

# **Cognitive and psychogenetic vulnerability markers of depression**

PhD theses

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## ***Introduction***

The disturbance of emotions and feelings is the primary symptom of affective disorders. Affective disorders are common and well-treatable. Recently genetic research has gained an important role in the research concerning the etiology of depression. Recently identification and functional characterization of polymorphisms became the main orientation of human genetic research. Several genetic and environmental factors play a role in the etiology of disorders with a complex inheritance such as depression. The association analysis of candidate genes is one of the most widespread approaches in the search for genetic predictors. The investigation of endophenotypes which can be associated with a gene variant with a higher chance, is in the focus of contemporary science. Also, recent studies aim at optimizing diagnostic systems, defining depression subtypes and thus expanding screening tests.

There is increasing evidence confirming the association of neuropsychological deficit and psychiatric diseases. The neuropsychological profile of major depression has not yet been fully described. Clinical associations can be found among the severity of illness, the cognitive deficit, the melancholic signs, and the age and gender of the patient. It is unclear whether the cognitive impairment is a significant predictor of the affective disorder.

Nowadays serotonin is the most widely investigated monoamine neurotransmitter in the central nervous system. One of the main candidate genes of the depression is the serotonin transporter gene (SLC6A4), with two well known functional polymorphic regions, the 5HTTLPR and STin2.

A non-synonymous single nucleotide polymorphism (SNP) of the P2RX7 gene (coding for the P2X7 purinergic receptor) has been also associated with major and bipolar depression.

### ***The objectives of our research were:***

- to investigate the neurocognitive processes in major depression.
- to determine if there is definite dysfunction within the global neurocognitive deficit characteristic of the depressive syndrome which may be a vulnerability marker of depression.

- to study the possible association between the neurocognitive dysfunction characteristic of depression and the STin2 polymorphism.
- If a cognitive vulnerability marker characteristic of depression can be identified, is it associated with the STin2 polymorphism influencing the activity of the serotonin transporter gene, and with which genotype?
- to investigate the effect of P2RX7 Gln460Arg SNP on depression and anxiety using dimensional scales, since quantitative assessment could facilitate the detection of small genetic effects.
- to investigate the gender differences in neurocognitive impairment in patients with depression and healthy controls.

### ***Methods***

The diagnosis of major depression and bipolar depression was based on DSM-IV criteria. Patients with any other organic or neurological disease and alcohol- and drug abusers were excluded from the study. All of the patients were assessed during the first four weeks of their current depressive episode. Healthy controls without psychiatric history were recruited. The study protocol was approved by the Health Science Board and the Local Ethical Committee. All participants provided written informed consent.

Clinical symptoms were assessed by the Montgomery-Åsberg Depression Rating Scale (MADRS), the Beck Depression Inventory (BDI), and the Hospital Anxiety and Depression Scale (HADS). Intellectual function was assessed by the RAVEN progressive matrix test. We measured neurocognitive functions associated with verbal learning and memory (Rey Auditive Verbal Learning Test), visual reconstruction and recall (Rey Osterreith Complex Figure Test), selective attention, executive functions and inhibitory control (Trail Making Test, Stroop Test).

Buccal epithelial cells were obtained by a non-invasive method. DNA was extracted and genotyped. The results were statistically analysed.

## ***Results***

### ***Comparative analysis of cognitive function***

There was no significant difference in the level intellectual functioning between patients and controls. The results indicated cognitive dysfunctions of the depressed patients in all tests compared to controls.

Patients performed worse in visual perception tasks compared to healthy controls. In the visual reconstruction test (ROFT „A”) the difference was significant between the clinical group and the controls ( $p=0.0003$ ). In the visual recall test (ROFT „B”) patient showed a non-significantly worse performance compared to controls. ( $0.0585$ ).

### ***Frequencies of the STin2 allele- and the genotype variants***

There was no significant difference in STin2 allele frequency between the study groups. The allele and genotype frequencies in our population showed no significant deviation from the Hardy-Weinberg equilibrium. We found a significantly higher frequency of the STin2 10/10 homozygous genotype in depressed patients compared to controls. There were no significant differences in heterozygous 10/12 and homozygous 12/12 genotype frequencies between the clinical and control groups.

### ***Association of the neurocognitive function and the STin2 genotype***

The clinical subgroup with at least one copy of the 10-repeat allele showed a decreased cognitive function in average. Average performance of the clinical subgroup without the 12-repeat allele proved to be significantly weaker in the working memory and recall tasks compared to patients having at least one copy of the 12-repeat allele.

### ***Association between depression and the Gln460Arg polymorphism of the P2RX7 gene***

A significant association was found between the P2RX7 polymorphism and the HADS scales in the clinical group. Both anxiety and depression scores increased depending on the number of the G-alleles. A significant interaction of clinical status and the P2RX7 polymorphism was also found for the depression scale. We could support the association between depressive disorder and the G-allele of the Gln460Arg polymorphism in the P2RX7 gene.

### ***Gender differences in the neurocognitive components of depression***

Depressed women performed significantly worse compared to depressed men in the test of visual recall (Rey-Osterreith Complex Figure Test). Depressed women performed significantly worse compared to depressed men in the test of cognitive interference threshold compared to depressed men (Stroop 3).

### ***Conclusion***

Our results confirm the accepted surmise that neurocognitive impairment can be detected in depression. Neurocognitive deficit have been demonstrated in almost all neurocognitive tests in the depressed group. The neurocognitive deficit can be demonstrated as a trait sign independent from clinical stage, and in remission and in healthy relatives of bipolar patients as well.

Remission and neurocognitive function are relatively independent of each other. The brain activation is different in fMRI during the cognitive interference test in euthymic bipolar patients and healthy controls. These data demonstrated the trait signs of neurocognitive function associated with depression. Our results confirm these findings, we found heavier impairment in selective attention, cognitive flexibility, executive function and working and verbal memory.

In the visual recall test there was no significant difference between the depressed patients and the controls. Our result confirm earlier results that there is intact short and long-term visual memory with impaired attention and executive function in remission. This information suggests intact hippocampal function during remission. The neuropsychological function was assessed in the first four weeks of the current episode, but not in the remission in our study. We suggest that the slightly impaired visual recall can be an important sign in the first period of the episode. Further studies are necessary to investigate the average neurocognitive deficit as a vulnerability marker of depression.

We found a significant difference in the frequency of the serotonin transporter gene STin2 genotype: the 10/10 homozygous genotype was twice more frequent in the clinical group compared to controls.

We established that the STin.2.10 allele showed a negative effect in some cognitive parameters in depression. These data suggest that there is an association between the homozygous STin2.10 allele and cognitive dysfunction in depression.

Case-control analysis did not show a significant difference between the groups concerning the P2X7 gene Gln460Arg polymorphism. Using the HADS scale as a dimensional scale we could support the association between depressive and depression-related anxiety symptoms and the G-allele. There was significant association between the clinical state (MD, BP, controls) and the P2RX7 gene G-allele in case of the depression subscale. It is not yet clearly understood what kind of mechanism the P2X7 receptors are involved in within the central nervous system. In the central and peripheral nervous system, the P2X7 purinergic receptors are expressed on microglial cells as well as on neurons and astrocytes. They take part in inflammatory responses, and the cross-talk between glia and neurons. The activated astrocytes can produce growth or trophic factors promoting neurogenesis or enhancing neuronal survival.

The symptoms of depression or anxiety are more common in women than in men. There are important differences between the female and male phenotypes of depression. It is well-known that healthy females perform better in verbal function and males perform better in visual function. A lot of studies report on the difference in the gender characteristic of the brain activation trends and in lateralization, which cause differences in cognitive strategies. In the light of neuroimaging studies our results suggest that in the background of gender differences we observed in depressed patients the lateralization of hippocampal function may play a role: in females the left and in males the right lateralization can be certified. This difference causes advantage in non-verbal functions in males. The neuroimaging assessments during the cognitive interference test (Stroop) show the hyperactivity of the rostral anterior cingulate cortex in healthy controls, and the left dorsolateral prefrontal cortex in unipolar depressed patients.

Our results are similar to the results from other reports. Depressed patients performed significantly worse in the word-colour incongruency tests compared to controls, and depressed females performed significantly worse in the same tests compared to depressed males.

### ***Journal articles related to the thesis***

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