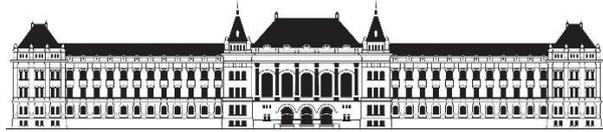


Budapest University of Technology and Economics

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M Ű E G Y E T E M 1 7 8 2

**AN EXAMINATION OF COGNITION AND CREATIVITY IN
A DIMENSIONAL NEUROPSYCHIATRIC AND A
PSYCHOPHARMACOLOGICAL FRAMEWORK**

Thesis booklet

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Introduction and main objectives

Broadly speaking, our goal was to investigate the cognitive correlates of neuropsychiatric disorder-like phenotypes occurring outside conventional diagnostic boundaries. More precisely, in our studies we mapped the relationship of neuropsychiatric disorder-like phenotypes with lower level indicators of exploration, such as latent inhibition and anomaly processing, and also with higher level cognitive abilities, such as executive functions and creative thinking skills. We studied two phenotypes in the general population that resemble neuropsychiatric disorders, namely attention-deficit/hyperactivity disorder-like traits and schizotypy (i.e. schizophrenia-like traits). Moreover, we examined schizotypy not only in the general population, but also in patients with Parkinson's disease who were treated with dopaminergic therapy.

What do these different phenotypes have in common? We argue that they are all related to the exploration-exploitation dilemma in some fashion. Briefly, by exploration we refer to the improvement of knowledge by approaching uncertainty, which also implies making decisions whose outcomes are less optimal or predictable. Exploration can be contrasted with exploitation, that is, the utilisation of already possessed knowledge, which implies favouring decision alternatives that are believed to lead to the optimal future states. Flexibility of mental representations, recognition of novel patterns, and coming up with original and useful ideas are some aspects of exploration that support adaptation to a changing environment. However, these benefits come at the expense of the stability mental representations, predictable behaviour and social conformity. With this in mind, it is easy to see that optimising the extent and the timing of exploration vs. exploitation is not only crucial to creativity and innovation, but it is also highly relevant to impulsivity, psychosis, or attentional dysfunction that are hallmarks of several neuropsychiatric disorders.

The neurotransmitter dopamine is assumed to be central to exploration, and it plays a key role in several cognitive functions such as motor and cognitive control, processing and approaching reward, novelty and uncertainty, and modulation of memory for adaptive future behaviour. Therefore, it is not surprising that signs and symptoms of a wide range of neuropsychiatric disorders, including attention-deficit/hyperactivity disorder, schizophrenia, and Parkinson's disease, have been related to disturbed dopaminergic neurotransmission. Accordingly, dopaminergic medications represent a major approach in the neurochemical treatment of the symptoms of these disorders.

Thesis point 1: The association between schizotypy and creativity may be mediated by alterations of basic, dopamine-dependent cognitive processes.

Schizotypy is a set of personality traits that resemble the symptoms and signs of schizophrenia (Ettinger, Meyhofer, Steffens, Wagner, & Koutsouleris, 2014). Whether the variance in schizotypy observed in the non-clinical population and in schizophrenia-spectrum disorders represent different points of a single population continuum, or stems from discrete latent subpopulations, is still a subject of debate (see Linscott & van Os, 2010). Nevertheless, positive schizotypy shows weak association with various indicators of creative achievements and potential (Acar & Sen, 2013). Moreover, large-scale population studies have shown that familial proximity to psychotic disorders is associated with greater likelihood of creative occupations (Kyaga et al., 2013).

In a literature review, we have argued that the association of positive schizotypy with creativity could be due to the overlap of neurocognitive correlates, some of which are modulated by dopamine. A prominent example is latent inhibition, that is, the well-established observation that repeated, non-reinforced presentation of a stimulus inhibits its later processing (Lubow, 2005). Latent inhibition biases cognition towards relevant information, therefore it is essentially connected to selective attention. Animal studies have demonstrated the key role of dopaminergic modulation in latent inhibition (Weiner & Arad, 2009). Importantly, reduced latent inhibition is not only associated with acute psychosis and schizotypy (Kumari & Ettinger, 2010), but also with openness (Peterson, Smith, & Carson, 2002) and real life creative achievements (Kéri, 2011), and openness is a robust predictor of creative thinking and achievements (Batey & Furnham, 2006). In addition, a positive correlation between openness and positive schizotypy has been documented in healthy (DeYoung, Grazioplene, & Peterson, 2012) and in clinical samples (Chmielewski, Bagby, Markon, Ring, & Ryder, 2014). We suggested that it would be beneficial to compare the developmental and neurocognitive aspects of openness and schizotypy.

Related article (written in Hungarian):

Polner, B., & Kéri, S. (2015). Individual differences in creative thinking: psychotic-like features in an adaptive context? *Hungarian Psychological Review*, 70(3), 537–555.
<http://doi.org/10.1556/0016.2015.70.3.3>

Thesis point 2: Attention-deficit/hyperactivity disorder-like traits are weakly and negatively associated with inhibition-related functions among healthy adults.

Growing evidence suggests that attention-deficit/hyperactivity disorder (ADHD) phenotypes are continuously distributed in the population (Marcus & Barry, 2011). Polymorphisms of genes related to the dopaminergic systems have been associated with ADHD (Faraone et al., 2005; Franke et al., 2012) and with ADHD-like traits in the general population as well (e.g. Tong et al., 2015). Patients with ADHD have frequently been reported to demonstrate impairment of inhibition-related executive functions (e.g. Hervey, Epstein, & Curry, 2004), and some studies have reported qualitatively similar, but subtler deficits in people without a diagnosis of ADHD but at increased genetic risk for ADHD (Slaats-Willemse, Swaab-Barneveld, De Sonnevile, Van Der Meulen, & Buitelaar, 2003) and/or with high levels of ADHD-like traits (Herrmann et al., 2009). Inhibition-related functions, including prepotent response inhibition and interference control, require active maintenance of certain task sets (Munakata et al., 2011). Thus an impairment of inhibition-related functions can mirror the difficulty of stabilising task set representations.

Therefore, we investigated whether performance on various tests of inhibition-related functions can predict ADHD-like traits in a large sample of healthy adults (N = 440). Attention-deficit/hyperactivity disorder-like (inattentive and hyperactive/impulsive) traits were measured with a self-report scale that is based on the DSM-IV TR ADHD criteria. Inhibition-related functions were assessed with a Stroop, a go/no-go, an antisaccade, an Eriksen flanker, a Simon, and a stop-signal task. Linear regression analyses revealed that worse performance on the Stroop task significantly predicted higher ADHD-like traits, over and above the effects of neuroticism, verbal intelligence, and demographic factors (i.e. age, gender, and education). In addition, increased go/no-go commission error rate was marginally associated with higher expression of ADHD-like traits (see Figure 1). Further analyses demonstrated that performance on the Stroop task predicted inattentive traits at trend level, while go/no-go error rate was significantly associated with hyperactive/impulsive traits. The effect size of the association between inhibition-related functions and ADHD-like traits were small: performance on the Stroop and the go/no-go task explained circa 1% of the variance in ADHD-like traits. Additionally, in each regression model, neuroticism consistently emerged as a significant and positive predictor of ADHD-like traits.

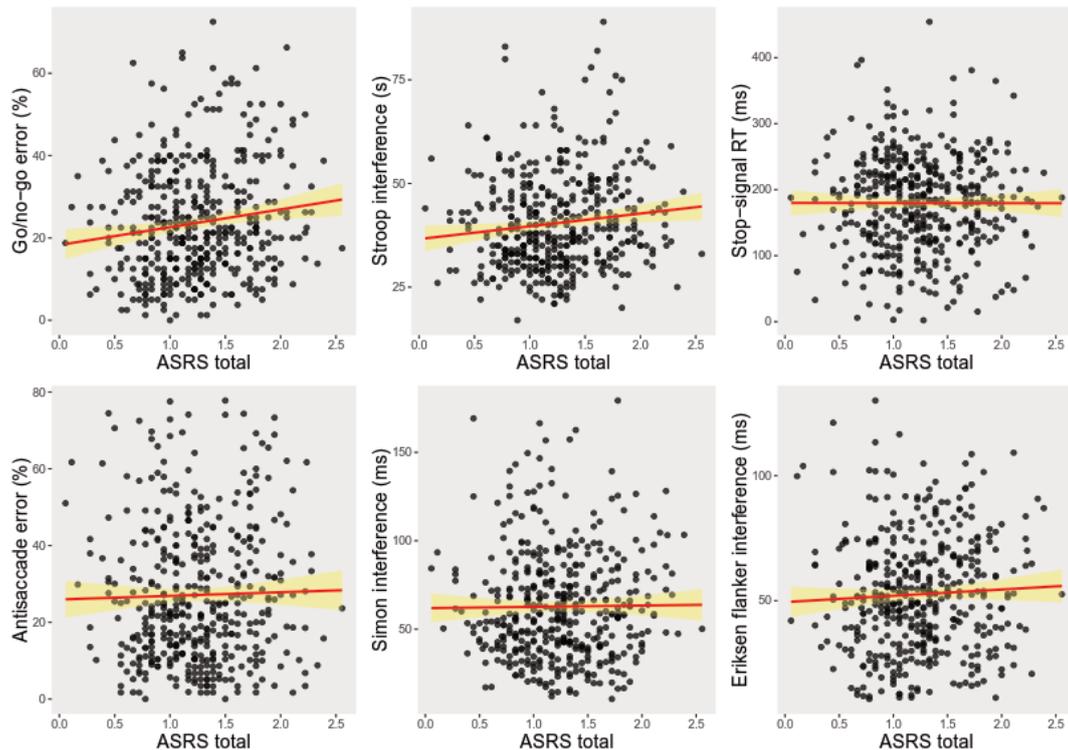


Figure 1. Association between inhibition-related functions and self-reported ADHD-like traits in a large healthy adult sample drawn from the general population. Performance on the Stroop task was significantly associated with ADHD-like traits, while performance on the go/no-go task predicted ADHD-like traits at trend level. Linear trend lines with 95% confidence intervals are shown. Higher scores on the y axis indicate worse inhibition-related functions. ASRS: ADHD Self-Report Scale.

All in all, we have found that a subtle proportion of the variance in ADHD-like traits can be predicted by performance on two tests tapping inhibition-related functions. Moreover, our analyses indicated that neuroticism, reflecting an increased tendency to experience negative emotions, is a robust correlate of ADHD-like traits in the general population. The underlying neurobiological and computational processes remain to be clarified by future psychopharmacological and neuroimaging studies.

Related article:

Polner, B., Aichert, D., Macare, C., Costa, A., & Ettinger, U. (2015). Gently restless: association of ADHD-like traits with response inhibition and interference control. *European Archives of Psychiatry and Clinical Neuroscience*, 265(8), 689–699. <http://doi.org/10.1007/s00406-014-0531-7>

Thesis point 3: Dopaminergic therapy increases positive and disorganised schizotypy, reduces latent inhibition, and improves anomaly processing in patients with Parkinson's disease.

Psychosis and related experiences are among the potential side effects of dopaminergic therapy in Parkinson's disease (Fénelon & Alves, 2010). Acute, but not chronic schizophrenia is associated with diminished latent inhibition, and several studies have found reduced latent inhibition to be associated with positive schizotypy in healthy participants as well (Kumari & Ettinger, 2010). Latent inhibition is the robust finding that repeated non-reinforced exposure to a stimulus can inhibit subsequent processing of the particular stimulus, and it is sensitive to pharmacological manipulations of the dopaminergic systems (Weiner & Arad, 2009). Importantly, lowered latent inhibition has additionally been associated with explorative behavioural tendencies (extraversion, openness, and creative achievement) in highly intelligent healthy samples (Kéri, 2011; Peterson et al., 2002). Another behavioural indicator of exploration is the processing of anomalies, as it demands updating of expectations about the environment. It can be argued that psychotic-like experiences represent a pathological form of exploration as they stem from perception of patterns in randomness (DeYoung, 2013).

We examined self-reported schizotypy, latent inhibition, and anomaly processing in two groups of patients with Parkinson's disease (N = 26 / 25) and in a healthy control group (N = 24). Latent inhibition was measured with a visual search task. In the anomaly processing task, participants had to identify a stimulus contradicting their expectations (i.e. a trick card, a black four of hearts, presented among regular playing cards). Furthermore, we investigated the dose-dependent effect of dopaminergic medications on the above measurements.

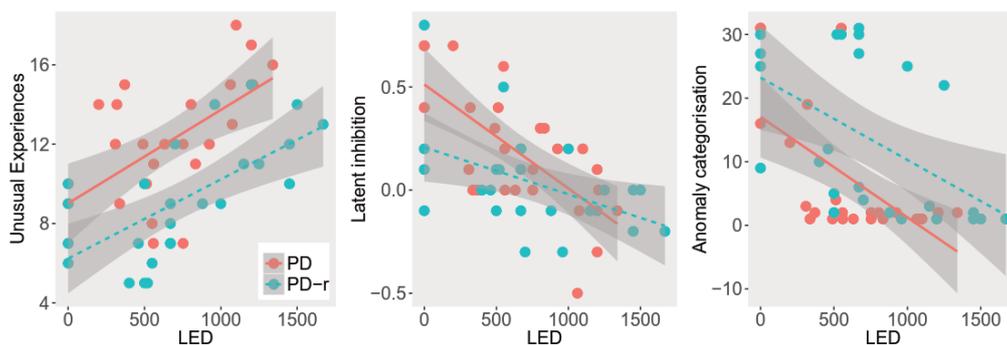


Figure 2. Dose-dependent effect of dopaminergic medications on positive schizotypy (as indicated by scores on the Unusual Experiences scale), latent inhibition, and anomaly categorisation in two groups of patients with Parkinson's disease. Linear trend lines with 95% confidence intervals are displayed for both samples. On the y axis of the right panel, the number of trials until correct categorisation are displayed. LED: levodopa-equivalent dose, PD: Parkinson's disease, PD-r: Parkinson's disease, replication sample.

Relative to the control group, we found higher disorganised schizotypy in both groups of patients. In addition, positive and impulsive schizotypy were increased in the first group of patients, and negative schizotypy was elevated in second group. Latent inhibition was diminished in both groups of patients, while it was intact in the control group. Anomaly processing was marginally enhanced in the first patient sample. In both groups of patients, larger levodopa-equivalent dopamine doses predicted more efficient anomaly processing, elevated disorganised and positive schizotypy, and reduced latent inhibition, despite clinical differences between the samples (see Figure 2).

In conclusion, we demonstrated that dopamine replacement therapy induces changes in cognition that can set the stage either for psychotic-like experiences or creative achievements. We suggest that while dopaminergic medications can alleviate the motor symptoms of Parkinson's disease, they might alter brain dynamics in a way that increases the likelihood of producing and perceiving novel patterns. Structural and functional neuroimaging might help to identify the neural substrates of the above proposed mechanisms.

Related article:

Polner, B., Moustafa, A. A., Nagy, H., Takáts, A., Györfi, O., & Kéri, S. (2016). Dopamine improves exploration after expectancy violations and induces psychotic-like experiences in patients with Parkinson's disease. *Neuroscience Letters*, *616*, 132–137. <http://doi.org/10.1016/j.neulet.2016.01.037>

Thesis point 4: Improvement of divergent thinking during dopamine agonist therapy in patients with Parkinson’s disease can be predicted from pre-treatment schizotypy and creative achievements.

Side effects of dopamine agonist treatment in Parkinson’s disease are a function of disease progression and also of pre-treatment factors. The unfolding of creative potentials after the initiation of dopaminergic therapy in patients with Parkinson’s disease is intriguing (e.g. Kulisevsky, Pagonabarraga, & Martinez-Corral, 2009). However, little is known about why it occurs only in within a limited set of patients: so far several case reports and even fewer systematic studies have addressed the mechanisms behind the “creativity side effect”. Researches in healthy participants have found that schizotypal traits can predict some behavioural and neural effects of dopaminergic drugs, and intellectual capacity has also been shown to predict the influence of dopaminergic compounds on cognitive and neural functions.

In our study, we examined whether intelligence, lifetime creative achievements, and schizotypy at pre-treatment can predict the change in aspects of divergent thinking in patients with Parkinson’s disease undergoing dopamine agonist therapy. Divergent thinking is considered to be an indicator of creative potentials, that is, a necessary but insufficient correlate of real-life creative achievements (Runco & Acar, 2012). We recruited a group of non-demented, never-medicated patients with Parkinson’s disease (N = 18) and a matched healthy control group (N = 19). Patients and controls were examined at baseline, and at a follow-up session twelve weeks after dopamine agonist therapy of the patients had been initiated. Divergent thinking was measured with the ‘Just suppose’ task from the Torrance Test of Creative Thinking (Torrance, 1974). In this task, participants are asked to list their ideas about what would be the consequences of an imaginary situation (e.g. ‘Just suppose clouds had strings attached to them which hang down to earth. What would happen?’). Responses are scored according to fluency (i.e. the number of ideas given), flexibility (i.e. the variability of ideas), and originality (i.e. statistical infrequency of the ideas in the sample).

In line with previous studies (Cools, Barker, Sahakian, & Robbins, 2003; Nagy et al., 2012), at follow-up we observed elevated rates of positive schizotypy and trait impulsivity in the patient group. Fluency and flexibility of divergent thinking were increased at trend level among the patients. However, we observed remarkable individual differences in change of divergent thinking. Improvement of originality was predicted by higher positive schizotypy at baseline, whereas improvement of flexibility was predicted by more lifetime creative achievements and higher disorganised schizotypy at pre-treatment (see Figure 3).

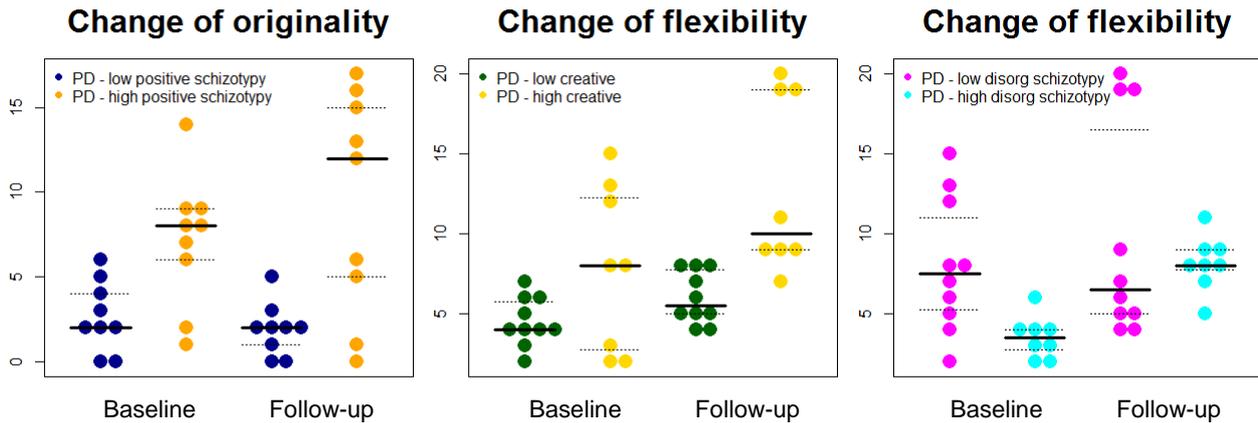


Figure 3. Individual differences in change of originality and flexibility of divergent thinking were predicted by baseline positive schizotypy (as indicated by scores on the Unusual Experiences scale, left panel), lifetime creative achievement (as mirrored by scores on the Creative Achievement Questionnaire, middle panel), and disorganised schizotypy (as reflected by scores on the Cognitive Disorganisation scale, right panel). Thick, continuous lines indicate the median, while thin, dashed lines indicate the 1st and 3rd quartiles. PD: Parkinson’s disease.

To the best of our knowledge, our study was the first to longitudinally assess the effect of dopamine agonists on divergent thinking. The results suggest that pre-treatment schizotypal personality traits and lifetime creative achievements might predict the development of divergent thinking in patients with Parkinson’s disease. Future studies should investigate to what extent are the observed associations due to variance in neural sensitivity to dopamine agonists (Woodward et al., 2011) or to differences in the ability of integrating unusual experiences and turning them into creative ideas (Nelson & Rawlings, 2010). It also remains to be clarified whether improved divergent thinking is associated with the emergence of novel creative activities and achievements in real life.

Related article:

Polner, B., Nagy, H., Takáts, A., & Kéri, S. (2015). Kiss of the muse for the chosen ones: de novo schizotypal traits and lifetime creative achievement are related to changes in divergent thinking during dopaminergic therapy in Parkinson’s disease. *Psychology of Aesthetics, Creativity and the Arts*, 9(3), 328–339. <http://doi.org/http://dx.doi.org/10.1037/a0039303>

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