have used cannabis in the last year, which corresponds to an average of 6.8 % of all 15- to 64-year-olds (EMCDDA, 2010 report). Additionally, an estimated 12.5 million Europeans used the drug in the last month prior to the interview, or 3.7 % (on average) of all 15- to 64-year-olds. Among the European 15- to 24-year-olds, estimated average prevalence rates are even higher ranging from 16 % for reported last year use to 8.4 % for reported last month use (EMCDDA, 2010 report). In Switzerland, the rates of young cannabis users that meet DSM-IV criteria for cannabis dependence is also quite high (see Cascone, Zimmermann, Auckenthaler, & Robert-Tissot, 2011 for overview). This relatively elevated prevalence rate amongst young adults is concerning when considering that cannabis use might go along with both cognitive attenuation (Barkus & Murray, 2010; Fernández-Serrano, et al., 2011) and an increased risk for mental health problems, in particular psychosis (Arseneault et al., 2002; Casadio, et al., 2011; Schimmelmann, et al., 2011; van Os, et al., 2002; Zammit, et al., 2002). Yet, not all studies unequivocally subscribe to these disconcerting messages, and other factors may influence the adverse consequences associated with cannabis use [see meta-analysis by Moore et al (2007)].

In the present study, our major focus was on the supposedly negative implications of cannabis use on cognitive functioning while accounting for associated licit drug use and individuals' schizotypy for the following reasons. Relatively pure cannabis users are reported to have attenuated frontal lobe functioning, e.g. immediate and delayed memory and reasoning (Fried, et al., 2005), verbal short-term memory (Wagner, et al., 2010), and mental flexibility (see also Fernández-Serrano, et al., 2011; Lundqvist, 2005 for overview; Pope & Yurgelun-Todd, 1996). Relatively common, researchers report on

the use of other illicit drugs, or exclude participants who used these (Fernández-Serrano, et al., 2011). Less common is the control for licit drugs such as alcohol and tobacco, although use of both drugs is elevated in cannabis users (see also Bélanger, Akre, Kuntsche, Gmel, & Suris, 2011; Fernández-Serrano, et al., 2011; Pape, Rossow, & Storvoll, 2009). When considering licit drug use in the just mentioned studies, it is observed that licit substance use (e.g. nicotine and alcohol use) was occasionally (Fried, et al., 2005; Pope & Yurgelun-Todd, 1996), but not always (C. J. A. Morgan, et al., 2010; Skosnik, et al., 2001) controlled for (either statistically, or by excluding participants who report additional drug use). Other groups asked participant to abstain from additional (licit and illicit) drug use before testing (Block & Ghoneim, 1993), or excluded participants reporting excessive alcohol use/ dependence (Pope, Gruber, Hudson, Huestis, & Yurgelun-Todd, 2001; Solowij et al., 2002). Alcohol, however, might result in cognitive attenuation much in the same way as suggested for cannabis involving functions such as verbal memory (Parada et al., 2011; Petros, Kerbel, Beckwith, Sacks, & Sarafolean, 1985; Poltavski, Marino, Guido, Kulland, & Petros, 2011), cognitive flexibility (Guillot, Fanning, Bullock, McCloskey, & Berman, 2010; Lyvers & Tobias-Webb, 2010) and working memory (Crego et al., 2010; Weissenborn & Duka, 2003; Yücel, Lubman, Solowij, & Brewer, 2007). The same can be said for nicotine with negative implications on working memory (M. Ernst, et al., 2001; Jacobsen, et al., 2005), verbal memory (Dunne, et al., 1986; Jacobsen, et al., 2005; Poltavski & Petros, 2005), and cognitive flexibility (Nesic, Rusted, Duka, & Jackson, 2011). Given the comparable implications of cannabis, alcohol, and nicotine on cognitive functioning, it is not possible to claim that impairments are specific to cannabis use.

In the present study, we also account for individuals' schizotypy, a thinking style that is qualitatively similar, but quantitatively attenuated to the one reported from psychotic patients. The schizotypy approach assumes that schizophrenia(-like) symptoms exist on a spectrum with severest symptoms being found in patients with schizophrenia and mildest sub-clinical symptoms being experienced in the least affected schizotypal individual in the general population (Meehl, 1962). Schizotypy is typically assessed in the general population using self-report questionnaires (L. J. Chapman, et al., 1994; Launay & Slade, 1981; Mason, et al., 1995; Raine, 1991; Rust, 1988; Stefanis et al., 2002; Venables, Wilkins, Mitchell, Raine, & Bailes, 1990) with high scores indicating enhanced psychosis-proneness (L. J. Chapman, et al., 1994; Gooding, et al., 2005). Support for the spectrum idea of schizophrenia comes from studies showing that the symptom dimensions proposed for patient populations can be replicated in the general population as revealed by a three-factor solutions consisting of positive schizotypy (e.g. cognitive-perceptual distortions, unusual experiences, magical thinking, paranoia etc.), negative schizotypy (e.g. social/physical anhedonia) and disorganization (e.g. odd speech and behavior, difficulties with decision-making and/or attention, etc.; Raine, 1991, 2006). Further support for the spectrum idea comes from studies showing that high schizotypes yield relatively impaired frontal lobe functioning (comparable with patient populations) as assessed from tasks on working memory (Park & McTigue, 1997; Pflueger, et al., 2007), verbal fluency (Tsakanikos & Claridge, 2005; Koychev et al., 2011), cognitive flexibility (Giraldez, et al., 1999), selective attention (Pflueger, et al., 2007) and verbal memory (Langdon & Coltheart, 2004; Simon, et al., 2007).

In the present context, we accounted for schizotypy, and by inference the schizophrenia spectrum, because individuals scoring high on schizotypy reveal an elevated substance

use of cannabis (Barkus & Lewis, 2008; A. S. Cohen, et al., 2011; Esterberg, et al., 2009; Fridberg, et al., 2011; Skosnik, et al., 2001), but also of nicotine (Esterberg, et al., 2009; Larrison, Briand, & Sereno, 1999), and alcohol (Esterberg, et al., 2009; Larrison, et al., 1999). This higher drug use is relevant for the schizophrenia spectrum, because patients as compared with controls also consume higher amounts of cannabis (Barkus & Murray, 2010; Zammit, et al., 2002), nicotine (de Leon, et al., 2002; Kumari & Postma, 2005), and alcohol (Cantor-Graae, et al., 2001; Gregg, Barrowclough, & Haddock, 2007; Mastrigt, Addington, & Addington, 2004). Given that drug use might have negative implications on the same cognitive functions also attenuated along the schizophrenia spectrum, and that more drugs are consumed along the schizophrenia spectrum, we cannot exclude the possibility that any influence cannabis might have on cognition is associated with individuals' higher schizotypal features. The most likely schizotypal symptom dimensions are cognitive disorganization (Barkus & Lewis, 2008; A. S. Cohen, et al., 2011; Esterberg, et al., 2009) and / or positive schizotypal features (Compton, Chien, & Bollini, 2009; Skosnik, et al., 2001; Verdoux, Sorbara, Gindre, Swendsen, & van Os, 2003), with predictions for negative schizotypy being hindered by heterogeneous findings (Bailey & Swallow, 2004; A. S. Cohen, et al., 2011; Compton, Chien, et al., 2009; Mass, Bardong, Kindl, & Dahme, 2001; Skosnik, Park, Dobbs, & Gardner, 2008). To note, the few studies that would provide a hint on the role of schizotypy on the link between cannabis use and cognition did not report on a potential effect of licit drug use (C. J. A. Morgan, et al., 2010; Skosnik, et al., 2001), e.g. nicotine and alcohol use.

The present study investigated the link between cognitive attenuation and cannabis use in pure cannabis users (CU) and non-using controls (nCU) accounting for the potential additional influence of licit drug use (alcohol, nicotine) and individuals' schizotypal

features. We expected CU to reveal cognitive attenuation as compared to nCU, but also that any cognitive attenuation might be associated with licit drug use, likely to be a more important factor than schizotypy (Herzig & Mohr, in press; Herzig, et al., 2010).

3. Method

Participants

Participants were recruited via advertisements distributed in the local University departments and venues, the University of Bristol 'Experimental Hours' scheme for course credits, and local websites ('Gumtree'). We recruited 83 healthy native English speaking participants, 35 of which were CU (23 males) and 48 nCU (20 males). Participants either received monetary compensation for travel expenses or course credits for taking part.

Screening

Prior to study inclusion, participants were made aware that they would have to hand in a urine sample for drug screening, and were then asked about regular illegal substance use (apart from cannabis) within two weeks prior to testing. They were also asked about their cannabis use habits in the past 30 days. The participants were kept unaware about the spectrum of drugs assessed with the urine test, which measured only THC-content. This was done to encourage volunteers to reveal use of other drugs before the testing, and verified the regularity of cannabis use as indicated by self-report. Participants were excluded when reporting additional illicit drug use (apart from cannabis use). CU with negative drug tests were classified as occasional users if it matched their self-report. If the self-report deviated from their urine test, their data were removed from further analysis. The nCU were healthy controls screened for regular nicotine use in the past three months. In both groups, people were excluded if they reported excessive alcohol

use (>50 units of alcohol/week for men, >35 units of alcohol/women), neurological, psychological or psychiatric history, or problems with their visual system (including dyslexia).

Procedure

Participants were firstly screened by means of the procedure outlined above. After this, participants had to come into the Department of Experimental Psychology for the testing session, which lasted about an hour. The CU were asked to abstain from cannabis use at least 2h prior to testing and nicotine use 30min prior to testing. All participants were given an information sheet before signing the consent form which informed them about the aims and procedure of the experiment. Afterwards, they handed in a urine test and then the testing session started. Subjects were firstly given the questionnaires on detailed drug use and schizotypy, and then performed the frontal lobe tasks outlined below[1]. The order of these tasks was randomized to avoid habituation- and/or fatigue effects. Finally, participants were debriefed and reimbursed for their time.

Questionnaires

(1) Schizotypy

The Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE; Mason & Claridge, 2006; Mason, et al., 1995) is a self-report instrument containing 159 questions. Positive schizotypy is assessed by 30 items pertaining to Unusual Experiences (UnEx, maximum score 30, including items such as 'Are your thoughts sometimes so strong that you can almost hear them?'), negative schizotypy is assessed by 27 items pertaining to Introvertive Anhedonia (IntAn, maximum score 27, including items such as 'Do you prefer watching television to going out with people?'), and

[1] We also assessed laterality with tachistoscopic lexical and facial decision tasks. For economy of presentation, these findings will be presented elsewhere, but data and findings from these tasks can be requested from the corresponding author.

Cognitive Disorganization is assessed by 24 items (CogDis, maximum score 24, including items such as ‘Are you easily confused if too much happens at the same time?‘). Finally, 23 items assess Impulsive Nonconformity (ImpNC, maximum score 23), which does not represent a schizotypy dimension (Mason, et al., 1995), but will be accounted for in the present study because of the strong link between impulsivity and addiction (Crews & Boettiger, 2009). Normative values can be found in Mason et al. (2006; 1995).

(2) Drug questions

Participants were asked to fill in drug use information, e.g. their alcohol, nicotine, cocaine, cannabis and amphetamine use. The questions were taken from the national household survey on drug abuse(United States Department of Health and Human Services, 1998), which asks detailed data of respondents’ prior drug use, with assessment of lifetime, past year and past month drug use assessed. Additionally, it taps into the DSM-IV criteria for drug dependence in the past 12 months by asking about e.g. time spent to obtain, use, or recover from the drug, tolerance (marked increase in amount; marked decrease in effect), substance taken in larger amount and for longer period than intended, persistent desire or repeated unsuccessful attempt to quit, and important social, occupational, or recreational activities given up or reduced due to drug use. Additionally, it enquires about psychological and physical problems caused by the drug in question (e.g. withdrawal symptoms such as depression). For each of these symptoms indicated in the past 12 months, participants received 1 point (maximum score 7), and higher values indicate higher substance dependence.

Behavioural measures

(3) Frontal lobe functioning[2]

i. Trail making task (TMT)

The TMT is used to test executive functioning. It was originally part of the Army Individual Test Battery (1944), and was incorporated into the Halstead–Reitan Battery (Reitan & Wolfson, 1985). In the Trail making test A, participants have to draw a line on numbered circles in chronological order (1 to 25), as fast as possible. On TMT B participants are presented with circles containing numbers and letters, and are instructed to draw a line in chronological order from 1 to 13, and A to L, but to switch back and forth between numbers and letters. Therefore, participants have to draw a line from 1 to A, from A to 2, from 2 to B etc. The reaction time of both tasks is recorded, and an index subtracting RT's of TMT-A from RT's of TMT-B results in an estimate of cognitive flexibility (Lezak, 1995) adjusted for individual differences in motor functioning and visual search strategies (Reitan & Wolfson, 1985). Norm values are available from Tombaugh (2004).

ii. Verbal short term memory (Story-recall/logical memory)

Verbal short term memory was tested with a subtest of the revised version of the Wechsler adult intelligence scale (Wechsler, 1987). We asked participants to immediately repeat a 60 words story that was read to them by the experimenter, and recall as many details as possible. The story details were given in units. For each correctly recalled unit the participant received 1 point. Half a point was given if information was paraphrased despite the wording being slightly different. For instance, if the sentence was: "*The Officers, / touched by the woman's story, / had a collection /*

[2] We measured a computerised Go NoGo task as well. Due to an overall ceiling performance, we omitted this task from all further analysis. Detailed information on this task can, however, be requested from the first author.

for her.", and participants literally repeated "*touched by the woman's story"* as a unit, they would receive 1 point. If they paraphrased the unit, e.g. by saying "*felt sorry for the woman*", they would receive half a point. A total of 23 possible points could be acquired. Normative data for young adults and University samples can be found in Bowden et al. (1999) and Ivison (1993), respectively.

iii. Verbal working memory (2-back task)

Comparable to previous published reports (Owen, et al., 2005; Schoofs, et al., 2008), participants saw 64 digits, (ranging from 1 – 9), sequentially presented, in the middle of the computer screen (white on black background, font Arial, size 16). Participants were instructed to press a given response key when the current digit (*n*) was identical to the digit *n*-2 (target trials). In all non-target trials, participants had to press another response key. Half the participants responded with the left SHIFT-key for target trials and the right SHIFT-key for non-target trial. Response key allocation was reversed for the other half of participants.

A third of the trials ($n = 20$) were target trials, and the remaining trials were non-target trials [$n = 44$ (e.g. Schoofs, et al., 2008)]. To increase task difficulty intrusion trials were added, ensuring that participants were not able to restart memorizing after each successful identification of a target, as sometimes targets occurred twice in a row. Each stimulus was presented for 2 seconds, with an inter-stimulus interval of 500ms (Barch, Sheline, Csernansky, & Snyder, 2003). Presentation of the stimuli was continuous, and if participants did not respond within this time, the next digit was presented and the response was counted as an omission. No feedback was given to participants about their performance. All participants performed 16 practice trials. We measured the percentage of the correctly identified targets, as well as mean RTs for target trials (e.g. Jonides et al., 1997; Schoofs, et al., 2008).

Data analysis

To determine if cannabis use affects frontal lobe functioning, we conducted separate univariate ANOVAs with group (CU, nCU) as between-subjects factor on the percentage of correct responses [(amount of correctly identified target stimuli *100)/total of targets] and RT in the 2-back task, the TMT-index (TMT B scores – TMT A scores) and the percentage of correctly identified units in the story recall task [(amount of correctly identified units *100)/total of units)].

In order to establish an effect of drug use and schizotypy on frontal lobe functioning, we firstly investigated the demographic characteristics of our population, and found that the sex distribution differed between the drug groups (see result section for details). We then correlated age and handedness with the outcome measures to determine the relevance of these control variables for the regression model (see result section for details). Since neither age nor handedness significantly correlated with frontal lobe functioning, we performed hierarchical regressions as follows. Sex was entered in the first step, drug dependence (nicotine, alcohol and cannabis) was entered in the second step, and schizotypy (UnEx scores, CogDis scores IntAn scores, Imp scores) in the third step. Thus, three blocks of predictors were entered in nested blocks, meaning that each subsequent block contained all prior predictors and the additional predictors from the current block. Presentation of results however will only include the new predictors entered, for economy of presentation. The full model can be found in the Appendix of this dissertation (see Table 25). Because all tolerance values were above .2 (Menard, 1995), and all independent variables were mean-centered, multi-collinearity between the independent variables was considered negligible. The dependent variables were: i) percentage correctly identified targets and mean RT for correctly identified targets and

non-targets in the 2-back task; ii) TMT-index and iii) percentage of correctly recalled units in the story recall task.

Kolmogorov–Smirnov tests for the groups separately revealed normal distribution for all behavioral measures. All *p*-values were two-tailed and the α-level was set at .05.

4. Results

Participants

Of the 83 healthy native English speaking controls, 35 pure cannabis-using participants were identified, six occasional users (17%) with negative THC-urine tests, 11 regular users (31%) and 18 (51%) frequent users, the latter two groups with positive urine tests for THC-content. Frequent use was defined as using cannabis at least four times per week, regular use as using cannabis between once and three times per week, and occasional use was defined as using cannabis less than once/week, but within the past three months. Within the CU group, 13 people were educated to college level (37%), one to secondary school (3%), and 21 to University degrees (60%). Of the 48 people in the control group, there were 12 people with finished college degrees (25%) and 36 with University degrees (75%). A chi-square test indicated that the two groups did not differ from each other in terms of highest finished education level [$X^2(df = 2) = 3.03$, $p = .22$]. However, there were significantly more males ($n = 23$) in the cannabis using group as compared to the non-using group [$n = 20$; $X^2(df = 1) = 4.69$, $p = .03$].

As can be seen from Table 8, participants did not differ in age and handedness. However, CU as compared to nCU scored higher on UnEx (as a trend) and ImpNC,

cigarettes per week, joints per week, nicotine dependence, alcohol dependence, and cannabis dependence.

Table 8. *Demographical and drug use statistics for the total sample as well as CU and nCU, separately. Values were compared between groups using independent t-tests. We report the statistical results in this table (t-values, df = 81; p-values). Significant group differences are highlighted in bold.*

	All (*N*=83)		**Cannabis users (*N*=35)**		**Controls (*N*=48)**			
Variables	***Mean***	***SD***	***Mean***	***SD***	***Mean***	***SD***	***t***	***p***
Age	22.02	4.54	22.51	5.63	21.67	3.56	0.84	0.40
Handedness	11.36	0.90	11.49	0.85	11.27	0.94	1.07	0.29
UnEx [a]	6.36	4.92	7.63	6.04	5.44	3.71	1.90	**0.06**
CogDis [b]	10.61	5.28	10.46	5.75	10.73	4.97	-0.23	0.82
IntAn [c]	4.54	3.67	4.26	3.53	4.75	3.78	-0.60	0.55
ImpNC [d]	9.06	3.70	9.97	4.11	8.40	3.25	1.95	**0.05**
Cigarettes/week	10.40	22.16	24.66	28.67	0.00	0.00	5.09	**0.00**
Joints/week	4.70	9.59	11.14	12.16	0.00	0.00	5.42	**0.00**
Nicotine dependence	0.87	1.55	1.94	1.86	0.08	0.45	5.78	**0.00**
Cannabis dependence	1.25	1.94	2.97	1.95	0.00	0.00	9.03	**0.00**
Alcohol dependence	1.72	1.67	2.29	1.84	1.31	1.42	2.72	**0.01**

[a] Unusual experiences; [b] Cognitive Disorganisation; [c] Introvertive Anhedonia; [d] Impulse Non-conformity;

Frontal lobe functioning

The separate univariate ANOVAs with cannabis use (CU, nCU) as between subject factor on the outcome measures in the frontal lobe tasks revealed that CU performed significantly worse in the story recall task and slightly worse on the working memory

task as compared to nCU (Table 9). The results for the remaining tasks were not significant (Table 9).

Table 9. *Descriptives and values from the multivariate ANOVA. Significant values are highlighted in bold, trends in grey.*

	All (*N*=83)		**CU (*N*=35)**		**nCU (*N*=48)**				
Variables	***Mean***	***SD***	***Mean***	***SD***	***Mean***	***SD***	***F(1,81)***	***p***	***Partial eta²***
2-back % target correct	88.61	10.86	86.00	13.49	90.52	8.07	3.62	**0.06**	0.04
2-back mean RT	821.90	188.30	822.57	164.00	821.42	205.92	0.00	0.98	<0.01
TMT [a] index	23.65	15.30	23.77	13.58	23.56	16.58	0.00	0.95	<0.01
Story recall % correct	62.44	14.40	55.90	14.78	67.21	12.19	14.55	**<0.01**	0.15

[a] Trail making task;

Regression

Correlations between scale scores revealed that neither age nor handedness related to frontal lobe functioning (all *p*-values > .10), and therefore these variables will not be considered further in the analyses. However, due to the significantly higher proportion of males in the CU group, sex will be entered as a control variable.

As can be seen from Table 10, sex significantly predicted verbal short-term memory performance. Post-hoc independent *t*-tests revealed that women were significantly better than men in the story recall task [women: *m* = 66.63%, *SD* = 12.08, men: *m* = 58.54%, *SD* = 15.39; *t*(81) = -2.65, *p* = .01]. Entering drugs in the second step predicted significant amounts of variance in the outcome measures. Here, alcohol dependence predicted lower working memory performance, and cannabis predicted reduced verbal short-term memory on top of sex. Entering schizotypy in the third step predicted

additional variance on top of the drug variables and sex only in story recall (see Table 10). Here, higher ImpNC values predicted better story recall.

Table 10. *Regression assessing the effect of sex (step 1), drug dependence (nicotine, alcohol and cannabis dependence; step 2), and schizotypy (Unusual Experiences, Cognitive Disorganisation, Introvertive Anhedonia and Impulse Non-conformity; step 3) on frontal lobe functioning.*

Outcome variables	**Step**	**Significant predictor**	***β*-value**	**Total R^2**	**ΔR^2**	***F* for ΔR^2**
2-back % target correct	2	Alcohol	**-0.24***	**0.14****	**0.14****	**4.25****
2-back mean RT	1	Sex	**-0.21†**	**0.04†**	**0.04†**	**3.61†**
	2	Alcohol	**0.39*****	**0.18****	**0.13****	**4.19****
Story recall % correct	1	Sex	**0.28****	**0.08****	**0.08****	**7.02****
	2	Cannabis	**-0.37****	**0.28*****	**0.20*****	**7.22*****
	3	CogDis[a]	**-0.21***	**0.39***	**0.11***	**3.34***
	3	ImpNC[b]	**0.36****	**SAA***	**SAA**	**SAA**

*† p≤.10; * significant at p≤.05; ** significant at p≤.01; *** significant at p≤.001*

[a] Cognitive disorganization; [b] Impulsive Non-Conformity; [c] Same as above

5. Discussion

Cannabis is one of the most frequently used substances amongst European youth, and its use has been associated with negative implications such as cognitive attenuation (Barkus & Murray, 2010; Fernández-Serrano, et al., 2011) and an elevated risk for psychosis (Arseneault, et al., 2002; Casadio, et al., 2011; Schimmelmann, et al., 2011; van Os, et al., 2002; Zammit, et al., 2002). However, the relationship is not as clear-cut

as some authors have pointed out. For instance, in patients with schizophrenia using cannabis, cognitive functions seem superior to non-using patients (Rabin, et al., 2011). Also, most individuals using cannabis will never develop a psychotic illness (e.g. Andreasson, et al., 1987; Arseneault, et al., 2002; Hall & Degenhardt, 2000; Schimmelmann, et al., 2011; van Os, et al., 2002; Zammit, et al., 2002; Zammit et al., 2008). Additionally, cannabis is rarely used alone, being usually associated with alcohol and nicotine use, but these have rarely been taken into account in the triadic investigation of cannabis use, cognition, and psychosis (-risk). To investigate whether cannabis use hampers cognitive performance, or whether cognitive attenuation is better explained by associated licit drug use and psychotic-like features (schizotypy), we here investigated CU and nCU on cognitive functions commonly associated with the frontal lobe, accounting also for alcohol and nicotine use, as well as individuals' self-reported schizotypal features. The main findings from this study were that i) CU as compared to nCU performed worse on story recall and slightly worse on the 2-back task, but not on the TMT, ii) regression analysis showed that enhanced alcohol use predicted impaired working memory deficits, whereas enhanced cannabis use predicted decreased verbal short-term memory, and iii) none of the schizotypy subscales explained any additional variance in frontal lobe functioning (apart from ImpNC and CogDis for story recall), iv) CU scored higher than nCU on positive schizotypy (as a trend), ImpNC and drug use other than cannabis. The implications of these findings are discussed below.

The role of cannabis use

Our results showed that the implications of cannabis use are rather negative than positive (or neutral) because our CU performed worse than nCU on tasks measuring verbal short term memory, and showed a reduced performance in verbal memory (story recall) with increasing cannabis use. This is in line with previous studies (Fernández-

Serrano, et al., 2011; Ranganathan & D'Souza, 2006; Wagner, et al., 2010). Our results also showed that these relatively negative cognitive implications were not further enhanced with individuals' self-reported schizotypy. However, story recall (verbal memory) was the only task that was affected by cannabis use, whereas relative impaired performance on another cognitive task (working memory as assessed with the 2back-task) was related to enhanced alcohol use instead. Previous studies have indicated that cannabis use should have a negative impact on working memory performance (see Ranganathan & D'Souza, 2006 for overview) and mental flexibility (see also Fernández-Serrano, et al., 2011; Lundqvist, 2005 for overview) as well. Our findings suggest that these previous findings on cannabis were potentially confounded by concomitant alcohol use (see Fernández-Serrano, et al., 2011 for overview; Zeigler et al., 2005).

Despite some evidence that cannabis use is still associated with cognitive impairments after adjusting for alcohol use (Medina, Hanson, et al., 2007), independent studies (Schimmelmann, et al., 2011) report that cannabis users tend to consume higher amounts of other drugs as well. This additional drug use, because it is frequently not assessed, might have led to misleading conclusions about the effect of cannabis use on cognitive functioning. Particularly licit drug use like alcohol seems to be a relevant confound. For instance, whereas in some studies alcohol use is either statistically controlled for (Fried, et al., 2005; Pope & Yurgelun-Todd, 1996), or subjects with alcohol abuse are excluded from participating (Wagner, et al., 2010), other studies do not do this (Skosnik, et al., 2001). Worse, alcohol and cannabis are thought to exert comparable effects on cognition, i.e. cognitive attenuation in verbal memory (Parada, et al., 2011; Petros, et al., 1985; Poltavski, et al., 2011), cognitive flexibility (Guillot, et

al., 2010; Lyvers & Tobias-Webb, 2010) and working memory (Crego, et al., 2010; Weissenborn & Duka, 2003; Yücel, et al., 2007). Therefore, future studies should aim to include this variable as potential confound when investigating the effects of cannabis use on cognition.

The role of schizotypy

Of additional significance was the observation that schizotypy did not explain variance in most cognitive tasks beyond what was already explained by drug use. We do not think that this finding can be explained by deviant features of our sample, because we replicated many previous observations that CU as compared to nCU scored slightly higher on measures of positive schizotypy (e.g. A. S. Cohen, et al., 2011; Compton, Chien, et al., 2009; Fridberg, et al., 2011; Skosnik, et al., 2008; Skosnik, et al., 2001; Verdoux, et al., 2003) and measures of impulsivity (e.g. ImpNC; Chamberlain & Sahakian, 2007; Crews & Boettiger, 2009; Koob & Volkow, 2010; Verdejo-García, Lawrence, & Clark, 2008) reflecting the populations' representativeness, at least in these regards. The lack of the schizotypy measures to be importantly related to frontal lobe functioning would indicate that impairments in frontal lobe functioning like working memory (Park & McTigue, 1997; Pflueger, et al., 2007), verbal fluency (Kopp, Wolff, Hruska, & Reischies, 2002; Laurent et al., 2000; Tsakanikos & Claridge, 2005; Voglmaier et al., 2005; Voglmaier, Seidman, Salisbury, & McCarley, 1997), cognitive flexibility (Blanchard et al., 2010; Diforio, et al., 2000; Giraldez, et al., 1999; Laurent, et al., 2000; Voglmaier, et al., 1997), and verbal memory (Langdon & Coltheart, 2004; Simon, et al., 2007) may not be due to individuals' schizotypal symptoms but result at least partially from co-morbid drug use.

When trying to follow up this argument, unfortunately the above mentioned studies did not report on drug use (Blanchard, et al., 2010; Diforio, et al., 2000; Giraldez, et al., 1999; Langdon & Coltheart, 2004; Park & McTigue, 1997; Simon, et al., 2007; Tsakanikos & Claridge, 2005), or only screen for substance use history without specifying the substances controlled for (Kopp, et al., 2002; Laurent, et al., 2000; Pflueger, et al., 2007; Voglmaier, et al., 2005; Voglmaier, et al., 1997). It is thus possible that substances (e.g. illicit as well as licit) influenced the relationship between schizotypal symptoms and the frontal/executive functions assessed in these experiments (e.g. Herzig & Mohr, in press; Herzig, et al., 2010). In particular, our results would suggest that cannabis may be more relevant than schizotypy for the cognitive attenuations in verbal short-term memory, and alcohol to be more relevant than schizotypy for the cognitive attenuations in working memory performance.

The specific effects of cannabis use on story recall, but not the 2-back or trail making task may also suggest that not all cognitive functions are equally sensitive to cannabis related attenuations. Even though many studies observe CU to show impairments compared to nCU on tasks measuring working memory (see Ranganathan & D'Souza, 2006 for overview) and mental flexibility (see also Fernández-Serrano, et al., 2011; Lundqvist, 2005 for overview), this may not always be the case [working memory (Grant, Chamberlain, Schreiber, & Odlaug, 2012), cognitive flexibility (Solowij, et al., 2002)]. Due to this lack of specificity many researchers use set scores / composite scores of test batteries (see Barrantes-Vidal et al., 2003; Brewer et al., 2006 for overview), or look at changes in the correlations between different cognitive markers as indicators of pathological processes (Cadenhead & Braff, 2002). These approaches may

be useful tools to consider in subsequent studies on the link between cannabis, cognition and psychosis.

Additionally, different meta-analyses draw inconsistent conclusions about which cognitive functions qualify as cognitive markers, or endophenotypes for pathological changes. Not only are findings in cannabis users inconsistent, but also along the schizophrenia spectrum. For instance, studies report consistent verbal memory impairments in psychosis (Heinrichs, 2004; Mesholam-Gately, Giuliano, Goff, Faraone, & Seidman, 2009) and cannabis use (see also Crean, Crane, & Mason, 2011; Solowij & Michie, 2007 for overview), whereas others find cognitive flexibility to be impaired in relatives (Sitskoorn, Aleman, Ebisch, Appels, & Kahn, 2004) or psychosis patients (Mesholam-Gately, et al., 2009), or consistent working memory impairments in both patient populations and cannabis users (Crean, et al., 2011; Mesholam-Gately, et al., 2009; Solowij & Michie, 2007). One problem when investigating this triad of cannabis, cognition and psychotic-like thinking is the complexity of the relationship between these factors and others influencing it. For instance, many factors such as genetic predisposition (Ho, Wassink, Ziebell, & Andreasen, 2011), IQ (Pope et al., 2003) and neurochemical peculiarities such as dopamine receptor availability (Bossong et al., 2009; Kuepper et al., 2010) may influence the effect cannabis exerts on cognitive functions. These factors are also relevant for the link between psychosis and drug use, e.g. genetic predisposition (Caspi et al., 2005; Estrada et al., 2011), IQ (Khandaker, Barnett, White, & Jones, 2011; Leeson, Barnes, Hutton, Ron, & Joyce, 2009 for overview; Matheson & Langdon, 2008), and neurochemical peculiarities such as dopamine receptor availability (see Kuepper, et al., 2010 for overview). However, it is impossible to account for all putatively influential variables, and hence additional

studies need to be conducted to replicate the importance of drug use in schizotypy research, be it clinical, experimental and/or epidemiological studies.

Study limitations and future research

While it may be close to impossible to find a Western sample of cannabis users that does not also use alcohol, the co-use of nicotine seems even more unavoidable. Cannabis is mostly used in combination with nicotine, a procedure known as 'mulling' (Bélanger, et al., 2011). Cannabis use might predict future nicotine use (Suris, Berchtold, Akre, Belanger, & Michaud, 2010), and those who also consume nicotine without cannabis might show lower educational attainment than those who only use nicotine in combination with cannabis (Suris, Akre, Berchtold, Jeannin, & Michaud, 2007). To what extent this differential influence of nicotine on cognitive functioning might relate to the direct neurochemical influences of nicotine and cannabis, or to indirect socio-educational mechanisms remains to be seen. For instance, higher intelligence seems to be a protective factor from the negative impact of psychopathology and/or drug use (Zammit, Lewis, Dalman, & Allebeck, 2010). What can be conjectured is that nicotine itself might have important influences on cognitive functioning, that might either worsen the implications of cannabis (Suris, et al., 2007), or potentially counteract them (Adler, et al., 1993; see Heishman, Kleykamp, & Singleton, 2010 for overview; Kumari & Postma, 2005; Zabala, et al., 2009). We would therefore suggest that future studies should elucidate the role of nicotine and cannabis more directly.

Gender imbalance is frequent in studies similar to ours, and we found an unequal distribution of females and males in the two groups (CU, nCU), which could have

affected the group differences on story recall. Typically, females perform better on verbal short-term memory tasks than males (see Kaushanskaya, Marian, & Yoo, 2011 for recent summary of relevant studies), a finding also observed in the present study. Since the nCU group consisted of more females than the CU, it could be argued that this could alternatively explain the worse story recall in CU. However, since cannabis use related to worse story recall performance on top of sex in the regression analysis, we deem it unlikely that the group differences are solely due to effects associated with the unequal sex distribution. Nevertheless, future studies on drug use and cognition should aim to control for sex differences.

A final limitation also frequently mentioned is the sample size. Obviously, a larger sample would always be advisable. Yet, it has turned out to be a true challenge to recruit pure CU. A potential reason could be firstly, that these individuals are either extremely difficult to motivate, or secondly, that pure users of drugs are rather difficult to find. The latter could be due to the recent trend, with many designer drugs being available on the market. Yet, if sample descriptions of the last 30 years are considered, it is also obvious that many studies inferred on the influence of cannabis use on cognition and mental health risk without necessarily ensuring that individuals not also used other legal and illegal drugs. We thus face the future challenge to disentangle what impact a specific drug, or even synergetic drug effects (Perez-Reyes, Hicks, Bumberry, Robert Jeffcoat, & Cook, 1988; Ramaekers et al., 2011; Ronen et al., 2010) might have on cognition and mental health.

Conclusion

While pure cannabis use seems associated with adverse effects on frontal lobe functioning, other risk factors such as alcohol and nicotine use may also contribute to this. Schizotypy, on the other hand, did not seem to consistently relate to attenuated frontal lobe functioning on top of drug dependence. The results suggest that it is important to control for substance use when assessing the effect of schizotypal symptoms and/or cannabis use on cognition. Moreover, heterogeneity of cannabis-related attenuations of specific frontal lobe functions may be avoided by calculating set-scores reflecting more generalized versus specific deficits in future studies, and controlling for additional factors potentially influencing the relationship between cannabis, cognition and psychosis (-risk).

6. Acknowledgements

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D. Study 3: Mephedrone / Polydrug use

Running title

Mephedrone, polydrug use and cognition

Reference

Herzig, D. A., Brooks, R., Mohr, C. (submitted). The cocktail (party) phenomenon: Inferring about individual drug effects on cognitive functioning in polydrug using mephedrone users before and after clubbing.

1. Abstract

Mephedrone has been recently made illegal in the UK, but little is known about its impact on cognitive functions. Filling this gap was the first aim of this study. Additionally, chronic drug use (including mephedrone) and personality features such as schizotypal thinking have been associated with cognitive attenuations, but the relationship between drug use, schizotypy and cognitive functioning is not well explored. Investigating this relationship was the second aim of this study. Volunteers (n = 26) performed cognitive measures twice (verbal learning, verbal fluency and cognitive flexibility), i.e. before (pre-clubbing) and after (post-clubbing) a clubbing experience. All filled in self-report questionnaires detailing demographic information, drug use, schizotypal symptoms (O-LIFE), depression, and premorbid IQ. Results showed that i) 10 volunteers had used mephedrone (post-clubbing, assessed via self-report), ii) mephedrone users performed worse than controls pre-clubbing, and deteriorated post-clubbing, iii) other pre-clubbing drug use (cannabis, amphetamine) predicted attenuation in cognitive functioning, iv) Post-clubbing, depression scores predicted attenuation in cognitive functioning, and v) schizotypy was largely unrelated to cognitive functioning, apart from a negative relationship between cognitive disorganisation and verbal fluency pre- clubbing. These results suggest that polydrug use and subjectively experienced depressive symptoms negatively affect cognitive functioning. The finding on cognitive disorganisation supports independent notions that this schizotypy dimension in the general population might be the most relevant to a pathological cognitive profile reported along the psychosis dimension.

Keywords: New-wave drugs, cognition, psychosis spectrum, substance dependence, cathinone

2. Introduction

Drugs are feared to threaten our mental health facilitating politics that criminalise their distribution and use (Nutt, King, & Phillips, 2010). While we increasingly know about the clinical, cognitive, and physical implications when individuals use "conventional" licit and illicit psychoactive substances (e.g. heroine, cocaine, nicotine; Fernandez-Serrano, Perez-Garcia, Rio-Valle, & Verdejo-Garcia, 2010; Fernández-Serrano, et al., 2011; Nutt, et al., 2010), we are yet to accumulate a comparable knowledge on so called "new wave" designer drugs. New wave designer drugs encompass a range of modern psychoactive substances, which have been both specifically marketed and synthesized for the aim of providing an intoxicating high. Since they are new, legislations have not yet been established, making the use of many of these substances officially legal and therefore attractive. The most popular of these drugs are based on the substance "cathinone", a compound found in the khat plant (see Schifano, et al., 2010 for overview). One derivate of cathinone is a substance widely known as "mephedrone", which is also known as 4-MMC, MMCat, Meow/Miaow Miaow, Bubbles, Meph, Rush, Drone, Plant Feeder etc., and which has been relatively popular in the clubbing scene in recent years (Winstock et al., 2011).

Cathinone substances have a chemical structure similar to amphetamine (Dal Cason, Young, & Glennon, 1997; Hoffman & Al'Absi, 2010), a similarity that is also reflected in the observation that they seem to mimic the physiological and psychological actions of amphetamines (Kalix, 1992; Schifano, et al., 2010). For instance, both cathinones and amphetamines prevent the uptake and stimulate the presynaptic release of dopamine, serotonin and noradrenalin (see Kalix, 1992 for overview). Importantly, similarly to amphetamines, high doses of mephedrone can induce hallucinations (ACMD, 2010; James, et al., 2010; Vardakou, et al., 2011). To assess the physiological

and psychological effects of cathinones, Brenneisen et al. (1990) investigated the effects of intravenous administration of cathinone in human participants and discovered that the drug markedly increased heart rate and blood pressure in comparison to placebo. Furthermore, participants reported an increased sense of euphoria and sociability, which is comparable to independent reports on the psychological effects of mephedrone (Morris, 2010). Reports such as these certainly facilitated a fierce debate on the potential risks and harmfulness of mephedrone prior to the prime minister elections in the UK in 2010, and its use was recently made illegal in the UK (see Vardakou, et al., 2011 for overview; Winstock, et al., 2011) and other European countries (EMCDDA, 2010).

Despite some scientific explorations on the physiological and psychological effects of cathinones (ACMD, 2010; Brenneisen, et al., 1990; James, et al., 2010; Morris, 2010; Vardakou, et al., 2011), studies on the cognitive effects of these substances are surprisingly sparse (Hoffman & Al'Absi, 2010), and to our knowledge have only recently started to be investigated. For instance, impairments in working memory and cognitive flexibility have been reported as a function of khat use (Colzato, Ruiz, van den Wildenberg, & Hommel, 2011). Given the similarities between amphetamines and cathinones in chemical structure (Dal Cason, et al., 1997) and subjective reports (ACMD, 2010; Brenneisen, et al., 1990; James, et al., 2010; Morris, 2010; Vardakou, et al., 2011), it seems justified to expect cathinone use to result in similar cognitive peculiarities to those reported after amphetamine use. If this reasoning is indeed considered feasible, we can infer from previous experimental research into the cognitive harms of amphetamines (see Fernández-Serrano, et al., 2011; Kalechstein, et al., 2007 for overview) that mephedrone (and other derivates of cathinones) might negatively affect various aspects of cognition such as working memory (Curran & Travill, 1997),

verbal fluency (Hanson & Luciana, 2004), cognitive flexibility (King, et al., 2010), verbal learning (Gonzalez, et al., 2004; Laws & Kokkalis, 2007; McCardle, et al., 2004; Parrott & Lasky, 1998), and mood (Curran & Travill, 1997; Parrott & Lasky, 1998). Given that these predictions are based on inferences from research on amphetamines, we here aimed to test more directly whether cognitive impairments reported from amphetamine use might also be observed for mephedrone use, or other drug use more broadly.

While the question on cognitive impairments as a function of drug use seems straightforward, it misses out on the equally important question on who would be most prone to use such drugs in the first place, or who might have a higher risk of experiencing harmful consequences from drug consumption. Knowing about these influential factors should indeed be of interest to clinicians and society more broadly, because early detection might help reduce negative long-term consequences for mental health (Bird, et al., 2010; Larsen, et al., 2011; M. Marshall & Rathbone, 2006). One factor associated with enhanced drug use is schizotypy (see Barkus & Murray, 2010 for overview), a personality construct that has also been associated with an enhanced risk for psychiatric conditions (L. J. Chapman, et al., 1994; Gooding, et al., 2005).

Schizotypy is thought to describe subjective experiences in the general population that are reminiscent of those reported from patients with schizophrenia, but in a milder form (Meehl, 1962). Such similarities are not only evident on the phenomenological level, but are also found for cognitive functions. In more detail, cognitive impairments that are common in patients with psychosis are also found along the psychosis dimension, although less severe, such as in individuals with a schizotypal personality disorder [see Reichenberg & Harvey (2007) for overview], and individuals from the general population scoring relatively high on self-report schizotypy questionnaires (Burch,

Hemsley, & Joseph, 2004; Krabbendam, et al., 2005; Laurent et al., 2001; Poreh, Ross, & Whitman, 1995; Vollema & Postma, 2002). Most important to the present study, cognitive functions relying on the frontal lobes such as cognitive flexibility (Blanchard, et al., 2010; Diforio, et al., 2000; Laurent, et al., 2000; Voglmaier, et al., 1997), working memory (Kopp, et al., 2002; Park & McTigue, 1997; Voglmaier, et al., 2005; Voglmaier, et al., 1997) and verbal fluency (Laurent, et al., 2000; Tsakanikos & Claridge, 2005; Koychev et al., 2011) seem attenuated along the psychosis spectrum including schizotypy (see also Reichenberg & Harvey, 2007 for overview).

A potential problem of the above described study lines is that only few investigated cognition, drug use and schizotypy simultaneously, i.e. studies either investigated the influence of a particular drug on cognition, the link between drug use and schizotypy, or the relationship between schizotypy and cognitive functioning. Yet, in the latter case, individuals with elevated schizotypy are also likely to be subject to relative enhanced polydrug use, without this drug consumption being accounted for in most scientific reports. We found 16 studies investigating the link between schizotypy and cognitive functioning; nine of them did not report drug use (Burch, Hemsley, Corr, & Gwyer, 2006; Dinn, Harris, Aycicegi, Greene, & Andover, 2002; Giraldez, Caro, Rodrigo, Pineiro, & Gonzalez, 1999; Kerns & Becker, 2008; Laws, Kondel, Clarke, & Nillo, 2011; Lenzenweger & Korfine, 1994; Park, Holzman, & Lenzenweger, 1995; Schmidt-Hansen & Honey, 2009; Tsakanikos & Claridge, 2005), and the others varied in their drug control criteria (Daneluzzo, Bustini, Stratta, Casacchia, & Rossi, 1998; Kaczorowski, Barrantes-Vidal, & Kwapil, 2009; Kim, Oh, Hong, & Choi, 2011; Koychev et al., 2011; Matheson & Langdon, 2008; Poreh, et al., 1995; Suhr, 1997). It is thus possible that substances (e.g. illicit as well as licit substances) influenced the relationship between schizotypal symptoms and the cognitive functions assessed

(Herzig & Mohr, in press; Herzig, et al., 2010). As will be shown in the following, the present study took this reasoning into account.

We investigated the potential role of current mephedrone use (but also of other common drugs) on cognitive functioning, and how this relationship might be influenced by individuals' schizotypy. In particular, we adopted a "natural" design in which a group of participants was tested twice, before (pre-clubbing) and after (post-clubbing) their clubbing experience. Because mephedrone was a preferred clubbing drug at the time of testing, we expected that some participants would consume new wave designer drugs such as mephedrone. This experimental design not only allowed to account for changes of cognitive functioning over the course of a clubbing experience (short-term) but also whether individuals using mephedrone have a more severe overall drug history (polydrug use) potentially implying that their cognitive functioning is already relatively impaired at the pre-clubbing stage (long-term effects).

Given the similarity between the physiological and emotional effects of cathinones and amphetamines, we predict that mephedrone users as compared to non-users should show relatively impaired cognitive functioning already reported from amphetamine users (cognitive flexibility, verbal learning and verbal fluency). Moreover, we considered the possibility that drug use rather than schizotypy would be the dominant predictor of these relatively impaired cognitive functions (Herzig & Mohr, in press; Herzig, et al., 2010). Because of the reported links between various drugs of abuse, mood and sleep patterns on cognition we also controlled for possible influential variables such as depression (Curran & Travill, 1997; Davison & Parrott, 1997; Deykin, Levy, & Wells, 1987; MacInnes, Handley, & Harding, 2001) and sleep (Carhart-Harris, Nutt, Munafo, & Wilson, 2008; Curran & Travill, 1997). By accounting for these variables a 'purer' measure of the effects of drug use on cognition is expected to derive.

3. Methods

Participants

Participants were recruited using a combination of snowballing sample method and advertisements, distributed at local businesses and university departments in the Bristol area. It was made explicitly clear that only members of the clubbing community were eligible to take part in the study, although no mention was made of drug use. Participants were excluded if they were not educated to at least degree level, and/or reported on major psychiatric illness or chronic health problems. Furthermore, participants were excluded if they were currently taking psychoactive medication (such as antidepressants, analgesics or neuroleptics), and/or had suffered from any form of organic head injury according to self-report. No pressure was placed on participants to consume psychoactive drugs at any point during the research, and no reimbursement was given for participants' time. Instead, they were entered into a prize draw to win £100 worth of vouchers to spend in a Bristol based business enterprise. We were able to recruit 26 native English speakers who were willing to participant shortly before and after their clubbing experience. Of these 26 participants, 10 reported having used mephedrone at the post-clubbing session.

The study was approved by the ethics committee of the University of Bristol, Department of Experimental Psychology.

Procedure

Participants completed a total of two experimental sessions, lasting approximately an hour each. The pre-clubbing session took place (mostly) on the Friday, in a quiet laboratory in the Department of Experimental Psychology, University of Bristol. This session acted as a baseline for measuring participants' cognitive performance when

abstinent from current psychoactive drugs (baseline cognitive functioning). Drug use information was not collected during this session, rendering the experimenter blind to participants' drug history. During this session participants completed all of the cognitive tasks and questionnaires (details are given below). Following completion of these tasks participants were instructed to engage in their usual clubbing experience. It is important to note that participants were not aware that the study was assessing the link between mephedrone use and cognition, therefore preventing to stimulate participants' motivation to consume drugs to be eligible for this study. The post-clubbing session was arranged approximately 48 hours after the night that they went clubbing (e.g. if they went clubbing on Friday the next testing session would be on Sunday). Participants were considered mephedrone users if they reported mephedrone use in the 48 hours between the pre-clubbing and post-clubbing testing session. The post-clubbing testing session involved exactly the same cognitive measures and tests that were completed in session 1. Considering the likely poly-drug use of clubbers, participants also filled out additional questionnaires that measured their current and past psychoactive drug use (including any drugs taken in the period between testing sessions).

Tasks

(1) Cognitive tests[3]

iv. Premorbid verbal intelligence: The national adult reading scale (NART)

To ensure groups were matched on IQ, participants completed the NART at the beginning of the pre-clubbing session. The NART is designed to provide a measure of verbal IQ, through the visual presentation of a list containing 50 irregular words, which the participant is required to pronounce in serial order (H. E. Nelson, 1982). The NART

[3] We measured a computerised Go NoGo task as well. Due to an overall ceiling performance, we omitted this task from all further analysis. Detailed information on this task can be requested from the first author.

is a widely used and reliable test that takes advantage of the correlation between reading ability and intelligence in the normal population (Wiens, Bryan, & Crossen, 1993). The greater the number of correctly pronounced words the higher a participant's verbal IQ. Normative values for the English version in healthy adults can be found in Crawford et al. (1989).

v. *Verbal learning and memory: The Rey Auditory verbal memory task (RAVLT)*

The RAVLT (e.g. Spreen & Strauss, 1998) is an easy to administer task assessing verbal learning as well as immediate and delayed recall. A series of 15 nouns are read aloud to the participant (separated by one second intervals) for five consecutive trails. Each trial is followed by an immediate free recall test. We assessed the number of correctly recalled words over the five trails (maximum 75). Finally, after a delay of 25 minutes, participants are again asked to recall the original word list (delayed recall). We calculated percentages of the correctly recalled words for both immediate and delayed recall. Pre-clubbing and post-clubbing, participants received alternative versions with the order of the two versions having been counterbalanced between participants. Normative values for both versions can be found in Badcock et al. (2011).

vi. *Verbal fluency (COWAT)*

The COWAT (= Controlled Word Association Task) was originally developed by Bechtold, Benton et al. (1962), and is a measure of left frontal lobe functioning (Newman, Trivedi, Bendlin, Ries, & Johnson, 2007; A. G. Wood, Saling, Abbott, & Jackson, 2001). It tests participants' ability to produce as many words as they can that begin with pre-determined sequentially presented letters (in this study: F, A and S) or categories (in this study: animals, vegetables and fruit) within a minute. In the present study, only letters were presented. We assessed the number of correctly generated words across all three letters. Proper nouns and changing of suffixes and prefixes were not

included (for example ‘See’ would be correct but subsequently saying ‘seeing’ would not). The test has been found to have reasonable test-retest reliability (Ruff, Light, Parker, & Levin, 1996), and updated normative data can be found in Ruff et al. (1996).

vii. *Trail making task (TMT)*

The TMT is used to test cognitive flexibility. It was originally part of the Army Individual Test Battery (1944), and was incorporated into the Halstead–Reitan Battery (Reitan & Wolfson, 1985). In the TMT participants are presented with a sheet of paper, filled with circles. These circles are either filled with numbers (TMT-A), or with numbers and letters (TMT-B). In version A, participants have to draw a line from circle 1 to circle 25 in chronological order, as fast as possible. In TMT B participants have to draw a line in chronological order from 1 to 13, and A to L, but to switch back and forth between numbers and letters. Therefore, participants draw a line from 1 to A, from A to 2, from 2 to B etc. The reaction time (RT) of both tasks are recorded, and an index subtracting RT’s of TMT A from RT’s of TMT B results in an estimate of cognitive flexibility (Lezak, 1995) adjusted for individual differences in motor functioning and visual search strategies (Reitan & Wolfson, 1985). Norm values are available from Tombaugh (2004).

Questionnaires

(2) The Becks Depression Inventory (BDI)

The BDI (Beck, Erbaugh, Ward, Mock, & Mendelsohn, 1961) is a 21 item questionnaire designed to measure depressive symptoms. Each item comprises a 4 choice statement differing in the extent of depressive loading. For example (0) I don’t have thoughts of killing myself, (1) I have thoughts of killing myself but I would not carry them out, (2) I would like to kill myself, (3) I would kill myself if I had the

chance. Each of the 4 choice statements provides a score that gauges how depressed the person feels from 0 to 3. The total depression score is the sum of the scores of each of the 21 items. Scores between 0–9 indicate that a person is not depressed, 10–18 indicates mild-moderate depression, 19–29 indicates moderate-severe depression and 30–63 indicates severe depression (Beck, et al., 1961; Sotiropoulos et al., 2008). In this experiment, we asked participants to answer the questionnaire by referring to how they generally felt in the past two weeks (pre-clubbing) and to how they feel currently (post-clubbing).

(3) The Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE; short version)

The short O-LIFE questionnaire (Mason, et al., 2005) is a validated 43-item self-report questionnaire assessing schizotypy in terms of four dimensions. Positive schizotypy is assessed by 12 items pertaining to Unusual Experiences (UnEx, maximum score 12, including items such as ‘Are your thoughts sometimes so strong that you can almost hear them?’), negative schizotypy is assessed by 10 items pertaining to Introvertive Anhedonia (IntAn, maximum score 10, including items such as ‘Do you prefer watching television to going out with people?’), and Cognitive Disorganization is assessed by 11 items (CogDis, maximum score 11, including items such as ‘Are you easily confused if too much happens at the same time?‘). Finally, 10 items assess Impulsive Nonconformity (Imp, maximum score 10), which does not represent a schizotypy dimension (Mason, et al., 1995), but will be accounted for in the present study because of the significant link between impulsivity and addiction (Crews & Boettiger, 2009). For each item, participants have to indicate whether the statement is true or false. The number of positive responses (some items are reversely formulated) is summed so that higher scores indicate higher schizotypy. Normative values can be

found in Mason et al. (2005) and the scale has shown good internal consistency as well as high correlations with the original O-Life questionnaire (Mason, et al., 1995; Mason, et al., 2005).

(4) Drug use and sleep patterns

On the post-clubbing testing session participant were asked to fill in the drug questionnaires of the national household survey on drug abuse (United States Department of Health and Human Services, 1998). The national household survey on drug abuse (NHSDA) gives detailed data of respondents' prior drug use, and an adapted version was administered to assess use of nicotine, alcohol, cannabis, mephedrone, amphetamine, cocaine, ketamine and benzodiazepine use during the clubbing experience (amount used), and in the past 30 days (times used). Additionally, participants indicated their total amount of average hours of sleep, as well as how much they slept between the pre- and the post-clubbing experience (total amount of hours).

Data analysis Mephedrone use vs. Control

In a first set of analysis, in which we focused on recent mephedrone use, we calculated separate 2 x 2 mixed sample ANOVAs with day (pre-clubbing, post-clubbing) as the related samples factor and drug use group (mephedrone, control) as the independent samples factor on the total % correct responses in the RAVLT (measuring verbal learning) as well as total amount correct items named in the COWAT (measuring verbal fluency). In the TMT (measuring cognitive flexibility) an index (TMT B –TMT A) was calculated and used as an outcome measure, with higher values indicating reduced cognitive flexibility. Post-hoc tests were performed using paired samples tests. Effect sizes are reported for all ANOVA results.

In order to establish if schizotypy is explaining an additional amount of variance on top of drug use and demographic / control variables, we firstly explored which variables are relevant to the regression models. We correlated age, BDI scores, hours of sleep (average amount and total sum of hours between pre- and post-clubbing), NART-scores, drug use variables and schizotypy sub-scale scores with the outcome measures of the cognitive tasks. For regression analyses, we only kept variables that were significantly related to at least one outcome measure. Subsequently, two separate regression models were run, corresponding to the two times of assessment (see result section for details). Blocks of predictors were entered into the regression model, with the first one containing control variables (if none of these correlated with the outcome measures, this step was omitted), the subsequent step including drug use information, and the final step containing schizotypy measures. These blocks were entered in nested blocks, meaning that each subsequent block contained all prior predictors and the additional predictors from the current block. Presentation of results however will only include significant predictors as in Fridberg et al. (2011), for economy of presentation. The full model will be presented, however, in the Appendix of this dissertation (see Tables 26-27). Because all tolerance values were above .2 (Menard, 1995), and all independent variables were mean-centered, multi-collinearity between the independent variables was considered negligible. The dependent variables were i) total percentage correctly recalled items in the RAVLT, for immediate and delayed recall, ii) the total amount of correctly named items in the verbal fluency task, and iii) TMT index scores.

Kolmogorov–Smirnov tests for the groups separately revealed normal distribution for all behavioral measures, NART, BDI and schizotypy scores. All *p*-values were two-tailed and the α-level was set at .05.

4. Results

Participants and self-report questionnaires

As is evident from Table 11, mephedrone users used more amphetamine, mephedrone, and nicotine as compared to the control group in the past 30 days, as well as more mephedrone and alcohol during the clubbing experience. Furthermore, mephedrone users as compared to controls scored higher on BDI scores, CogDis and ImpNC. A mixed-samples ANOVA with BDI scores (pre-clubbing, post-clubbing) as the repeated measures, and group (mephedrone, control) as the between subjects factor indicated that there was a significant effect of day of testing [$F(1,24)=6.69$, $p=.02$, *partial* $\eta^2= .22$], with BDI scores being generally higher post-clubbing than pre-clubbing (see Table 11). There also was a significant interaction between group * day of testing [$F(1,24)=17.83$, $p<.001$, *partial* $\eta^2= .43$]. Post-hoc paired samples t-tests split by group revealed that this rise in BDI scores was only significant in the mephedrone using group [$t(9)=-3.70$, $p<.01$], but not in the control group [$t(15)= 1.50$, $p=.16$; see Table 11]. All other measures did not differ between groups (Table 11).

Table 11. *T-test values and descriptives for demographic variables, average sleep and total hours sleep between test sessions, BDI scores, schizotypy scores, and substance use in mephedrone users (n = 10 participants) and non-mephedrone using controls (n = 16 participants). Significant values are highlighted in bold.*

	Total		**Mephedrone (*N*=10)**		**Control (*N*=16)**		***T*-test statistics**	
Variable	***Mean***	***SD***	***Mean***	***SD***	***Mean***	***SD***	***t(24)***	***p***
Age	23.42	5.54	21.40	0.84	24.69	6.80	-1.91	0.07
Verbal IQ	32.96	5.44	33.60	5.42	32.56	5.59	0.47	0.65
Average hours sleep	7.58	1.03	7.60	1.06	7.56	1.03	0.09	0.93
Total hours sleep between sessions	19.35	4.99	19.80	4.10	19.06	5.58	0.36	0.72
BDI[a] pre[b]	8.15	7.25	11.90	5.53	5.81	7.36	2.24	**0.03**
BDI post[c]	8.77	7.63	14.50	5.70	5.19	6.48	3.73	**0.00**
UnEx[d]	3.35	2.71	4.60	2.41	2.56	2.66	1.97	0.06
CogDis[e]	5.15	3.46	6.80	3.26	4.13	3.26	2.03	**0.05**
IntAn[f]	1.73	1.80	2.00	1.89	1.56	1.79	0.59	0.56
ImpNC[g]	3.42	2.48	5.30	1.57	2.25	2.24	3.76	**0.00**
Amphetamine past 30 days	0.19	0.49	0.50	0.71	0.00	0.00	2.24	**0.05**
Mephedrone past 30 days	0.62	1.10	1.60	1.26	0.00	0.00	4.00	**0.00**
Nicotine past 30 days	12.77	14.33	22.00	13.17	7.00	12.08	2.98	**0.01**
Cannabis past 30 days	2.31	4.35	4.80	6.12	0.75	1.53	2.05	0.07
Alcohol past 30 days	9.62	6.54	9.20	5.29	9.88	7.37	-0.25	0.80
Mephedrone between test sessions	0.54	0.76	1.40	0.52	0.00	0.00	8.57	**0.00**
Cannabis between test sessions	0.27	1.00	0.70	1.57	0.00	0.00	1.41	0.19
Alcohol between test sessions	16.08	7.03	20.50	7.75	13.31	5.02	2.88	**0.01**
Age of first use: Amphetamine	18.75	1.86	19.00	1.66	18.00	2.65	0.79	0.45
Age of first use: Mephedrone	n/a	n/a	20.67	0.50	n/a	n/a	n/a	n/a
Age of first use: Nicotine	16.00	3.12	15.38	1.19	16.63	4.31	-0.79	0.44
Age of first use: Cannabis	17.56	4.06	16.60	1.78	18.75	5.75	-1.12	0.28
Age of first use: Alcohol	14.85	1.93	14.70	1.57	14.94	2.17	-0.30	0.77

Note: [a] Beck's Depression Inventory; [b] Pre-clubbing experience; [c] Post-clubbing experience; [d] Unusual Experiences; [e] Cognitive Disorganisation; [f] Introvertive Anhedonia;[g] Impulse Non-conformity;

Results in the behavioural tasks

(1) RAVLT

For the immediate recall measure, we found that mephedrone users performed worse than controls ($F(1,24) = 10.43$, $p < .01$, *partial η2*= .30; see Table 12). The interaction

between group and day ($F(1,24)= .85$, $p= .37$, *partial* $\eta^2 = .03$) and the effect of day ($F(1,24) = 1.99$, $p = .17$, *partial* $\eta^2= .08$; see Table 12) were both not significant. For the delayed recall measure, we found that mephedrone users performed significantly worse than controls ($F(1,24) = 12.33$, $p < .01$, *partial* $\eta^2= .34$; see Table 12). Whereas the effect of day ($F(1,24) = .73$, $p = .40$, *partial* $\eta^2 = .03$; see Table 12) was not significant, the analysis revealed a significant interaction between group and day ($F(1,24) = 7.72$, $p = .01$, *partial* $\eta^2 = .24$). Post-hoc paired samples t-tests split by group revealed that in the control group there was no difference in scores between pre- and post clubbing [$t(15) = -1.30$, $p = .21$]. However, the mephedrone group showed a significant decrease in delayed recall performance between pre- and post-clubbing [$t(9) = 4.33$, $p < .01$; see Table 12].

Table 12. *Means and standard deviations (SD) of task performance for the total sample and the two groups separately.*

	All		**Mephedrone**		**Control**	
Variables	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
RAVLT[a] % Immediate[b] pre[c]	79.85	10.07	74.50	11.37	83.19	7.78
RAVLT % Immediate post[d]	78.27	9.09	71.30	8.60	82.63	6.38
RAVLT % Delayed[e] pre	82.81	17.03	74.60	19.39	87.94	13.60
RAVLT % Delayed post	82.27	19.27	66.00	19.18	92.44	10.54
COWAT[f] pre	45.88	9.09	42.40	10.29	48.06	7.81
COWAT post	44.69	10.20	38.20	8.70	48.75	9.07
TMT[g] index pre	16.49	9.39	14.61	5.80	17.66	11.10
TMT index post	15.62	7.41	14.92	5.81	16.06	8.41

Note: [a] Rey Auditory verbal memory task; [b] Immediate Recall; [c] Pre-clubbing; [d] Post-clubbing; [e] Delayed Recall; [f] Verbal Fluency Task; [g] Trail Making Task;

(2) COWAT

There was a significant main effect for group ($F(1,24) = 5.32$, $p = .03$, *partial* $\eta^2 = .18$), with mephedrone users performing significantly worse than controls (see Table 12). Additionally, there was a significant effect of day ($F(1,24) = 6.77$, $p = .02$, *partial* $\eta^2 = .22$; see Table 12), and interaction between group and day ($F(1,24) = 13.11$, $p < .01$, *partial* $\eta^2 = .35$). Post-hoc paired samples t-tests split by group revealed that in the mephedrone group values significantly decreased from pre- to post-clubbing [$t(9) = 5.00$, $p < .01$; see Table 12), whereas there was no day difference in the control group [$t(15) = -.74$, $p = .47$; see Table 12).

(3) TMT

There were no significant findings (group: $F(1,24) = .39$ $p = .54$, *partial* $\eta^2 = .02$; day: $F(1,24) = .60$, $p = .45$, *partial* $\eta^2 = .02$, interaction between group * day: $F(1,24) = 1.31$, $p = .26$, *partial* $\eta^2 = .05$; see Table 12).

Regressions: Severity of drug use and schizotypy as predictors of performance

To further investigate the possibility that schizotypy may be relevant to cognitive functioning on top of drug use, multivariate step-wise regressions were conducted. Exploratory correlation analyses (Table 13) showed that pre-clubbing amphetamine, mephedrone and cannabis use, as well as CogDis scores correlated with cognitive functioning. Therefore, for the pre-clubbing session amphetamine, mephedrone and cannabis use in the past 30 days was entered in the first step, and CogDis scores in the second step.

Table 13. *Correlations between potential predictor variables and outcome measures pre- clubbing. Significant values are highlighted in bold.*

Variables	RAVLT[h] % Immediate[i] pre	RAVLT % Delayed[j] pre	TMT[k] index pre	COWAT[l] pre
Age	0.30	0.04	0.23	0.24
NART[a]	0.15	0.08	-0.22	**0.35†**
BDI[b] pre[c]	-0.27	-0.26	-0.08	**-0.34†**
Average sleep	0.05	0.29	-0.02	-0.16
UnEx[d]	-0.22	-0.25	0.03	-0.25
CogDis[e]	**-0.47***	-0.13	0.04	**-0.65*****
IntAn[f]	0.14	0.21	-0.13	0.17
ImpNC[g]	-0.17	-0.17	0.09	**-0.37†**
Amphetamine past 30 days	**-.49***	**-0.52****	-0.21	-0.30
Mephedrone past 30 days	**-.48***	-0.18	0.01	-0.29
Nicotine past 30 days	-0.21	-0.31	-0.18	0.04
Cannabis past 30 days	**-0.63*****	**-0.34†**	0.02	**-0.39***
Alcohol past 30 days	0.20	-0.07	-0.12	0.28

*†p≤.10; * significant at p≤.05; ** significant at p≤.01; *** significant at p≤.001*

Note: ; [a] National Adult Reading Test; [b] Beck's Depression Inventory; [c] Pre-clubbing experience; [d] Unusual Experiences; [e] Cognitive Disorganization; [f] Introvertive Anhedonia; [g] Impulsive Non-conformity; [h] Rey Auditory verbal memory task; [i] Immediate Recall; [j] Delayed Recall; [k] Trail Making Task; [l] Verbal Fluency Task;

For the post-clubbing session (Table 14) BDI scores, total hours of sleep between test sessions, mephedrone use and schizotypy scores (UnEx, CogDis and ImpNC scores) were correlated with at least one of the outcome measures. Therefore, BDI scores post-clubbing and total hours of sleep between test sessions were entered in the first step, mephedrone use between test sessions in the second, and schizotypy subscales (UnEx, CogDis and ImpNC) in the third step.

Table 14. Correlations between potential predictor variables and outcome measures post-clubbing. Significant values are highlighted in bold.

Variables	RAVLT [h] % Immediate[i] post	RAVLT % Delayed [j] post	TMT [k] index post	COWA T[l] post
Age	0.32	0.04	0.07	**0.36†**
NART [a]	0.24	-0.02	-0.32	0.30
BDI [b] post[c]	**-0.49***	**-0.55****	0.02	**-0.44***
Total hours sleep between test sessions	**-0.36†**	-0.22	0.13	**-0.39***
UnEx [d]	-0.31	**-0.54****	0.09	-0.23
CogDis [e]	**-0.52****	**-0.47***	0.15	**-0.59****
IntAn [f]	-0.23	0.05	0.03	0.19
ImpNC [g]	**-0.40***	**-0.47***	0.10	**-0.40***
Alcohol between test sessions	0.02	-0.22	-0.06	-0.08
Cannabis between test sessions	-0.26	**-0.35†**	-0.29	-0.29
Mephedrone between test sessions	**-0.58****	**-0.52****	0.00	**-0.43***

*†p≤.10; * significant at p≤.05; ** significant at p≤.01; *** significant at p≤.001*

Note: ; [a] National Adult Reading Test; [b] Beck's Depression Inventory; [c] Post-clubbing; [d] Unusual Experiences; [e] Cognitive Disorganization; [f] Introvertive Anhedonia; [g] Impulsive Non-conformity; [h] Rey Auditory verbal memory task; [i] Immediate Recall; [j] Delayed Recall; [k] Trail Making Task; [l] Verbal Fluency Task;

The results from the regression on the pre-clubbing session are displayed in Table 15. We found that immediate recall in the RAVLT was reduced with increasing cannabis use and delayed recall in the RAVLT was reduced with increasing amphetamine use. Additionally, increasing CogDis scores related to a decreasing number of words produced in the COWAT.

Table 15. *Regression analysis assessing the effect of cannabis, mephedrone and amphetamine use (step 1) and CogDis (step 2) on cognitive functioning at the pre-clubbing session. Only significant ΔR²-values and their corresponding coefficients (β-values) are reported.*

Outcome variables	Step	Significant predictor	β-value	Total R^2	ΔR^2	F for ΔR^2
RAVLT [a] % immediate [b]	1	Cannabis	**-0.60***	**0.48****	**0.48****	**6.85****
	1	Amphetamines	**-0.33†**	**SAA**	**SAA**	**SAA**
RAVLT % delayed [c]	1	Amphetamines	**-0.53***	**0.35***	**.035***	**3.99***
COWAT [d]	2	CogDis [e]	**-0.58****	**0.45****	**0.26****	**9.76****

*† p≤.10; * significant at p≤.05; ** significant at p≤.01; *** significant at p≤.001*
Note: [a] Rey Auditory verbal memory task; [b] Immediate Recall; [c] Delayed Recall; [d] Verbal Fluency Task; [e] Cognitive Disorganisation;

The results from the regression on post-clubbing session are presented in Table 16. Results indicate that increasing BDI scores predicted lower RAVTL performance (immediate and delayed recall) as well as less words produced in the COWAT. Additionally, a higher amount of hours slept between test-sessions related to lower immediate recall performance in the RAVTL and less words produced in the COWAT. Adding drugs or schizotypy in later steps did not explain additional variance in cognitive functioning.

Table 16. *Regression assessing the effect of total hours of sleep between test sessions and depression (Beck´s Depression Inventory/BDI; step 1), mephedrone use between test sessions (step 2), and schizotypy (Unusual Experiences, Cognitive Disorganisation, and Impulse Non-conformity; step 3) on cognitive functioning post-clubbing. Only significant ΔR²-values and their corresponding coefficients (β-values) are reported.*

Outcome variables	**Step**	**Significant predictor**	***β*-value**	**Total R^2**	**ΔR^2**	***F* for ΔR^2**
RAVLT % [a] immediate [b]	1	BDI [e] post [f]	**-0.55****	**0.42****	**0.42****	**8.45****
	1	Total hours of sleep between test sessions	**-0.43***	**SAA** [g]	**SAA**	**SAA**
RAVLT % delayed [c]	1	BDI post	**-0.59****	**0.39****	**0.39****	**7.40****
COWAT [d]	1	BDI post	**-0.50****	**0.39****	**0.39****	**7.49****
	1	Total hours of sleep between test sessions	**-0.46***	**SAA**	**SAA**	**SAA**

** significant at p≤.05; ** significant at p≤.01;*

Note: [a] Rey Auditory verbal memory task; [b] Immediate Recall; [c] Delayed Recall; [d] Verbal Fluency Task; [e] Beck's Depression Inventory; [f] Post- clubbing; [g] Same as above;

5. Discussion

Drug policies are aimed to prevent harm to people by making access to these drugs more difficult. To avoid the problem of the illegality of drugs, new drugs are frequently developed that are little or not yet regulated. Among those drugs are popular new wave designer drugs such as mephedrone. These provide "legal highs" without knowing much about their harmfulness or factors that might predict it. We here investigated whether mephedrone use might have a negative impact on cognitive functioning, and whether any such relationship might be influenced by individuals' schizotypal features. We tested cognitive functions that were formerly associated with amphetamine use and elevated schizotypy, i.e. cognitive flexibility, verbal learning and verbal fluency.

Importantly, we were able to recruit volunteers in a "natural" setting, i.e. before (pre-clubbing) and after (post-clubbing) a clubbing experience during which drugs such as mephedrone are commonly consumed. The advantage of this design consists in the assessment of i) participants' baseline functioning (i.e. the cognitive level at which individuals with different drug histories entered the study), and ii) how the drug use of the clubbing experience affected their cognitive performance (i.e. short-term effects). The main findings of the present study were that i) mephedrone users performed worse than controls at baseline and their performance decreased pre- to post-clubbing in tasks measuring cognitive functioning, ii) cannabis and amphetamine use related to decreased cognitive performance in the pre-clubbing session, whereas mephedrone did not, iii) depression rather than drug use or schizotypy was the most consistent predictor of cognitive attenuations in the post-clubbing session, and iv) schizotypy did not explain variance in cognitive functioning (apart from CogDis in the pre-clubbing session) when controlling for drug use. These findings will be discussed in the following sections.

We argued that the cognitive consequences of mephedrone use should mirror those of amphetamine use, because studies reported on physiological, chemical and psychological similarities between the consequences of amphetamine (such as ecstasy) and cathinone use (ACMD, 2010; Brenneisen, et al., 1990; Dal Cason, et al., 1997; Hoffman & Al'Absi, 2010; James, et al., 2010; Kalix, 1992; Morris, 2010; Schifano, et al., 2010; Vardakou, et al., 2011).

For our pre-clubbing session, we already observed that mephedrone users performed worse than the control group for immediate and delayed verbal recall, and verbal fluency. Our group results also showed that performance in all but the TMT task became worse over the pre-clubbing to post-clubbing session in our mephedrone users

as compared to controls. If we would have only performed these group comparisons, we would have concluded that recent mephedrone use negatively affects cognitive functioning. We have, however, obtained more detailed information on other drug use as well, and this additional drug use was important to cognitive functioning.

When taking additional drug use into consideration, we firstly found that mephedrone users as compared to controls had consumed more amphetamines and nicotine in the 30 days prior to testing. Secondly, when looking at the individual contribution of drug use (regression analysis) on cognitive functioning, we found that enhanced cannabis and amphetamine use was related to memory impairments, whereas mephedrone use was not. These latter results are in line with studies on the cognitive effects of amphetamines (see Gouzoulis-Mayfrank & Daumann, 2009; Hoshi et al., 2007; Kuypers & Ramaekers, 2005; M. J. Morgan, 2000; G. Rogers et al., 2009 for overview), cathinones (Colzato, et al., 2011), and cannabis (Fernández-Serrano, et al., 2011) indicating impairments in verbal recall, verbal learning and/or fluency as a function of these drugs' consumption. Our findings and the previous literature would thus suggest that mephedrone consumption does not necessarily exert a negative impact on cognitive functioning by itself. Instead, mephedrone users are likely those individuals who are prone consuming or having consumed other drugs before. It might be this polydrug use that makes these individuals more vulnerable to the observed attenuations in the cognitive tasks. In line with this rational, it seems difficult to find pure users of any one substance alone (Fernández-Serrano, et al., 2011), and our sample has been no exception.

The implication of polydrug use when trying to understand the influence of a particular drug on cognition is thus far-reaching. For instance, those who have a risk for negative

implications of drug use on mental health are likely polydrug users (Bondi, Drake, & Grant, 1998; Hakansson, Schlyter, & Berglund, 2011). Findings from psychopharmacological studies who have pre-selected their participants according to drug naivety might thus not provide very representative results for a clinically relevant population. Moreover, when only use of one particular drug is targeted (see Fernández-Serrano, et al., 2011 for overview), we might neglect and miss out on the influence of other drugs on the relationship we are interested in. Based on these considerations, we here conjecture that it might be impossible to infer about the impact of a single drug on cognition in a research context as the present one. Instead, we should take polydrug use more thoroughly into account, as former polydrug use might also explain long-term effects on cognitive functioning in substance users.

Polydrug use and not only single drug use might also be relevant for cognition and mood in the short-term, as was found here when considering post-clubbing performance and mood. In the regression analysis, we explored additional factors that could influence cognitive measures post-clubbing more thoroughly. Strikingly, we found that higher BDI scores and prolonged sleep (rather than drug use or schizotypy) predicted a relative drop in cognitive performance. While not our a priori focus, the role of depression is worthwhile considering. To start with, our mephedrone users as compared to controls showed higher BDI scores both pre-clubbing and post-clubbing. Moreover, schizotypy scores showed no additional influence on cognitive functioning post-clubbing, and the influence of actual drug use seemed to become marginal when BDI scores were considered. We thus conjecture that depression might be a major confound in previous schizotypy and drug studies that targeted cognitive functions, because depression levels are commonly not assessed (e.g. Herzig, et al., 2010; Skosnik, et al.,

2001). The same can be said for studies testing non-clinical populations (and thus non-clinical depression) on the influence of particular drugs, where potentially relevant depression ratings have not been reported in relatively pure cannabis users (Fried, et al., 2005), alcohol users (Ratti, Bo, Giardini, & Soragna, 2002) or psychostimulant users (Bolla et al., 2003). Depression rates are, however, relatively elevated in e.g. amphetamine users (M. J. Morgan, 2000; G. Rogers, et al., 2009 for overview), alcohol users (Weitzman, 2004) or cannabis users (Hayatbakhsh et al., 2007; Patton et al., 2002). Consequently, if depression is a major confound in studies such as the present one, we would expect that depression influences cognitive functioning directly (primary influence) or indirectly (secondary influence through e.g. loss of motivation), much as we have originally expected this to be the case for drug use and / or schizotypy.

Studies that tested the link between depression and cognitive functioning indeed report that clinical depression in young adults is accompanied by relatively impaired cognitive functioning including those we tested here (see Castaneda, Tuulio-Henriksson, Marttunen, Suvisaari, & Lönnqvist, 2008 for overview). Even in healthy subjects, negative mood can lead to reduced brain activity during verbal (not spatial) working memory tasks (Aoki et al., 2011). Finally, the mood-behavior model (Gendolla, 2000) predicts that negative mood results in disengagement and little resource mobilization when facing difficult tasks, as demands would be perceived as being too high (Silvestrini & Gendolla, 2009). Given that negative mood is frequently a characteristic of depression, it is possible that task performance decreases the more individuals are depressed, due to decreased motivation (Engelmann, Damaraju, Padmala, & Pessoa, 2009; Locke & Braver, 2008).

Another possibility, though not necessarily independent of motivational factors, could be that the clubbing experience (including the drug consumption) resulted in neurochemical changes related to depression via serotonergic pathways, or more specifically through an attenuation of serotonergic functioning (Bhagwagar et al., 2006; Meyer et al., 2004; Meyer et al., 2003). Serotonin is a neurotransmitter, importantly linked to depression, to amphetamine use (see Walstab, Rappold, & Niesler, 2010 for overview), and the interaction between depression and amphetamine use (see Darke, Kaye, McKetin, & Duflou, 2008 for overview; McCardle, et al., 2004; M. J. Morgan, 2000; G. Rogers, et al., 2009). In all cases, a reduction in serotonin availability seems to have negative consequences. For instance, taking amphetamines such as ecstasy is related to a drop in mood, observable about two days after its consumption (Curran & Travill, 1997; Parrott & Lasky, 1998), presumably via reductions in serotonin-receptor density and binding [McCann et al. (1998; 2008)]. These changes in serotonin functioning have also been related to verbal memory performance (Reneman et al., 2001). Interestingly, serotonin receptor functioning has been implicated in the rewarding effects of THC as well (Maldonado, Berrendero, Ozaita, & Robledo, 2011), and some studies suggest that the effect of amphetamine and cannabis on memory functions is accumulative when consumed in parallel (see Mohamed, Hamida, Cassel, de Vasconcelos, & Jones, 2011 for overview). Taken together, these findings suggest that amphetamine and cannabis use may have altered susceptibility to mood-related cognitive attenuations, either via motivational factors, neurochemical modulations, or both.

To summarize, drug use was a consistent predictor of task performance in the long-term (pre-clubbing), and may have induced mood-related attenuations in cognitive

functioning in the short-term (post-clubbing). Schizotypy, on the other hand, was largely irrelevant to cognitive functioning on top of (poly-)drug use. The only significant schizotypy finding was that enhanced CogDis scores related to reduced verbal fluency. If we consider this single significant finding to be meaningful, the question arises whether some schizotypy dimensions are pathologically more relevant than others. Indeed, several researchers have indicated that CogDis is related to perceiving unusual experiences as unpleasant (Schofield & Claridge, 2007), or related to cognitive attenuations and poor emotional processing (Kerns & Becker, 2008). A problem is certainly the lack of consideration of disorganised symptoms in studies that found attenuated cognitive functioning relating to positive symptoms (Hoshi, Scoales, Mason, & Kamboj, 2011; Laws, et al., 2011; Lenzenweger & Korfine, 1994), and that most of the psychometric tools used in these studies do not distinguish between the two symptom dimensions (L. J. Chapman, et al., 1976; L. J. Chapman, et al., 1978; Eckblad & Chapman, 1983; Eysenck & Eysenck, 1975; Peters, Joseph, & Garety, 1999; Winterstein, et al., 2011).

If cognitive disorganisation is considered to be a separate symptom dimension, it seems more relevant to cognitive performance than the positive symptom dimension. For instance, in a study by Rawlings and Goldberg (2001) performance in a continuous performance task was affected by higher cognitive disorganization, but not as consistently by other schizotypy dimensions. Similar conclusions on the role of symptom dimensions have also been drawn from studies in other schizotypal samples (Bejaoui & Pedinielli, 2010; Chan et al., 2011; Steffen Moritz, Andresen, Naber, Krausz, & Probsthein, 1999) and in patients with schizophrenia (Kebir et al., 2008; Lucas et al., 2004). With regard to schizotypy, positive symptoms have even been associated with performance benefits in creativity tasks (Batey & Furnham, 2008;

Mohr, Graves, Gianotti, Pizzagalli, & Brugger, 2001; B. Nelson & Rawlings, 2010). It might be the case that only scoring high on positive schizotypy relates to a well-adapted cognitive profile, while high scores in CogDis alone and/or in combination with high scores in positive schizotypy might yield the most disadvantageous cognitive profile (Schofield & Claridge, 2007). Our results would support this notion.

Study limitations and implications

Our study population consisted of volunteers who were willing to come to the laboratory twice, shortly before and after a clubbing night. Moreover, testing had to be completed within two months. These study constraints reduced the number of possible participants, and by inference the overall sample size. Given our naturalistic designs, we nevertheless argue that our results are informative (Fernández-Serrano, et al., 2011), and stress that we could retain a considerable number of participants despite their clubbing activity, and decreased mood. These volunteers committed themselves to be tested twice around their clubbing experience, turning this sample and the measurements into a valuable data pool. Only with this naturalistic design were we able to assess the long-term (pre-clubbing) and short-term (post-clubbing) effects of drug use as it might occur in everyday situations. We do suggest that the current study, its design and results revealed important new findings that should be followed up in future studies, including laboratory ones (the role of depression, changes in results due to the emotional consequences of the clubbing / drug experience not observable in laboratory tests of drug exposure, the problem of poly-drug use).

Illicit drug use and depression are associated, but so are licit drugs. For instance, alcohol negatively influences mood, and the accumulation of this effect could be related to the depression rate increase seen in mephedrone users as well. According to recent meta-

analyses, alcohol increases the risk for depression (Boden & Fergusson, 2011), is related to impairments in memory and verbal fluency (see Fernández-Serrano, et al., 2011 for overview; Manning et al., 2008; Wendt & Risberg, 2001; Zeigler, et al., 2005), and hangovers are usually associated with low mood (Howland et al., 2010). Moreover, alcohol seems to affect serotonin-receptor functioning, similarly to amphetamines (McHugh, Hofmann, Asnaani, Sawyer, & Otto, 2010; Vengeliene, Bilbao, Molander, & Spanagel, 2008). Given that alcohol has been used more frequently between test sessions in our sample, we assume important interaction effects with alcohol.

It is also possible that the effects of mephedrone become more pronounced in chronic users, or those that use the drug at a high frequency, as in our sample use was relatively low (about 1.5 times/month). Additionally, it could have been advantageous to test the effects of mephedrone use in a sample of less educated subjects. IQ may have the potential to protect from adverse situations in e.g. psychiatric illnesses (MacCabe & Murray, 2004; Moore, et al., 2007; Sørensen et al., 2010) or substance use (Pope, et al., 2003; Zammit, et al., 2010). However, in our sample most participants were students, or educated to at least degree level. Therefore, more variance in subjects' educational level/IQ could be informative in subsequent studies.

Conclusion

We set out to investigate the effects of mephedrone use on cognition, and elucidate the relationship between drug use, schizotypal symptoms and cognitive functioning. Results showed that even before clubbing mephedrone users performed worse than non-users on cognitive tasks. In mephedrone users but not in controls, performance in verbal learning and fluency decreased over the clubbing experience. Additional analysis on the use of other drugs and psychological factors, however, indicated that the changes in cognitive

functioning were likely due to prior polydrug use (amphetamine, cannabis and alcohol use in particular), and related psychological consequences (enhanced depression rates). Schizotypal traits were rather unrelated to cognitive performance, apart from CogDis. This schizotypy subscale may therefore represent a pathologically more relevant symptom dimension. The present study shows that polydrug use should be considered in future studies on drug effects on cognition, as well as relevant associated psychological concepts (depression, schizotypy). Given the political interest in preventing the population from harmful drug effects, knowing when and who is really under an elevated risk is warranted, also because a more regulated drug policy has been called for from various professional domains (Bennett & Holloway, 2010; Nutt, et al., 2010).

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E. Study 4: Compensatory behaviours

Running title

Compensatory behaviours, schizotypy and hemispheric asymmetry

Reference

Herzig, D. A., & Mohr, C. (in press). Stressing schizotypy: The modulating role of stress-relieving behaviours and intellectual capacity on functional hemispheric asymmetry. *Laterality: Asymmetries of Body, Brain and Cognition*, 1-27.

1. Abstract

Relative cognitive impairments are common along the schizophrenia spectrum reflecting potential psychopathological markers. Yet stress, a vulnerability marker in schizophrenia (including its spectrum), is likewise related to cognitive impairments. We investigated whether one such cognitive marker (attenuated functional hemispheric asymmetry) during stressful life periods might be linked to individuals' schizotypal features or rather to individuals' stress-related experiences and behaviours. Fifty-eight students performed a left (lateralized lexical decisions) and right (sex decisions on composite faces) hemisphere dominant task. In order to account for individual differences in stress sensitivity, we separated participants into groups of high or low cognitive reserve according to their average current marks. In addition, participants filled in questionnaires on schizotypy (short O-LIFE), perceived stress, stress response, and a newly adapted questionnaire that enquired about potential stress compensation behaviour (elevated substance use). The most important finding was that enhanced substance use and cognitive disorganisation contributed to a right and left hemisphere shift in language dominance, respectively. We discuss that i) former reports on right hemisphere shifts in language dominance with positive schizotypy might be explained by an associated higher substance use and ii) cognitive disorganisation relates to unstable cognitive functioning that depend on individuals life circumstances, contributing to published reports on inconsistent laterality – schizotypy relationships.

Keywords: Stress, drug dependence, schizophrenia spectrum, cognitive reserve, hemispheric asymmetry

2. Introduction

Relative cognitive impairments are common in patients with psychosis as well as in less severely affected individuals along the schizophrenia spectrum. This includes individuals with a schizotypal personality disorder [see Reichenberg & Harvey (2007) for overview], and those scoring high on schizotypy questionnaires (Burch, et al., 2004; Krabbendam, et al., 2005; Laurent, et al., 2001; Poreh, et al., 1995). For instance, higher cognitive functions that rely on the frontal lobes (e.g. working memory, fluency) seem impaired along the schizophrenia spectrum, including schizotypy (Laurent, et al., 2001; Reichenberg & Harvey, 2007; Tsakanikos & Claridge, 2005). Supporting the likely brain correlates of such behavioural findings, the frontal lobes have long been discussed as a target area of psychopathology along the schizophrenia spectrum (Buchsbaum, et al., 2002).

Most relevant to the present study are those reports that link common patterns of functional hemispheric asymmetry to intact frontal and temporal lobe functioning (Rossell, Bullmore, Williams, & David, 2001). In particular, the common hemispheric asymmetry pattern seems to be disrupted along the schizophrenia spectrum with reduced left hemisphere dominance for language or a reduced right hemisphere dominance for face processing reported from patients with schizophrenia (Bleich-Cohen, et al., 2009; Kucharska-Pietura, et al., 2002; Mitchell & Crow, 2005; Phillips & David, 1997; Sommer, et al., 2001) and healthy individuals with elevated self-reported schizotypy (Broks, 1984; Brugger, et al., 1993; Løberg, et al., 2006; Mason & Claridge, 1999; Mohr, Krummenacher, et al., 2005; Suzuki & Usher, 2009). It is considered that cognitive impairments (such as those specified here) might be a reflection of the illness, or even be a marker of the schizophrenia spectrum (Crow, 2000; Noguchi, et al., 2008).

In addition to above, the stress response system seems to be implicated along the schizophrenia spectrum as well. Firstly, the hypothalamic-pituitary-adrenal (HPA) axis, one of the primary neural systems triggered by stress exposure, may be hyperactive in psychotic patients (Walker, Mittal, & Tessner, 2008). Secondly, increases in the stress-hormone cortisol can elevate psychotic symptoms in patients with schizophrenia [see Walker et al. (1997; 2008) for overview]. Drugs that increase cortisol serum levels induced mild psychotic symptoms and perceptual disturbances in healthy individuals (D'Souza et al., 2006). Thirdly, an elevated stress response has also been found in schizotypy (Soliman et al., 2008; see van Winkel, Stefanis, & Myin-Germeys, 2008 for overview), which may explain why individuals scoring high on positive schizotypy show sensitivity to threatening (stressful) stimuli (Fisher et al., 2004).

Stress has not only been linked to the schizophrenia spectrum, but also to the cognitive functions associated with it. For instance, cortisol administration disrupts verbal memory functions (Newcomer et al., 1999). Naturalistic stressors such as exam stress cause increased cortisol levels in some (Lucini, Norbiato, Clerici, & Pagani, 2002; Morgan III, Rasmusson, Pietrzak, Coric, & Southwick, 2009) though not all studies (Vedhara, Hyde, Gilchrist, Tytherleigh, & Plummer, 2000). Naturalistic stressors associate with shifts in hemispheric functioning such that relatively greater left frontal EEG-activity during low examination stress, shifts to relatively greater right frontal activity during high examination stress [see also Gruzelier and Phelan (1991)]. This shift is associated with increasing health complaints [(Lewis, Weekes, and Wang (2007)].

Given these cross-links between the schizophrenia spectrum, stress, and cognition, we investigated whether shifts in hemispheric asymmetry would be influenced by elevated

stress rather than by participants' self-reported psychotic and psychotic-like thinking (Broks, 1984; Brugger, et al., 1993; Løberg, et al., 2006; Mason & Claridge, 1999; Mohr, Krummenacher, et al., 2005; Suzuki & Usher, 2009). We also accounted for individual differences in stress responses and evaluations by asking about stress-related behaviours / experiences and cognitive reserve for the following reasons. Stress-related behaviours and experiences such as smoking (Finkelstein, Kubzansky, & Goodman, 2006) and drug use (Goeders, 2003) have been found to increase in times of elevated stress including periods before / during exams (Kassel, Stroud, & Paronis, 2003; Ng & Jeffery, 2003; Steptoe, Wardle, Pollard, Canaan, & Davies, 1996; Umberson, Liu, & Reczek, 2008) because they might have stress-alleviating properties (henceforth referred to as compensatory behaviours). Such compensatory behaviours may influence cognition [e.g. Scarmeas and Stern (2003)], and seem to occur more frequently along the schizophrenia spectrum (Cantwell et al., 1999; Kavanagh, McGrath, Saunders, Dore, & Clark, 2002; Regier et al., 1990). Cognitive reserve (also referred to as cognitive resilience, and sometimes linked to IQ), can be understood as an efficient dynamism with which the brain balances out threatening situations and challenges in order to maintain efficient cognitive functioning (Katzman et al., 1989; Stern, 2002). Cognitive reserve may protect from adverse situations in psychiatric illnesses (MacCabe & Murray, 2004; Moore, et al., 2007; Sørensen, et al., 2010) including post-traumatic stress disorder (see Buckley, Blanchard, & Neill, 2000 for overview).

In the present study, we investigated whether uncommon patterns of hemispheric asymmetry might relate to an abnormal or overactive stress response rather than to individuals' self-reported schizotypy. We assessed whether reduced hemispheric asymmetry in a left (lateralized lexical decisions) and right (sex decisions in visual

composite faces) hemisphere dominant task is affected by individuals' experienced stress / compensatory behaviours and cognitive reserve rather than by their self-reported schizotypy. If stress is a more important predictor of hemispheric asymmetry than schizotypy, we expect that higher stress levels and higher stress-related compensatory behaviours will relate to a reduced hemispheric asymmetry for function, in particular in those with less cognitive reserve (relatively lower marks).

3. Methods

Participants

This native English speaking student sample (n = 58, n = 16 males) reported normal or corrected to normal vision, and was right-handed according to a standardized handedness questionnaire [Oldfield (1971), scoring criteria see also Kita, de Condappa and Mohr (2007)]. The sample consisted of MSc students (n = 29) and BSc students at the University of Bristol. Their mean age (years, ±SD) was 20.33 (±2.35). Participants took part to obtain course credit or were recruited via a local internet advertising system. The study was approved by the local ethics committee. All participants provided written informed consent prior to participation. As indicated by self-report, none of the participants reported a previous history of psychiatric or neurological illness (Mohr, et al., 2006).

Self-report questionnaires

(1) Perceived stress scale

This 14-item scale (S. Cohen, Kamarck, & Mermelstein, 1983) measures global levels of perceived stress tapping into the key components of perceived stress, namely how uncontrollable, unpredictable and overloading (Averill, 1973; Houston, 1972; Monat, Averill, & Lazarus, 1972; Schulz, Kirschbaum, Prüßner, & Hellhammer, 1998) respondents found their lives in the past month. Participants answer on a 5-point Likert scale ranging from 'never', 'almost never', 'sometimes', 'fairly often' and 'very often'. After coding all items so that higher scores indicate higher perceived stress levels, scores range from 0 to 56. The perceived stress scale has adequate internal validity, construct validity and test-retest-reliability (S. Cohen, et al., 1983; Ramirez & Hernandez, 2007). Normative values can be found in Ramirez & Hernandez (2007).

(2) Stress response inventory

This 39-item stress response inventory (Koh, Park, Kim, & Cho, 2001) measures emotional, somatic, cognitive, and behavioural stress responses tapping into different stress-response domains such as tension (6 statements), aggression (4 statements), somatisation (3 statements), anger (6 statements), depression (8 statements), fatigue (5 statements) and frustration (7 statements). People indicate how much each statement applied to them in the past month on a 5-point Likert scale with the response options being 'Not at all' (scored '0'), 'Somewhat' (scored '1'), 'Moderately' (scored '2'),'Very much' (scored '3'), or 'Absolutely' (scored '4'). After coding all items so that higher scores indicate a higher stress response, scores range from 0 to 156. The stress response inventory is considered to have adequate internal consistency and test-retest reliability, and normative values for different populations can be found in Koh et al. (2001).

(3) Short O-LIFE

The short O-LIFE questionnaire (Mason, et al., 2005) is a validated 43-item self-report questionnaire assessing schizotypy in terms of four dimensions. Positive schizotypy is assessed by 12 items pertaining to Unusual Experiences (UnEx, maximum score 12,), negative schizotypy is assessed by 10 items pertaining to Introvertive Anhedonia (IntAn, maximum score 10), and Cognitive Disorganization is assessed by 11 items (CogDis, maximum score 11). Finally, 10 items assess Impulsive Nonconformity (Imp, maximum score 10), which does not represent a schizotypy dimension (Mason, et al., 1995), but will be accounted for in the present study because of the strong link between impulsivity and addiction (Crews & Boettiger, 2009). For each item, participants have to indicate whether the statement is true or false. The number of positive responses (some items are reversely formulated) is summed so that higher scores indicate higher schizotypy. Normative values can be found in Mason et al. (2005) and the scale has shown good internal consistency as well as high correlations with the original O-LIFE questionnaire (Mason, et al., 1995; Mason, et al., 2005).

(4) Compensatory behaviours

This adapted questionnaire (see Appendix, part A) is based on Ogden et al.'s (1997) 'Exercise Dependence Questionnaire', and is aimed to assess the severity or extent of substance based compensatory behaviours (henceforth referred to as substance-CB, 16 items). To avoid stigmatization, reduce associations with clinically relevant dependence, ethical concerns and socially desirable answers, we did not ask for drug use or drug addiction, but focussed on the need, or habit to consume a given substance (see the questionnaire instructions in Appendix, part A). Nevertheless, the items assess a variety of life-domains commonly affected by clinically relevant dependency, such as 'interference with social / family life' (3 statements), 'withdrawal symptoms' (3

statements), 'insight into problem' (2 statements), 'positive reward' (3 statements), 'loss of control' (2 statements) and behaviour salience (3 statements). On a 5-point Likert scale, individuals indicate how often they think each statement applied to them in the past month, with response options being 'Never' (scored '0'), 'Sometimes' (scored '1'), 'Often' (scored '2'), 'Nearly always' (scored '3') and 'Always'(scored '4'). Thus, scores range from 0 to 64 with a higher score indicating a higher 'dependence' on substance-CB.

(5) Cognitive reserve

To estimate cognitive reserve, participants indicated their current average mark. Answers were provided in percentages (0-100% scale), where 50% is a pass, 70% – 100% (for taught components and dissertations, respectively) is a first or distinction. Higher scores indicate higher marks and by inference higher cognitive reserve. The link between higher marks and higher IQ/cognitive reserve is well established (see Buckley, et al., 2000 for overview; Spinath, Harald Freudenthaler, & Neubauer, 2010; Stern, 2002).

Hemi-field studies [4]

We assessed hemispheric asymmetry with two lateralized lexical and facial decision tasks used before (Herzig, et al., 2010). Details can be found in this reference, whereas we will only briefly describe the tasks here.

(6) Lateralized Lexical Decision Task (LDT)

The stimulus material consisted of 24 abstract words and 72 pronounceable non-words. The stimuli consisted of four- and five-letter words and were matched for

[4] We also assessed verbal and figural fluency performance. For economy of presentation, these findings will be presented elsewhere. Data and findings from the fluency tasks can also be requested from the corresponding author.

neighbourhood and CELEX frequency (Coltheart, 1981). Each word was matched with a non-word of the same length. The remaining non-words were matched to result in an additional set of non-word pairs. There were 72 trials with three 24-trial conditions (word left/non-word right, non-word left/word right, and non-word/non-word as the control condition). Participants were instructed to indicate whether they saw a meaningful English word on the left or right, or did not see a meaningful English word at all by pressing the shift key ipsilateral to the word with the index finger, or space bar with both thumbs if they did not see a meaningful string of letters on the screen. Prior to the experimental task each participant undertook a practice block consisting of 10 trials with words and non-words not used in the experimental trial. The order of the stimuli was randomized within blocks and between participants, and trials were doubled according to suggestions by Hunter & Brysbaert (2008), resulting in a total of 144 trials. We assessed the number of correct lexical decisions and the mean reaction times for correct lexical decisions for the left (LVF) and right (RVF) visual field separately.

(7) Lateralized Facial Decision Task (FDT)

Participants were presented with emotionally neutral facial stimuli against a grey background on the computer screen. In the control condition, 20 whole faces (=WF, 10 male, 10 female) were presented. From these, 20 sexually dimorphic composite faces were constructed with an equal number of female and male half-faces appearing in each visual field. These composite faces were also presented mirror-reversed resulting in 40 composite faces. Participants were instructed to press one of the two shift keys to indicate the sex of the picture. The allocation of face sex to the two shift keys was counterbalanced between participants. Prior to the test trials participants were presented with a practice block of 10 trials consisting of two whole faces and eight composite faces that were not included in the experimental trials. The order of stimuli was

randomized within blocks and between participants, and trials were doubled according to suggestions by Hunter and Brysbaert (2008), resulting in 120 trials in total. We assessed the number and response time of facial decisions towards the left visual field (LF decisions) and right visual field (RF decisions).

Data cleaning and analysis

We excluded individual response latencies that were faster than 2xSD from the individual means of the different conditions in the LDT and FDT. To test for differences in performance as a function of cognitive reserve, we split the whole group into a group of high and low cognitive reserve at the median current average mark. Using these measures we calculated separate 2x2 mixed-samples ANOVAs with visual field (LVF, RVF) as the repeated factor and cognitive reserve (high, low) as the independent factor on i) mean reaction times of correct responses (LVF/RVF in the LDT), and ii) percent correct responses (LVF/RVF in the LDT). For the FDT (see Herzig, et al., 2010 for detailed rational), we performed a mixed-samples ANOVA on percent correct (WF) and percent LF decisions (composite faces) as repeated measure and the cognitive reserve group as between-subject measure. In addition (see Herzig, et al., 2010 for detailed rational), we performed a mixed-samples ANOVA on mean reaction time for sex decisions with face type (correct decisions for WF, LF decisions, RF decisions) as a repeated measure and the cognitive reserve group as a between-subject measure. Post-hoc tests correcting for multiple comparisons were performed using Tukey HSD tests. Effect sizes (*partial* η^2) are reported for all ANOVA results.

We also tested whether, within each cognitive reserve group, the tasks resulted in lateralized performance at all (Herzig, et al., 2010; Mason & Claridge, 1999; Mohr, et al., 2006) using conventional laterality indices (J. C. Marshall, et al., 1975) by

subtracting inferior performance from superior performance, and dividing this difference by its sum. Accordingly, positive values indicated an advantage of the normally dominant hemisphere (LDT: left hemisphere/LH; FDT: right hemisphere/RH), and negative values an advantage of the normally sub-dominant hemisphere. In order to obtain indices that would be comparable in this respect, the index for i) accuracy in the LDT, and ii) reaction times in the FDT was *[(RVF–LVF)/ (LVF+RVF)]*100*, while the index for reaction times in the LDT was *[(LVF–RVF)/ (LVF+RVF)]*100*. For accuracy in the FDT, we needed only the percentage of LF decisions (as LF and RF decisions added up to 100%). These indices were calculated for each cognitive reserve group separately, with one sample *t*–tests against chance level (zero for both LDT indices and the FDT RT index, 50% for the FDT LF percentage index).

To establish an effect of schizotypy over and above age, cognitive reserve (average mark), substance-CB and stress (perceived stress scale, stress response inventory) on hemispheric asymmetry, we performed hierarchical regressions as follows. Age was entered in the first step (Amirkhan & Auyeung, 2007; Brallier, Palm, & Gilbert, 2007; see also Tables 21 and 22), cognitive reserve (average mark) was entered in the second step, substance-CB in the third step, stress measures (perceived stress scale, stress response inventory) in the fourth step, and schizotypy (UnEx scores, CogDis scores IntAn scores, Imp scores) in the fifth step. Thus, five blocks of predictors were entered in nested blocks, meaning that each subsequent block contained all prior predictors and additional predictors from the current block. In line with Fridberg et al. (2011), the presentation of results will be restricted to significant ΔR^2-values and their corresponding significant coefficients. The full model can be found in the Appendix of this dissertation (see Table 28). We considered multi-collinearity between independent

variables negligible, because all tolerance values were above .2 (Menard, 1995), and all independent variables were mean-centered. Separate regression analyses were applied to the same dependent variables included in the ANOVAs described above (see also Herzig, et al., 2010). Kolmogorov–Smirnov tests for the groups separately revealed normal distribution for all behavioural measures and questionnaire scores. All *p*-values were two-tailed and the α-level was set at .05.

4. Results

Participants and self-report questionnaires

Most participants did not report any particularly stressful previous life events (n = 44). Self-report measures were compared to previous normative samples via calculations of Cohen's *d* (1992) with values of ± 0.2 / ± 0.5 / ± 0.8 being indicative of a small / medium / large effect size, respectively (see Table 17). These comparisons showed that the present sample was largely comparable with normative samples, apart from CogDis scores and perceived stress scale scores that were elevated and IntAn scores and stress response inventory scores that were reduced in our as compared to the normative sample (see Table 17).

Table 17. *Means, SDs and effect sizes (Cohen's d), comparing the normative sample values with our sample.*

		Norm values			**Our sample**		
Questionnaire	**Published norms by**	***m***	***SD***	***N***	***m***	***SD***	**Cohen's *d***
O-LIFE: UnEx[a]	Mason et al., 2005	3.35	2.92	2072	3.67	1.89	-0.11
O-LIFE: CogDis[b]	Mason et al., 2005	4.42	2.90	2094	6.16	2.55	-0.60
O-LIFE: IntAn[c]	Mason et al., 2005	2.46	2.01	2073	1.40	1.41	0.53
O-LIFE: Imp[d]	Mason et al., 2005	2.60	1.99	2098	2.78	1.52	-0.09
PSS[e]	Ramirez & Hernandez (2007)	21.90	7.03	365	28.21	8.00	-0.88
SRI[f]	Koh et al. (2001)	68.50	23.40	215	41.96	20.79	1.16

Note: [a] Unusual experiences; [b] Cognitive Disorganisation; [c] Introvertive Anhedonia; [d] Impulse Non-conformity; [e] Perceived Stress Scale; [f] Stress Response Inventory;

Regarding the cognitive reserve groups, the median-split (median of 65%) on the average mark (in percent) resulted in 31 students (23 women) belonging to the high cognitive reserve group (marks ≥ 65%, range 65%-80%, *m* = 68.55, *SD* = 4.12), and 27 students (19 women) belonging to the low cognitive reserve group (marks < 65%, range 40%-64%, *m* = 56.44, *SD* = 6.70). Separate t-tests on age, schizotypy scores, substance-CB scores, perceived stress scale scores, and stress response inventory scores with cognitive reserve group as a between-subject measure showed that the high as compared to low cognitive reserve group was older, and had lower CogDis scores (Table 18). None of the other group comparisons were significant (Table 18).

Table 18. *Means and SD for age and self-report questionnaire scores for the whole sample, and for the two cognitive reserve groups separately. The results of the t-tests are presented.*

	Total (N = 58)		**High (N = 31)**		**Low (N = 27)**			
Dependent variable	***Mean***	***SD***	***Mean***	***SD***	***Mean***	***SD***	***t(1, 56)***	***p***
Age	20.33	2.35	20.97	2.87	19.59	1.25	2.42	**0.02**
UnEx[a]	3.67	1.89	3.26	1.71	4.15	1.99	-1.83	0.07
CogDis[b]	6.16	2.55	5.55	2.59	6.85	2.35	-1.99	**0.05**
IntAn[c]	1.40	1.41	1.42	1.29	1.37	1.57	0.13	0.90
Imp[d]	2.78	1.52	2.71	1.47	2.85	1.61	-0.35	0.73
SCB[e]	12.38	8.60	11.61	7.41	13.26	9.87	-0.72	0.47
PSS[f]	28.21	8.00	27.52	7.31	29.00	8.80	-0.70	0.49
SRI[g]	41.96	20.79	39.19	18.34	45.13	23.23	-1.09	0.28

Note: [a] Unusual experiences; [b] Cognitive Disorganisation; [c] Introvertive Anhedonia; [d] Impulse Non-conformity; [e] Substance-based compensatory behaviours; [f] Perceived Stress Scale; [g] Stress Response Inventory;

Correlations between self-report questionnaire scores

The correlations between schizotypy measures showed positive correlations between UnEx, Imp and CogDis scores, but no correlations with IntAn scores (Table 19). The stress response inventory scores were positively correlated with perceived stress scale scores (Table 19). Correlations between schizotypy and stress-relevant measures showed that increasing UnEx scores, CogDis scores, and Imp scores all related to increasing perceived stress scale scores and stress response inventory scores. Substance-CB scores were positively correlated with CogDis scores (Table 19). An inverse relationship between the extent of schizotypal traits and IQ is sometimes reported [e.g. (Matheson & Langdon, 2008; Noguchi, et al., 2008)], even though IQ is generally believed to be spared in schizotypy (Raine, 2006). In this sample none of the correlations between schizotypy and average mark were significant (Table 19).

Table 19. *Pearson correlations between scale scores.*

	UnEx	**CogDis**	**IntAn**	**Imp**	**SCB**	**PSS**	**SRI**	**Average Mark**
UnEx[a]	1.00	**0.37****	-0.02	**0.36****	0.18	**0.32***	**0.42*****	-0.18
CogDis[b]	**0.37****	1.00	0.02	**0.44*****	**0.46*****	**0.45*****	**0.56*****	**-0.22†**
IntAn[c]	-0.02	0.02	1.00	**0.24†**	-0.01	0.05	0.01	**0.23†**
Imp[d]	**0.36****	**0.44*****	**0.24†**	1.00	0.13	**0.33***	**0.36****	-0.08
SCB[e]	0.18	**0.46*****	-0.01	0.13	1.00	0.19	**0.24†**	-0.14
PSS[f]	**0.32***	**0.45*****	0.05	**0.33***	0.19	1.00	**0.69*****	-0.20
SRI[g]	**0.42*****	**0.56*****	0.01	**0.36****	**0.24†**	**0.69*****	1.00	**-0.23†**
Average mark	-0.18	**-0.22†**	**0.23†**	-0.08	-0.14	-0.20	**-0.23†**	1.00

*†p≤.10; * significant at p≤.05; ** significant at p≤.01; *** significant at p≤.001*

Note: [a] Unusual experiences; [b] Cognitive Disorganisation; [c] Introvertive Anhedonia; [d] Impulse Non-conformity; [e] Substance-based compensatory behaviours; [f] Perceived Stress Scale; [g] Stress Response Inventory;

Hemispheric asymmetry tasks

(1) LDT

The ANOVA on accuracy showed that performance was superior for RVF as compared to LVF presentations ($F(1,56) = 16.97$, $p < .001$, *partial* $\eta^2 = .23$; see Table 20). The interaction between group and visual field ($F(1,56) = .27$, $p = .60$, *partial* $\eta^2 < .01$) and the main effect of group ($F(1,56) = 1.21$, $p = .28$, *partial* $\eta^2 = .02$; see Table 20) yielded no significant result. The ANOVA on reaction times showed no significant result, neither for the main effect visual field ($F(1,56) = .08$, $p = .78$, *partial* $\eta^2 < .01$), nor the main effect group ($F(1,56) = .14$, $p = .71$, *partial* $\eta^2 < .01$), nor the interaction visual field * group ($F(1,56) = 1.84$, $p = .18$, *partial* $\eta^2 = .03$].

The comparisons against chance level for the laterality indices were significant for percent accuracy (t [57] = 3.66, $p < .001$), but not for reaction times (t [57] = .12, p = .91). The difference remained stable when calculated for the cognitive reserve groups separately (high cognitive reserve group: accuracy: t [30] = 2.62, p = .01; reaction time:

t [30] = -.70 *p* = .49); low cognitive reserve group: accuracy: *t* [26] = 2.52, *p* = .02; reaction time: *t* [26] = .99, *p* = .33; Table 20). The positive laterality indices point to a RVF (LH) advantage in the LDT.

(2) FDT

The ANOVA on percentage of sex decisions showed a main effect for face type with sex decisions for WF being more accurate than the proportion of LF decisions (*F* [1,56] = 443.85, *p* < .001, *partial* η^2 = .89, Table 20). The interaction between face type and group (*F* [1, 56] = 1.76, *p* = .19, *partial* η^2 = .03) and the main effect for group (*F* [1, 56] = 3.43, *p* = .07, *partial* η^2 = .06) were not significant. The ANOVA on reaction times showed a significant main effect for face type (*F* [2,112] = 76.63, *p* < .001, *partial* η^2 = .58), due to slower responses for both RF-decisions (*p* < .001) and LF decisions (*p* < .001) as compared to WF decisions (Table 20). However, participants were equally fast for LF and RF decisions (*p* = .15). The main effect for cognitive reserve (*F* [1, 56] = .20, *p* = .66, *partial* η^2 < .01), and the interaction between cognitive reserve and visual field were both not significant (*F* [2, 112] = .45, *p* = .61, *partial* η^2 = .01). The comparisons against chance level for the laterality indices showed a significant finding for percent LF decisions (*t* [57] = 6.95, *p* < .001; see Table 20) as well as the reaction time index (*t* [57] = 2.79, *p* = .01). The analogue comparisons for the cognitive reserve groups separately were significant for the high (*t* [30] = 6.94, *p* < .001) and low (*t* [26] = 3.23, *p* < .01) group on percent LF decisions, but only for the high group (*t* [30] = 2.39, *p* = .02, low group: *t* [26] = 1.46, *p* = .16, Table 20) on the reaction time index. Percent LF decisions above 50% represent a LF (RH) bias.

Table 20. *Mean and SD of lateralized task performance for the total sample and the two groups separately.*

		All (N=58)		High (N=31)		Low (N=27)	
		Mean	***SD***	***Mean***	***SD***	***Mean***	***SD***
LDT[a]	LDT LVF[c] %[d]	62.14	20.99	64.85	21.28	59.03	20.60
	LDT RVF[e] %	74.43	15.87	75.67	14.60	72.99	17.38
	LDT NoW[f] %	72.05	10.56	73.19	10.63	70.76	10.52
	LDT index[g] %	10.34	21.52	9.50	20.18	11.30	23.32
	LDT LVF RT	695.71	108.57	691.93	92.85	700.05	125.93
	LDT RVF RT	693.24	102.81	705.59	104.76	679.06	100.58
	LDT NoW RT	834.16	133.27	843.38	118.29	823.57	150.25
	LDT index RT	0.10	6.74	-0.88	6.96	1.23	6.41
FDT[b]	FDT LF[h] %	59.03	9.89	61.37	9.12	56.34	10.22
	FDT WF[i] %	90.82	7.03	91.29	6.98	90.28	7.18
	FDT LF RT	678.82	124.37	683.47	132.41	673.49	116.74
	FDT RF[j] RT	702.28	145.31	713.25	155.59	689.69	134.35
	FDT WF RT	597.47	98.74	601.31	104.21	593.05	93.84
	FDT index RT	1.47	4.01	1.86	4.34	1.02	3.64

Note: [a] Lexical decision task; [b] Facial decision task; [c] Left visual field; [d] Percentage correct; [e] Right visual field; [f] Two non words displayed on either side of the screen; [g] Laterality index; [h] Left face decisions; [i] Whole face decisions; [j] Right face decisions

Regressions: Severity of compensatory behaviours, stress and schizotypy as predictors of performance in the LDT and FDT

(3) LDT

Neither age nor cognitive reserve significantly predicted variance in the LDT (see Table 21). Compensatory behaviours explained a significant amount of variance in the LDT outcome variables, with increasing substance-CB scores predicting an increase in LVF % and a decrease in the index % (Table 21, see also Herzig et al., 2010). Adding the two

stress scores in the fourth step only helped to explain variance in the reaction times for correct lexical decisions in the RVF. More specifically, faster RVF reaction times were predicted by increasing perceived stress scale scores (Table 21). Schizotypy explained a significant amount of variance in the reaction time index only with higher CogDis scores enhancing the typical LH-dominant response pattern (see Table 21).

Table 21. *Beta-weights and ΔR² for the LDT outcome variables for the whole sample, assessing the effect of schizotypy (step 5) on LDT performance on top of age (step 1), cognitive reserve (step 2), compensatory behaviours (step 3) and stress (step 4). Only significant ΔR²-values and their corresponding significant coefficients (β-values) are reported.*

Outcome variables	**Step**	**Significant predictor**	***β*-value**	**Total R^2**	**ΔR^2**	***F* for ΔR^2**
LVF[a] %[b]	3	SCB[d]	**0.39****	**0.18****	**0.14****	**9.20****
Index[c]	3	SCB	**-0.29***	**0.10***	**0.08***	**4.80***
RVF RT	4	PSS[e]	**-0.38***	**0.14***	**0.13***	**3.97***
RT Index	5	CogDis[f]	**0.39***	**0.28***	**0.21***	**3.45***

** significant at p≤.05; ** significant at p≤.01; *** significant at p≤.001*

Note: [a] Left visual field; [b] Percentage correct; [c] Laterality index; [d] Substance-based compensatory behaviours; [e] Perceived Stress Scale; [f] Cognitive Disorganisation;

(4) FDT

As Table 22 indicates, only age and stress predicted an additional significant amount of variance on top of the other variables in the FDT RT index. More specifically, increasing age predicted a reduction in the typical RH bias for face processing. The stress measures predicted variance in the FDT RT index in opposite directions: Whereas perceived stress predicted a stabilization of the RH face processing bias, the stress response predicted a decrease in RH bias (see Table 22).

Table 22. *Beta-weights and ΔR² for the FDT outcome variables for the whole sample, assessing the effect of schizotypy (step 5) on FDT performance on top of age (step 1), cognitive reserve (step 2), compensatory behaviours (step 3) and stress (step 4). Only significant ΔR²-values and their corresponding significant coefficients (β-values) are reported.*

Outcome variable	Step	Significant predictor	*β*-value	Total R^2	ΔR^2	*F* for ΔR^2
RT index[a]	1	Age	**-0.26***	**0.07***	**0.07***	**4.20***
	4	PSS[b]	**0.39***	**0.21***	**0.13***	**4.19***
	4	SRI[c]	**-0.52****	**SAA**[d]	**SAA**	**SAA**

** significant at p≤.05; ** significant at p≤.01; *** significant at p≤.001*

Note: [a] Laterality index; [b] Perceived Stress Scale; [c] Stress Response Inventory; [d] Same value as above;

5. Discussion

Relative cognitive impairments along the schizophrenia spectrum might be associated with stress rather than those processes related to the symptoms of the schizophrenia spectrum. To test this idea, we measured functional hemispheric asymmetry in a student population varying in schizotypal thoughts around their end of year exam period. We assessed hemispheric asymmetry, because its attenuation has been related to enhanced psychotic (clinical populations) or psychotic-like (schizotypal) thinking styles (Broks, 1984; Brugger, et al., 1993; Mason & Claridge, 1999; Reichenberg & Harvey, 2007; Suzuki & Usher, 2009). To account for individual differences in perceived and experienced stress (Dallman, 2010; Ensel & Lin, 2004; Finkelstein, et al., 2006; Goeders, 2003; Krause, Goldenhar, Liang, Jay, & Maeda, 1993; Scarmeas & Stern, 2003), we assessed perceived stress and stress response (S. Cohen, et al., 1983; Koh, et al., 2001), stress-related compensatory behaviours (substance use), and potential cognitive reserve. If stress is a more important predictor of hemispheric asymmetry than schizotypy, we expected higher stress levels and higher stress-related compensatory

behaviours, in particular in those with less cognitive reserve (relative lower marks), relate to reduced hemispheric asymmetry for function.

Our data supported these predictions only partially, i.e. enhanced substance-CB contributed to a reduced LH dominance for language (see also Herzig, et al., 2010) but enhanced perceived stress was associated with increased hemispheric asymmetry. We did not find any consistent changes in performance due to cognitive reserve or the stress response. Regarding schizotypy, increasing CogDis scores were associated with enhanced LH language dominance. Before discussing the relevance of these findings, we would like to point out that we tested a seemingly representative population because we firstly observed the commonly reported LH bias in the LDT and the RH bias in the FDT (Brugger, et al., 1993; Mason & Claridge, 1999; Regard, Landis, & Graves, 1985) and secondly, that self-report measures were largely comparable to normative values, apart from some scores that were relatively higher in our sample for the perceived stress scale and CogDis subscale and relatively lower for the stress response inventory and IntAn subscale.

Hemispheric asymmetry and its' relation to substance-CB

A major finding was that increased substance-CB related to a reduced LH language dominance supporting previous notions that drug use relates to a cognitive profile resembling the one seen along the schizophrenia spectrum, namely an attenuated hemispheric asymmetry pattern (Bleich-Cohen, et al., 2009; Broks, 1984; Brugger, et al., 1993; Kucharska-Pietura, et al., 2002; Løberg, et al., 2006; Mason & Claridge, 1999; Mitchell & Crow, 2005; Mohr, Krummenacher, et al., 2005; Phillips & David, 1997; Sommer, et al., 2001; Suzuki & Usher, 2009). Thus, an attenuated hemispheric asymmetry seems not only related to enhanced nicotine dependence in healthy

populations (Hahn, Pogun, & Güntürkün, 2010; Herzig, et al., 2010) and patients with schizophrenia (Hahn, et al., 2011), but might relate to a generally enhanced drug use. Indeed, participants in these latter nicotine studies are likely to have consumed other drugs (e.g. licit and illicit) as well (Degenhardt, et al., 2001; Martinez-Ortega, et al., 2006), stressing the possibility that the present RH shift in language processing with increasing substance-CB is not restricted to a particular substance (Herzig, et al., 2010). Enhanced substance-CB as a potential indicator of a "pathological" profile would also be supported by the observation that elevated substance-CB predicted more cognitive disorganisation. This schizotypy subscale was also linked with lower cognitive reserve and higher perceived stress in the present and independent samples (Cuesta & Peralta, 1995; Ventura, Thames, Wood, Guzik, & Hellemann, 2010; Walker, et al., 2008) and with deteriorating mental health in the long-term (Goulding & Ödéhn, 2009; Schofield & Claridge, 2007).

As a final note, we found the relationship between attenuated hemispheric asymmetry and enhanced substance dependence only for the LDT [but see (Herzig et al., 2010)], potentially because language is the cognitive function that most reliably yields lateralized findings in healthy populations (Hugdahl & Westerhausen, 2010; Resnick, Lazar, Gur, & Gur, 1994).

Hemispheric asymmetry and its' relation to stress

Perceived stress was associated with a LH shift in the LDT and FDT, whereas the stress response predicted a reduction in RH face processing for one outcome variable only. Such a LH-shift, in particular for the more reliable LH language functions, may point to a favourable cognitive profile with enhanced perceived stress. Some authors argue that stress is advantageous for general survival (see Lupien, Maheu, Tu, Fiocco, & Schramek, 2007 for overview) or performance abilities (Lewis, Nikolova, Chang, &

Weekes, 2008; McEwen & Sapolsky, 1995; Yerkes & Dodson, 1908). Supporting different, opposing conclusions for results on substance-CB above, and stress-measures here, these two measures were not related with each other. By inference, perceived stress may be related to a relatively "healthy" pattern of brain functioning while the need to engage in substance-CB during times of enhanced stress (exams) may be linked to a relatively "unhealthy" pattern of brain functioning (Herzig, et al., 2010).

Hemispheric asymmetry and its' relation to schizotypy

Increasing CogDis scores were associated with an increase in LH language dominance for the RT measure. This result is contrary to our initial prediction and might thus be spurious. Caution is also warranted when considering that CogDis relates to poor verbal abilities (Chan, et al., 2011; Cuesta & Peralta, 1995; Lucas, et al., 2004; Stefanis, et al., 2006). Taking into account that high CogDis is indicative of a rather disadvantageous cognitive profile (see above), that it was related to elevated stress perception and drug use, we are hesitant to conclude that CogDis favours the most common and by inference, "normal" cognitive profile. We would like to speculate instead, that CogDis may be particularly sensitive to environmental changes, based on the following reasoning. Previous findings investigating the link between CogDis and language laterality have been inconsistent in the literature. A reduction in language laterality is most consistently reported from samples taken from the general population (Mason & Claridge, 1999; Suzuki & Usher, 2009). Inconsistent findings on the relationship between CogDis and language laterality, on the other hand, emerge frequently for student samples, be it decreases in LH processing (Herzig, et al., 2010; Kravetz, et al., 1998), increases in LH processing (Liouta, et al., 2008 and this study), or no differences between hemispheres (Nunn & Peters, 2001). Purportedly, as compared to the individuals from the general population, students have unique features not observed in

the general population that predispose them to fluctuations in laterality patterns, such as during confined periods of exam stress. We are unaware of any published report linking CogDis, stress and laterality but do know that stress is associated with psychotic-like symptoms [e.g. (H. Lee & Schepp, 2009; van Os, et al., 2009; Walker & Diforio, 1997; Walker, et al., 2008)]. It may be the case that relatively elevated CogDis might turn exam periods into particularly stressful situations. We actually found that higher CogDis was associated with higher perceived stress. This enhanced stress may elevate revision time in students high on CogDis exposing them to more verbal stimuli and consequently increase LH language laterality (Marcel, Katz, & Smith, 1974; Rutherford, 2006; Wey, Cook, Landis, Regard, & Graves, 1993). On the other hand, during periods of low exam stress, low revision time, and lower exposure to verbal material, CogDis might have related to the expected hemispheric asymmetry pattern, i.e. a reduced LH language dominance. The present argumentation is admittedly highly conjectural but constructive enough to trigger future studies in which participants' situational variables are accounted for.

The influence of drug use on the link between schizotypy and cognition

Substance-use is elevated along the schizophrenia spectrum for a large variety of drugs, such as i) tobacco use in schizotypy (Esterberg, et al., 2009; J. H. Williams, Wellman, Allan, et al., 1996) and patients with schizophrenia (de Leon, et al., 2002), ii) cannabis in schizotypy (Barkus, et al., 2006; Skosnik, et al., 2001; J. H. Williams, Wellman, & Rawlins, 1996) and schizophrenia (Archie, et al., 2007; Moore, et al., 2007), iii) amphetamines/stimulants in schizotypy (Curran & Morgan, 2000) and schizophrenia (Barkus & Murray, 2010), and iv) caffeine in schizotypy (Jones & Fernyhough, 2009) and schizophrenia (Gurpegui, et al., 2004). In our present study, it was not schizotypy but substance use that associated with a reduced LH language dominance, indicating

that substance use might be the major determinant to measures of cognitive functioning. The present study and its design are unsuited to infer which variable (schizotypy, substance use, or yet unspecified variables) is the most likely to cause a reduced LH language dominance. Reports on legal or illegal substance are still uncommon in the schizotypy literature when investigating the effects of psychotic (-like) thinking on hemispheric asymmetry (Broks, 1984; Brugger, et al., 1993; Mason & Claridge, 1999; Mohr, Krummenacher, et al., 2005; Suzuki & Usher, 2009), despite the recent evidence that the extent of substance use is important in this regard (Hahn, et al., 2011; Hahn, et al., 2010; Herzig, et al., 2010). The necessity to control for substance use is not exclusive to the study of hemispheric asymmetry but is relevant to cognitive functions more broadly (Rodriguez-Jimenez et al., 2010). Only by taking the influence of substance use on cognitive functions in schizotypy studies more seriously will we find out whether our focus on schizotypal symptoms has been overvalued.

Limitations

While we have aimed to control and account for important variables to test our study question, we are aware of short-comings and improvements, such as i) the pre-selection of right-handed participants, ii) inferring cognitive reserve from the current mark, iii) assessing substance-CB without knowing anything about the substance(s), iv) unbalanced sex distribution. Concerning the first point, we pre-selected participants for their right-handedness as is common in experiments on hemispheric asymmetry in general (Bourne, 2006) and on schizotypy in particular (e.g. Mason & Claridge, 1999; Mohr, Krummenacher, et al., 2005; Suzuki & Usher, 2009) and general hemispheric asymmetry (Bourne, 2006). However, if we acknowledge reduced right-handedness in schizophrenia (Dragovic & Hammond, 2005) and schizotypy (H. L. Chapman, Grimshaw, & Nicholls, 2011; Somers, et al., 2009), we are likely to exclude relevant

participants. Future studies should investigate a more representative sample that encompasses a wider range of hand preferences (e.g. Shaw, et al., 2001; Somers, et al., 2009). Concerning the second point, we tested a highly performing student group because all had to have three As (in A-level exams) when admitted to the local Psychology course. Using participants from a wider educational background might yield more systematic relationships between task performance and study performance (i.e. marks) than the one observed here. Concerning the third point, the substance-CB questionnaire did not ask about specific substances that could nevertheless have yielded different effects on hemispheric asymmetry. For instance, some of the substances might have stress-alleviating properties (e.g. anxiolytic medication), having counteracted otherwise detrimental effects of stress on cognition. The advantage of the present questionnaire is its lowered risk of socially desirable responding. Moreover, as argued above, results from the questionnaire replicated previous findings on specific drugs such as nicotine. Concerning the fourth point, studies on laterality and schizotypy frequently observed effects in male populations only (see Hausmann & Güntürkün, 2000 for overview; McGlone, 1980), hence we cannot exclude stronger and more consistent findings if we had excluded female participants. However, due to unequal sex distribution in the current sample we could not further account for this factor.

Conclusions

We here aimed to disentangle whether stress and stress-related behaviours or schizotypal symptoms influence reduced hemispheric asymmetry for function as formerly reported along the schizophrenia spectrum. Results from two lateralized tasks (LDT, FDT) were not fully supportive of either perspective, but revealed that stress, stress-related behaviour and schizotypal symptoms contributed differently to cognitive performance. Most importantly, our findings indicated that i) a RH shift in language

dominance might be explained by enhanced substance dependence, and less so by individuals' schizotypal features, ii) perceived stress related to a LH shift, and iii) inconsistent findings on laterality and schizotypy might be population and context dependent.

In practical terms, the implications of these results are that future studies assessing the link between schizotypy and cognition should control for legal and illegal substance use, in which participants' life situations are measured (stressful life situation or not) and whether students or non-students of various educational backgrounds are targeted. We also argue that the current implications are not only relevant to studies on hemispheric asymmetry, but to cognition more generally and on frontal lobe functioning more particularly (Buchsbaum, et al., 2002; Laurent, et al., 2001; Reichenberg & Harvey, 2007; Tsakanikos & Claridge, 2005).

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III. General discussion

A. Interpretations of findings

The presented four studies support the original notion of the current thesis that cognitive attenuations formerly linked to schizotypal symptoms might be significantly associated with enhanced drug consumption. The notion that drugs can influence cognition is known (see section I. C. 2.), as is the observation that drug use is elevated in schizotypal populations (see section I. C. 1.). Despite these different streams of research, studies on the relationship between schizotypy and cognition have shown little efforts so far to consider both legal and illegal drug use. In Table 30 (see Appendix), we listed studies that investigated schizotypy and cognition, including the information if and how they controlled for licit (nicotine, alcohol) and illicit substance use (e.g. via assessment, exclusion, statistically controlling for drug use). As Table 30 shows, the majority of studies did not report controlling for drug use. Sixty-seven percent (%) of the findings are reported without considering drug use, whereas the remaining ones vary in the criteria applied (see Table 30 in Appendix), potentially contributing additional noise to the analysis. For instance, in the 33% of findings where drug use is taken into account (either by reporting on it, excluding participants with a drug use history, or statistically controlling for it), the majority (72%) report decreased performance as a function of schizotypy, followed by 28% reporting no effect of schizotypy on cognition. A relatively elevated performance as function of schizotypy is not shown in this group of findings. For findings where participants' drug use is not reported, 11% show an improved performance due to relatively elevated schizotypy, 30% report no effect of schizotypy, and the majority (59%) find relatively impaired cognitive performance as a function of elevated schizotypy.

It is therefore possible that the lack of adequately assessing drug use (e.g. via questionnaires, interviews, drug test) and responding accordingly (e.g. excluding drug using individuals, statistically controlling for drug use), or the diversity in methods used (e.g. according to DSM-criteria, self-report or drug tests, see Table 30 in Appendix) explains why results on the effects of schizotypal symptoms, in particular on hemispheric asymmetry and frontal lobe functioning, are frequently heterogeneous between studies (Giraldez, et al., 1999; Park & McTigue, 1997; Laws, et al., 2008; Liouta, et al., 2008; Spitznagel & Suhr, 2002). As detailed in sections I. C.1. and I. C.2., drug use affects those cognitive functions that are also thought to be affected along the schizophrenia spectrum with the use of such drugs being elevated in high schizotypes as well. This is also true for licit drugs like alcohol, which is rarely asked for in studies on schizotypy (see also Table 30 in Appendix). Since alcohol rather than schizotypy emerged as an important predictor for cognitive attenuations in our studies, alcohol potentially relates to cognitive attenuations formerly associated with schizotypal symptoms. In the next paragraph we will try to lend further support to this idea by elaborating on the effect of alcohol on frontal lobe functioning and hemispheric asymmetry, functions reported to be attenuated along the schizophrenia spectrum (see also section I. B. 1. and I. B. 2.).

1. Alcohol

Alcohol and schizophrenia spectrum

It could be the case that alcohol played a role in previous studies assessing cognition along the schizophrenia spectrum, because independent studies reported on an elevated use in schizophrenia and other psychotic disorders [(Cantor-Graae, et al., 2001; Gregg, et al., 2007; Mastrigt, et al., 2004; Sevy et al., 2001), but see (Brown, Birtwistle, Roe, &

Thompson, 1999; Roick et al., 2007)]. A relative enhanced alcohol consumption can also be observed when studies are accounted for that assess populations along the schizophrenia spectrum, i.e. schizotypal individuals (Kwapil, 1996). Some studies also reported alcohol use to relate to schizotypal symptoms, e.g.lower negative and higher positive schizotypy as a function of alcohol use (Barrantes-Vidal, Lewandowski, & Kwapil, 2010; Nunn, Rizza & Peters, 2001), lower positive schizotypy (Larrison, et al., 1999) or higher positive, negative and disorganized schizotypy as a function of alcohol (Esterberg, et al., 2009). These findings stress the relevance of this substance along the schizophrenia spectrum, particularly when assessing cognitive functions along the schizophrenia spectrum. Given that the effect of alcohol on cognitive functioning has emerged as important in the present doctoral thesis over the course of testing, in the following we account in more detail on previous experiments investigating the influence of alcohol on cognition, in particular those that have been tested in the present studies (see also section I. B. 1. and I. B. 2.).

Alcohol and frontal lobe functioning

Enhanced alcohol use is related to impairments in memory and verbal fluency (see Fernández-Serrano, et al., 2011 for overview; Manning, et al., 2008; Wendt & Risberg, 2001; Zeigler, et al., 2005). In the case of acute alcohol intoxication, studies showed impairments in prose recall (Parada, et al., 2011; Petros, et al., 1985; Poltavski, et al., 2011) or working memory impairments in populations frequently exposed to high doses of alcohol (Parada, et al., 2011; Parada et al., 2012; Parker, Birnbaum, & Noble, 1976). Additionally, verbal fluency (Wendt & Risberg, 2001), and cognitive flexibility or set shifting (Trail making and WCST) attenuations have been reported with increasing doses of alcohol (Guillot, et al., 2010; Lyvers & Tobias-Webb, 2010). These functional impairments are probably due to alterations in brain structure and activation in alcohol

using individuals. For instance, brain imaging studies reported on brain volume deficits and activity levels in prefrontal areas of alcoholics (see Zahr, Pitel, Chanraud, & Sullivan, 2010 for overview). Additionally, increased left frontal and right cerebellar activation was reported in alcoholics when they performed a verbal working memory task (Desmond et al., 2003). The increased activation seemed to support the theory that more effort is needed in this population to compensate for functional impairments.

Alcohol and hemispheric asymmetry

The literature on functional hemispheric asymmetry in alcohol use is sparse. However, there are some studies suggesting a reduction of hemispheric asymmetry as a function of alcohol. For instance, an older study investigating lateralization effects of alcohol (Kostandov, Arsumanov, Genkina, Restchikova, & Shostakovich, 1982) revealed performance decreases in the left visual field (right hemisphere) as a function of acute ethanol administration. Another experiment found deficits in a lateralized emotional word recognition task in alcoholics (Hutner & OscarBerman, 1996) suggesting a decrease in right hemisphere bias as well. Additionally, others studies point to a decrease in left hemisphere functioning as a function of alcohol, e.g. a decreased left hemisphere bias under acute ethanol influence as compared to placebo in occasional social drinkers (Leone & McCourt, 2009). Anatomical and brain imaging studies also reported a reduced left hippocampal volume in alcohol users as compared to non-using controls (Medina, Schweinsburg, Cohen-Zion, Nagel, & Tapert, 2007), and this effect increased with higher alcohol use. EEG-studies showed that in alcohol dependent subjects the left anterior frontal activation was reduced relative to the right when compared to non-dependent control subjects (Hayden et al., 2006). Taken together, the findings suggest that the harmful effects of alcohol use may be associated with a reduction in typical hemispheric asymmetry for function and brain anatomy.

Given our initial working hypothesis of attenuated cognitive performance as a function of schizotypal symptoms (see section I. B.), we would here conjecture that elevated alcohol use (see section III. A. 1.) could serve as an alternative explanation for attenuations in laterality patterns and frontal lobe functioning.

2. Polydrug use

Legal (e.g. alcohol) as well as illegal drug use affect cognitive functioning, but if this relates to the specific substances used, or whether or not it is the amount of drugs consumed simultaneously (polydrug use) we will elucidate here. Many studies have shown that cannabis users (Barkus, et al., 2006; Pape, et al., 2009) or ecstasy/MDMA users (Brecht, Huang, Evans, & Hser, 2008; Scholey et al., 2004) are frequently not pure users of this particular substance, but consume a multitude of substances (see also Fernández-Serrano, et al., 2011). We now elaborate in how far this polydrug use is related to the schizophrenia spectrum, and how it may influence cognitive functioning.

Polydrug use and the schizophrenia spectrum

Patients with schizophrenia show elevated consumption of a variety of drugs as compared to the general population, e.g. amphetamines, alcohol, nicotine etc. (Barkus & Murray, 2010; Degenhardt & Hall, 2001; Regier, et al., 1990). In high-risk samples, this elevated drug use as compared to the general population also corresponds to increased symptom severity (Miller et al., 2001). In the general population, users of several illicit drugs also score higher on measures of schizotypy than those only consuming one illicit drug (e.g. cannabis), or only legal drugs (van Dam, Earleywine, & DiGiacomo, 2008).

Polydrug use and cognitive functioning

Polydrug use affects the cognitive functions that have been of major relevance to the present doctoral thesis (see section I. B. 1. and I. B. 2.). Polydrug users have frequently been shown to exhibit more functional frontal lobe attenuations as compared to those only using one drug and/or non-users (see Fernández-Serrano, et al., 2011; Mohamed, et al., 2011 for overview). For instance, memory functions and learning (Gouzoulis-Mayfrank et al., 2000), or semantic word fluency (de Sola LLopis et al., 2008) are impaired in polydrug users as compared to uni-drug users or non-using controls. As is also evident from section I. C. 2., certain substances influence hemispheric asymmetry, but how polydrug use relates to functional hemispheric asymmetry remains to be investigated. The scarcity of studies on the relationship between polydrug use (including licit and illicit drugs) and cognition, and the relevance of these studies to cognitive functioning along the schizophrenia spectrum reflects the lack of knowledge we have in this domain. Our results would provide some initial indications that different drugs might affect different cognitions, but also that some might have synergetic influences. Obviously, these findings and conjectures are based on findings from healthy student populations. Whether our conjectures and observations might also have clinical relevance will be discussed just below.

B. General Conclusions

Our results indicated that drug use is mainly responsible for cognitive attenuations formerly ascribed to schizotypal symptoms. The question is whether or not the findings would extend to all populations along the schizophrenia spectrum, including at-risk populations and patients with schizophrenia. If this would be the case, cognitive impairments in patients with schizophrenia may not be illness-related per se, but may be importantly influenced by enhanced drug use as seen along the schizophrenia spectrum

as well. While this effect of drug use on cognition has to our knowledge not been tested systematically in e.g. patients with schizophrenia before, we will review cognitive functions and their relation to drug use in individuals at the 'high' end of the schizophrenia spectrum (e.g. in schizotypal personality disorder, or patients with schizophrenia) in the following paragraphs.

In individuals with schizotypal personality disorder or schizophrenia, cognitive functioning is affected when compared to healthy controls across a variety of cognitive domains (Mesholam-Gately, et al., 2009; R. E. Nielsen, 2011; Siever et al., 2002), even in those not taking illicit drugs (Cadenhead, Perry, Shafer, & Braff, 1999; Coulston, Perdices, & Tennant, 2007; McClure et al., 2007; R. E. Nielsen, 2011). Moreover, the influence of drugs seems to be different in patients with schizophrenia than in drug users from the general population in terms of cognitive functioning (e.g. Jockers-Scherubl et al., 2007). For instance, cannabis using patients with schizophrenia outperform non-using patients on a variety of cognitive functions (see Rabin, et al., 2011 for overview), whereas chronic cannabis users in the general population normally yield cognitive attenuations when compared to non-cannabis using individuals (see section I. C. 2. b). It could be argued that this performance superiority is only reported amongst specific classes of drugs, e.g. cannabis. However, in schizophrenia this cognitive performance superiority is by no means specific to cannabis, and extends to polydrug using patients with schizophrenia as compared to non-using ones as well (Coulston, et al., 2007). Medication in patients with schizophrenia does not seem to relate to cognitive functioning in this population (see R. E. Nielsen, 2011 for meta-analysis), even though there may be adverse interaction between substance use and medication response (A. I. Green et al., 2004).

This indicates that the influence of drug use on the relationship between schizophrenia symptoms and cognition may be different for healthy versus mentally ill individuals. If cognitive dysfunctions are related to symptoms in schizophrenia, but not schizotypy after controlling for drug use, cognitive attenuations may not be reliable risk markers of pathology before illness-onset (see also discussion study 2). However, future studies should try to elucidate the relationship between drugs, cognition and symptoms in patient populations to shed light on this issue.

As a final remark, concerning is the fact that substance abuse in patients is associated with higher rates of hospitalization and relapse (Cantor-Graae, et al., 2001; Mueser, Bellack, & Blanchard, 1992; Swofford, Kasckow, Scheller-Gilkey, & Inderbitzin, 1996). As a result, independent of which factors will be revealed as the most predictive for pathological changes in future studies, treatments or interventions for both illegal and legal drug use along the schizophrenia spectrum could be useful to facilitate amelioration or recovery from symptomatology (see also Hahn, et al., 2011; Kerfoot et al., 2011).

C. Alternative explanations

Due to several studies being conducted in parallel, we were mostly unable to take ongoing results (e.g. emerging relevant factors) for subsequent studies into account. Therefore, we elucidate some alternative explanations to our findings by discussing the relevance of factors emerging from our studies that have not systematically been accounted for, such as depression and its relationship to drug use, psychotic disorders and cognitive functioning. Additionally, we will try to cover IQ as potential explanation for the multitude of null-results in most of the drug group comparisons on cognitive outcome measures (contrary to previous research).

1. Depression

Depression and drug use

Recent debates in the UK have revolved around which objective means are useful to assess harmfulness of drug use on e.g. mood disorders due to the users' lifestyle or drug use itself (Nutt, et al., 2010). The effect of drug use on mood may be interesting when cognitive functions as those outlined in this project are assessed. For instance, various studies confirm that depression and substance use frequently co-occur (see Swendsen & Merikangas, 2000 for overview). Furthermore, certain studies even suggest that drug use (e.g. cannabis) follows the development of depression in adolescents (Libby, Orton, Stover, & Riggs, 2005). In independent studies investigating the influence of particular drugs, potentially relevant depression ratings are frequently not reported such as in relatively pure cannabis users (Fried, et al., 2005; Skosnik, et al., 2001), nicotine smokers (Herzig, et al., 2010), alcohol users (Ratti, et al., 2002) or psychostimulant users (Bolla, et al., 2003). Depression rates are, however, relatively elevated in drug users including amphetamine users (M. J. Morgan, 2000; G. Rogers, et al., 2009 for overview), alcohol dependent individuals (Conner, Pinquart, & Gamble, 2009; Davidson, 1995), smokers (Breslau, Kilbey, & Andreski, 1991; Klungsøyr, Nygård, Sørensen, & Sandanger, 2006) or cannabis users (Hayatbakhsh, et al., 2007; Patton, et al., 2002). We and others cannot exclude the possibility that depression rates could partially explain the effects of drug use on cognitive functioning known to be attenuated along the schizophrenia spectrum. This argument will be elaborated upon in the following section, by looking at the relationship between depression and cognition.

Depression and cognitive functioning

Studies that tested the link between depression and frontal lobe functioning report that clinical depression in young adults is accompanied by relative dysfunctional frontal lobe functions including those we tested here (see Castaneda, et al., 2008 for overview). Even in healthy subjects, negative mood can lead to reduced prefrontal lobe activity during verbal (not spatial) working memory tasks (Aoki, et al., 2011). Additionally, there is some evidence for a right hemisphere deficit in depressed patients as well. For instance, depressed patients show longer RTs in the right hemisphere in a divided visual field task (Liotti, Sava, Rizzolatti, & Caffarra, 1991). This decreasing right hemisphere processing advantage in depressed patients is also found in verbal dichotic listening tasks (Pine et al., 2000), verbal divided field studies (Min & Oh, 1992) or face processing tasks (Heller, Etienne, & Miller, 1995).

Overall, the above mentioned studies point to the possibility of depression being a more robust predictor of cognitive attenuations than drugs. To what extent this link between depression and cognition is relevant for individuals along the schizophrenia spectrum is elaborated on now.

The link between depression and the schizophrenia spectrum

There is substantial overlap between depression and psychotic experiences (Hartley, Haddock, & Barrowclough, 2012). Some authors argue that depression and schizophrenia often co-occur, with depression symptoms appearing on average four years before admission with schizophrenia (Häfner et al., 2005). Even in healthy individuals from the general population schizotypal traits correlate considerably with measures of depression/anxiety (Wolfradt & Straube, 1998), and in adolescence depression and anxiety (amongst other factors) modulate the expression of positive schizotypal symptoms (Debbané, Van der Linden, & Eliez, 2008). Taken together, these

findings suggest that depression may be an important variable to consider in future research on drug use, schizotypy and cognition.

2. IQ

The majority of participants tested in our studies were students recruited from the University of Bristol. If we assume that marks are indicators of intellectual capacities (Lagerström, Bremme, Eneroth, & Janson, 1991; Rindermann & Neubauer, 2004; Spinath, et al., 2010), our population is characterised by a high IQ as students are preselected according to their high marks before they are granted access to this University. As also discussed in detail in study 4, IQ is linked to cognitive reserve, an efficient dynamism with which the brain balances out threatening situations and challenges to maintain efficient cognitive functioning (Katzman, et al., 1989; Stern, 2002). As a result, these high functioning subjects may have been affected differently by drug use and schizotypal symptoms than those with lower intellectual capacity. This argument we will outline in the following sections by looking at the relationship between IQ and the schizophrenia spectrum, and between IQ and cognitive functioning.

IQ and schizophrenia spectrum

Intelligence seems diminished in patients with schizophrenia and schizophrenia spectrum disorders as compared to healthy controls (see Khandaker, et al., 2011; see Leeson, et al., 2009 for overview). Even in psychometrically defined schizotypy, symptoms seem to relate to intelligence (Matheson & Langdon, 2008; Noguchi, et al., 2008) with higher IQ generally relating to lower schizotypal symptoms. Intelligence may protect from adverse situations in psychiatric illnesses, a finding replicated by several studies (MacCabe & Murray, 2004; Moore, et al., 2007; Sørensen, et al., 2010).

IQ and cognitive functioning

IQ, or general intelligence, has been frequently linked to cognitive functioning, in particular frontal lobe functioning (Garcia-Molina, Tirapu-Ustarroz, Luna-Lario, Ibanez, & Duque, 2010). For instance, higher IQ frequently relates to better performance on tasks measuring frontal lobe functions such as verbal memory, working memory, verbal fluency, and cognitive flexibility (Colom, Abad, Rebollo, & Chun Shih, 2005; J. R. Gray, Chabris, & Braver, 2003; Roca et al., 2010). However, evidence regarding intelligence and hemispheric asymmetry is sparse, and laterality dependent effects of intelligence can only be inferred. Generally, increased laterality for language goes along with better performance in verbal functions (potentially related to verbal IQ), e.g. reading proficiency (Marcel, et al., 1974; Rutherford, 2006; Wey, et al., 1993). Additionally, handedness can be used to infer about hemispheric asymmetry (Crow, 2000; Crow, Crow, Done, & Leask, 1998), with increasing handedness scores usually relating to a more pronounced hemispheric asymmetry. As such, individuals closer to equal hand skill (and consequently a reduction in hemispheric asymmetry) show deficits in verbal, non-verbal, and mathematical ability and reading comprehension as compared to those showing either strong left or right handedness (Crow, et al., 1998). Therefore, it is likely that higher intelligence (in particular verbal IQ) may go along with stronger laterality patterns.

IQ and drug use

Intelligence also seems to relate to drug use, with higher drug use being generally associated with lower IQ. For instance, higher IQ relates to later-life non-smoking status (Wennerstad et al., 2010). Using cannabis before the age of 18 years reduces peoples expected years of education (see Casadio, et al., 2011 for overview) suggesting lower educational attainment. It should be noted, that this phenomenon may depend on the

frequency of cannabis use and complementary nicotine use, as occasional cannabis use without additional nicotine consumption is associated with higher academic success (Suris, et al., 2007). The effect of chronic cannabis use on general intelligence over time seems rather unclear, with some studies reporting a decline in general intelligence (Fried, et al., 2005), and others reporting no change (Lyketsos, Garrett, Liang, & Anthony, 1999). However, it seems feasible to assume that IQ is a protective factor for the adverse effects of drugs, and may therefore predict cognitive functioning more consistently than schizotypy and/or drug use.

D. General limitations

Apart from additional risk factors that could be relevant to studies on drug use and cognition along the schizophrenia spectrum (Rössler, Vetter, et al., 2011) the research studies conducted here have certain limitations that we would like to discuss in the following: i) the reliability of findings given the sample size and statistical methods chosen; ii) the validation of the O-LIFE; iii) the preselection of risk factors; and iv) the specificity of cognitive attenuations to schizophrenia.

Regarding the first point, a general limitation to the current analyses could be the low sample size. It is difficult to determine the appropriate sample size, and guidelines vary. Green (S. B. Green, 1991) suggested the amount of variables included in the regression model should follow the formula (50 + 8x N variables; Field, 2009; Tabachnik & Fidell, 2001). However, others suggest a minimum sample size of 10 participants per predictor variable (Harris, 1985), adding to the general variety of approaches and guidelines. Crucially, many studies do not pre-select participants according to relatively rare characteristics (in the present case the consumption of cannabis use only) enhancing the

ease with which to have a larger sample size, but at the same time adding unwanted noise. Fernandez et al (2011) reviewed the evidence on the specialized effects of a variety of drugs recently.

According to their review, the sample sizes vary considerably in the published articles, reflecting the difficulties researchers face when trying to recruit minority samples (e.g. drug users in general), or pure users of individual drugs in particular (Fernández-Serrano, et al., 2011). For instance, in relatively pure users of cannabis, recruitment rates may vary between 16-19 participants, or between five and 28 participants for MDMA/psychostimulant users. This implies that power analyses can result in the recommendation of unrealistically large sample sizes when dealing with minority samples.

The difficulty of facing naturally low sample sizes also affects the choice of statistical analysis. In small samples, the population distribution of a variable cannot be estimated reliably. As such, using these parametric tests (assuming a normal distribution) may have resulted in less reliable results than non-parametric tests which do not assume a normal distribution of data (Field, 2009). Yet, the use of parametric tests such as ANOVAs and regressions, based on the assumption of normality, are fairly robust to violations of normality assumptions in general (Lindman, 1974; Schmider, Ziegler, Danay, Beyer, & Bühner, 2010), whereas the risk in non-parametric tests is often a false rejection of significant effects with small sample sizes (McCluskey & Lalkhen, 2007). Hence, parametric tests were given preference in our studies to reduce the risk of inflated false negative rates.

On a similar note, the multiple comparisons performed in our analyses could have profited from a more conservative statistical approach, e.g. using Bonferroni-

corrections. These were originally developed as part of the statistical test theory, proposed by Neyman and Pearson in 1928 (Neyman & Pearson, 1928). This theory was supposed to aid practical decision making in industrial settings, e.g. considering the rejection of lots (based on defective multiple samples within each lot, where an inflated rejection rate would lead to higher financial loss), but was actually not developed for assessing evidence in scientific data sets (Feise, 2002; Perneger, 1998). Whereas these methods reduce the risk of a type I error, they can be specifically problematic if a researcher is testing specific hypotheses in one study (Perneger, 1998). This is due to the fact that Bonferroni-corrections -whilst reducing the Type I risk- also inflate the false negative rates. Applying this method results in loss of power to detect significant differences to such an extent that behavioural studies with small to medium expected effect sizes have a lower than chance level likelihood to detect significant differences (Jennions & Møller, 2003; Nakagawa, 2004). Consequently, we abstained from applying a Bonferroni correction in our studies, as this would have likely resulted in rejection of important results. The fact that we drew comparable conclusions across our studies seems to justify using a less conservative approach.

Regarding the second limitation: the original O-LIFE was developed using factor analyses of scales for item selection, and internal consistency and reliability were verified (Mason, et al., 1995). The short version of this questionnaire that we used in the majority of our studies did not follow strict psychometric validation (Mason, et al., 2005), and internal consistency ratings were rather low in the normative sample. Therefore, by not adhering to strict psychometric standards for validation of questionnaires (Aluja, García, Rossier, & García, 2005; Steinman & Teachman, 2011) there is a risk that the O-LIFE does not reflect the concept of schizotypy very well. On the other hand, our own analysis on the O-LIFE scales indicate a rather sufficient

internal consistency (see Table 29 in Appendix). Moreover, a recent study would suggest that the short versions of the O-LIFE (Mason, et al., 2005) and the schizotypal personality questionnaire - another widely used schizotypy questionnaire (Raine & Benishay, 1995)- measure schizotypy in a similar way (Asai, Sugimori, Bando, & Tanno, 2011). This may support the possibility that these questionnaires adequately measure the schizotypy construct, though direct evidence for this is still warranted (Compton, Goulding, Bakeman, & McClure-Tone, 2009).

The third limitation concerns the multitude of factors associated with the development of psychosis, with higher risk for individuals that e.g. experienced adverse life events (see Wiles et al., 2006 for overview), live in urban rather than rural surroundings (Takei, Sham, Ocallaghan, Glover, & Murray, 1995), and have a genetic predisposition to psychosis, e.g. a relative with a psychotic illness (K. W. Lee, Woon, Teo, & Sim, 2012). Our study on two preselected factors revealed that drug use is a more consistent predictor of cognitive attenuation than schizotypy. However, future studies should aim to incorporate a more encompassing selection of variables to disentangle their complex interactions, as well as detect those being particularly important for the development of psychotic-like cognitive profiles.

Regarding the fourth point, another factor that could be potentially relevant is the specificity of cognitive impairments along the schizophrenia spectrum. Specificity is warranted as it can firstly help to identify the unique underlying pathophysiology of the disease, and secondly because once specific cognitive (dys-)functions are identified they could aid as diagnostic tools along the schizophrenia spectrum. Behavioural cognitive markers are relatively easy, quick and cheap to assess in comparison to lengthy diagnostic interviews usually required to diagnose any mental illness, or brain imaging techniques. Consequently, the convenience associated with using behavioural cognitive

functions as so-called “endophenotypes” for schizophrenia has fuelled a wealth of research in the past couple of years (see Allen, Griss, Folley, Hawkins, & Pearlson, 2009 for overview). For any behavioural cognitive measure to qualify as cognitive vulnerability marker of the disease, it must fulfill certain criteria. Though definitions may vary (Cadenhead & Braff, 2002), they most likely include the following conditions: (i) association with the illness (higher rates of the endophenotype in people with the illness as compared to the general population or other psychiatric disorders); (ii) state independence (presence irrespective of the disease state); (iii) familial association (present at higher rates in unaffected family members than in the general population); (iv) co-segregation (higher prevalence in ill relatives of ill probands than in well relatives of ill probands); and (v) heritability (the extent of variation of the endophenotype that is attributable to the genetic variation; Gottesman & Gould, 2003).

Among cognitive tasks, hemispheric asymmetry and frontal lobe/executive dysfunctions have been discussed as vulnerability markers. For instance, patients with schizophrenia often perform two standard deviations below healthy matched participants in tasks on frontal lobe/executive functioning (Heinrichs & Zakzanis, 1998; Saykin et al., 1991), and these deficits are present before the onset of the disorder (Erlenmeyer-Kimling et al., 2000). Moreover, they seem relatively stable over time (Albus et al., 2002). For hemispheric asymmetry the same picture emerges, with a reduction of hemispheric asymmetry usually being present to a higher degree in patients with schizophrenia and healthy relatives of patients with schizophrenia as compared to the general population (Crow, 2000; Sharma et al., 1999), being present before illness onset (Cannon, Jones, Murray, & Wadsworth, 1997; Crow, Done, & Sacker, 1996) and these reductions only normalize when patients are medically treated or in remission (Løberg, Jørgensen, & Hugdahl, 2002). Certainly problematic to the idea of such measures to be appropriate

endophenotypes, hypofrontality and reduced laterality have also been observed in patients suffering from other mental illnesses, such as depression (Heller, et al., 1995; Medved, Petrovic, Isgum, Szirovicza, & Hotujac, 2001; Oertel-Knöchel & Linden, 2011; M. A. Rogers et al., 2004), or bipolar disorder (Borkowska & Rybakowski, 2001; Ketter et al., 2001; Oertel-Knöchel & Linden, 2011).

Taken together, frontal lobe functioning and hemispheric asymmetry may not be particularly specific to schizophrenia, and therefore may not serve as reliable diagnostic tools along the schizophrenia spectrum. However, schizophrenia is a rather heterogeneous disease, and shares common features (e.g. psychotic symptoms) with other mental illnesses (Kendell, 1991). In the case of complex mental conditions, the cognitive dysfunctions are often numerous, and thus unspecific to schizophrenia, but specific to widespread brain dysfunctions (Keri & Janka, 2004). Hence, using unspecific cognitive markers may nevertheless be relevant to understand the etiology underlying the schizophrenia spectrum (Cadenhead & Braff, 2002; Tandon, Nasrallah, & Keshavan, 2009).

E. Summary of conclusions

Our research indicates that specific drugs, as well as general substance dependence may influence the relationship between schizotypy and cognition, suggesting that previous reports on attenuations in high schizotypes could be explained (at least partially) by enhanced substance use. This may also suggest that cognitive markers for the disease are rather unreliable as indicators of risk for psychosis pathology. Additionally, more research is warranted to establish the nature of the relationship between drugs, psychotic (-like) thinking and cognition, and potential modulator variables such as IQ and

depression. Subsequent studies in patient populations are deemed valuable to acquire this comprehensive overview over the most reliable predictors of pathological changes.

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V. Appendices

A. Questionnaires

1. Compensatory behaviour questionnaire

Please think about a rewarding habit you cannot imagine living without. This habit should be substance-based (like caffeine, chocolate, nicotine or illicit drugs).

Please answer the following questions regarding your habit in the past month, using the scales below.

Substance-based habit					
Do you need the habit in order to perform/ feel well?	❑ Never	❑ Sometimes	❑ Often	❑ Nearly always	❑ Always
Do you find yourself thinking about when you will next be able to perform your habit?	❑ Never	❑ Sometimes	❑ Often	❑ Nearly always	❑ Always
Does your pattern of performing your habit interfere with your social life?	❑ Never	❑ Sometimes	❑ Often	❑ Nearly always	❑ Always
Do you plan your days around performing your habit?	❑ Never	❑ Sometimes	❑ Often	❑ Nearly always	❑ Always
Do you feel that your need for performing this habit is too strong to control?	❑ Never	❑ Sometimes	❑ Often	❑ Nearly always	❑ Always
Do you feel agitated or irritable when you cannot perform your habit?	❑ Never	❑ Sometimes	❑ Often	❑ Nearly always	❑ Always
Do you need your habit in order to relieve stress?	❑ Never	❑ Sometimes	❑ Often	❑ Nearly	❑ Always

Is performing your habit more important than anything else you might do during the day?	❑ Never	❑ Sometimes	❑ Often	❑ Nearly always	❑ Always
Do you feel you cannot cope with life without that habit?	❑ Never	❑ Sometimes	❑ Often	❑ Nearly always	❑ Always
Are you feeling more positive about yourself and/or life after performing your habit?	❑ Never	❑ Sometimes	❑ Often	❑ Nearly always	❑ Always
Do you perform your habit in higher amounts/ frequency than intended?	❑ Never	❑ Sometimes	❑ Often	❑ Nearly always	❑ Always
Does your habit interfere with your study?	❑ Never	❑ Sometimes	❑ Often	❑ Nearly always	❑ Always
Do you find it difficult to cope with life without your habit?	❑ Never	❑ Sometimes	❑ Often	❑ Nearly always	❑ Always
Do you feel guilty about performing your habit?	❑ Never	❑ Sometimes	❑ Often	❑ Nearly always	❑ Always
Do you have little energy for your family and friends due to your habit?	❑ Never	❑ Sometimes	❑ Often	❑ Nearly always	❑ Always

2. Oxford* - Liverpool Inventory of feelings and experiences (O-LIFE, original)

Please Read the Instructions Before Continuing:

This questionnaire contains questions that may relate to your thoughts, feelings, experiences and preferences. There are no right or wrong answers or trick questions so please be as honest as possible. For each question place a circle around either the "YES" or the "NO". Do not spend too much time deliberating any question but put the answer closest to your own.

Please do not discuss the questionnaire with anyone who may also complete it as this may affect their answers. It is best completed in private, without the need to hurry.

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1	Do you prefer reading to meeting people?	YES	NO
2	Do you often hesitate when you are going to say something in a group of people whom you more or less know?	YES	NO
3	Are you always willing to admit it when you have made a mistake?	YES	NO
4	Do you hate being alone?	YES	NO
5	Do you often overindulge in alcohol or food?	YES	NO
6	Do you often feel that people have it in for you?	YES	NO
7	Are the sounds you hear in your daydreams really clear and distinct?	YES	NO
8	Do you enjoy many different kinds of play and recreation?	YES	NO
9	Do your thoughts sometimes seem as real as actual events in your life?	YES	NO
10	Does it often happen that nearly every thought immediately and automatically suggests an enormous number of ideas?	YES	NO
11	When in a group of people do you usually prefer to let someone else be the centre of attention?	YES	NO
12	If you say you will do something do you always keep your promise no matter how inconvenient it might be?	YES	NO
13	Do you frequently have difficulty in starting to do things?	YES	NO
14	Has dancing or the idea of it always seemed dull to you?	YES	NO

15	When you catch a train do you often arrive at the last minute?	YES NO
16	Is trying new foods something you have always enjoyed?	YES NO
17	Do you always wash before a meal?	YES NO
18	Do you believe in telepathy?	YES NO
19	Do you often change between intense liking and disliking of the same person?	YES NO
20	Have you ever cheated at a game?	YES NO
21	Are there very few things that you have ever really enjoyed doing?	YES NO
22	Do you at times have fits of laughing or crying that you can't control?	YES NO
23	Do you at times have an urge to do something harmful or shocking?	YES NO
24	Do you often worry about things you should not have done or said?	YES NO
25	Are your thoughts sometimes so strong that you can almost hear them?	YES NO
26	Do you usually take the initiative in making new friends?	YES NO
27	Do your thoughts ever stop suddenly causing you to interrupt what you are saying?	YES NO
28	Are you usually in an average sort of mood, not too high and not too low?	YES NO
29	Would you take drugs which may have strange or dangerous effects?	YES NO
30	Do you think you could learn to read other's minds if you wanted to?	YES NO
31	When in a crowded room, do you often have difficulty in following a conversation?	YES NO
32	No matter how hard you try to concentrate do unrelated thoughts always creep into your mind?	YES NO
33	Are you easily hurt when people find fault with you or the work you do?	YES NO
34	Do you stop to think things over before doing anything?	YES NO
35	Have you ever felt that you have special, almost magical powers?	YES NO
36	Are you much too independent to really get involved with other people?	YES NO
37	Do you ever get nervous when someone is walking behind you?	YES NO

38	Do ideas and insights sometimes come to you so fast that you cannot express them all?	YES	NO
39	Do you easily lose your courage when criticised or failing in something?	YES	NO
40	Can some people make you aware of them just by thinking about you?	YES	NO
41	Does a passing thought ever seem so real it frightens you?	YES	NO
42	Do you always practice what you preach?	YES	NO
43	Do you often have periods of such great restlessness that you aren't able to sit still for more than a very short time?	YES	NO
44	Have you ever blamed someone for doing something you know was really your fault?	YES	NO
45	Are you a person whose mood goes up and down easily?	YES	NO
46	Does your voice ever seem distant or faraway?	YES	NO
47	Do you think having close friends is not as important as some people say?	YES	NO
48	Do you like doing things in which you have to act quickly?	YES	NO
49	Are you rather lively?	YES	NO
50	Do you feel at times that people are talking about you?	YES	NO
51	Are you sometimes so nervous that you are "blocked"?	YES	NO
52	Do you find it difficult to keep interested in the same thing for a long time?	YES	NO
53	Do you dread going into a room by yourself where other people have already gathered and are talking?	YES	NO
54	Have you ever felt that you were communicating with someone telepathically?	YES	NO
55	Does it often feel good to massage your muscles when they are tired or sore?	YES	NO
56	Do you sometimes feel that your accidents are caused by mysterious forces?	YES	NO
57	Do you like mixing with people?	YES	NO
58	On seeing a soft thick carpet have you sometimes had the impulse to take off your shoes and walk barefoot on it?	YES	NO
59	Do you frequently gamble money?	YES	NO
60	Do you often have difficulties in controlling your thoughts?	YES	NO

61	Do you feel that you cannot get “close” to other people?	YES	NO
62	Do the people in your daydreams seem so true to life that you sometimes think they are real?	YES	NO
63	Do other people think of you as being very lively?	YES	NO
64	Are people usually better off if they stay aloof from emotional involvements with people?	YES	NO
65	Does life seem entirely hopeless?	YES	NO
66	Can just being with friends make you feel really good?	YES	NO
67	Do you enjoy meeting new people?	YES	NO
68	Is your hearing sometimes so sensitive that ordinary sounds become uncomfortable?	YES	NO
69	Have you often felt uncomfortable when your friends touch you?	YES	NO
70	When things are bothering you do you like to talk to other people about it?	YES	NO
71	Do you ever have the sensation that your body or a part of it is changing shape?	YES	NO
72	Do you have many friends?	YES	NO
73	Are all your habits good and desirable ones?	YES	NO
74	Do you tend to keep in the background on social occasions?	YES	NO
75	Would being in debt worry you?	YES	NO
76	Have you ever felt when you looked in a mirror that your face seemed different?	YES	NO
77	Do you think people spend too much time safeguarding their future with savings and insurance?	YES	NO
78	Do you believe that dreams can come true?	YES	NO
79	Do you ever have the urge to break or smash things?	YES	NO
80	Do you often feel that there is no purpose to life?	YES	NO
81	Do things sometimes feel as though they were not real?	YES	NO
82	Do you worry about awful things that might happen?	YES	NO
83	Have you ever felt the urge to injure yourself?	YES	NO

84	Would it make you nervous to play the clown in front of other people?	YES	NO
85	Do you prefer watching television to going out with other people?	YES	NO
86	Have you felt that you might cause something to happen just by thinking too much about it?	YES	NO
87	Have you had very little fun from physical activities like walking, swimming or sports?	YES	NO
88	Do you ever have suicidal thoughts?	YES	NO
89	Have you ever said anything bad or nasty about anyone?	YES	NO
90	Do you feel so good at controlling others that it sometimes scares you?	YES	NO
91	Are you easily distracted from work by daydreams?	YES	NO
92	Are you easily confused if too much happens at the same time?	YES	NO
93	Do you ever have a sense of vague danger or sudden dread for reasons that you do not understand?	YES	NO
94	Is it true that your relationships with other people never get very intense?	YES	NO
95	Do you feel that you have to be on your guard even with your friends?	YES	NO
96	Have you sometimes had the feeling of gaining or losing energy when certain people look at you or touch you?	YES	NO
97	When coming into a new situation have you ever felt strongly that it was a repeat of something that had happened before?	YES	NO
98	Do you worry too long after an embarrassing experience?	YES	NO
99	Do you love having your back massaged?	YES	NO
100	Do you consider yourself to be pretty much an average kind of person?	YES	NO
101	Have you ever taken advantage of someone?	YES	NO
102	Would you like other people to be afraid of you?	YES	NO
103	Have you ever thought you heard people talking only to discover that it was in fact some nondescript noise?	YES	NO
104	Have you occasionally felt as though your body did not exist?	YES	NO
105	Do you often feel lonely?	YES	NO

106	Do you often have an urge to hit someone?	YES	NO
107	Do you often experience an overwhelming sense of emptiness?	YES	NO
108	On occasions, have you seen a person's face in front of you when no one was in fact there?	YES	NO
109	Do you feel it is safer to trust nobody?	YES	NO
110	Is it fun to sing with other people?	YES	NO
111	Do you often have days when indoor lights seem so bright that they bother your eyes?	YES	NO
112	Have you wondered whether the spirits of the dead can influence the living?	YES	NO
113	Do people who try to get to know you better usually give up after a while?	YES	NO
114	Do you often feel "fed up"?	YES	NO
115	Have you felt as though your head or limbs were somehow not your own?	YES	NO
116	Do you ever become oversensitive to light or noise?	YES	NO
117	When you look in the mirror does your face sometimes seem quite different from usual?	YES	NO
118	Do people who drive carefully annoy you?	YES	NO
119	Do you like telling jokes and funny stories to your friends?	YES	NO
120	Are your thoughts about sex often odd or bizarre?	YES	NO
121	Are you very hurt by criticism?	YES	NO
122	Do you feel lonely most of the time, even when you're with people?	YES	NO
123	Would you call yourself a nervous person?	YES	NO
124	Can you usually let yourself go and enjoy yourself at a lively party?	YES	NO
125	Do you ever feel that your thoughts don't belong to you?	YES	NO
126	Do you ever suddenly feel distracted by distant sounds that you are not normally aware of?	YES	NO
127	As a child, did you do as you were told immediately and without grumbling?	YES	NO
128	Do you sometimes talk about things you know nothing about?	YES	NO

129	When you are worried or anxious do you have trouble with your bowels?	YES	NO
130	When in the dark do you often see shapes and forms even though there's nothing there?	YES	NO
131	Do you often have vivid dreams that disturb your sleep?	YES	NO
132	Do you like plenty of bustle and excitement around you?	YES	NO
133	Have you sometimes sensed an evil presence around you, even though you could not see it?	YES	NO
134	Is it hard for you to make decisions?	YES	NO
135	Do you find the bright lights of a city exciting to look at?	YES	NO
136	Does your sense of smell sometimes become unusually strong?	YES	NO
137	Do you usually have very little desire to buy new kinds of food?	YES	NO
138	Are you often bothered by the feeling that people are watching you?	YES	NO
139	Do you ever feel that your speech is difficult to understand because the words are all mixed up and don't make sense?	YES	NO
140	Do you often feel like doing the opposite of what people suggest, even though you know they are right?	YES	NO
141	Do you like going out a lot?	YES	NO
142	Do you feel very close to your friends?	YES	NO
143	Are you sometimes sure that other people can tell what you're thinking?	YES	NO
144	Do you ever feel sure that something is about to happen, even though there does not seem to be any reason for you thinking that?	YES	NO
145	Do you often feel the impulse to spend money which you know you can't afford?	YES	NO
146	Are you easily distracted when you read or talk to someone?	YES	NO
147	Are you a talkative person?	YES	NO
148	Do everyday things sometimes seem unusually large or small?	YES	NO
149	Do you feel that making new friends isn't worth the energy it takes?	YES	NO
150	Have you ever taken the praise for something you knew someone else had really done?	YES	NO

3. Oxford* - Liverpool Inventory of feelings and experiences (O-LIFE, short version)

Please Read the Instructions Before Continuing:

This questionnaire contains questions that may relate to your thoughts, feelings, experiences and preferences. There are no right or wrong answers or trick questions so please be as honest as possible. For each question place a circle around either the "YES" or the "NO". Do not spend too much time deliberating any question but put the answer closest to your own.

Please do not discuss the questionnaire with anyone who may also complete it as this may affect their answers. It is best completed in private, without the need to hurry.

*Prof G Claridge & Dr O Mason, Depart Exp Psychol, South Parks Road, Oxford

1	When in the dark do you often see shapes and forms even though there is nothing there?	YES	NO
2	Are you easily confused if too much happens at the same time?	YES	NO
3	Are you much too independent to get involved with other people?	YES	NO
4	Do you at times have an urge to do something harmful or shocking?	YES	NO
5	Is trying new foods something you have always enjoyed?	YES	NO
6	Do you think that you could learn to read other's minds if you wanted to?	YES	NO
7	Have you ever felt the urge to injure yourself?	YES	NO
8	Has dancing or the idea of it always seemed dull to you?	YES	NO
9	Do you dread going into a room by yourself where other people have already gathered and are talking?	YES	NO
10	Do you feel that your accidents are caused by mysterious forces?	YES	NO
11	Do you often feel the impulse to spend money which you know you can't afford?	YES	NO
12	Do you ever feel that your speech is difficult to understand because the words are all mixed up and don't make sense?	YES	NO
13	Do you often overindulge in alcohol or food?	YES	NO

14	Have you often felt uncomfortable when your friends touch you?	YES	NO
15	Do you ever have a sense of vague danger or sudden dread for reasons that you do not understand?	YES	NO
16	Are you a person whose mood goes up and down easily?	YES	NO
17	Do you often have difficulties in controlling your thoughts?	YES	NO
18	Do ideas and insights sometimes come to you so fast that you cannot express them all?	YES	NO
19	Do you feel very close to your friends?	YES	NO
20	Would you like other people to be afraid of you?	YES	NO
21	Do you prefer watching television to going out with people?	YES	NO
22	Do you find it difficult to keep interested in the same thing for a long time?	YES	NO
23	Can some people make you aware of them just by thinking about you?	YES	NO
24	Do you stop to think things over before doing anything?	YES	NO
25	Are there very few things that you have ever enjoyed doing?	YES	NO
26	When in a crowded room, do you often have difficulty in following a conversation?	YES	NO
27	Does a passing thought ever seem so real it frightens you?	YES	NO
28	Do you love having your back massaged?	YES	NO
29	When you look in the mirror does your face sometimes seem quite different from usual?	YES	NO
30	Are you usually in an average kind of mood, not too high and not too low?	YES	NO
31	Do you find the bright lights of a city exciting to look at?	YES	NO
32	Does your sense of smell sometimes become unusually strong?	YES	NO
33	Are your thoughts sometimes so strong that you can almost hear them?	YES	NO
34	Do you like mixing with people?	YES	NO
35	Do you often feel like doing the opposite of what other people suggest even though you know they are right?	YES	NO
36	Are you easily distracted when you read or talk to someone?	YES	NO

37	Do you ever have the urge to break or smash things?	YES	NO
38	Have you ever thought that you had special, almost magical powers?	YES	NO
39	Do you frequently have difficulty in starting to do things?	YES	NO
40	Have you sometimes sensed an evil presence around you, even though you could not see it?	YES	NO
41	Are you easily distracted from work by daydreams?	YES	NO
42	Do you consider yourself to be pretty much an average sort of person?	YES	NO
43	Is it hard for you to make decisions?	YES	NO

B. Regression Tables

1. Nicotine paper

Table 23. *Group status*

Variables	Statistics	Group (Sm/nSm)	UnEx[j]	CogDis[k]	IntAn[l]	UnEx*Group	CogDis*Group	IntAn*Group	Model total
LDT [a] index %[b]	*β*	-0.11	-0.13	-0.30	0.16	0.21	-0.10	-0.01	n/a
	p	0.51	0.55	0.15	0.40	0.34	0.64	0.97	0.38
LDT index RT[c]	*β*	-0.12	0.08	-0.54	0.22	-0.05	0.20	0.26	n/a
	p	0.46	0.68	**0.01**	0.21	0.81	0.31	0.14	**0.09**
FDT[d] index RT	*β*	0.10	-0.30	0.20	-0.18	0.19	-0.02	-0.04	n/a
	p	0.60	0.19	0.36	0.37	0.40	0.91	0.82	0.84
LDT LVF [e] %	*β*	0.10	0.18	0.16	-0.12	-0.05	0.02	-0.04	n/a
	p	0.60	0.42	0.47	0.53	0.83	0.91	0.82	0.78
LDT RVF [f] %	*β*	-0.02	0.13	-0.35	0.09	0.19	-0.10	-0.06	n/a
	p	0.93	0.57	0.11	0.66	0.41	0.65	0.74	0.73
LDT LVF RT	*β*	-0.14	-0.09	0.05	0.08	-0.04	0.18	0.27	n/a
	p	0.45	0.71	0.83	0.69	0.86	0.40	0.16	0.68
LDT RVF RT	*β*	-0.03	-0.14	0.53	-0.07	0.01	0.05	0.13	n/a
	p	0.87	0.50	**0.01**	0.71	0.98	0.82	0.47	0.21
FDT LF [g] %	*β*	0.05	-0.12	-0.08	-0.32	-0.18	0.28	-0.03	n/a
	p	0.75	0.57	0.70	**0.09**	0.41	0.19	0.88	0.36
FDT WF [h] %	*β*	0.22	-0.17	0.11	-0.10	-0.26	0.25	0.41	n/a
	p	0.17	0.38	0.58	0.56	0.19	0.18	**0.02**	**0.05**
FDT LF RT	*β*	0.05	-0.20	0.40	0.26	0.01	-0.11	0.44	n/a
	p	0.75	0.32	**0.05**	0.14	0.97	0.56	**0.01**	**0.09**
FDT RF [i] RT	*β*	0.08	-0.30	0.46	0.17	0.11	-0.10	0.39	n/a
	p	0.61	0.15	**0.02**	0.34	0.58	0.61	**0.03**	0.12
FDT WF RT	*β*	-0.13	-0.08	0.40	0.13	0.14	-0.07	0.18	n/a
	p	0.44	0.71	**0.05**	0.49	0.51	0.71	0.30	0.20

Note: [a] Lexical decision task; [b] Percentage correct; [c] Reaction time; [d]Facial decision task; [e]Left visual field; [f] Right visual field; [g] Left face decisions; [h] Whole face decisions; [I] Right face decisions; [j] Unusual Experiences; [k] Cognitive Disorganization; [l] Introvertive Anhedonia;

Table 24. *Nicotine dependence*

Outcome variables	*Value*	Predictor variables							
		ND[j]	**UnEx[k]**	**CogDis[l]**	**IntAn[m]**	**UnEx*ND**	**CogDis*ND**	**IntAn*ND**	**Model total**
LDT [a] index %[b]	*β*	-0.03	0.00	-0.30	-0.02	0.47	-0.16	0.05	
	p	0.95	0.99	0.39	0.93	0.17	0.62	0.89	0.62
LDT index RT[c]	*β*	0.84	0.04	-0.31	0.39	0.26	0.06	0.67	
	p	**0.02**	0.89	0.24	**0.08**	0.31	0.79	**0.03**	**0.06**
FDT[d] index RT	*β*	0.38	-0.15	0.14	0.00	-0.45	0.18	0.49	
	p	0.37	0.68	0.69	0.99	0.20	0.59	0.21	0.74
LDT LVF [e] %	*β*	-0.54	0.12	0.01	0.08	-0.69	0.05	-0.26	
	p	0.15	0.70	0.97	0.73	**0.03**	0.87	0.44	0.31
LDT RVF [f] %	*β*	-0.88	0.11	-0.48	0.10	-0.27	-0.23	-0.30	
	p	**0.03**	0.73	0.14	0.70	0.37	0.43	0.38	0.30
LDT LVF RT	*β*	0.61	-0.19	0.42	0.16	0.48	-0.15	0.46	
	p	0.11	0.55	0.19	0.53	0.12	0.61	0.18	0.31
LDT RVF RT	*β*	0.09	-0.20	0.66	-0.05	0.32	-0.15	0.07	
	p	0.82	0.58	**0.07**	0.85	0.33	0.64	0.86	0.59
FDT LF [g] %	*β*	0.74	-0.13	0.10	-0.09	-0.44	0.45	0.42	
	p	**0.05**	0.68	0.73	0.69	0.13	0.12	0.20	0.18
FDT WF [h] %	*β*	0.30	-0.24	0.27	0.19	0.09	0.10	-0.14	
	p	0.48	0.51	0.45	0.50	0.79	0.76	0.72	0.71
FDT LF RT	*β*	-0.30	-0.38	0.30	0.42	0.27	-0.60	-0.06	
	p	0.36	0.21	0.29	**0.08**	0.32	**0.04**	0.84	0.13
FDT RF [i] RT	*β*	-0.02	-0.37	0.35	0.40	0.02	-0.50	0.22	
	p	0.95	0.23	0.24	0.10	0.94	**0.09**	0.48	0.18
FDT WF RT	*β*	-0.05	-0.15	0.33	0.21	0.09	-0.72	0.24	
	p	0.86	0.55	0.17	0.26	0.69	**0.01**	0.34	**0.02**

Note: [a] Lexical decision task; [b] Percentage correct; [c] Reaction time; [d]Facial decision task; [e]Left visual field; [f] Right visual field; [g] Left face decisions; [h] Whole face decisions; [I] Right face decisions; [j] Fagerström Test for Nicotine Dependence; [k] Unusual Experiences; [l]Cognitive Disorganization; [m]Introvertive Anhedonia;

2. Cannabis

Table 25. *Full regression model.*

	Outcome variables							
Predictor variables	**2-back % target correct**		**2-back mean RT**		**TMT [e] index**		**Story recall % correct**	
Predictor variables	*β*	*p*	*β*	*p*	*β*	*p*	*β*	*p*
Sex	-0.20	0.09	-0.15	0.21	-0.12	0.35	0.15	0.16
Nicotine dependence	-0.14	0.30	-0.03	0.81	-0.05	0.76	-0.18	0.14
Alcohol dependence	-0.31	**0.01**	0.37	**0.00**	0.26	**0.05**	0.08	0.44
Cannabis dependence	-0.20	0.18	-0.01	0.95	0.00	1.00	-0.45	**0.00**
UnEx [a]	-0.04	0.74	0.01	0.92	0.06	0.65	0.07	0.52
CogDis [b]	0.01	0.95	0.03	0.83	-0.01	0.91	-0.21	**0.05**
IntAn [c]	0.09	0.44	-0.15	0.21	-0.12	0.34	0.06	0.59
ImpNC [d]	0.32	**0.01**	-0.07	0.55	-0.07	0.58	0.36	**0.00**
Model total	n/a	**0.01**	n/a	**0.03**	n/a	0.35	n/a	**0.00**

[a] Unusual experiences; [b] Cognitive Disorganisation; [c] Introvertive Anhedonia; [d] Impulse Non-conformity; [e] Trail making Task;

3. Mephedrone

Table 26. *Pre- clubbing full regression model.*

Predictor variables	RAVLT [b] % Immediate [c] pre		RAVLT % Delayed [d] pre		TMT[e] index pre		COWAT[f] pre	
	β	***p***	***β***	***p***	***β***	***p***	***β***	***p***
Amphetamine past 30 days	-0.28	0.12	-0.56	**0.01**	-0.29	0.25	-0.06	0.77
Mephedrone past 30 days	0.11	0.66	0.38	0.17	0.10	0.78	0.06	0.81
Cannabis past 30 days	-0.53	**0.04**	-0.49	**0.08†**	0.01	0.99	-0.19	0.47
CogDis [a]	-0.18	0.30	0.14	0.49	0.11	0.65	-0.57	**0.01**
Model total	n/a	**0.00**	n/a	**0.04**	n/a	0.83	n/a	**0.01**

[a] Cognitive Disorganisation; [b] Rey's auditory verbal learning task; [c] Immediate recall; [d] Delayed recall; [e] Trail making Task; [f] Verbal Fluency Task;

Table 27. *Post- clubbing full regression model.*

Predictor variables	RAVLT [f] % Immediate[g] post		RAVLT % Delayed [h] post		TMT [i] index post		COWAT [j] post	
	β	*p*	*β*	*p*	*β*	*p*	*β*	*p*
BDI [a] after[b]	-0.18	0.55	-0.18	0.55	-0.20	0.65	-0.11	0.72
Total weekend sleep	-0.30	0.12	-0.31	0.11	0.12	0.65	-0.29	0.14
Mephedrone weekend	-0.43	**0.06**	-0.26	0.24	-0.06	0.83	-0.22	0.34
UnEx [c]	-0.06	0.78	-0.44	**0.06**	0.14	0.66	0.07	0.75
CogDis [d]	-0.25	0.35	0.09	0.73	0.15	0.70	-0.47	0.11
ImpNC [e]	0.15	0.52	-0.08	0.73	0.11	0.74	0.06	0.80
Model total	n/a	**0.02**	n/a	**0.01**	n/a	0.98	n/a	**0.03**

[a] Beck's Depression Inventory; [b] After the weekend; [c] Unusual Experiences; [d] Cognitive Disorganisation; [e] Impulsive Non-conformity; [f] Rey's auditory verbal learning task; [g] Immediate recall; [h] Delayed recall; [i] Trail making Task; [j] Verbal Fluency Task;

4. Stress paper

Table 28. *Full regression model.*

	Statistics	Age	Cognitive reserve	SCB[i]	PSS[j]	SRI[k]	UnEx[l]	CogDis[m]	IntAn[n]	ImpNC[o]	Model total
LDT[a] index[b] %	*β*	-0.20	-0.11	-0.29	0.02	0.03	-0.18	0.01	0.04	0.07	n/a
	p	0.23	0.47	**0.07**	0.90	0.88	0.24	0.95	0.78	0.65	0.59
LDT index RT	*β*	-0.26	-0.16	-0.32	0.07	-0.17	-0.28	0.39	0.24	0.10	n/a
	p	**0.09**	0.25	**0.03**	0.69	0.39	**0.06**	**0.03**	**0.08**	0.52	**0.06**
FDT[c] index RT	*β*	-0.40	0.10	-0.05	0.39	-0.52	-0.01	0.03	-0.13	0.00	n/a
	p	**0.01**	0.49	0.74	**0.04**	**0.02**	0.96	0.85	0.35	0.99	0.16
LDT LVF[d] %	*β*	0.22	0.24	0.36	0.00	0.16	-0.01	0.06	-0.13	-0.09	n/a
	p	0.15	**0.09**	**0.02**	0.99	0.45	0.92	0.76	0.34	0.57	0.18
LDT RVF[e] %	*β*	-0.08	0.12	0.03	-0.03	0.24	-0.22	0.12	-0.01	0.00	n/a
	p	0.61	0.41	0.86	0.88	0.30	0.18	0.52	0.96	0.99	0.77
LDT LVF RT	*β*	-0.11	-0.13	-0.17	-0.30	-0.12	-0.23	0.36	0.08	0.08	n/a
	p	0.48	0.36	0.26	0.11	0.56	0.13	**0.05**	0.55	0.63	0.20
LDT RVF RT	*β*	0.13	0.03	0.15	-0.38	0.04	0.00	-0.01	-0.13	-0.02	n/a
	p	0.41	0.85	0.34	**0.05**	0.86	0.98	0.95	0.35	0.90	0.44
FDT LF[f] %	*β*	-0.08	0.13	-0.05	-0.01	0.02	-0.11	-0.01	0.25	-0.02	n/a
	p	0.62	0.38	0.74	0.95	0.93	0.50	0.95	0.10	0.89	0.74
FDT WF[g] %	*β*	-0.03	0.08	-0.10	-0.36	0.11	-0.04	0.10	-0.10	0.20	n/a
	p	0.86	0.61	0.51	**0.07**	0.62	0.81	0.60	0.51	0.23	0.69
FDT LF RT	*β*	0.02	0.01	-0.11	-0.30	-0.04	-0.25	0.25	0.10	0.17	n/a
	p	0.89	0.93	0.49	0.12	0.85	0.10	0.17	0.49	0.30	0.30
FDT RF[h] RT	*β*	-0.15	0.07	-0.10	-0.08	-0.25	-0.22	0.25	0.04	0.12	n/a
	p	0.36	0.65	0.52	0.67	0.27	0.16	0.20	0.81	0.46	0.53
FDT WF RT	*β*	-0.01	-0.03	-0.08	-0.11	-0.08	-0.17	0.16	0.29	0.04	n/a
	p	0.97	0.86	0.60	0.56	0.72	0.28	0.40	**0.05**	0.80	0.54

Note: [a] Lexical decision task; [b] Laterality index; [c] Facial decision task; [d] Left visual field; [e] Right visual field; [f] Left face decisions; [g] Whole face decisions; [h] Right face decisions; [i] Substance-based compensatory behaviours; [j] Perceived Stress Scale; [k] Stress Response Inventory; [l] Unusual experiences; [m] Cognitive Disorganisation; [n] Introvertive Anhedonia; [o] Impulse Non-conformity;

C. Cronbach's Alpha Questionnaires

Table 29. *Internal consistency for the questionnaires used in the experiments.*

Questionnaire	Cronbach's α
O-LIFE [a] 150 items	0.89
O-LIFE 43 items	0.72
SCB[b]	0.75
PSS[c]	0.75
SRI[d]	0.75

[a]Oxford - Liverpool Inventory of Feelings and Experiences; [b]Substance-based compensatory behaviours; [c]Perceived Stress Scale; [d]Stress Response Inventory;

D. Literature Review

Table 30. *Review of studies investigating psychometrically defined schizotypy and cognition, including their control for substance use. Results are sorted alphabetically by cognitive function*. All abbreviations used can be found below the table**.*

Function	Task	Author	Year	Title	Groups/N	Schizotypy scale	Control illegal drugs	Control tobacco	Control alcohol	Analyses	Results as a function of schizotypy ***	Symptom dimension relevant?
CF	IED	Laws et al.	2011	Delusion-prone individuals: Stuck in their ways?	100 healthy participants	PDI-21	Not reported	Not reported	Not reported	Group comparisons	↓	Positive schizotypy
CF	TMT	Dinn et al.	2002	Positive and negative schizotypy in a student sample: neurocognitive and clinical correlates	103 students	SPQ	Not reported	Not reported	Not reported	Group comparisons	↓	Negative schizotypy
CF	TMT	Giraldez et al.	1999	Assessment of essential components of schizotypy by means of neurocognitive measures	82 healthy adolescents	MSTQ	Not reported	Not reported	Not reported	Group comparisons	↓	Negative schizotypy
CF	TMT	Kim et al.	2011	Neuropsychologic profile of college students with schizotypal traits	59 healthy females	SPQ	Controlled for drug/alcohol abuse DSM-IV	Controlled for drug/alcohol abuse DSM-IV	Controlled for drug/alcohol abuse DSM-IV	Group comparisons	=	n/a
CF	TMT	Matheson & Langdon	2008	Schizotypal traits impact upon executive working memory and aspects of IQ	100 healthy students	SPQ	Self-reported cannabis and ecstasy use 12 months	Self-reported cannabis and ecstasy use 12 months	Self-reported cannabis and ecstasy use 12 months	Correlational analyses	=	n/a

Function	Task	Author	Year	Title	Groups/N	Schizotypy scale	Control illegal drugs	Control tobacco	Control alcohol	Analyses	Results as a function of schizotypy ***	Symptom dimension relevant?
CF	TMT	Poreh et al.	1995	Reexamination of executive functions in psychosis-prone college students	19 psychosis prone (pp); 19 normal	PAS; MIS; STA	Substance abuse	Substance abuse	Substance abuse	Group comparisons	↓	Positive schizotypy
CF	WCST	Aguirre et al.	2008	Emotional intelligence and social functioning in persons with schizotypy	96 healthy students, 40 high schizotypes 56 low schizotypes	SPQ-B	Not reported	Not reported	Not reported	Group comparisons	=	n/a
CF	WCST	Daneluzzo et al.	1998	Schizotypal personality questionnaire and wisconsin card sorting test in a population of DSM-III-R schizophrenic patients and control subiects	48 healthy students	SPQ	Controlled for substance dependence DSM-III	Controlled for substance dependence DSM-III	Controlled for substance dependence DSM-III	Correlational analyses	↓	Total score
CF	WCST	Kim et al.	2011	Neuropsychologic profile of college students with schizotypal traits	59 healthy females	SPQ	Controlled for drug/alcohol abuse DSM-IV	Controlled for drug/alcohol abuse DSM-IV	Controlled for drug/alcohol abuse DSM-IV	Group comparisons	↓	Total score
CF	WCST	Jahshan & Sergi	2007	Theory of mind, neurocognition, and functional status in schizotypy	92 healthy students; 40 low-schizotypy ; 52 high schizotypy	SPQ-B	Not reported	Not reported	Not reported	Group comparisons	=	n/a

Function	Task	Author	Year	Title	Groups/N	Schizotypy scale	Control illegal drugs	Control tobacco	Control alcohol	Analyses	Results as a function of schizotypy ***	Symptom dimension relevant?
CF	WCST	Lenzenweger & Korfine	1994	Perceptual Aberrations, Schizotypy, and the Wisconsin Card Sorting Test	51 healthy students, 23 high schizotypy, 28 low schizotypy	PAS	Not reported	Not reported	Not reported	Group comparisons + correlational analyses	↓	Positive schizotypy
CF	WCST	Noguchi et al.	2008	Schizotypal traits and cognitive function in healthy adults	124 healthy adults	SPQ	Not reported	Not reported	Not reported	Correlational analyses	=	n/a
CF	WCST	Park et al.	1995	Individual Differences in Spatial Working Memory in Relation to Schizotypy	51 healthy students, 28 high schizotypes, 23 low schizotypes	PAS	Not reported	Not reported	Not reported	Group comparisons	↓	Positive schizotypy
CF	WCST	Poreh et al.	1995	Reexamination of executive functions in psychosis-prone college students	19 psychosis prone (pp); 19 normal	PAS; MIS; STA	Substance abuse	Substance abuse	Substance abuse	Group comparisons	↓	Positive schizotypy
CF	WCST	Suhr	1997	Executive functioning deficits in hypothetically psychosis-prone	56 healthy students	PAS; MIS	Self-reported substance abuse	Self-reported substance abuse	Self-reported substance abuse	Group comparisons	↓	Positive schizotypy

Function	Task	Author	Year	Title	Groups/N	Schizotypy scale	Control illegal drugs	Control tobacco	Control alcohol	Analyses	Results as a function of schizotypy ***	Symptom dimension relevant?
LAT	FDT	Mason & Claridge	1999	Individual Differences in Schizotypy and Reduced Asymmetry Using the Chimeric Faces Task	52 healthy adults	O-LIFE	Not reported	Not reported	Not reported	Correlational analyses	↓	Positive schizotypy
LAT	FDT	Luh & Gooding	1999	Perceptual Biases in Psychosis-Prone Individuals	210 healthy students, 98 high positive schizotypes, 40 high negative schizotypes, 112 low schizotypes	PAS; MIS; PA	Not reported	Not reported	Not reported	Group comparisons	↓	Negative schizotypy
LAT	DL	Asai et al.	2009	Schizotypal personality traits and atypical lateralization in motor and language functions	46 university students	STA; AHES; O-LIFE	Not reported	Not reported	Not reported	Group comparisons + correlational analyses	↓	Positive schizotypy
LAT	DL	Broks	1984	Schizotypy and hemisphere function--IV : Story comprehension under binaural and monaural listening conditions	36 normal schizotypes	STA	Not reported	Not reported	Not reported	Group comparisons	↓	Positive schizotypy
LAT	DL	Castro & Pearson	2011	Lateralisation of language and emotion in schizotypal personality: Evidence from dichotic listening	132 healthy adults: high schizotypy (n = 64), low (n = 68)	SPQ	Not reported	Not reported	Not reported	Group comparisons	=	n/a

Function	Task	Author	Year	Title	Groups/N	Schizotypy scale	Control illegal drugs	Control tobacco	Control alcohol	Analyses	Results as a function of schizotypy ***	Symptom dimension relevant?
LAT	DL	Overby	1992	Perceptual asymmetry in psychosis-prone college students: Evidence for left-hemisphere overactivation.	47 University students (20 high, 27 low)	PAS; MIS; RSAS; ImpNC	Not reported	Not reported	Not reported	Group comparisons	↑	Positive schizotypy
LAT	DL	Raine & Andrews	1989	Interhemispheric transfer in schizophrenics, depressives, and normals with schizoid tendencies	13 schizophrenics 15 depressives 15 schizoid ; 17 normal controls	PAS; HP; SchzPhr; STA	Not reported	Not reported	Not reported	Group comparisons	↑	Positive schizotypy
LAT	DL	Rawlings & Borge (study 2)	1987	Personality and hemisphere function: Two experiments using the dichotic shadowing technique	30 students	EPQ	Not reported	Not reported	Not reported	Group comparisons	↓	Positive schizotypy
LAT	CS	Gruzelier et al.	1995	Patterns of cognitive asymmetry and syndromes of schizotypal personality	140 students	SPQ	Not reported	Not reported	Not reported	Group comparisons	↓	Negative schizotypy
LAT	CS	Nunn & Peters	2001	Schizotypy and patterns of lateral asymmetry on hemisphere-specific language tasks	90 students	O-LIFE	Not reported	Not reported	Not reported	Correlational analyses	↓	Positive and disorganized schizotypy

Function	Task	Author	Year	Title	Groups/N	Schizotypy scale	Control illegal drugs	Control tobacco	Control alcohol	Analyses	Results as a function of schizotypy ***	Symptom dimension relevant?
LAT	DVFT	Brugger et al.	1993	Functional hemispheric symmetry and belief in ESP - Towards a neuropsychology of belief	30 healthy students	EPS	Not reported	Not reported	Not reported	Group comparison	↓	Positive schizotypy
LAT	DVFT	Mohr et al.	2005	Psychometric schizotypy modulates levodopa effects on lateralized lexical decision performance.	40 healthy men	MIS; PA	Self-reported abstinence from alcohol and drug use 24h prior to testing	Self-reported abstinence from alcohol and drug use 24h prior to testing	abstinence from alcohol and drug use 24h	Correlational analyses	↓	Positive schizotypy
LAT	DVFT	Rawlings & Claridge	1984	Schizotypy and hemisphere function—III : Performance asymmetries on tasks of letter recognition and local-global processing	20	EPQ; STA	Not reported	Not reported	Not reported	Group comparisons	↓	Positive schizotypy
LAT	DVFT	Suzuki & Usher	2009	Individual differences in language lateralisation, schizotypy and the remote-associate task	53 healthy participants; 25 low-schizotypy ; 26 high schizotypy	O-LIFE- B	Not reported	Not reported	Not reported	Correlational analyses	↓	Total score
LAT	SP	Mohr et al.	2006	Lateralized semantic priming: modulation by levodopa, semantic distance, and participants' magical beliefs	40 healthy pps	MIS	Self-reported abstinence from alcohol and drug use 24h prior to testing	Self-reported abstinence from alcohol and drug use 24h prior to testing	reported abstinence from alcohol and drug use 24h prior to	Group comparisons	↓	Positive schizotypy

Function	Task	Author	Year	Title	Groups/N	Schizotypy scale	Control illegal drugs	Control tobacco	Control alcohol	Analyses	Results as a function of schizotypy ***	Symptom dimension relevant?
VF	C&L	Kim et al.	2011	Neuropsychologic profile of college students with schizotypal traits	59 healthy females	SPQ	Controlled for drug/alcohol abuse DSM-IV	Controlled for drug/alcohol abuse DSM-IV	Controlled for drug/alcohol abuse DSM-IV	Group comparisons	=	n/a
VF	C&L	Koychev et al.,	2011	A validation of cognitive biomarkers for the early identification of cognitive enhancing agents in schizotypy: A three-center double-blind placebo-controlled study	237 healthy adults, 117 high, 120 average schizotypes	SPQ-B and SPQ	urine test	<5 cigarettes/ day	breathtest	Group comparisons + correlational analyses	↓	Dis-organization
VF	C&L	Laws et al.	2008	Awareness of everyday executive difficulties precede overt executive dysfunction in schizotypal subjects	65 undergraduate students; 32 low SPQ-B group , 29high SPQ-B group	SPQ-B	Not reported	Not reported	Not reported	Group comparisons	=	n/a
VF	C&L	Poreh et al.	1995	Reexamination of executive functions in psychosis-prone college students	19 psychosis prone (pp); 19 normal	PAS; MIS; STA	Substance abuse	Substance abuse	Substance abuse	Group comparisons	↓	Positive schizotypy
VF	L	Dinn et al.	2002	Positive and negative schizotypy in a student sample: neurocognitive and clinical correlates	103 students	SPQ	Not reported	Not reported	Not reported	Group comparisons	↓	Negative schizotypy

Function	Task	Author	Year	Title	Groups/N	Schizotypy scale	Control illegal drugs	Control tobacco	Control alcohol	Analyses	Results as a function of schizotypy ***	Symptom dimension relevant?
VF	L	Giraldez et al.	1999	Assessment of essential components of schizotypy by means of neurocognitive measures	82 healthy adolescents	MSTQ	Not reported	Not reported	Not reported	Group comparisons	↓	Negative schizotypy
VF	L	Tsakanikos & Claridge	2005	More words, less words: Verbal fluency as a function of `positive' and `negative' schizotypy	190 healthy students	O-LIFE B	Not reported	Not reported	Not reported	Correlational analyses	=	Total schizotypy
VF	L	Tsakanikos & Claridge	2005	More words, less words: Verbal fluency as a function of `positive' and `negative' schizotypy	190 healthy students	O-LIFE B	Not reported	Not reported	Not reported	Correlational analyses	↓	Negative schizotypy
VF	L	Tsakanikos & Claridge	2005	More words, less words: Verbal fluency as a function of `positive' and `negative' schizotypy	190 healthy students	O-LIFE B	Not reported	Not reported	Not reported	Correlational analyses	↑	Positive schizotypy
VM	CVLT	Aguirre et al.	2008	Emotional intelligence and social functioning in persons with schizotypy	96 healthy students, 40 high schizotypes. 56 lopw schizotypes	SPQ-B	Not reported	Not reported	Not reported	Group comparisons	=	n/a

Function	Task	Author	Year	Title	Groups/N	Schizotypy scale	Control illegal drugs	Control tobacco	Control alcohol	Analyses	Results as a function of schizotypy ***	Symptom dimension relevant?
VM	CVLT	Kim et al.	2011	Neuropsychologic profile of college students with schizotypal traits	59 healthy females	SPQ	Controlled for drug/alcohol abuse DSM-IV	Controlled for drug/alcohol abuse DSM-IV	Controlled for drug/alcohol abuse DSM-IV	Group comparisons	=	n/a
VM	CVLT	Jahshan & Sergi	2007	Theory of mind, neurocognition, and functional status in schizotypy	92 healthy students; 40 low-schizotypy ; 52 high schizotypy	SPQ-B	Not reported	Not reported	Not reported	Group comparisons	=	n/a
VM	IWL	Burch et al.	2006	The relationship between incidental learning and multi-dimensional schizotypy as measured by the Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE)	75 undergraduate students	O-LIFE B	Not reported	Not reported	Not reported	Group comparisons	↓	Positive schizotypy
VM	SR	Langdon & Coltheart	2004	Recognition of metaphor and irony in young adults: the impact of schizotypal personality traits	36 students; 8 low-schizotypal (lo-S) adults and a group of 18 high-schizotypal (hi-S) adults.	SPQ	Not reported	Not reported	Not reported	Group comparisons	↑ as trend	Negative schizotypy
VM	SR	LaPorte et al.	1994	Psychosis-proneness and verbal memory in a college student population	409 healthy students	MIS; PAS, PA	Self-reported drug and alcohol use	Self-reported drug and alcohol use	Self-reported drug and alcohol use	Group comparisons + correlational analyses	=	Positive schizotypy

Function	Task	Author	Year	Title	Groups/N	Schizotypy scale	Control illegal drugs	Control tobacco	Control alcohol	Analyses	Results as a function of schizotypy ***	Symptom dimension relevant?
VM	WAIS-R	Noguchi et al.	2008	Schizotypal traits and cognitive function in healthy adults	124 healthy adults	SPQ	Not reported	Not reported	Not reported	Correlational analyses	=	n/a
VM	WR	Kaczorowski et al.	2009	Neurological soft signs in psychometrically identified schizotypy	177 healthy students	PAS; MIS; PA; RSAS	Self-reported medication, drug and alcohol use	Self-reported medication, drug and alcohol use	Self-reported medication, drug and alcohol use	Correlational analyses	↓	Negative schizotypy
WM	LNS	Lenzenweger & Gold	2000	Auditory working memory and verbal recall memory in schizotypy	57 healthy students; 31 schizotypic and 26 normal controls	PAS	Not reported	Not reported	Not reported	Group comparisons	=	n/a
WM	LNS	Matheson & Langdon	2008	Schizotypal traits impact upon executive working memory and aspects of IQ	100 healthy students	SPQ	Self-reported cannabis and ecstasy use 12 months	Self-reported cannabis and ecstasy use 12 months	Self-reported cannabis and ecstasy use 12 months	Correlational analyses	↓	Positive + Negative schizotypy
WM	n-back	Kerns & Becker	2008	Communication disturbances, working memory, and emotion in people with elevated disorganized schizotypy	66 healthy students; 32 high schizotypes, 34 low schizotypes	CSS	Not reported	Not reported	Not reported	Group comparisons	↓	Dis-organizatio n

Function	Task	Author	Year	Title	Groups/N	Schizotypy scale	Control illegal drugs	Control tobacco	Control alcohol	Analyses	Results as a function of schizotypy ***	Symptom dimension relevant?
WM	n-back	Koychev et al.,	2011	A validation of cognitive biomarkers for the early identification of cognitive enhancing agents in schizotypy: A three-center double-blind placebo-controlled study	240 healthy adults, 120 high, 120 average schizotypes	SPQ-B and SPQ	urine test	<5 cigarettes/ day	breathtest	Group comparisons + correlational analyses	↓	Dis-organization
WM	n-back	Schmidt-Hansen & Honey	2009	Working memory and multidimensional schizotypy: Dissociable influences of the different dimensions	289 healthy students	O-LIFE	Not reported	Not reported	Not reported	Group comparisons	↓	Positive schizotypy
WM	MUT	Avons et al.	2003	Executive function assessed by memory updating and random generation in schizotypal individuals	59 healthy students; 27 low UnEx, 32 high UnEx	O-LIFE: UnEx	Not reported	Not reported	Not reported	Group comparisons	=	Positive schizotypy
WM	Spatial	Park & McTigue	1997	Working memory and the syndromes of schizotypal personality	89 healthy students	SPQ	Not reported	Not reported	Not reported	Correlational analyses	↓	Negative schizotypy
WM	Visual	Giraldez et al.	1999	Assessment of essential components of schizotypy by means of neurocognitive measures	82 healthy adolescents	MSTQ	Not reported	Not reported	Not reported	Group comparisons	↓	Negative schizotypy

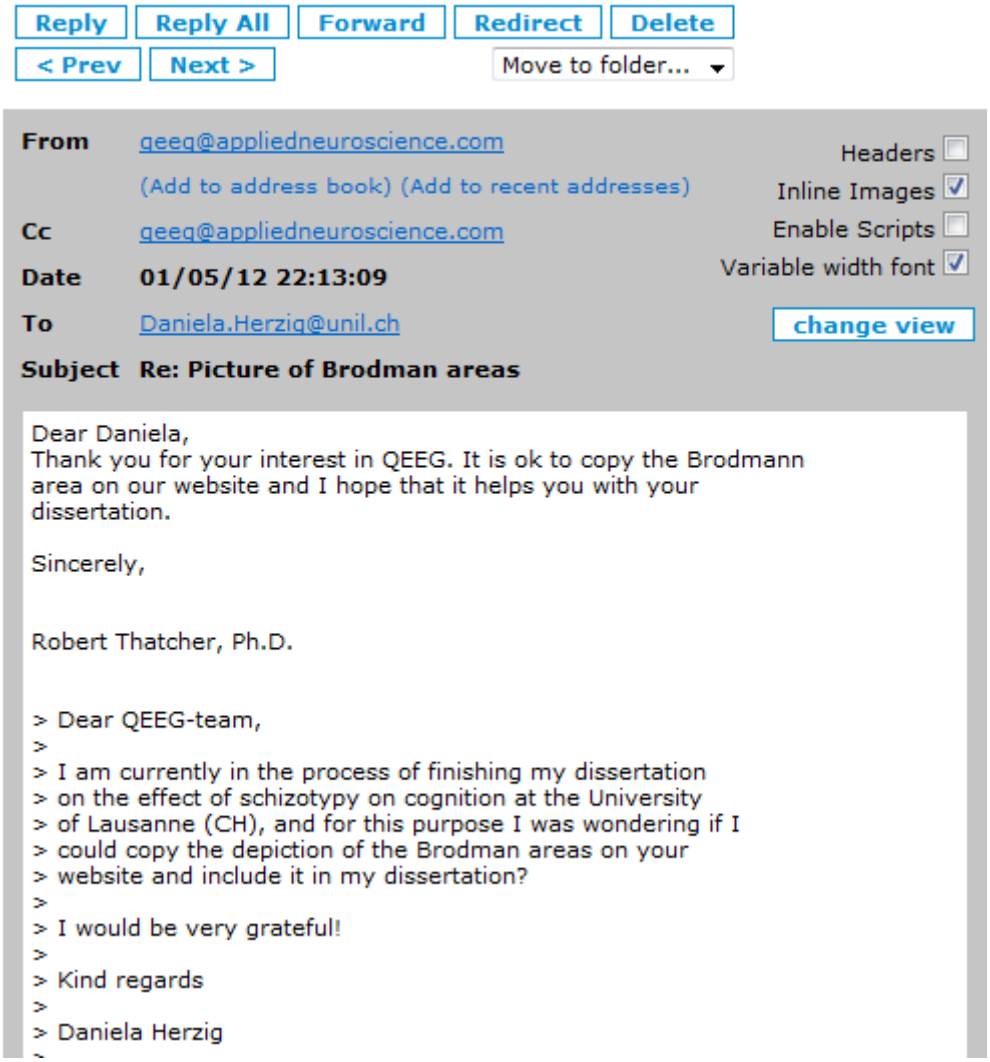
***** To note: Some studies reported more than one finding on schizotypy and cognition. This table represents a listing of findings, and as such the number of findings exceeds the number of studies.

***Note:* Abbreviations used in table 1 (sorted alphabetically). **AHES** = Auditory Hallucination Experience Scale (Onari, 1998); **CF** = Cognitive flexibility; **C&L** = Categories and letters; **CS** = composite score for discrepancy between left and right hemisphere dominant task (language laterality); **CSS** = Cognitive Slippage Scale (Miers & Raulin, 1987); **CVLT** = California Verbal learning test (verbal learning); **DL** = Dichotic Listening (language laterality); **DVFT** = Divided visual field task (language laterality); **EPQ** = Eysencks Personality Questionnaire (Eysenck & Eysenck, 1975); **EPS** = Extrasensory perception Scale; **FDT** = Facial decision Task (Face processing, Laterality); **HP** = hallucinatory predisposition (Launay & Slade, 1981); **IED** = Intra–extradimensional set shift (cognitive flexibility); **ImpNC** = Impulsive Non-conformity scale (L. J. Chapman et al., 1984); **IWL** = incidental word learning (verbal learning); **L** = Letters only; **LAT** = Laterality; **LNS** = letter number sequencing (working memory); **LNST** = letter number span task (verbal memory); **MIS** = Magical Ideation Scale (Eckblad & Chapman, 1983); **MSTQ** = Multidimensional Schizotypal Traits Questionnaire (Rawlings & MacFarlane, 1994); **MUT** = memory updating task (working memory); **n/a** = not applicable; **O-LIFE** = Oxford and Liverpool Inventory for Feelings and Experiences (Mason, et al., 1995); **O-LIFE -B** = Oxford and Liverpool Inventory for Feelings and Experiences - Brief (Mason, et al., 2005); **PA** = Physical Anhedonia (L. J. Chapman, et al., 1976); **PAS** = Perceptual Abberation Scale (L. J. Chapman, et al., 1978); **PDI** = Peters Delusional Inventory (Peters, et al., 1999); **RSAS** = Revised Social Anhedonia Scales (Eckblad, et al., 1982); **SchzPhr =** schizophrenism (Faily & Venables, 1986); **SP** = Semantic priming (Language laterality); **SPQ** = Schizotypal Personality Questionnaire (Raine, 1991); **SPQ -B** = Schizotypal Personality Questionnaire - Brief (Raine & Benishay, 1995); **SR** = Story recall (verbal memory); **STA** = Schizotypy Traits Questionnaire (Claridge & Broks, 1984); **SWM** = Spatial working memory task; **TMT** = Trail making task (cognitive flexibility); **UnEx** = Unusual Experiences Scale; **VF** = Verbal fluency; **VL** = Verbal Learning; **VM** = Verbal memory; **VWM** = Visual working memory; **WAIS-R** = Wechsler adult intelligence scale verbal memory task; **WCST** = Wisconsin Card Sorting Test (cognitive flexibility); **WM** = Working memory; **WR** = word recall (verbal memory).

***** „↓“ = Relatively decreased performance as a function of schizotypy; „=“ = Equal performance as a function of schizotypy; „↑“ = Relatively elevated performance as a function of schizotypy;To note: the direction of effect (increase, decrease or equal performance) is related to Table 30, and does not necessarily represent within-subjects effects.

E. Copyright documents

1. Figure 3



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From qeeg@appliedneuroscience.com

(Add to address book) (Add to recent addresses)

Cc qeeg@appliedneuroscience.com

Date 01/05/12 22:13:09

To Daniela.Herzig@unil.ch

Subject Re: Picture of Brodman areas

Headers ☐ Inline Images ☑ Enable Scripts ☐ Variable width font ☑

change view

Dear Daniela,
Thank you for your interest in QEEG. It is ok to copy the Brodmann area on our website and I hope that it helps you with your dissertation.

Sincerely,

Robert Thatcher, Ph.D.

> Dear QEEG-team,
>
> I am currently in the process of finishing my dissertation
> on the effect of schizotypy on cognition at the University
> of Lausanne (CH), and for this purpose I was wondering if I
> could copy the depiction of the Brodman areas on your
> website and include it in my dissertation?
>
> I would be very grateful!
>
> Kind regards
>
> Daniela Herzig
>

2. Figure 4

Daniela Herzig 1. Mai (vor 13 Tagen)

an bruno.dubuc

Dear Institute of Neuroscience-team,

I am currently in the process of finishing my doctoral thesis on the effect of schizotypy on hemispheric asymmetry at the University of Lausanne (CH), and for this purpose I was wondering if I could copy the depiction of the two hemispheres including their individual function specializations (e.g. face recognition, word processing) on your website and include it in my dissertation?

I would be very grateful!

Kind regards

...

bruno.dubuc@videotron.ca 2. Mai (vor 12 Tagen)

an mich

Englisch > Deutsch Nachricht übersetzen Deaktivieren für: Englisch

Hi Daniela,

No problem to use our material for academic use.
So feel free to do so.

Cordially,
Bruno Dubuc

----- Message d'origine -----
De: Daniela Herzig <amygdalas@googlemail.com>
Date: Mardi, 1 Mai 2012, 4:17 pm
Objet: Picture copyright request
À: bruno.dubuc@videotron.ca

F. Curriculum Vitae

PERSONAL INFORMATION

Name:	Daniela Herzig
Current address:	Route de Prilly 7, 1004 Lausanne, Switzerland
Telephone:	+41 799438317
Private e-mail:	amygdalas@googlemail.com
Professional email:	Daniela.Herzig@unil.ch
Born:	11th August 1981 in Dinslaken, Germany
Citizenship:	German

LANGUAGES

German:	Mother tongue
Dutch:	Excellent
English:	Excellent
Spanish:	Advanced
French:	Beginner
Latin:	7 years in school

EDUCATION

09/2001 until 08/2003	Radboud University of Nijmegen/Netherlands, BSc in General Psychology.
09/2003 until 03/2006	Radboud University of Nijmegen/Netherlands, MSc in Neuropsychology and Rehabilitationpsychology.
09/2004 until 01/2005	MSc thesis on egocentric and object-centred neglect (direct Supervisor: Dr. Paul Eling, Radboud University Nijmegen/ Netherlands).

11/ 2004	Short-term traineeship in the context of my MSc thesis (East Bremen clinic, Bremen/Germany, Supervisor: Prof. Dr. phil. Hildebrandt).
02/2005 until 07/2005	University of Granada/Spain as part of an ERASMUS exchange program. Courses on Exercise Psychology and the Philosophy of Psychology.
09/2005 until 03/2006	Internship at the University Hospital Aachen/Germany (Department of Neuropsychology, Supervisors: Prof. Dr. Walter Sturm, Dr. Bruno Fimm, Dr. Markus Thimm).
10/2006 until 02/2011	PhD (1st year part-time) in the Department of Experimental Psychology, University of Bristol/UK. Supervision by Prof. Christine Mohr, 2nd Supervisor Prof. Marcus Munafo.
02/2007 until 11/2007	Part-time research assistant (Supervisors: Dr. Angela Rowe, Prof. Marcus Munafo) at the Department of Experimental Psychology in Bristol. Work included material preparation, recruitment and testing of participants, data input and preparation for statistical analysis (SPSS/Excel).
03/2010 until 07/2010	Part-time research assistant (Supervisors: Prof. Christine Mohr, Prof. Hans Stassen, University Hospital Zurich) assessing speech and mood in healthy adults (part of a EU-funded project "OPTIMI"). Work included obtaining ethical approval, study planning (including stimuli preparation), recruitment and testing of participants, transfer of sensitive study equipment to Spain, training of research assistant in Spain.
02/2011 until present	Finishing the doctoral thesis (started at the University of Bristol) in the Department of Psychology, University of Lausanne, Switzerland. Supervision by Prof. Christine Mohr

(internal viva successfully passed, public defense date: 14.06.2012).

TEACHING EXPERIENCE

ACADEMIC TEACHING

2006 until 2009	Experimental laboratory Demonstrator at the University of Bristol, Department of Experimental Psychology, during three consecutive years. Tutorial-style teaching of scientific methods, experimental designs, writing skills, marking of and providing feedback on written experimental laboratory reports to 1st, 2nd and 3rd year undergraduate students.
2007 until 2010	Assisting Prof. Christine Mohr in the supervision of BSc and MSc projects (study design, programming in and handling of DMDX, data preparation and analysis with Excel/SPSS, as well as general support) at the Department of Experimental Psychology (University of Bristol).
2009 until present	Lectures on the neural correlates of addiction (four one-hour lectures to undergraduate students) as part of a Neuropsychology module at the Department of Experimental Psychology (University of Bristol), and the Institute of Psychology (University of Lausanne).
2011 until present	Experimental laboratory demonstrator to MSc students at the École Polytechnique Fédérale de Lausanne (EPFL). Tutorial-style teaching of scientific methods, experimental designs, writing skills, marking of and providing feedback on written experimental laboratory reports to MSc students.

OTHER TEACHING ACTIVITIES

03/2006 until 09/2006	Volunteer work as an assistant teacher at the Dr. Muhajir school for Mapuche children in Temuco/Chile. Teaching children with cognitive impairments, ages 10-15 years.
03/2009 until 10/2009	Running and chairing biweekly Neuropsychiatry meetings attended by undergraduate and postgraduate students as well as academic staff (discussion of recent articles, coordination of presentation and discussion of current research projects) at the Department of Experimental Psychology (University of Bristol).

DISSEMINATION OF SCIENTIFIC WORK

PEER-REVIEWED PUBLICATIONS

Herzig, D.A., Tracy, J., Munafò, M., & Mohr, C. (2010). The influence of tobacco consumption on the relationship between schizotypy and hemispheric asymmetry. *Journal of Behavior Therapy and Experimental Psychiatry, 41*(4), 397-408.

Herzig, D.A., Sullivan, S., Evans, J., Corcoran, R., Mohr, C. (in press). Hemispheric asymmetry and theory of mind: Is there an association? *Cognitive Neuropsychiatry:* 1-26.

Herzig, D.A., Mohr, C. (in press). Stressing schizotypy: the modulating role of stress-relieving behaviours and intellectual capacity on functional hemispheric asymmetry. *Laterality: Asymmetries of Body, Brain and Cognition:* 1-27.

Herzig, D.A., Nutt, D., Mohr, C. (under revision). Does cannabis use impair frontal lobe functioning? The role of alcohol, nicotine, and schizotypy.

Herzig, D.A., Brooks, R., Mohr, C. (submitted). The cocktail (party) phenomenon: Inferring about individual drug effects on frontal lobe functioning in polydrug using mephedrone users before and after clubbing.

Sullivan, S., Herzig, D.A., Mohr, C., Lewis, G., Corcoran, R., Drake, R. & Evans, J. (in press). Theory of mind and social functioning in first episode psychosis patients and their relatives. *Cognitive Neuropsychiatry.*

Cappe, C., Herzog, M., Herzig, D.A., Mohr, C. (under revision). Cognitive disorganisation in schizotypy is associated with deterioration in visual backward masking.

POSTERS

Herzig, D.A., Tracy, J., Munafò, M., & Mohr, C. Nicotine, hemispheric asymmetry, and schizotypy. Meeting of the Experimental Psychological Society in Cambridge, UK (April, 2008).

Herzig, D.A., Sullivan, S., Evans, J., Corcoran, R., Mohr, C. Hemispheric asymmetry and theory of mind: Is there an association? Paper presented at the ISSID, UCL London, UK (July 2011).

Herzig, D.A., Nutt, D., Mohr, C. Cannabis, frontal lobe functioning and schizotypy – What is the nature of the association? Poster presented at the ESCoP, BCBL San Sebastian, Spain (September/October, 2011).

Herzig, D.A., Sullivan, S., Lewis, G., Corcoran, R., Drake, R., Evans, J. & Mohr, C. Hemispheric asymmetry in first-episode psychosis and schizotypy: What´s left for cannabis? Poster to be presented at the SIRS conference in Florence, Italy (April 2012).

ORAL PRESENTATIONS

07/2007	University of Bristol Departmental annual PhD Conference. Title: Personality, cognition and cannabis.
07/2008	University of Bristol Departmental annual PhD Conference. Title: Cannabis, cognition and personality.
07/2009	University of Bristol Departmental annual PhD Conference. Title: Cannabis, cognition and psychotic(-like) thinking.
11/2009	The 15th Biennial Winter Workshop in Psychoses, Barcelona, Spain. Title: No reduced functional hemispheric asymmetry after a first psychotic episode or regular cannabis consumption.
02 & 05/2011	Cannabis, cognition and psychotic (-like) thinking. Talks presented at the Colloquia of the Faculté des sciences sociales et politiques, Lausanne.
09/2011	Cognitive impairment in schizotypy: Take a look at the drug side. Talk held at the Swiss Psychological Society (SSP – SGP) conference in Fribourg (CH).

CONFERENCES ATTENDED

07/2007	Experimental Psychological Society conference in Edinburgh (UK).
04/2008	Experimental Psychological Society conference in Cambridge (UK).
06/2008	Mini symposium in Oxford at the University Natural History Museum. Title: "Did Paul Broca have the answer to the Huxley Owen argument?: Cerebral Asymmetry as the defining feature of the human brain". University of Oxford (UK).
11/2008	Out of Body Experiences event at the Science Museum's Dana Centre, London (UK).

11/2009	The 15th Biennial Winter Workshop in Psychoses, Barcelona, Spain.
07/2011	Conference of The International Society for the Study of Individual Differences (ISSID), at University College London (UK).
09/2011	12th bi-annual congress of the Swiss Psychological Society (SSP-SGP), at the University of Fribourg (CH).
09 & 10/2011	17th European Society for Cognitive Psychology (ESCoP) Conference, Donostia, San Sebastian (Spain).

OTHER TRANSFERABLE SKILLS

2006 until present	Collaboration in multi-centre study on early psychosis (MRC-funded project "PsyGrid"), sub-section: "social cognition and hemispheric asymmetry" (work included study planning, programming, training of collaborators and ongoing support regarding experimental run system DMDX, data input and analysis, write-up for scientific publications, participation in regular meetings).
2007 until present	Supporting peers, students, and academic staff with DMDX-related problems.
08/2010 until 09/2010	Text translation German - English (part-time): www.maasberg.ch for Prof. Hans Stassen, University of Zurich.

ADDITIONAL COURSES ATTENDED

10/2006	Staff development course: Getting started with Excel (University of Bristol).
03/2007	Staff development course: Further Excel (University of Bristol).
07/2007	Workshop "Postgraduates who teach" (University of Bristol).

10/2007	Postgraduate Research Network, Title: Qualitative Research Methods. Statistics According to Hugh (University of Bristol).
10/2007	Staff development course: Getting started with the SPSS statistics package (University of Bristol).
06/2008	Presentation Skills Training (University of Bristol).
07/2009	Matlab workshops (University of Bristol).
06/2010	ESRC Mock panel: Exercise for better grant writing (University of Bristol).
06/2010	CELT seminar. Title: Getting Published: Exploring The Issues And Dispelling The Myths (Newport).