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Salience learning: a common framework for schizophrenia, parkinsonian cognition, and normal variability in personality

Ph.D. Dissertation

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LIST OF ABBREVIATIONS

ANOVA: analysis of variance

Anx: anxious

BOLD: blood oxygen level dependent

CognDis: cognitive disorganization

CONT: controls

CPZ: chlorpromazine-equivalent dose

CS+: conditioned stimulus, relevant

CS-: conditioned stimulus, irrelevant

Cyclo: cyclothymic

D: dopamine

Depr: depressive

DSM: Diagnostic and Statistical Manual of Mental Disorders

fMRI: functional magnetic resonance imaging

GAF: Global Assessment of Functioning

Gen: general symptoms

HAM-A: Hamilton Anxiety Rating Scale

HAM-D: Hamilton Depression Rating Scale

Hyper: hyperthymic

IntAnh: introvertive anhedonia

ImpNon: impulsive nonconformity

Irrit: irritable

L-DOPA: L-3,4-dihydroxy-L-phenylalanine

Neg: negative symptoms

O-LIFE: Oxford-Liverpool Inventory of Feelings and Experiences

PANSS: Positive and Negative Syndrome Scale

PD: Parkinson's disease

Pos: positive symptoms

RM: reward magnitude

RT: reaction time

S: stimulus

SCR: skin conductance response

SCZ: schizophrenia

SD: standard deviation

TEMPS-A: Temperament Evaluation of Memphis, Pisa, Paris and San Diego – Autoquestionnaire

UnEx: unusual experiences

UPDRS: Unified Parkinson's Disease Scale

WAIS-R: Wechsler Adult Intelligence Scale, revised

YMRS: Young Mania Rating Scale

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1. INTRODUCTION

1.1. Reward/salience learning and the neurocognitive model of schizophrenia

Since the pioneering experiments and theoretical formulations of Watson, Skinner, and Pavlov, it has been widely acknowledged that human individuals acquire and form stimulus-response associations based on trial-to-trial feedback, which can be a reward or a punishment (Baum, 2005). There are multiple evidences from experimental psychology and computational modelling that reward/punishment learning can be defined depending on the availability or absence of internal cognitive models. When we talk about model-based strategies, there are goal-directed choices employing a model or cognitive-style representation, which means an internal model of stimuli and associated responses happened during a training phase (Daw et al., 2005). The internal model is useful in the prospective assessment of the consequences of actions, predictions of errors, and attentional control mechanisms to compensate behavioral dysfunctions. On the other hand, model-free strategies provide no consciously available internal representations about stimulus-response associations and their context in space and time. It is a simple cumulative experience about the utilities of outcomes based on previous stimulus-response associative learning during a longer period of time, which provides automatic rules for behavior encountered on past interactions with the environment. Model-free mechanism can generate all-or-none rules for behavioral schemes, propensities for performing specific actions, which are based on predictions deriving from long-run values of actions. Model-based mechanisms produce a higher level of cognitively flexible, goal-directed behavior, meanwhile model-free mechanisms produce automatic instrumental stimulus-response habits (Daw et al., 2005).

Both model-based and model-free mechanism play an important role in the neurocognitive mechanisms of schizophrenia. Although in the DSM-5 schizophrenia is still recognized and defined as a collection of sign and symptoms based on the work of Kraepelin (negative symptoms), Bleuler (loosened associations and disorganized thinking and speech), and Schneider (imperative hallucinations, delusion of control and other first-rank symptoms) (American Psychiatric Association, 2013). The National Institute of Mental Health put emphasis on cognitive mechanisms so as to better describe the neurobiological correlates and translational potential of the observable

clinical phenotype (Insel, 2014). In the Research Domain Criteria system, there is a separate subcategory for reward-related processes, called the Positive Valence Systems, which includes functions involved in positive motivational situations and contexts, such as stimulus seeking (exploratory behavior), consummation, and reward-habit learning (Hess et al., 2016). Beyond stimulus-response associations, the Positive Valence System describes approach motivation, reward and effort evaluation, action selection, expectancy of behavioral outcomes and prediction error, and finally a more sustained behavioral pattern based on long-run reinforcement learning and the formation of stimulus-response habits. By definition, habits are sequential, repetitive, motor, or cognitive phenomena (e.g., during problem solving and categorization), which are triggered by external of internal events, but when initiated, the whole sequence of behavior or cognition can be completed with a minimal level of conscious control. Habit formation is usually a consequence of reward learning, but later the expression of behavior/cognition can become resistant to changes in outcome values and environmental contingencies due to overtraining and behavioral fixation (Packard and Knowlton, 2002).

Reward learning has a special significance in the schizophrenia literature since the seminal publication of Shitij Kapur on salience syndrome. By reframing the classic dopamine hypothesis of schizophrenia, Kapur (2003) claimed that dopamine mediates the salience of environmental events (e.g., the basis of stimulus-response associations) and their internal representations (the cognitive models of associations). In this sense, salience is a consequence of inadequately provided or exaggerated reward during a natural learning process. In a disturbed phasic hyper-dopaminergic state, as it has been supposed in schizophrenia, there is an aberrant assignment of salience to the building blocks of the cognitive representations of the external world, and delusions, the fixed false beliefs of the patients, are nothing else but the patients' efforts to make sense of the aberrantly salient and enhanced experiences. When an internal representation of a sensory event or a memory trace gains an extreme salience, the patient will experience hallucinations, that is, sensory-like experiences in the absence of external stimuli (Kapur, 2003). The salience hypothesis also explains how antipsychotic medications work. These drugs reduce and dampen the salience of anomalous experiences simply by

inhibiting D_2 dopamine receptors with a special reference to the nucleus accumbens (ventral striatum), a main structure for reward and salience (Kapur and Mamo, 2003).

However, it is essential to understand that salience and reward are not the same. From an evolutionary point of view, everything is salient that will predict reward or help avoid aversive conditions (punishments). Functional neuroimaging evidence from humans suggests that salience predictions (awaiting reward and avoiding punishment) are related to the activation of the ventral striatum regardless of the value of the stimuli (Jensen et al., 2007). On the other hand, the orbitofrontal cortex and anterior insula coded the valence of appetitive-rewarding/aversive-punishing characteristics of stimuli (Jensen et al., 2007). Since the ventral striatum links the motor and cognitive system (basal ganglia and its frontostriatal circuits) and the limbic system, it is essential in the encoding of motivationally salient stimuli and its association with certain responses, and hence it may play a key role in the neurocognitive mechanisms of schizophrenia.

There is experimental evidence that the mechanisms described above are dysfunctional in schizophrenia. Jensen et al. (2008) measured blood oxygen level dependent (BOLD) responses in a functional magnetic resonance imaging (fMRI) paradigm when patients with schizophrenia and control subjects were presented with colored circles served as conditioned stimulus (CS+) with a loud noise served as the unconditioned stimulus. Importantly, there were neutral stimuli (CS-) when the circles were not linked to a salient loud noise. As expected according to the model of Kapur (2003), patients with schizophrenia showed large BOLD activations in the ventral striatum even to CS- stimuli, as compared to the healthy controls. In accordance with this neural evidence of aberrant salience attribution and learning, patients consciously attributed a high significance to CS- stimuli, and their skin galvanic responses, a marker of implicit autonomous nervous system activation for salient events, were also exaggerated. Altogether, these results suggest that patients with schizophrenia aberrantly assign motivational salience to otherwise neutral stimuli, and this abnormal salience attribution can be tracked at the level of subjective reports and learning, skin galvanic responses, and neural activation in the ventral striatum (Jensen et al., 2008).

It is especially interesting to note what happens when drug-naïve patients with schizophrenia anticipate reward in an experimental game where they can win or lose money. Surprisingly, during reward anticipation patients had a marked decrease in

neuronal activation in an extended network of salience attribution, including the mesencephalic dopaminergic center (ventral tegmentum), ventral striatum, and anterior cingulate cortex. BOLD signal attenuation in ventral striatum was correlated with the degree of hallucinations and delusions (Nielsen et al., 2012). Therefore, there is a double-mechanisms in non-medicated patients: an enhanced response to non-salient events, and a dampened response to salient events, both are related to the positive symptoms of schizophrenia.

If we take into consideration the significance of the findings discussed above, it is not surprising that several studies have attempted to investigate this type of feedback-driven reinforcement and reward learning in schizophrenia. However, at the behavioral level the results are heterogeneous and non-conclusive with some unexpected features. Patients with schizophrenia show very similar subjective experiences to that of the healthy controls when positive emotions are elicited, but this subjective experience is not in accordance with behavioral action selection patterns: subjectively desirable responses are omitted, and less desirable ones are performed (Gold et al., 2008). It seems that the patients are not able to adequately represent the value of different choices, which is especially apparent in rapid learning on the basis of trial-to-trial feedback. Extended and gradual learning, which can be considered as a model-free function, is more preserved, although there are some exceptions discussed below (Gold et al., 2008). At the neuronal level, the orbital and dorsal prefrontal structures may be the most compromised, which are important in the flexible integration and rapid modulation of the value of outcomes and plans (model-based learning). In contrast, the slow, model-free learning by the integration of reward signals during a long period of training are less disrupted in the basal ganglia (Strauss et al., 2014).

Despite these extensive investigations, the predictors of reward learning functions in schizophrenia are still unclear. In outpatients with schizophrenia, our research group previously found intact feedback-driven reward learning (Kéri et al., 2000), while in patients with primary negative symptoms, such as apathy, anhedonia, and blunted affect, we observed significant impairments well beyond the general cognitive status and loss of motivation (Farkas et al., 2008; Polgár et al., 2008). Polgár et al. (2008) developed an entertaining computer game in which the player should navigate a cartoon character (“Kilroy”) through four rooms by learning to choose the

open door from three colored doors. The aim of the game was to learn the open doors in each room and to navigate the character to a nice garden. Despite the fact that even less motivated and cognitively impaired individuals can learn the task easily, schizophrenia patients with prominent negative symptoms (the so-called deficit type) showed sever impairments. Replicating and extending our results, Weiler et al. (2009) demonstrated a reward learning deficit in patients with schizophrenia with negative symptoms. Importantly, Weiler et al. (2009) also showed that reward learning impairment cannot be explained by low IQ and working memory deficits, which are commonly observed in schizophrenia.

Waltz et al. (2007) proposed a hypothesis that reinforcement learning is disrupted in schizophrenia only when reward is provided, whereas patients can learn for punishment signals. In a study integrating clinical, cognitive, and computational approaches, it was revealed that schizophrenia patients with severe negative symptom demonstrated impaired learning from rewards but intact acquisition of loss-avoidance learning, and they were unable to distinguish rewarding stimuli from loss-avoiding (lack of punishment) stimuli. Computational models indicated that patients with severe negative symptoms attempted to mechanically learn stimulus-response associations, whereas patients with low negative symptoms and controls based their decision of the expected value of their actions (Gold et al., 2012). These findings are in accordance with neuroimaging results revealing abnormal activation and dopamine receptor binding in the mesencephalon, ventral/dorsal striatum, anterior cingulate cortex, and dorsolateral prefrontal cortex (Deserno et al., 2016).

The potential effect of D_2 inhibiting antipsychotics must also be taken into consideration. Beninger et al. (2003) and Kéri et al. (2005) reported that patients receiving first-generation antipsychotics, which exert a potent inhibition on D_2 receptors, show disrupted reward learning, which is not the case for patients receiving second-generation drugs with lower D_2 affinity or fast-off receptor binding mechanism. Harris et al. (2009) found spared basal ganglia-dependent procedural learning in drug-naïve patients with schizophrenia, which was disrupted when antipsychotic treatment was initiated. Regarding medications, clozapine may be special providing a more optimal treatment for negative symptoms. In a Pavlovian learning paradigm, it has recently been shown that clozapine is able to ameliorate reward processing impairment,

probably by the enhancement of the connectivity between the striatum and prefrontal cortex (Albrecht et al., 2016).

One of the most important and reproducible results in the cognitive literature of schizophrenia is that general functioning is a robust predictor of cognitive performance such as attention, executive functions, and declarative memory (Green et al., 2004; Keefe, 2007). In other words, the schizophrenia patients' ability to meet everyday demands including self-care, social rhythm and contacts, internalization and application of norms and rules, and working capacity are more consistently related to the cognitive functions than that we can see in the case of specific symptoms of the illness. Despite this observation, it has not been explored how reward learning is related to general functioning. Our first aim in this work was to fill this surprising gap in the literature by assessing the correlation between reward/reinforcement learning and everyday psychosocial functioning in chronic schizophrenia patients.

1.2. Reward/salience learning and Parkinson's disease

Mathias Pessiglione and his colleagues (2006) were the first to demonstrate the neuronal and cognitive bases of the common clinical observation of reciprocity between schizophrenia and Parkinson's disease (PD): antipsychotic medications potently inhibiting dopamine D2 receptors result in parkinsonian symptoms (e.g., bradykinesia, cogwheel rigidity, and resting tremor), whereas dopamine substitution in PD is associated with psychosis-like symptoms in some patients (e.g., hallucinations and delusions). The researchers administered the dopamine progenitor L-DOPA (3,4-dihydroxy-L-phenylalanine) or the potent D_2 antagonist haloperidol to healthy individuals before a reward learning task. At the behavioral level, subjects receiving L-DOPA tended to choose the most rewarding action (gaining money in an experimental game) relative to subjects treated with haloperidol. At the neuronal level, these behavioral phenomena were associated with the magnitude of the BOLD response in the striatum (left posterior putamen and ventral striatum). At the computational level, when applying an in silico learning algorithm, the reward prediction error measured in the brain accurately reproduced the behavioral decision of the participants under L-DOPA and haloperidol conditions (Pessiglione et al., 2006).

There are many studies clearly indicating that different aspects of reward learning are specifically impaired in PD (Knowlton et al., 1996; Swainson et al., 2000; Czerenczki et al., 2002; Frank et al., 2004; Cools et al., 2006; Nagy et al., 2007; Rowe et al., 2008; Bódi et al., 2009). In a seminal study, Knowlton et al. (1996) used the Weather Prediction Task in which four cards are presented to the participant and he/she is asked to try to figure out whether the cards predicted rainy or shiny weather. Each correct answer is rewarded, and during a large number of trials, subjects gradually learn to make correct predictions based on the numerous combinations of cards that are difficult to consciously memorize. Knowlton et al. (1996) found that amnesic patients were able to learn the weather prediction task, whereas PD patients failed to do so. Since the deficit was independent on higher-level prefrontal functions, Knowlton et al. (1996) postulated that such slow learning guided by cumulative reward signals is mediated by the human striatal habit learning system impaired in PD. This interpretation received an excessive criticism (e.g., Kemény and Lukács, 2013), but the Weather Prediction Task is still the prototype of reward leaning paradigms.

In an advanced paradigm, Frank et al. (2004) used Chinese characters to build a category learning task in which different combinations of the characters should be classified into distinct groups. Each decision is followed by positive or negative feedback (reward or punishment, gaining or losing points and credits). PD patients who did not receive dopaminergic medications before the test were better at avoiding category decisions that lead to the loss of points than at gaining rewards. When the test was repeated after L-DOPA intake, patients became more sensitive to reward. Frank et al. (2004) also created a computational model to explain their results in which the mesencephalic dopaminergic center, the striatum, and the premotor cortex were represented as distinct nodes with multiple layers. In this system, “Go” signals were linked to increased dopaminergic tone and reward (direct pathway in the corticostriatal system regulated by D_1 receptors), whereas “No-Go” signals referred to decreased dopaminergic tone and punishment (indirect pathway, D_2 receptors). The model performed similarly to PD patients on and off dopaminergic replacement therapy (Frank et al., 2004).

As expected after the consideration of behavioral and neuropsychological data, there is a differential response at the neuronal level in PD and controls in reward

learning tasks, namely, controls tend to activate frontal, cingulate, and striatal areas, whereas in PD activation is shifted towards a compensatory network including the cerebellum (Künig et al., 2000; Goerendt et al., 2004). By using (123)I-FP-CIT Single Photon Emission Computed Tomography, Aarts et al. (2012) showed that dopaminergic neuronal loss was associated cognitive inflexibility and aberrant reward processing in PD. Interestingly, PD patients were not able to maintain a task goal when a high reward was provided, suggesting paradoxical reward-related impulsivity. Moreover, L-DOPA may have a negative impact on reward processing by enhancing cognitive flexibility (task switching) and disrupting ventral striatal reward prediction, possibly by local overdosing in this brain region (Aarts et al., 2014).

It is essential to make a distinction among higher cognitive functions (e.g., attentional modulation, problem solving, task switching), elementary reward processing (e.g., monetary rewards in a gambling-like task), and motors functions, which are differentially affected in PD and by dopaminergic medications (Rowe et al, 2008). Neuroimaging evidence suggests a non-linear U-shape relationship between lateral prefrontal – caudate activation and the severity of motor symptoms, which is modified by dopaminergic medications. On the other hand, anterior cingulate activation during reward expectation declined with more severe disease. Surprisingly, when brain activation associated with the current reward was measured, there was a positive relationship between disease severity and activation, which may refer to a shift from goal-directed to actions guided by immediate actual rewards (Rowe et al., 2008). There is a widely cited model in which the L-DOPA or dopamine agonist dose sufficient to restore motor symptoms disrupts reward processing in the ventral striatum by "overdosing" dopamine (Gotham et al., 1988; Cools et al., 2001; Shohamy et al., 2006; Jahanshahi et al., 2010; MacDonald et al., 2011; Aarts et al., 2014).

Shohamy et al. (2006) showed how L-DOPA can disrupt discrimination learning while sparing generalization to novel features. Participants were presented with two objects differing in shape or color, and the task was to were predict which of two objects was associated with reward (gaining points). Each pair of objects differed in either color or shape, so that there was one relevant and one irrelevant dimension (i.e., the color dimension was important to learn which object is rewarded but the shape dimension was not). In the generalization/transfer phase, the pairs of objects continued

to differ according to previously relevant dimension (i.e., color remained the dimension that should have been used to choose the rewarded object), but the irrelevant dimension changed (i.e., new shapes appeared). Therefore, the subject should transfer previous knowledge (i.e., color signs reward) to new shapes. Results indicated that L-DOPA administration was associated with impaired reward learning, but the medicated PD patients showed intact generalization/transfer to novel shapes (Shohamy et al., 2006). In other words, feedback-based learning was specifically disrupted by dopamine "overdose" in ventral striatum, whereas more abstract features of the task (transfer/generalization) were intact.

These findings may have a clinical relevance in the interpretation of non-motor symptoms of PD. As early as 1984, Fibiger postulated that the mesolimbic-mesocortical dopaminergic projections known in animals may be important in humans, too. Reduced ability to experience pleasure after a rewarding event is a key feature of depression, and due to the degeneration of the mesolimbic and mesocortical dopamine projections in PD there may be an increased vulnerability to depression. Bódi et al. (2009) showed that in newly diagnosed, drug-naïve PD patients without clinical depression there is a reduced novelty seeking personality style, which is linked to less effective reward learning. This pattern is reversed and even over-stimulated by dopamine agonists. Now it is known that not only depression, but impulse control disorders (gambling, substance misuse, compulsive sexual behavior, compulsive buying, binge-eating, and hoarding) are frequently diagnosed in PD in association with depression, anxiety, obsessive thinking, novelty seeking, and worse higher-level cognition (Voon et al., 2009; Weintraub and Nirenberg, 2013; Napier et al., 2015). Impulse controls disorder often co-occurs with dyskinesias after a prolonged dopaminergic treatment, called the dopamine dysregulation syndrome. According to the synthesis of neuroimaging data, there is an enhanced dopamine release in the ventral striatum following incentive cues indicating immediate and large rewards, whereas top-down inhibition from the orbitofrontal cortex is diminished leading to poor risk evaluation and response inhibition (Voon et al., 2009; Weintraub and Nirenberg, 2013; Napier et al., 2015).

Much less is known about psychosis in PD. The overall prevalence is 20-60%, which is higher in elderly patients, comorbid depression, and higher antiparkinsonian medication doses (Weintraub et al., 2007; Forsaa et al., 2010). In early stages of PD, the

one-year prevalence is 3% rising to 7.7% one year later (Morgante et al., 2012). There is some evidence that visual hallucinations, rapid eye movement sleep behavioral disorder, and cognitive dysfunctions share common mechanisms. From a structural point of view, atrophy in the hippocampus and parahippocampal regions are typical, and cholinergic abnormalities may mediate all symptoms clusters (Lenka et al., 2016). However, it is plausible to hypothesize that dopaminergic "overdose" in the ventral striatum may be important in PD psychosis with a similar salience attribution mechanism as described in schizophrenia (Maia and Frank, 2011).

As discussed above, conditioned stimuli associated with reward (CS+) evoke phasic dopamine response in the striatum (Schultz, 2007). CS+ stimuli also elicit faster responses, which is linked to dopamine in the ventral striatum (Wyvell and Berridge, 2000). This phenomenon is incentive salience, when a neutral stimulus (CS-) becomes associated with a motivational value (Berridge, 2007). King et al. (1984) was the first to raise the idea that abnormal dopaminergic signals can cause chaotic stimulus-reward associations, which may then lead to psychotic experiences and behavior in PD patients receiving dopaminergic drugs. This is very similar to the hypothesis of aberrant saliance attribution in schizophrenia (Miller, 1993; Kapur, 2003; Roiser et al., 2009). Housden et al. (2010) reported that medicated PD patients are not only characterized by an impulsive preference for immediate reward, but these patients also exhibit psychosis-like experiences at a clinically subthreshold level. Although these symptoms are not frank hallucinations, delusions, and disorganization, their clinical significance must be taken into consideration. For example, many patients on dopaminergic medications report enhanced unusual experiences (illusions, perceptual distortions, unusual impression and intuitions, magical ideations), mild dysfunctions in thinking (loosened associations and poor concentration), loss of social interest and blunted affect, or, contrary, impulsive non-conformity (eccentric, aggressive, and asocial impulses) (Housden et al., 2010).

One problem with the classic reward learning tasks, as described at the Knowlton et al. (1996) and Frank et al. (2004) studies, is that these procedures are less dominantly investigate automatic conditioning processes and require the cooperation of higher-level decision making processes. When testing salience learning mechanisms, researchers need a Pavlovian rather than a Skinnerian learning framework in which the

response requirements of the subjects are minimal, for example, by limiting the task to an over-trained pressing of a single button. Attentional control for the outcome of the task can be minimized by a speeded reaction time task in which the participant focuses on the speed of the response (to press the button as fast as possible) instead of the outcome (i.e., whether the decision was correct or not).

If we take into consideration the task demands, implicit and explicit salience can be distinguished, both with adaptive or aberrant features (Roiser et al., 2009). Implicit and explicit salience parameters are measured by reaction time and consciously decided visual-analogue scales, respectively. Implicit adaptive salience can be defined as the difference between the reaction time when the probability of the reward is low and when it is high. Larger differences in reaction time indicate faster responses on trials with high reward probability, which refers to implicit adaptive salience. Explicit adaptive salience is measured by increases in rating on the visual-analogue scale for high reward trials relative to low reward ones. In other words, subjects are not only faster for rewarded stimuli, but they consciously feel that the stimulus is more salient (relevant and important for behavioral purposes) (Roiser et al., 2009).

Implicit and explicit aberrant salience is determined in a similar way, but in this case reaction time and visual-analogue scale scores are measured for the task-irrelevant stimulus dimension which is not rewarded. For example, color signs reward and hence it is used for the assessment of adaptive salience, and shape is not rewarded and hence it is used to measure aberrant salience. In the case of a perfectly rational learner, aberrant salience is zero because there is no reason to respond faster to a certain shape or value a certain shape as more important and relevant because shape is not associated with reward. However, people are not perfectly rational learners and they attribute some salience even to non-relevant stimulus dimensions. An extreme level of such abnormal or aberrant salience attribution can be a marker of psychotic disintegration (Kapur, 2003). Aberrant salience attribution will lead to dysfunctional predictions about reality. During such predictive coding the brain performs Bayesian inference about the external world by combining sensory data, conditioned associations, and higher-order beliefs. This inferential hierarchy is disrupted in psychosis biasing inference towards sensory data and irrelevant conditionings and away from cognitive beliefs (Adams et al., 2016).

Our second question therefore refers to the effect of dopaminergic medications in PD. We will explore how these medications may affect adaptive and aberrant salience, and how these changes are related to subclinical psychosis-like experiences. If the abnormal salience attribution of schizophrenia (Kapur, 2003) can be generalized to other disorders, we will obtain enhanced aberrant salience in medicated PD patients, which will show a positive correlation with psychosis-like experiences.

1.3. Reward/salience learning and normal variation in personality

The traditional views of psychosis, based on the approach of Kraepelin, states that there is a clear boundary between psychotic states characterized by the disruption of reality testing and normal mental functioning. This approach is different from that of Bleuler who proposed a continuity between psychosis as an extreme form of unusual perception and thinking and less definitive variations present in non-clinical individuals (Boyle, 1990). According to Meehl (1962) in some persons we can see a collection of enduring personality traits, called schizotypy, which is a consequence of dysfunctions of integrative neuronal processes (schizotaxia). In Meehl's approach this condition is genetically determined and it is a risk factor of real schizophrenia. In contrast, Eysenck's psychoticism concept is less dominantly categorical and pathological: psychosis-like features such as odd behavior, unusual experiences, magical ideation, and suspiciousness is very similar to other personality traits and shows a continuum in the population without any strict categorical boundary between normal and abnormal. The roots of psychoticism are less genetically determined, and environmental factors and psychosocial development also play a significant role (Eysenck and Eysenck, 1976).

There are many models of schizotypal personality structure. Based on the concepts of Crow (1980) to schizophrenia dimensions, initially schizotypal traits were also divided into a positive and negative cluster (Kendler and Hewitt, 1992), and later a third disorganized factor was included in the models (Raine et al., 1994). Others suggested that paranoid ideas and social dysfunctions are separate dimensions of schizotypy (Venables and Rector, 2000). In the Fogelson et al. (1999) five-factor model paranoid, positive, schizoid, avoidant, and disorganized dimensions are differentiated. Finally, Stefanis et al. (2004) proposed a four-factor model with conceptual/perceptual,

negative, disorganized, and paranoid factors. The conceptual/perceptual factor contains unusual perceptual experiences and magical ideation; the paranoid factor is associated with ideas of reference social anxiety, and suspiciousness; the negative factor is related to suspiciousness, social anxiety, lack of close friends, and constricted affect; the disorganized factor contains odd speech and behavior (Stefanis et al., 2004).

There is evidence that many schizotypal traits are quite common in the general population and show a normal or half-normal distribution (Johns et al., 2001). Moreover, 5-8% of the non-clinical population experience transient psychotic symptoms, which is a much higher proportion as previously thought (van Os et al., 2009). Schizotypal traits correlate with measures used to describe "normal" personality, which indicates a high degree of overlap. For example, unusual experiences in the positive/conceptual/perceptual factor of schizotypy correlates with openness to experiences from the Big Five personality measure and self-transcendence (openness to spirituality) from the Temperament and Character Inventory of Cloninger (Laidlaw et al., 2005; Asai et al., 2011). In this framework, low cooperativeness and self-directedness together with high self-transcendence represents a less advantageous schizotypal combination with withdrawal from reality and poor social adaptation. However, if high self-transcendence is associated with higher cooperativeness and self-directedness, a more advantageous face of schizotypy can be observed (Smith et al., 2008).

By integrating results from the literature and investigating a large number of people from the general population, Gordon Claridge and his colleagues defined and operationalized common forms and dimensions of subclinical schizotypal/psychosis-like experiences, which are considered as normal variations by most of the scholars today (Mason et al., 1995; Mason and Claridge, 2006). The first dimension of unusual experiences, also included in many other classifications, refer to sensory illusions and distortions, sometimes overt visions and voice-hearing, as well as magical and superstitious beliefs that are all parts of human spirituality. Cognitive disorganization describes the form of thinking, including derailed, circumstantial, and tangential trains of thought, less focused concentration, and lapses in memory. Introverted anhedonia is subclinical variation of the negative symptoms of schizophrenia, including introversion, low social interest and pleasure, and less colorful affective reactions. Finally, impulsive

non-conformity is a collection of traits of unstable mood and difficulties in the regulation of impulses to meet social rules and conventions (Mason et al., 1995; Mason and Claridge, 2006).

Not only the phenomenology of schizophrenia served as a framework for the description of personality trait, but similar models were created by using the symptoms of mood disorders (major depressive disorder and bipolar disorder), which are strictly separated from schizophrenia in the traditional diagnostic approach. According to this approach, we can distinguish depressive, anxious, hyperthymic, cyclothymic, and irritable dimensions (Akiskal et al., 2005; Rózsa et al., 2008).

Despite the fact that schizotypal traits show a considerable level of overlap with schizophrenia in terms of phenomenology and neurobiology, no studies have been done to investigate the relationship between schizotypal traits and salience learning. It is of particular relevance how different dimensions of schizotypy are related to salience learning and whether there is a clear separation between schizotypy and temperament features based on the structure of mood disorder. Although salience learning and reward prediction disturbances may seem to be specific for the schizophrenia-spectrum, this is probably not the case. Using a reward learning task, Gradin et al. (2011) contrasted reward prediction errors in depression and schizophrenia. In depression, they found reduced prediction errors in the striatum and midbrain, which correlated with the severity of depressive anhedonia. In schizophrenia, the authors observed a more widespread decrease of prediction error signals, including the caudate nucleus, thalamus, insula and amygdala-hippocampal complex in correlation with the psychotic symptoms (Gradin et al., 2011). These results indicate that the different magnitude and localization of reward prediction signals, a key marker for salience learning, may be associated with both mood alterations and impairments in reality testing. Therefore, if we want to elucidate the relationship between schizophrenia-related personality traits and salience learning, we must take into consideration that similar mechanisms could be included in mood disorder-related traits. In addition to schizotypal traits, as defined Mason et al. (1995), we assessed cyclothymic, hyperthymic, depressive, and irritable personality traits to compare these with results from a classic conditioning paradigm based on the measurement of skin conductance responses.

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2. AIMS

In this thesis, we wanted to answer three main questions:

1. We assessed instrumental learning in patients with schizophrenia by using a computerized categorization game in which stimulus-response associations were acquired via reward and punishment (gaining and losing points for correct and incorrect decisions, respectively). We asked whether clinical symptoms or general psychosocial functions are the better predictors of learning performance. Our hypothesis was that beyond the clinical symptoms general functioning is a significant predictor of learning performance.

2. We assessed implicit/explicit adaptive and aberrant salience in PD before and after the initiation of medications, with a special reference to dopamine receptor agonists. Subclinical psychosis-like symptoms were also scaled. We hypothesized that after dopaminergic medications there are increased psychosis-like experiences and that these experiences are associated with higher aberrant, but not adaptive, salience.

3. We used an aversive Pavlovian conditioning with relevant (conditioned) and irrelevant (non-conditioned) stimuli in healthy individuals, together with the administration of personality questionnaires for schizotypal and affective temperament traits. We predicted that skin conductance responses to irrelevant stimuli would be associated with schizotypal traits connected to reality distortion, whereas blunted responses would be associated with decreased affective reactivity, a common feature of negative schizotypy and depressive anhedonia.

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3. METHODS

3.1. Participants

3.1.1. Patients with schizophrenia

Forty patients with schizophrenia and 30 matched healthy volunteers were enrolled at the Semmelweis University, Department of Psychiatry and Psychotherapy, Budapest (2007-2009) after obtaining a permission from the institutional ethics board. The study was conducted in accordance with the Declaration of Helsinki, and all participants gave written informed consent. The patients were clinically stable and received psychosocial rehabilitation. The control volunteers were employees of the hospital and their acquaintances and friends.

In addition to the full clinical record of the patients, we used the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998) to verify the DSM-IV criteria of schizophrenia (American Psychiatric Association, 1994). Individuals with psychoactive substance misuse or organic brain disorders were excluded from the study. General psychosocial functioning was assessed with the Global Assessment of Functioning (GAF) scale (American Psychiatric Association, 1994). The GAF is a 1-100 scale to characterize the social, occupational, and general psychological adaptive functions. Scores above 90 sign no symptoms and superior functioning. Scores of 51-60 indicate moderate symptoms or moderate difficulty in social and occupational functions (e.g., social isolation, recurrent conflicts with family members and co-workers). Scores below 20 indicates dangerous behavior (e.g., suicide attempts and violent actions), failure to maintain personal hygiene, and grossly disorganized speech and behavior. In addition to GAF, the Positive and Negative Syndrome Scale (PANSS) was used for the assessment of schizophrenia symptoms (Kay et al., 1987).

The chlorpromazine-equivalent antipsychotic dose was 363.4 mg/day (SD = 232.4) (Woods, 2003) (only six patients received first-generation drugs).

The description of the participants is presented in Table 1.

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Table 1. Demographic and clinical characteristics of the schizophrenia patients and controls

	Schizophrenia (n=40)	Controls (n=30)
Male/female	17/23	10/20
Age (years)	36.6 (10.0)	37.0 (9.6)
Education (years)	12.4 (2.4)	12.6 (2.7)
Duration of illness (years)	8.0 (6.6)	-
Number of episodes	5.6 (4.3)	-
GAF	54.7 (17.1)	-
PANSS-positive	12.0 (4.6)	-
PANSS-negative	15.6 (6.8)	-
PANSS-general	27.3 (8.2)	-

Notes: Shown are the mean values (standard deviation). PANSS – Positive and Negative Syndrome Scale, GAF – Global Assessment of Functioning

3.1.2. Patients with Parkinson's disease

We recruited 20 newly diagnosed, never-medicated patients with PD and the same number of healthy controls at the Semmelweis University, Department of Neurology, Budapest (2007-2011) after obtaining a permission from the institutional ethics board. The study was conducted according to the Declaration of Helsinki, and all participants gave written informed consent. The patients met the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria (Hughes et al., 1992).

The following scales were used for the assessment: Hoehn-Yahr Scale (Hoehn and Yahr, 1967), Unified Parkinson's Disease Scale (UPDRS) (Lang and Fahn, 1989), Hamilton Depression Rating Scale (HAM-D), Hamilton Anxiety Rating Scale (HAM-A) (Mountjoy and Roth, 1982), Young Mania Rating Scale (YMRS), Hollingshead Four-Factor Index for socioeconomic status (Cirino et al., 2002), and the Wechsler Adult Intelligence Scale (WAIS-R) (Wechsler, 1981).

We administered the Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE) questionnaire was used to assess subclinical psychosis-like experiences (Mason et al., 1995). The test consists of 159 items: Unusual Experiences (perceptual aberrations, magical thinking, trasnient hallucinations), Introvertive Anhedonia (decreased motivation and enjoyment for social and physical sources of pleasure), Cognitive Disorganization (loosened associations, impaired concentration), and Impulsive Nonconformity (eccentric, aggressive, and asocial features).

There were two assessment sessions. The first was at the baseline, non-medicated state, and the second one was 12 weeks later during which PD patients received dopamine agonists (pramipexole: n=12, mean dose at follow-up: 4.0 mg/day, 2.0-6.0 mg/day; ropinirole: n=8, mean dose at follow-up: 8.5 mg/day, 4.0-11.5 mg/day). The patients rated their overall subjective state using a -10 - to - +10 Likert-type scale (-10: feeling very bad relative to the non-medicated state; +10 feeling very good relative to the non-medicated state; 0 – no changes after medication).

The clinical and demographic data are shown in Tables 2 and 3.

Table 2. Characteristics of the Parkinson's patients and controls

	Parkinson's	Controls
Number of participants (male/female)	20 (14/6)	20 (14/6)
Age (years)	45.8 (6.0)	46.3 (7.9)
Education (years)	14.3 (7.0)	14.2 (6.3)
Time since onset of first symptoms (months)	20.3 (9.6)	-
Full-scale IQ (WAIS-R)	107.4 (12.9)	109.6 (10.5)
Socioeconomic status (Hollingshead)	38.5 (16.9)	37.9 (15.2)
No. of patients in Hoehn-Yahr Stage	1.0: 3 1.5: 2 2: 14 2.5: 1	-

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Table 3. Changes in clinical symptoms during the follow-up period in Parkinson's disease and controls

	Parkinson' (n=20)	Controls (n=20)
UPDRS total		
Baseline	34.4 (9.8)	-
Follow-up	26.7 (8.8)[a]	-
UPDRS III (motor)		
Baseline	25.5 (6.4)	-
Follow-up	20.5 (7.5)[b]	-
HAM-D		
Baseline	3.9 (2.2)	3.7 (3.3)
Follow-up	3.8 (2.3)	3.7 (2.9)
HAM-A		
Baseline	3.4 (1.9)	3.0 (2.5)
Follow-up	3.4 (2.0)	3.1 (2.7)
YMRS		
Baseline	1.0 (0-4)	1.0 (0-2)
Follow-up	2.5 (0-8)[c]	1.0 (0-2)
O-LIFE		
Unusual Experiences		
Baseline	8.5 (3.0)	9.0 (3.5)
Follow-up	11.6 (3.3)[d]	8.9 (3.3)
Cognitive Disorganization		
Baseline	8.9 (4.2)	9.1 (4.0)
Follow-up	8.6 (4.2)	9.1 (4.1)
Introvertive Anhedonia		
Baseline	4.8 (3.7)	4.7 (2.6)
Follow-up	4.0 (3.3)	4.9 (2.8)
Impulsive Nonconformity		
Baseline	6.9 (4.5)	7.6 (4.4)
Follow-up	7.1 (4.6)	7.1 (4.6)

Notes: Data are mean (standard deviation) with the exception of YMRS where median and range are shown. HAM-A – Hamilton Anxiety Scale; HAM-D – Hamilton Depression Scale; O-LIFE - Oxford-Liverpool Inventory of Feelings and Experiences; UPDRS – Unified Parkinson's Disease Rating Scale; PD – Parkinson's disease; WAIS-R - Wechsler Adult Intelligence Scale, revised; YMRS – Young Mania Rating Scale; [a-d] $p < 0.05$, baseline vs. follow-up

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3.1.3. Healthy volunteers in the personality assessment

One hundred healthy individuals (42 male, 58 female) with negative family and personal history of mental disorders were recruited via student and community networks at the University of Szeged (2011). The study was approved by the institutional ethics board, and written informed consent was obtained from each participant.

In addition to the O-LIFE, we administered the Temperament Evaluation of Memphis, Pisa, Paris and San Diego - Autoquestionnaire (TEMPS-A), which is a 110 item tool with five subscales: Depressive (e.g., low self esteem, pessimistic, sensitivity) Cyclothymic (e.g., variability, cyclicity, intensity), Hyperthymic (e.g., fun loving, risk taking, high self esteem), Irritable (e.g., restlessness, critical attitude, aggression), and Anxious (e.g., worrying about kin, fear prone, inability to relax) (Rózsa et al., 2008).

Participants also received a standard IQ test (Wechsler, 1981). Demographic characteristics and scale scores are shown in Table 4.

Table 4. Characteristics of the participants from the skin conductance response experiment (N=100)

	Mean	Standard Deviation	Range
Age (years)	36.8	13.9	18-70
Education (years)	12.1	2.6	8-18
IQ	102.5	11.1	90-140
		O-LIFE	
Unusual Experiences	8.5	4.1	3-18
Introvertive Anhedonia	6.2	3.1	6-11
Cognitive Disorganization	10.0	6.3	5-17
Impulsive Nonconformity	7.8	3.8	4-12
		TEMPS-A	
Cyclothymic	7.1	3.5	4-15
Hyperthymic	10.9	4.8	1-20
Depressive	6.5	3.2	2-15
Irritable	5.7	3.0	0-13
Anxious	6.4	3.1	0-14

Notes: O-LIFE - Oxford-Liverpool Inventory of Feelings and Experiences; TEMPS-A - Temperament Evaluation of Memphis, Pisa, Paris and San Diego - Autoquestionnaire

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3.2. Experimental procedure

3.2.1. Reward/punishment learning in schizophrenia patients

The experimental task was programmed under SuperCard (Allegiant Technologies, San Diego, CA) on a MacBook. During the task, participants viewed one of four images (S1-S4) (Figure 1). When an image was presented, the participant was asked to guess whether it belonged to category A (S1 and S3 with 80% probability) or category B (S2 and S4 with 80% probability) by pressing one of two buttons.

At the beginning of the test, choices were trial-by-error types. When S1 and S2 were correctly categorized, a reward of +25 points was delivered, but if the participant guessed incorrectly, no feedback was provided. Therefore, no punishment was linked to S1 and S2. Stimuli S3 and S4 were used in a similar way, but in this case incorrect category-decisions were followed by a loss of 25 points, and no feedback appeared for correct decisions.

The task included a total of 160 trials (four blocks of 40 trials). Each block contained reward and punishment trials in a pseudo-randomized order. Each stimulus appeared 10 times/block, eight times with the high probability outcome and two times with the low probability outcome. The dependent measure was the proportion of correct category decisions.

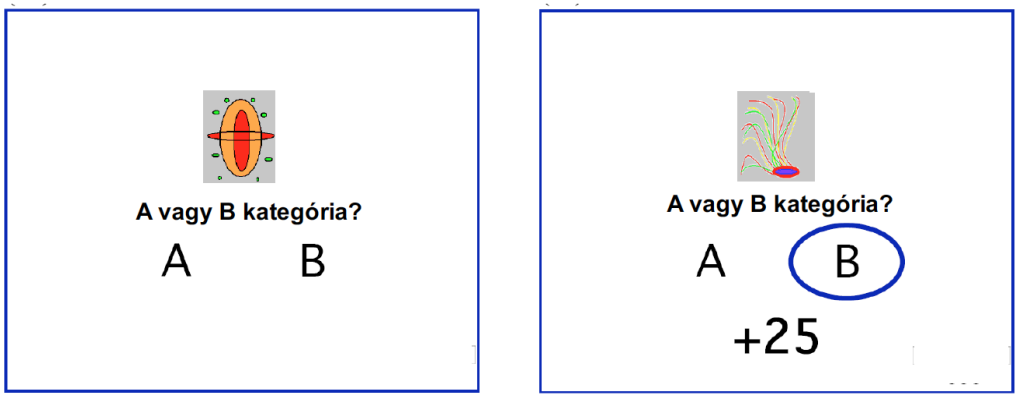

Figure 1. Illustration of an experimental trial.
A correct decision of "category B" resulted in 25 points gain (Somlai et al., 2011).

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3.2.2. Salience learning in Parkinson's disease: a classical conditioning paradigm

We used a VPC221 workstation (ViewSonic, Walnut, CA) for stimulus generation, presentation, and response collection. The task was to press a button as quickly as possible when a probe stimulus (black square) appeared on the screen. The probe stimulus was predicted by conditioned stimuli (colored shapes) predicting the probability of reward (gaining money) after the motor response. The sequence of screen events was as follows: (1) a fixation cross for 1 sec, (2) conditioned stimuli until the end of the trial, (3) an interval of 0.5-1.5 sec, (4) the probe stimulus (Figure 2).

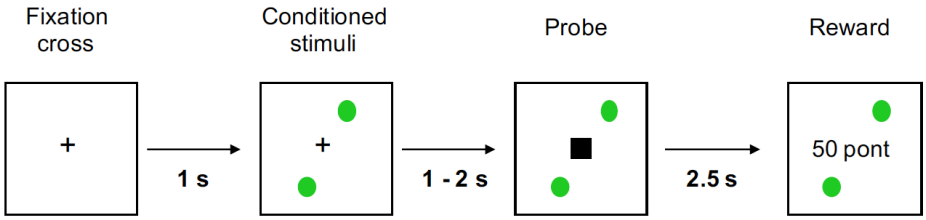

Figure 2. The sequence of the events during the salience learning task (Nagy et al., 2012)

The duration of the probe stimulus was determined for each participant in a separate training session during which conditioned stimuli were not presented and reward was not delivered (a simple reaction time task). First, the probe was presented with variable durations (0.5 - 1.5 sec, mean: 1 s). Feedback was given after 2 sec indicating whether the response was too slow or too early. Next, probe stimulus duration was adjusted according to the reaction time of the participant. We calculated the standard deviation (SD) of the reaction time from the faster 50% of trials, and the mean probe stimulus duration was set at the mean duration of the reaction time. The maximum and minimum values were from the mean reaction time +/- 2SD.

The test consisted of 100 trials. Reward (winning points) followed each second trial. Reward probability was signaled by the conditioned stimuli, which has different shapes and colors (green or red and circle or triangle). To separate adaptive and aberrant conditioning, only shape or color was relevant. For example, green predicted reward on 40/50 trials (80%) (green circle and green triangle), whereas the other color signed

reward on 10/50 trials (20%) (red circle and red triangle). Shape was irrelevant: circles and triangles predicted reward with an equal probability.

Reward was presented in points in a 5 - 100 range (Pence exchanged to Hungarian Forints) depending on the latency of the response. Premature or late responses won 5 points. Otherwise reward depended on the speed of the response:

$$RM = 10 + 90 \times (RT[training] - RT[trial]) / 3 \times SD$$

RM – reward magnitude
RT[training] – mean reaction time from the second training session
RT[trial] – actual reaction time from the main test
SD - standard deviation of the mean reaction time from the faster half of the trials in the second training session

At the end of the test, participants reported how they experienced the probability of reward for each stimulus by clicking on a 10 cm visual-analog scale. In addition to reaction time, this subjective rating was used to describe adaptive and aberrant salience developed during the conditioning:

1. Implicit adaptive salience: the difference between the reaction time on trials with low reward probability and that on trials with high reward probability
2. Explicit adaptive salience: the increase in rating on the visual analogue scale for trials with high reward probability in comparison with trials with low reward probability

For the calculation of implicit and explicit aberrant salience, reaction time and visual analogue scale scores are defined by using the task-irrelevant stimulus dimension. For each participant, “high” and “low” reward probabilities are determined only by the subjective experience or responses: “high” is the irrelevant stimulus dimension to which the individual responded faster or rated higher on the visual-analogue scale. For a perfectly rational learner with zero aberrant salience, there is no “high” and “low” reward probabilities in the case of irrelevant stimulus dimensions (e.g., they respond with the same speed to and rate equally circles and triangles because

circles and triangles predict reward with a 50-50% probability when color is the relevant dimension).

3.2.3. Salience learning and skin conductance responses to conditioned alarming stimuli

The test ran on a VPC221 workstation (ViewSonic, Walnut, CA) programmed with an E-Prime software (Psychology Software Tools, Inc., Pittsburg, PA). The unconditioned alarming stimulus was an aversive sound (loud car horn embedded in urban noise for 800 msec). The intensity of the sound was determined for each participant to achieve an unpleasant but tolerable level. Tolerance calibration started at 40 dB with 5 dB steps upwards. The CSs+ (colored circles) predicting the unconditioned stimulus were presented in a 50% partial reinforcement schedule with a duration of 1 sec. CSs- were circles of a different color and not followed by the unconditioned stimulus. The CS+ - unconditioned stimulus interval was 5 sec, and the intertrial interval was 9 sec. There were 40 CS + and 40 CS- trials.

SCRs were registered by placing silver/silver chloride electrodes on the index and middle fingers. SCRs were measured at 10 Hz (BIOPAC system, Inc., Goelta, CA). SCRs threshold was 0.05 μS (Jensen et al., 2008). Following the conditioning, participants completed a simple reaction time task in which CS+ and CS- were presented alone.

3.3. Data analysis

We used STATISTICA software for data analysis (StatSoft Inc., Tulsa). To determine group differences across different experimental conditions, we used repeated measures or mixed model analyses of variance (ANOVAs) in the general linear model panel of STATISTICA. Tukey's Honestly Significant Differences (HSD) or Scheffé's tests were used for post hoc comparisons. To determine the relationship and prediction among different measures, we used Pearson's and Spearman's correlation coefficients (for normally and non-Gaussian data, respectively), or linear regression analysis to control co-variance among multiple variables. For non-normally distributed data, we

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applied Mann-Whitney U tests to conduct between-group comparisons. For the same purposes, two-tailed Student's t tests were used if the data were normally distributed. The level of statistical significance was alpha $\alpha < 0.05$, which was corrected for multiple comparisons with the Bonferroni method (α/n).

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4. RESULTS

4.1. Reward/punishment learning in schizophrenia

The ANOVA revealed no statistically significant main effect of group ($F(1,68)=2.38$, $p=0.13$), which indicates statistically unimpaired learning in schizophrenia. The effect of feedback-type (reward vs. punishment) was not significant ($F(1,68)=2.83$, $p=0.10$), and there was no interaction between group and feedback-type ($F(1,68)=0.08$, $p=0.78$) (Figure 3).

Table 5 shows the correlation coefficients. When performance from the reward learning task was included in a linear regression analysis, only the GAF scores retained significance ($F(1,38)=7.8$, $p=0.008$, $R^2=0.17$). The other potential predictors were not significant any more (education: $R^2=0.01$, $p=0.5$; antipsychotic dose: $R^2=0.02$, $p=0.3$; PANSS positive: $R^2=0.00$, $p=0.8$; PANSS negative: $R^2=0.03$, $p=0.2$; PANSS general: $R^2=0.02$, $p=0.3$). A similarly significant prediction of GAF was found in the case of punishment learning ($F(1,38)=6.21$, $p=0.02$, $R^2=0.14$) (Figures 4 and 5).

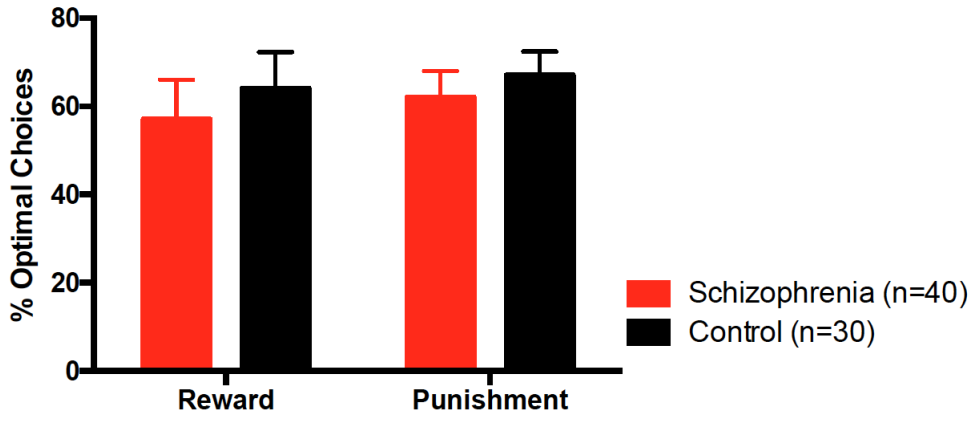

Figure 3. Reward and punishment learning in schizophrenia (SCZ) and controls (error bars are 95% confidence intervals) (Somlai et al., 2011)

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Table 5. Correlations from the reward/punishment learning task in schizophrenia

	Reward	Punish-ment	Education	CPZ	GAF	Pos	Neg	Gen
Reward	-	0.12	0.19	-0.29	0.41*	-0.28	-0.38*	-0.37*
Punishment	0.12	-	0.25	-0.10	0.37*	-0.13	-0.14	-0.24
Education	0.19	0.25	-	-0.14	0.42*	-0.15	-0.49*	-0.17
CPZ	-0.29	-0.10	-0.14	-	-0.40*	0.23	0.27	0.29
GAF	0.41*	0.37*	0.42*	-0.40*	-	-0.64*	-0.76*	-0.71*
Pos	-0.28	-0.13	-0.15	0.23	-0.64*	-	0.44*	0.73*
Neg	-0.38*	-0.14	-0.49*	0.27	-0.76*	0.44*	-	0.61*
Gen	-0.37*	-0.24	-0.17	0.29	-0.71*	0.73*	0.61*	-

Notes: CPZ – chlorpromazine-equivalent dose; GAF – Global Assessment of Functioning; Pos – positive symptoms; Neg – negative symptoms; Gen – general symptoms. *p<0.05.

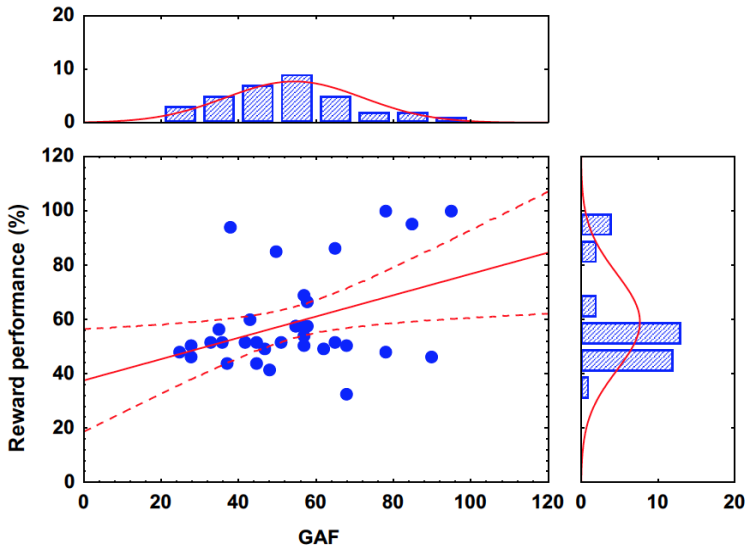

Figure 4. Relationship between reward learning performance and Global Assessment of Functioning (GAF) scores

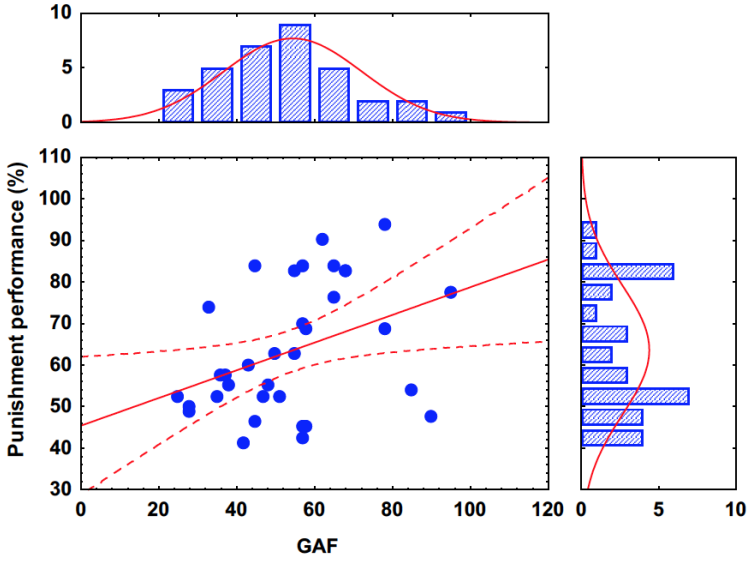

Figure 5. Relationship between punishment learning performance and Global Assessment of Functioning (GAF) scores

4.2. Salience learning in Parkinson's disease

4.2.1. Clinical changes during the dopamine agonist treatment

The UPDRS scores were significantly increased during the treatment. We also observed statistically significant increase in YMRS and O-LIFE unusual experiences (Table 3). The general subjective state of the patients was improved by the end of the follow-up period (mean: 5.4, SD=3.4).

4.2.2. Reaction time

We conducted an ANOVA: experimental group (controls vs. PD) was the between-subject factor and testing time (baseline vs. follow-up) and CS reward predicting (high vs. low) were the within-subject factors. We found a significant main effect of reward predicting value ($F(1,38)=38.55$, $p<0.0001$). There were interactions between testing time and group ($F(1,38)=17.61$, $p=0.0002$) and testing time and reward predicting value ($F(1,38)=12.30$, $p=0.001$). The three-way interaction among group, testing time, and reward predicting value was also significant ($F(1,38)=24.81$, $p<0.0001$).

Healthy controls were faster when the probe stimulus was preceded by CS with high reward predicting value relative to CS with low value ($p<0.05$). This effect was present in PD only at follow-up on dopamine agonist therapy ($p<0.001$) (Figure 6). For the irrelevant stimulus dimension, the ANOVA indicated a significant main effect of testing time ($F(2,37)=7.89$, $p=0.002$), as well as a two-way interaction between group and testing time ($F(2,37)=7.53$, $p=0.002$). PD patient were faster at follow-up relative to baseline ($p<0.001$) (Figure 6).

4.2.3. Explicit rating

There were significant main effects of group ($F(1,38)=32.26$, $p<0.0001$), testing time ($F(1,38)=6.10$, $p=0.02$), and reward predicting value ($F(1,38)=83.68$, $p<0.0001$). There were two-way interactions between group and testing time ($F(1,38)=6.09$, $p=0.02$), and group and predictive value ($F(1,38)=9.63$, $p=0.004$). Critically, the three-way interaction was significant ($F(1,38)=5.03$, $p=0.03$).

Dopamine agonists increased explicit rating in PD patients for high reward predicting stimuli ($p<0.01$). At baseline, PD patients displayed lower scores for high reward predicting stimuli compared to controls ($p<0.001$) (Figure 7).

For the irrelevant stimulus dimension, there was a significant main effect of testing time ($F(2,37)=10.39$, $p<0.001$), and an interaction between group and testing time ($F(2,37)=11.50$, $p=0.0001$). PD patients displayed a significantly increased rating at follow-up relative to baseline ($p<0.001$). In the medicated state, they displayed higher scores relative to controls ($p<0.01$) (Figure 7).

Figure 7 also suggests that at high predicting stimuli there is an inverse pattern of performance in PD and controls. At baseline, PD patients showed a significant reduction for relevant stimuli ($t(38)=-6.54$, $p<0.001$), but not for irrelevant stimuli ($p=0.3$). This suggest reduced adaptive salience and normal aberrant salience in non-medicated PD. At follow-up, PD patients still showed lower ratings for relevant stimuli, although the difference in relation to controls was smaller ($t(38)=-3.64$, $p<0.01$). Strikingly, there was a robust increase for task-irrelevant stimuli, suggesting heightened aberrant salience in medicated PD ($t(38)=3.85$, $p<0.01$).

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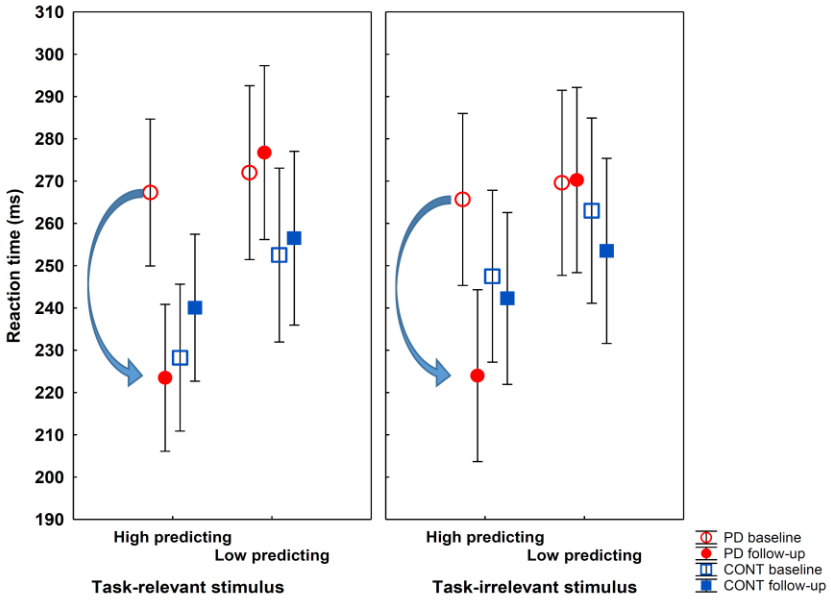

Figure 6. Reaction time from the salience learning task.

Parkinson's disease (PD, n=20), healthy controls (CONT, n=20). Error bars: 95% confidence intervals. The arrow indicates significant drop in reaction time ($p<0.01$, PD baseline vs. follow-up, Tukey's test).

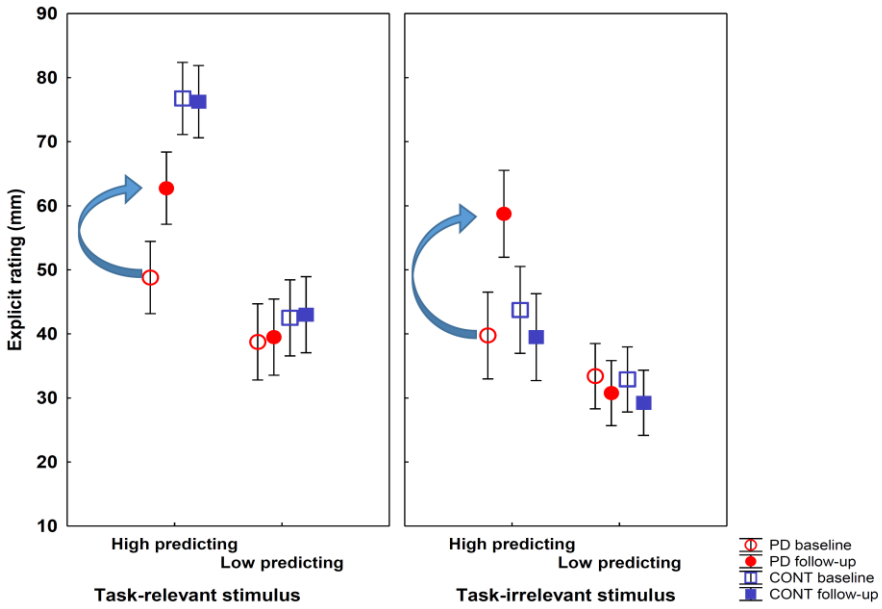

Figure 7. Explicit ratings from the salience learning task

Parkinson's disease (PD, n=20), healthy controls (CONT, n=20). Error bars: 95% confidence intervals. The arrow indicates significant increases in ratings ($p<0.01$, PD baseline vs. follow-up, Tukey's test).

4.2.4. Relationship between salience and psychosis-like experiences

In PD patients receiving dopamine agonists faster responses and higher ratings for task-irrelevant stimuli were correlated with increased O-LIFE unusual experiences (reaction time: $r=-0.65$, $p<0.005$; rating: $r=0.57$, $p<0.05$). For task-relevant stimuli, we found no such correlations ($r<0.1$). There were no significant correlations with YMRS scores ($r<0.1$).

4.3. Salience learning and schizotypal traits

SCRs were more prevalent for CSs+ (mean: 61.2%, SD=14.7) than for CSs (mean: 33.5%, SD=9.4) ($t(198)=15.92$, $p<0.001$) (Figure 8a). Participants responded faster for CSs+ (mean reaction time: 615.4, SD=149.8) than for CSs- (mean reaction time: 824.0, SD=254.6) ($t(198)=-7.06$, $p<0.001$) (Figure 8b).

Table 6 shows the correlations between SCRs and scale scores. For CSs+ significant predictors were O-LIFE Introvertive Anhedonia ($b^*=-0.33$, $t(92)=-3.61$, $p<0.001$) and Unusual Experiences ($b^*=-0.44$, $t(92)=-4.09$, $p<0.001$); ($F(7,92)=6.26$, $p<0.001$, $R^2=0.27$). For CSs- significant predictors were IQ ($b^*=-0.19$, $t(92)=-2.01$, $p<0.05$) and O-LIFE Unusual Experiences ($b^*=0.31$, $t(92)=2.69$, $p<0.05$); ($F(7,92)=4.10$, $p<0.01$, $R^2=0.18$).

Figure 9. Illustrates the opposite relationships among OLIFE unusual experiences and SCR CS+/CS-. Higher levels of unusual experiences were associated with less efficient conditioning for relevant stimuli (CS+) ($r=-0.44$, $p<0.05$), whereas, paradoxically, more SCRs were observed for irrelevant stimuli predicting no unconditioned stimuli ($r=0.44$, $p<0.05$). Interestingly, cyclothymia showed the same pattern of correlation with CS+/CS- (Table 6), but it was due to its co-variance with unusual experiences.

For CSs+ reaction time the significant predictor was O-LIFE Introvertive Anhedonia ($b^*=0.61$, $t(92)=7.31$, $p<0.001$; $F(7,92)=9.30$, $p<0.001$, $R^2=0.37$), whereas for CSs- reaction time the significant predictor was O-LIFE Unusual Experiences ($b^*=-0.42$, $t(92)=-3.52$, $p<0.01$; $F(7,92)=2.91$, $p<0.05$, $R^2=0.11$).

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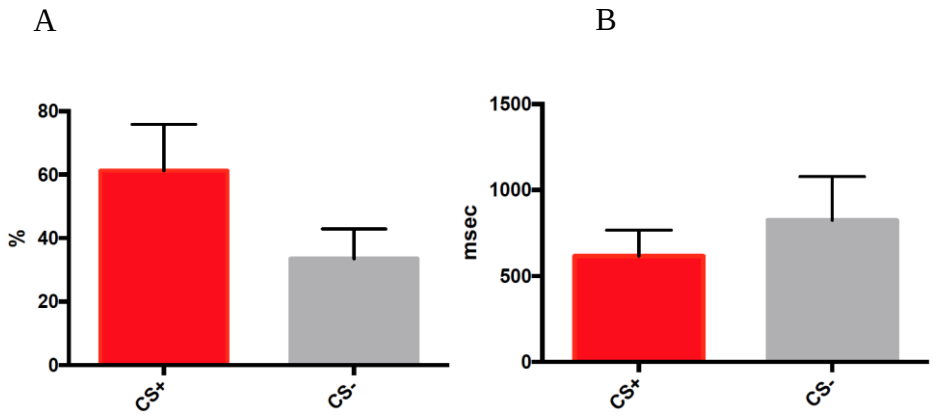

Figure 8. Skin conductance responses (% suprathreshold) (A) and reaction time (B) from the conditioning task

Mean, standard deviation (error bars). Significant differences between CS+ and CS- in both A and B, $p<0.001$, t tests

Table 6. Correlations between skin conductance responses and O-LIFE/TEMPS-A scores

	O-LIFE				**TEMPS-A**				
	UnEx	IntAnh	CognDis	ImpNon	Cyclo	Hyper	Depr	Irrit	Anx
SCR CS+	-0.44*	-0.34*	-0.01	0.04	-0.26*	0.10	-0.05	0.08	0.11
SCR CS-	0.40*	-0.10	0.14	0.03	0.27*	0.11	-0.03	0.02	0.13
RT CS+	0.18	0.64*	-0.05	0.07	0.22*	-0.12	0.13	0.01	0.05
RT CS-	-0.39*	0.07	-0.09	0.01	-0.12	-0.15	0.09	0.0	0.01

Notes: * $p<0.05$; O-LIFE - Oxford-Liverpool Inventory of Feelings and Experiences; TEMPS-A - Temperament Evaluation of Memphis, Pisa, Paris and San Diego; SCR - skin conductance response; CS - conditioned stimulus;+ - relevant; -- - irrelevant; RT – reaction time; UnEx -

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Unusual Experiences; IntAnh - Introvertive Anhedonia; CognDis - Cognitive Disorganization;, ImpNon – Impulsive Nonconformity; Cyclo - Cyclothymic; Hyper - Hyperthymic; Depr - Depressive; Irrit - Irritable; Anx - Anxious

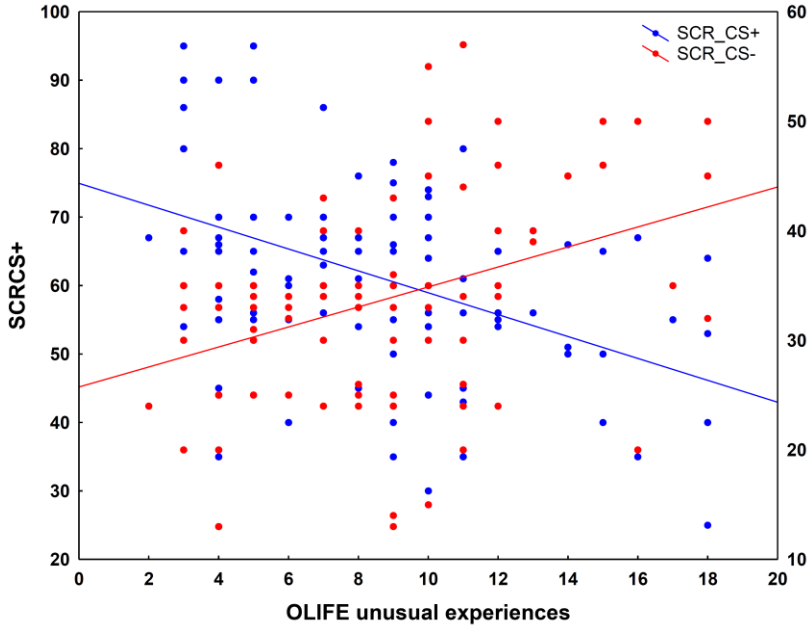

Figure 9. Correlations among unusual experiences and SCRs. O-LIFE - Oxford-Liverpool Inventory of Feelings and Experiences; TEMPS-A - Temperament Evaluation of Memphis, Pisa, Paris and San Diego; SCR - skin conductance response; CS - conditioned stimulus; ;+ - relevant; -- - irrelevant

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5. DISCUSSION

5.1. Key points of the results

The results of the present study indicate three main new aspects of salience learning in relation to schizophrenia, medication-induced psychosis-like symptoms in PD, and schizotypal personality traits:

1. In relatively well-functioning patients with chronic schizophrenia, there is no generalized deficit in instrumental learning, that is, performance decrement was not prominent in reward-based feedback (reward and punishment learning were not significantly deficient in the patients). The symptoms of schizophrenia and general psychosocial functioning were differentially related to reward and punishment learning: negative and general symptoms were related to reward learning, whereas general psychosocial functioning predicted both reward and punishment learning over and above the clinical symptoms and demographic characteristics.
2. In newly diagnosed PD patients, dopamine agonists elevated manic mood symptoms and unusual experiences, but these signs and symptoms remained at the subclinical level. Dopamine agonists also enhanced both adaptive and aberrant salience, but only aberrant salience was linked to unusual experiences.
3. Reality distortion, introvertive anhedonia, and cyclothymic personality traits negatively correlated with SCRs and reaction time for CSs+, which suggests that higher levels of these traits were linked to less conditioning.
4. Schizophrenia- and mood disorder-related personality traits showed a significant overlap, and when it was controlled, only reality distortion and introvertive anhedonia were significant for CS+. Critically, CS- responses were positively predicted by reality distortion, but not other personality traits. In other words, aberrant salience is associated with schizotypal personality traits in healthy individuals.

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5.2. General psychosocial functioning dominantly predicts reward and punishment learning in schizophrenia

General psychosocial functioning, as reflected by the GAF score, was the sole predictor of reward and punishment learning when education, PANSS scores, and chlorpromazine-equivalent doses of antipsychotics were included in the regression model, accounting for 14-17% of variance of task performance. Unexpectedly, schizophrenia patients displayed no significant reward- or punishment-learning deficits relative to healthy controls, which indicates that the learning capacity of the patients is rather diverse depending on their psychosocial impairments. This observation is highlighted in the literature: some studies found normal learning (Kéri et al., 2000; Weickert et al., 2002; Waltz and Gold, 2007; Murray et al., 2008a), whereas others found significant impairments (Foerde et al., 2008; Horan et al., 2008; Murray et al., 2008b; Weiler et al., 2009; Koch et al., 2010).

The behavioral studies discussed so far investigated performance (percentage of correct decisions) and/or reaction time. However, these measures are not independent in real-life tasks, and it is necessary to find mathematical models that are able to integrate them. Drift diffusion models provide insight into the details of decision-making processes. By reanalyzing our data, we found that patients with schizophrenia had slower encoding time, response caution, and a deficit in punishment, but not reward learning (Moustafa et al., 2015).

Weickert et al. (2002) proposed that different frontostriatal circuits can be assessed by specific tests in schizophrenia. In this model, the motor circuit, involving the premotor cortex and the putamen, is responsible for motor skill learning such as the pursuit rotor task. The cognitive circuit, including the dorsolateral prefrontal cortex and the dorsal caudate nucleus, mediates more abstract non-motor forms of habit learning such as feedback-based category learning guided by corrective reward and punishment signals. A prototypical example for cognitive skill learning is the Weather Prediction Task (Packard and Knowlton, 2002). Weickert et al. (2002) payed a special attention to the rate of the learning rather than the overall learning performance difference between patients and controls. There was a significantly lower learning rate in patients relative to the controls in the motor learning task but not in the cognitive skill learning task, which

was an unexpected finding given that it would be hypothesized that the cognitive circuit is more impaired. More surprisingly, when patients and controls were matched on general intellectual functioning, the difference in the learning rate was not observed any more (Weickert et al., 2002). The authors concluded that the cortical input to the striatum is impaired in schizophrenia (Weickert et al., 2002).

However, based purely on behavioral tests it is difficult to determine the neuronal substrates. Koch et al. (2010) used fMRI during a gambling task including cue-number associations with different probabilities (51, 81, and 100%). Healthy controls tend to show larger activations in the frontoparietal executive network when the probability between the cue and the number is lower, that is, the cue only uncertainly signifies the preceding number. This network does not show probability-dependent recruitment in schizophrenia. Moreover, during the expectancy phase of the task a superior frontal-cingular-putamen circuit was less active in schizophrenia patients (Koch et al., 2010). Therefore, a wide range of cortical and subcortical structures are implicated in the reinforcement learning deficit of schizophrenia patients, and the putamen is not exclusively included in the motor circuit.

Another critical question is the issue of antipsychotic medications. We found a negative relationship between reward learning and daily dose of antipsychotics, which is similar to our earlier results from another task (Fish-Face Association Task) (Kéri et al., 2005). It is notable that in this study the majority of patients received second-generation drugs with a lower affinity to dopamine D2 receptors, whereas the patients in the Fish-Face study received first-generation drugs. This is consistent with the results of Bódi et al. (2009) who found that a 12-week of dopamine agonist treatment normalized reward learning in PD. At the neuronal level, antipsychotics with low vs. high dopamine receptor affinity differentially modulate the ventral striatal reward system, i.e., higher D2 affinity medications induce dampened responses (Juckel et al., 2006a). Down-regulated activation of reward-related brain regions is associated with less effective feedback-based learning (Aron et al., 2004). The role of dopamine in these functions has also been confirmed by a combined dopamine depletion – fMRI approach (da Silva Alves et al., 2013).

Shohamy et al. (2010) also used the Fish-Face task, which is a memory generalization task; first, participants are involved in a trial-by-error associative learning

phase as it also happened in our study. In the next phase, it is tested how this knowledge can be generalized to new stimulus configurations. Critically, patients with schizophrenia exhibited a selective deficit on the generalization phase of the task. The trial-by-error learning phase was spared, which is in accordance with the data of our present study. Interestingly, Shohamy et al. (2010) were able to demonstrate the generalization deficit only in non-medicated schizophrenia patients, suggesting that antipsychotics facilitate generalization, a putative function of the hippocampal formation (Myers et al., 2003). The hippocampal formation, in turn, regulates the ventral striatum and affects emotional salience and reward learning via cannabinoid transmission (Loureiro et al., 2015).

An important question is how instrumental learning processes discussed above can be linked to salience learning in more details. Murray et al. (2008a) were the first who demonstrated this link by using fMRI during a gambling task. The participants were patients with first episode psychosis receiving no antipsychotics. Murray et al. (2008a) demonstrated abnormal reward prediction error responses in the mesencephalic dopaminergic centers, striatum, and limbic system. Moreover, the healthy control individuals responded faster to rewarded stimuli than to neutral (non-rewarded) ones in accordance with the development of normal adaptive salience during task conditioning. In contrast, this response acceleration was less pronounced in patients with psychosis, which may indicate that they developed an abnormal salience to neutral stimuli (Murray et al., 2008a). Schlagenhauf et al. (2009) replicated and extended these findings by showing a relationship between reward-related brain activation and delusions in non-medicated patients with schizophrenia (see also Esslinger et al., 2012; Gradin et al., 2013).

However, altered activation in the striatum is not only the sign of aberrant salience attributions. Negative symptoms, anhedonia, and apathy can be considered as a form of reduced salience when value and importance are not linked to non-relevant stimuli or internal representations (a basis of impaired reality testing in the model of Kapur (2003)), but relevant and important stimuli lose their meaning (i.e., decreased salience). Indeed, lower responses in the ventral striatum are associated with the negative symptoms of schizophrenia (Juckel et al., 2006b; Simon et al., 2010). In non-medicated persons with high psychosis risk syndrome, positive symptoms are correlated

with the reward anticipation signal, whereas negative and symptoms are correlated with the outcome-related signal in the ventral striatum (Wotruba et al., 2014).

Although higher-level cognitive functions, such as working memory, declarative memory, and attention are related to functional outcome in schizophrenia and hence forms a major target for treatment (Green et al., 2004; Keefe, 2007; Revell et al., 2015), the role of feedback-driven reinforcement learning has not been clarified until the present study. It is intuitive to suppose that reinforcement learning dysfunctions sign anomalies in emotion, motivation, and approach-avoidance behavior regulation that may result in shortcomings in general psychosocial functioning (Gold et al., 2008). One of the rare observations comes from Kawakubo et al. (2006) who demonstrated that performance on a feedback-based sensory-motor task (Mirror Reading Test) is related to nonverbal social skills in schizophrenia.

These findings have a direct relevance to therapy. Silverstein et al. (2009) developed an attention shaping method for the cognitive remediation of patients with highly scattered attention in social settings. The novel feature of this therapy is that it integrates reward learning with attentional control. Although this approach is novel in the light of current results from reward learning tasks, the basic principles are established by the pioneers of behaviorism (Braum, 2005).

Our study has the following limitations that must be taken into consideration in the final interpretation:

1. We used the GAF scale for the assessment of psychosocial functions, which is clinically relevant but simplistic and non-specific. More widespread and specific measures of different aspects of psychosocial functioning are warranted to further studies (e.g., occupation, interpersonal relationships, communication skills, role modelling, and social motivation).
2. We conducted no comprehensive neuropsychological assessment in this sample of patients with schizophrenia. Evidence suggests that higher-level cognitive functions are only loosely associated with feedback-driven reinforcement learning performances (Weickert et al., 2002; Kéri et al., 2005; Waltz et al., 2007; Weiler et al., 2009), and therefore it is less likely that we failed to target a specific cognitive domain.

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5.3. Dopamine agonists enhance both adaptive and aberrant salience, but only aberrant salience is related to reality distortion in Parkinson's disease

In this part of our research, we were interested in whether dopamine receptor agonists induce similar salience learning biases in PD to that observed in schizophrenia. It is clinically important given the prevalence of psychotic symptoms in PD, which is especially common in elderly patients with poor cognitive functions receiving higher doses of dopamine replacement therapies (Weintraub and Burn, 2011). The present study was the first to evaluate how dopamine agonists in previously never-medicated, young PD patients affect subjective subclinical experiences related to psychosis and how it is related to reward/salience learning. The key findings were that (i) dopamine agonists facilitate not only the acquisition of real stimulus-reward associations during conditioning, but the emergence of illusory and arbitrary associations (aberrant salience); (ii) speeded responses and higher subjective rating for task-irrelevant stimuli (aberrant salience) correlated with subthreshold psychotic-like feelings and experiences in PD patients receiving dopamine agonists. However, non of the PD patients developed frank psychosis, with an average of 27% increases in unusual experiences during the 12-week of dopamine agonist therapy. Manic-like symptoms were also slightly elevated, but it was independent of the unusual experiences.

Our results can be compared with data from patients with schizophrenia. As in our case, schizophrenia patients were asked to press a button as quickly as they can to earn money points when CSs with different colors and forms were presented. Only form or color was relevant/salient for reward prediction (Roiser et al., 2009). Patients with schizophrenia as a group showed reduced adaptive salience (i.e., successful conditioning), but interestingly they were not characterized by a higher level of aberrant salience when compared with the healthy controls. However, when the deluded patients were analyzed separately, Roiser et al. (2009) found increased aberrant salience relative to non-deluded patients and healthy control participants. Another interesting finding was that aberrant salience also correlated with negative symptoms in patients and introvertive anhedonia in controls. Therefore, results from PD patients receiving dopamine agonists and those from schizophrenia are only partially similar. The fact that in the study of Roiser et al. (2009) aberrant salience was also linked to negative

symptoms and O-LIFE introvertive anhedonia (reduced interest and social withdrawal) can be explained by abnormally high false negative phasic dopamine signal. This is based on the data of Knutson et al. (2004) who demonstrated that amphetamine unexpectedly decreased phasic ventral striatal responses in response to conditioned stimuli predicting reward (false negatives), which could result in decreased motivational salience and a general loss of volition and interest. Moreover, amphetamine caused phasic ventral striatal activation for conditioned stimuli that did not predict reward (false positives), which may be the physiological basis of aberrant salience (Knutson et al., 2004).

The effect of medication may be different in distinct kinds of reward learning tasks. Recently, Sharp et al. (2016) showed that dopaminergic medications have no effect on model-free reward learning, but they markedly remediate learning in PD when a model-based procedure is used requiring higher-level working memory functions. Such functions inhibit habit formation and behavioral/cognitive inflexibility in novel situations (Gillan et al., 2015).

In our study, dopamine receptor agonists increased both adaptive and aberrant salience, i.e., enhanced both real and noisy stimulus-reward associations, possibly by the stimulation of D_2 and D_3 dopamine receptors in the limbic striatum (Gerlach et al., 2003; Winstanley et. al, 2011). The ventral striatum is not the sole structure implicated in the formation of adaptive and aberrant salience; there is a close link with midbrain dopaminergic centers and prefrontal cortex (Roiser et al., 2010). Ishibasi et al. (2011) suggested that the dopamine agonist pramipexole may significantly bind to non-striatal regions in the brain, contributing to the antidepressant and behavioral effects of this drug. By using positron emission tomography, these authors showed that pramipexole significantly binds D_2 and D_3 dopamine receptors in the frontal cortex, amygdala, and thalamus even at a very low single dose of 0.25 mg. Ramayya et al. (2014) applied phasic microstimulation in the substantia nigra in PD patients under a deep brain stimulation surgery and found decreased reward learning together with the rigidity of reward-action associations. It seems that the subthalamic nucleus is a key structure to understand impulsivity and other neuropsychiatric symptoms in PD (Zavala et al., 2015).

The mechanism of psychosis-inducing ability of dopamine agonists are multiple. For example, these drugs enhance memory for angry faces in PD (Subramanian et al, 2010). Following the administration of dopamine agonists, some people may feel that their actions and the consequences and outcomes of these actions are dissociated, and hence they fail to control their own actions (Moore et al., 2010). The third psychosis-related mechanism may be attentional distraction. Cools et al. (2010a, 2010b) showed that attention was easily captured by stimuli from the external world in PD, whereas in the non-medicated state low dopamine in the striatum, together with higher frontal dopamine levels, may lead to better resistance against distracting external stimuli. Dopaminergic medications change this striatal/frontal dopamine ration in medicated PD patients, and in this way these drugs may enhance attentional distractibility (less resistance against incoming external stimuli) (Cools et al., 2010a, 2010b).

There are some differences between the results of the present study and the observations of Housden et al. (2010). These authors investigated salience, reward learning, and impulsivity in chronic PD patients receiving both L-DOPA and dopamine agonists. They demonstrated that PD patients with impulsive-compulsive behavior showed high reward learning, but there was no enhanced explicit aberrant salience and no correlations with O-LIFE unusual experiences scores. However, introvertive anhedonia was positively associated with explicit aberrant salience, and cognitive disorganization was similarly related to implicit aberrant salience. Notably, PD patients displayed higher O-LIFE unusual experiences and cognitive disorganization scores than seen in controls, which was the most dominant in PD patients with impulsive-compulsive symptoms with higher scores on all O-LIFE dimensions (Housden et al., 2010).

Housden et al. (2010) did not use the same task as we did, and the PD patients were chronic cases with a long history of many kinds of medications. This latter fact is especially critical. Moustafa et al. (2013) provided a computational model of frontostriatal connections and demonstrated that in some circumstances L-DOPA enhances but dopamine agonists impair or have no effect on both stimulus-response learning and working memory, requiring the integration of frontal and striatal information processing via dopamine D_1 receptors (Moustafa et al., 2013).

Our results should be interpreted by taking into account the following limitations:

1. We did not administer dopamine agonists to healthy controls, and therefore the potential interaction between medication and disease process is unclear. We do not know whether dopamine agonists have similar effect in PD and healthy individuals.
2. Second, the effect of dopamine agonist therapy was always assessed after a non-medicated baseline state, so there could be a session order effect. Future on-off medication studies should investigate whether the effects can be shown in a reverse order, that is, when medications are terminated.

5.4. Schizotypal traits correlate with Pavlovian conditioning indicating abnormal salience

We found that unusual experiences, introvertive anhedonia, and cyclothymia correlated with conditioning parameters related to abnormal salience learning: lower responses to CS+ and heightened responses to CS- (Jensen et al., 2008). The finding that an affective temperament trait was among the predictors of abnormal salience seems to be in contradiction with its specificity for reality distortion. However, it has been shown that scores on the O-LIFE and TEMPS-A scales show a significant degree of correlation, which means that the phenomena they measure are overlapping in the general non-clinical population (Claridge and Blakey, 2009). This is similar to the pre-Kraepelin era of psychosis concept, the unitary psychosis (Einheitpsychose) of Wilhelm Griesinger (1817-1868), in which schizophrenia and manic-depressive insanity were not categorically separated (Beer, 1996). However, when the co-variance between O-LIFE and TEMPS-A was taken into consideration, unusual experiences and introvertive anhedonia predicted reduced responses to CS+ (less effective conditioning - decreased adaptive salience), but only reality distortion predicted elevated responses to CS- (abnormal conditioning to irrelevant stimuli - increased aberrant salience).

The strength of the current paradigm is that it represents a more realistic setting for stress situations than other, more abstract laboratory paradigms (Tregellas et al., 2009; Lederbogen et al., 2011). We used a conditioned SCR paradigm that has been validated at the biological level. The goal of Jensen et al. (2008) was to investigate

ventral striatal activations while patients with schizophrenia and healthy controls learnt reward-related associations. The authors used fMRI (brain-level analysis), SCR (autonomous neuronal responses to aversive conditioning), and subjective reports from the participants. The advantage of the Pavlovian learning paradigm was that the participants were less required to make conscious efforts with a lower level of cognitive demands. Similar to our study, colored shapes were the conditioned stimuli (CS+), and a loud alarming noise was the unconditioned stimulus paired with the CS+ during conditioning. The same shapes with another color were not paired with and unconditioned stimulus (CS-), and hence these stimuli had no behavioral relevance. The central finding was that in patients with schizophrenia, the ventral striatum showed an abnormally enhanced response to CS-, a sign of aberrant salience learning. It was in accordance with SCRs and subjective ratings. Therefore, in an alarming conditioning context patients with schizophrenia tend to form aberrant associations, which may be linked to psychotic salience attribution (Jensen et al., 2008). The results were similar in the case of appetitive conditioning (monetary reward), showing an enhanced effective connectivity between striatum and hippocampus for CS- only in patients (Diaconescu et al., 2011). Full D_2 receptor antagonist drugs (haloperidol) and partial agonists (aripriprazole) differentially modify the responses of the ventral striatum (Bolstad et al., 2015).

Very little information is available on a potentially altered conditioning in schizotypal personality disorders. One possible candidate is cerebellum-dependent eyeblink conditioning, which is impaired in schizotypal personality disorder and in first-degree relatives of schizophrenia patients (Forsyth et al., 2012; Bolbecker et al., 2014). Freeman et al. (2013) studied associative blocking of reward-related cues (CS+) in ketamine users who display elevated schizotypal personality traits. As expected, ketamine user individuals were characterized by elevated delusional, schizotypal, and depressive symptoms. In the conditioning paradigm, they showed higher accuracy for blocked cues relative to the control participants, which indicates reduced stimulus blocking. This reduced blocking was especially significant in the case of drug-related cues (Freeman et al., 2013). Ettinger et al. (2013) used fMRI during a sequence learning task and found a significant association between the psychoticism subscale of the

Eysenck Personality Questionnaire and activation in the putamen, caudate nucleus, thalamus, insula, and frontal cortex.

There is a couple of methodological issues with this stduy that should be addressed. We analyzed the percentage of detected SCRs and not the amplitude of the responses. Our goal was to obtain data that are comparable to previous results in the literature (Jensen et al., 2008). It has been verified that thersholded SCRs can separate CS+ and CS-, and there is a relationship between these SCRs and subjective experiences, as well as brain activation. Raine et al. (2000) were the first to report that reduced grey matter in the frontal cortex of individuals with antisocial personality is correlated with a decreased potency of SCR conditioning. The amygdala is critical in the generation of the responses (Phelps et al., 2001), but now we know that the ventral striatum, which is classically interpreted as a "reward center", is also activated during aversive conditioning (Pohlack et al., 2012).

In accordance with the later findings of Pohlack et al. (2012), Jensen et al. (2007) found that neuronal activation in the ventral striatum correlated with prediction error for both aversive and appetitive stimuli. Dopamine regulates functional connectivity among striatal, limbic, and prefrontal areas during aversive conditioning (Diaconescu et al., 2010) and enhances responses to salient stimuli regardless whether it was rewarding or punishing (Wyvell and Berridge, 2000). Animal research indicates that some mesencephalic dopamine neurons' activity reflects the valence of the stimulus, whereas other cells encode general, value-independent motivational salience. Novel and alerting events activate both populations of neurons (Bromberg-Martin et al., 2010). Another microstructural pattern has recently been discovered regarding the reward vs. action selection regulating property of dopamine: neuronal terminals in ventral striatum is activated to reward delivery and reward-predicting stimuli, while those in the dorsal striatum are associated with motor choices from alternative behaviors (Parker et al., 2016).

The results of Roiser et al. (2009) might indirectly indicate that dopamine antagonist antipsychotic therapy reduces abnormal salience attribution, and we showed in PD patients that dopamine agonists have the opposite effect. In healthy controls, there is a correlation between introverted anhedonia and abnormal salience (Roiser et al., 2009; Schmidt and Roiser, 2009), which was contrasted in the present study: both

reality distortion and withdrawal traits were associated with reduced processing of salient stimuli (CSs+), but only reality distortion was associated with an enhanced processing CSs-. Woodward et al. (2011) showed that higher schizotypy was associated with increased dopamine release in the associative striatum following amphetamine administration. Disorganized schizotypy is associated with the striatal binding of D_2/D_3 receptors (Chen et al., 2012). The finding that dopaminergic mechanisms are important in cognitive alterations associated with schizotypal personality has relevance in therapy: D_1 receptor agonists are able to improve working memory is schizotypal personality disorder, possibly via acting on information processing in the prefrontal cortex (Rosell et al., 2015).

The general conclusion of our study is that schizotypal personality traits are specifically related to psychophysiological and behavioral responses to CSs+, which is similarly sensitive to dopaminergic mechanisms as it has been shown in the case of to prepulse inhibition, antisaccade performance, and and sequence learning (Ettinger et al., 2013). Although it is in accordance with the salience hypothesis of psychotic symptoms, that is, an anomalous association between behaviorally irrelevant internal and external events and unconditioned stimuli (Kapur, 2003), aberrant salience attribution can not explain the full range of psychosis-like experiences and schizotypal traits, for instance, anxiety and threat anticipation associated with reality distortions (Pankow et al., 2012). When future studies will be designed to separate these cognitive and affective factors, the limitations must be taken into consideration.

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6. CONCLUSIONS

Reward/salience learning paradigms are useful as tools to describe the neurocognitive mechanisms of (i) psychosocial impairments associated with schizophrenia, a severe psychotic disorder; the effects of dopamine agonists on information processing in PD; the correlation between salience learning and psychosis-like experiences in non-clinical individuals.

Based on the results, we have the following conclusions:

1. In a binary categorization task, in which each and every decision is made on a trial-by-error basis until the accumulation of a sufficient amount of reinforcement signals, patients with schizophrenia do not show a uniform deficit. Rather, their performance largely depends on general psychosocial functions, but not clinical symptoms.
2. Salience learning can be measured by reaction time (implicit aspect) and visual-analogue rating (explicit aspect). Within explicit and implicit salience learning, adaptive and aberrant types can be distinguished: in the former case, individuals respond faster and rate higher for stimulus-reward associations, whereas in the latter case there is a speeded response and higher rating for stimuli that do not predict reward.
3. In PD all types of salience learning (implicit, explicit, adaptive, and aberrant) are facilitated by dopamine agonists. However, there is a striking increase for aberrant salience, which is associated with higher levels of psychosis-like unusual experiences. This phenomenon may be useful in the prediction of vulnerability to real clinical psychosis in PD.
4. Psychosis-like experiences with low intensity are relatively frequent in the non-clinical general population. These experiences show similarities in their neurocognitive mechanisms to those seen in psychotic disorders (e.g., schizophrenia) and medication-induced psychosis (e.g., in PD).
5. Adaptive and aberrant salience attribution can be measured at the level of the activation of the autonomous nervous system: SCRs elicited by intensive auditory stimuli are valid indicators of salience acquired during classic conditioning.

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6. SCR measures, including the prevalence of suprathreshold responses and reaction time to CS+ and CS-, correlate with the level of unusual experiences in healthy individuals: indicative for aberrant salience, higher SCR rate and shorter reaction time for CS- are associated with higher levels of psychosis-like experiences.

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7. SUMMARY

Aims: We used reward/salience learning paradigms in order to characterize: (i) the psychosocial functional impairment in schizophrenia, (ii) the effects of dopamine agonists on subclinical psychosis-like experiences in Parkinson's disease, and (iii) the relationship between schizotypal traits and psychosis-like experiences in non-clinical community individuals.

Methods: We used three cognitive tasks in the above mentioned populations: (i) reward/punishment guided category learning; (ii) salience learning in a conditional context; (iii) skin galvanic responses modulated by alarming stimuli. Clinical symptoms, psychosocial functioning, and personality traits/subclinical experiences were measured with the Positive and Negative Syndrome Scale, Unified Parkinson's Disease Rating Scale, Global Assessment of Functioning (GAF), and Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE).

Results: In schizophrenia, the most important predictor of reward/salience learning was the GAF score. In Parkinson's disease, dopamine agonists increased both adaptive and aberrant salience, but only aberrant salience was related O-LIFE unusual experiences. In non-clinical individuals, aberrant salience measured during skin conductance response conditioning was also related to O-LIFE unusual experiences.

Discussion: Reward/salience learning may play an important role in the everyday psychosocial functioning of schizophrenia patients. Dopamine agonist medications used for the treatment of Parkinson's disease enhance psychosis-like experiences, which are related to aberrant salience, that is, the acquisition of arbitrary stimulus-reward associations. Finally, the level of aberrant salience may be important in the emergence of psychosis-like experiences and schizotypal traits in the general population.

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8. ÖSSZEFOGLALÁS

Célkitűzések: Vizsgálatainkban jutalomtanulással és kondicionálással kapcsolatos feladatokat használtunk három fő kérdés megválaszolásának céljából: (i) Milyen szerepet játszanak e folyamatok a szkizofrén páciensek pszichoszociális funkcióinak alakulásában? (ii) Milyen hatást gyakorolnak a Parkinson-kórban használt dopamin agonisták a szubklinikus pszichózis-szerű jelenségekre? (iii) Milyen kapcsolat mutatható ki egészséges személyek pszichózis-szerű élményeivel és szkizotípiás vonásaival?

Módszerek: Három paradigmát alkalmaztunk a fentiekben ismertetett populációknál: (i) jutalomszignál által vezérelt kategóriatanulás; (ii) klasszikus appetitív kondicionálás; (iii) bőrgalván-reflex modulációja erős hangingerek által. A klinikai tüneteket, a pszichoszociális funkciók szintjét és a szkizotípiás jegyeket/szubklinikus pszichózis-szerű élményeket a következő skálák segítségével számszerűsítettük: Pozitív és Negatív Tünetek Skálája, Egyesített Parkinson-kór Becslőskáka, Globális Funkcionális Skála és az Élmények - Tapasztalatok Oxford-Liverpool Skálája.

Eredmények: Szkizofrén páciensek esetében a kategóriatanulás legkiemelkedőbb prediktora a globális pszichoszociális funkciókat vizsgáló skálán elért pontszám volt. Parkinson-kórban a dopamin agonisták az adaptív és az abnormális inger-jutalom asszociációk kiemelkedését is elősegítették, de kizárólag az abnormális kiugrás kapcsolódott a pszichózis-szerű jelenségekhez. Végül egészséges személyeknél a bőrgalván-reflex kapcsán tapasztalt abnormális kiugrás szintén korrelált a szubklinikus pszichózis-szerű jelenségek és szkizotípiás vonások intenzitásával.

Megbeszélés: A megerősítéses tanulás során elért teljesítmény fontos szerepet tölthet be a szkizofrén páciensek mindennapi pszichoszociális funkcióiban. A Parkinson-kórban alkalmazott dopamin agonisták felerősítik a pszichózis-szerű jelenségeket, amelyek a tanulás során létrejött abnormális kiugrásokhoz (véletlenszerű inger-jutalom asszociációk kialakulása és megerősödése) kapcsolódnak. Az abnormális kiugrások hozzájárulhatnak az egészséges populációban megfigyelhető pszichózis-szerű élmények és szkizotípiás vonások létrejöttéhez is.

9. REFERENCES

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10. LIST OF OWN PUBLICATIONS

Publications related to the thesis

Somlai Z, Moustafa AA, Kéri S, Myers CE, Gluck MA. (2011) General functioning predicts reward and punishment learning in schizophrenia. Schizophr Res, 127: 131-136.

Nagy H, Levy-Gigi E, **Somlai Z**, Takáts A, Bereczki D, Kéri S. (2012) The effect of dopamine agonists on adaptive and aberrant salience in Parkinson's disease. Neuropsychopharmacology, 37: 950-958.

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Publications not directly related to the thesis

Moustafa AA, Kéri S, **Somlai Z**, Balsdon T, Frydecka D, Misiak B, White C. (2015) Drift diffusion model of reward and punishment learning in schizophrenia: Modeling and experimental data. Behav Brain Res, 291: 147-154.

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