

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

Ph.D. Thesis

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1. Introduction

Salience/reward (reinforcement) learning is one of the classic paradigms introduced by pioneers of behavioral sciences. There are two basic types of reinforcement learning. The first is a binary decision-making task in which participants are requested to make a conscious judgment, for example, about category membership. Initially, the behavior is based on trial-by-error responses – rewarded (correct and salient) decisions are enhanced, whereas punished (incorrect) responses are extinguished.

The second type is based on the classic Pavlovian conditioning paradigm. Participants are given an automatic task, for example, pressing a button as fast as they can when a probe stimulus is presented. The probe stimulus is preceded by conditioned stimuli (e.g., shapes with different colors) from which some are salient (they predict reward or punishment after the response), whereas others are not. When reward/punishment-predicting conditioned stimuli are presented, individuals tend to respond faster, which is called adaptive salience. However, non-predicting stimuli are also associated with

response enhancement at a certain degree, called aberrant salience.

The strengthening of aberrant salience is one of the leading neurocognitive mechanisms in the emergence of the psychotic symptoms of schizophrenia and other disorders, including delusions, hallucinations, and behavioral disorganization. In these cases, non-salient external stimuli and mental representations gain relevance and value in an arbitrary manner resulting in impaired reality testing. At the neuroanatomical and neurochemical level, this process may be induced by phasic dopamine release in the ventral striatum regulated by the frontal cortex (top-down inhibition) and hippocampus (behavioral context). It is not known, however, how reward/salience learning is associated with the psychosocial functions of schizophrenia patients and how dopaminergic drugs modulate these functions in clinical settings. Additionally, it is important to explore how aberrant salience participates in the emergence of mild psychosis-like experiences and schizotypal traits in the general population.

2. Aims

1. We investigated the relationship between reward/punishment learning and general psychosocial functions in patients with schizophrenia.
2. We tested how adaptive and aberrant salience are altered in Parkinson's disease (PD) patients receiving dopamine agonists. We also asked how psychosis-like experiences are related to these changes in PD.
3. We used a classic aversive conditioning paradigm by measuring skin conductance responses in healthy individuals. The critical question was the correlation between aberrant salience and psychosis-like experiences.

3. Methods

3.1. Participants

We tested two populations of patients: schizophrenia (n=40, mean age: 36.5 years, SD=10.0) and PD (n=20, mean age: 46.3 years, SD=7.9). PD patients were evaluated two times, a baseline non-medicated state and after 12 weeks of dopamine agonist therapy (pramipexole and ropinirole). Table 1 enlists the clinical scales and diagnostic tools that were used for the characterization of our samples. Both patient groups had healthy controls matched in age, gender, and education. In our third study, 100 healthy individuals participated (mean age: 36.8 years, SD=13.9).

These studies were approved by ethics boards (Semmelweis University and University of Szeged), and all participants gave written informed consent. The studies were done in accordance with the Declaration of Helsinki.

Table 1. Clinical scales and diagnostic tools

Scale/tool	Function
Mini-International Neuropsychiatric Interview	DSM-IV diagnosis of schizophrenia
Global Assessment of Functioning (GAF)	General psychosocial functioning
Positive and Negative Syndrome Scale (PANSS)	Clinical symptoms of schizophrenia
UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria	Diagnosis of PD
Unified Parkinson's Disease Scale (UPDRS)	Clinical symptoms of PD
Hamilton Depression/Anxiety Rating Scale	Severity of depression and anxiety
Young Mania Rating Scale (YMRS)	Severity of manic symptoms
Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE)	Schizotypal traits and subclinical psychosis-like experiences
Temperament Evaluation of Memphis, Pisa, Paris and San Diego Autoquestionnaire (TEMPS-A)	Affective temperament traits

3.2. Cognitive tasks

3.2.1. Reward/punishment guided category learning

Participants viewed one of four abstract images (S1-S4). 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. Each decision was followed by corrective feedback (reward – gaining points, punishment – losing points).

3.2.2. Salience attribution test

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

3.2.3. Conditioning of skin conductance responses

The unconditioned alarming stimulus was an aversive sound (loud car horn embedded in urban noise for 800 msec). Tolerance calibration started at 40 dB with 5 dB steps upwards. The conditioned stimuli (colored circles) predicting the unconditioned stimulus were presented in a 50% partial reinforcement schedule with a duration of 1 sec. The conditioned - unconditioned stimulus interval was 5 sec, and the intertrial interval was 9 sec.

4. Results

1. Reward and punishment learning performance correlated with the GAF scores in schizophrenia, and when other potential predictors were included in a general linear model, only the GAF score remained significant ($p=0.008$, $R^2=0.17$).
2. Dopamine agonists boosted both reaction time (implicit salience) and subjective visual-analogue rating (explicit salience) in PD. This effect was present for both adaptive and aberrant salience ($p<0.01$, PD non-medicated baseline vs. medicated follow-up, Tukey's test).
3. 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: $r=-0.65$, $p<0.005$; subjective 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. In healthy individuals, skin conductance responses for relevant conditioned stimuli were predicted by O-LIFE

introvertive anhedonia ($b^*=-0.33$, $p<0.001$) and unusual experiences ($b^*=-0.44$, $p<0.001$).

5. In the same population, irrelevant stimulus associated responses were predicted by the IQ ($b^*=-0.19$, $p<0.05$) and O-LIFE unusual experiences ($b^*=0.31$, $p<0.05$; full model: $p<0.01$, $R^2=0.18$).

5. Conclusions

Our results indicate that general psychosocial functioning is the best predictor of reward/punishment learning in schizophrenia. Regarding learning performance, patients show a high degree of heterogeneity.

We also revealed that dopamine agonists induce faster response times and higher subjective valuations for conditioned stimuli associated with reward in PD. Interestingly, a similar enhancing effect was found for irrelevant stimuli, indicating a degree of aberrant salience. This aberrant salience was related to subclinical psychosis-like experiences in PD, including perceptual distortions, magical thinking, and suspiciousness.

Aberrant salience can be detected in the general population, and not only in schizophrenia patients and PD patients under dopaminergic medications. Aberrant salience may be related to psychosis-like experiences and schizotypal traits of everyday life which are far from the intensity/frequency to require clinical attention.

These results highlight the clinical importance of psychosocial rehabilitation in schizophrenia including

cognitive remediation, and the relevance of subclinical psychosis-like signs and symptoms in medicated PD patients. Clinicians are encouraged to monitor these subthreshold psychosis-like experiences, or changes in schizotypal traits because these phenomena may be useful in the early detection of clinically relevant psychosis.

6. 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.

Balog Z, **Somlai Z**, Kéri S. (2013) Aversive conditioning, schizotypy, and affective temperament in the framework of the salience hypothesis. *Pers Individ Diff*, 54: 109-112.

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.