Neurocognition and psychogenetic vulnerability in depression

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The clinical symptoms of major depression are paralleled by typical neurocognitive deficits. The relation of STin2 - one of the polymorphisms of the serotonin transporter gene - to major depressive disorder (MDD) is less widely investigated. The aim of the present study was to measure the neurocognitive functions of major depressive patients and healthy controls, and identify vulnerability markers of the disease. The frequency of STin2 polymorphism and its effect on neurocognition was investigated in major depression. The gender differences in neurocognitive impairment in patients with major depressive disorder were also studied. Relative to controls, patients with depression showed significant impairment on most neurocognitive tasks, but not in tasks measuring visuo-spatial function, which may suggest intact hippocampal function in depression. We found a significantly higher frequency of the STin2 10/10 genotype in the MDD patient group compared to controls. Our results suggest that the presence of STin2.10 and absence of STin2.12 may be considered a possible genetic endophenotype for cognitive dysfunction detected in major depressive disorder. Depressed women performed significantly worse on tests of cognitive interference and visual recall threshold compared to depressed men. In the light of neuroimaging studies our results suggest that the lateralisation of hippocampal function may play an important role in the background of gender differences.

Keywords: depression, neurocognition, cognitive dysfunction, vulnerability marker, serotonin transporter, STin2 polymorphism, endophenotype, gender difference

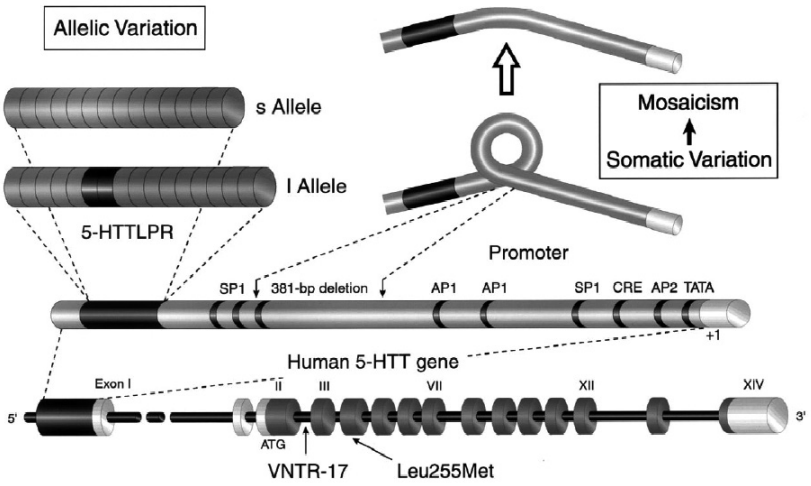
The disturbance of emotions and feelings is the primary symptom of affective disorders. Recently genetic research has gained an important role in the investigations concerning the etiology of depression and identification and functional characterization of polymorphisms associated with this disorder became the main orientation of 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 corresponding to a higher chance is in the main 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 deficits and psychiatric diseases (Nemeroff, 1999). The neuropsychological profile of major depression has not yet been fully described (Mayberg, 1997; Deverts, 2000; Brody, 2001). Clinical associations can be found between severity of illness, cognitive deficit, melancholic signs, and age and gender of the patient (Nelson, 1998; Austin, 1999; Sweeney, 2000; Grant, 2001; Landro, 2001). It is unclear whether the cognitive impairment is a significant predictor of affective disorder (Ottowitz, 2002).

Nowadays serotonin is the most widely investigated monoamine neurotransmitter in the central nervous system (Meneses, 1999; Lesch, 2001; van Kesteren and Spencer, 2003). One of the main candidate genes in depression research is the serotonin transporter gene (SLC6A4, Figure 1) (Heils, 1996; Du and Faludi, 1999; Najamura, 2000; Kato, 2007), with two well-known functional polymorphic regions, the 5HTTLPR

Figure 1. Allelic variation in the serotonin transporter gene (Lesch, 2001)



and STin2 (MacKenzie and Quinn, 1999; Fan and Sklar, 2005; de Lara, 2006; Sarosi, 2008). However, the role of this gene and its polymorphisms is not fully understood in the background of depression, and it is still to be established which processes mediate the effect of the presence of the polymorphic variants.

Therefore the primary aims of our research were as follows:

1. to investigate the neurocognitive processes in major depression.
2. 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.
3. to study the possible association between the neurocognitive dysfunction characteristic of depression and the STin2 polymorphism.
4. to determine if a cognitive vulnerability marker characteristic of depression can be identified, and if it is associated with the STin2 polymorphism influencing the activity of the serotonin transporter gene.
5. 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) (Montgomery-Åsberg, 1979), the Beck Depression Inventory (BDI) (Beck, 1961), and the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983). Intellectual function was assessed by the RAVEN Progressive Matrices Test (Szegedi, 1988). We measured neurocognitive functions associated with verbal learning and memory (Rey Auditive Verbal Learning Test) (Rey, 1969), visual reconstruction and recall (Rey Osterreith Complex Figure Test) (Osterreith, 1944; Rey, 1969), selective attention, executive functions and inhibitory control (Trail Making Test, Stroop Test) (Stroop, 1935; Spreen and Strauss, 1998).

Buccal epithelial cells were obtained by a non-invasive method. DNA was extracted and genotyped. The results were statistically analysed (Freemann, 1997; Boor, 2002; Cheng, 1998; Nemoda, 2001).

RESULTS

Comparative analysis of cognitive function

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

patients in all tests compared to controls. The mean MADRS score was 30.3±11.0; and the mean BDI score was 17.9±7.8 in the depressed group. (Table 1.)

Table 1. Montgomery-Åsberg Depression Rating Scale and Beck Depression Inventory main scores

	Depressed group (N=71)	
	Mean	*SD*
MADRS	30.3	11.0
BDI	17.9	7.8

Patients performed worse in visual perception tasks compared to healthy controls. In the visual reconstruction test (ROFT "A") the difference was significant between the depressed group and controls (p=0.0003). In the visual recall test (ROFT "B") patients showed a non-significantly worse performance compared to controls (0.0585). (Table 2.)

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. (Table 3.)

Association of neurocognitive function and STin2 genotype

The depressed subgroup with at least one copy of the 10-repeat allele showed overall decreased cognitive function. Average performance of the depressed 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. (Table 4., 5.)

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). (Table 6.)

Depressed women performed significantly worse compared to depressed men in the test of cognitive interference threshold compared to depressed men (Stroop 3). (Table 7.)

Table 2. Visual reconstruction test and visual recall test results of the depressed and control group

	Depressed group (N=71)		*Control group (N=30)*		*t test*
	Mean	*SD*	*Mean*	*SD*	*p*
ROFT A	32.7	3.7	35.3	1.1	0.0003
ROFT B	18.5	8.4	22.1	8.8	0.0585

Table 3. STin2 allele and genotype frequencies in depressed patients and controls

STin2 allele	*Controls*	*Patients*	*t*	*STin2 genotype*	*Controls*	*Patients*	*t*
9	3.3%	1.2%	n.s.	**9/12**	5.7%	2.5%	n.s.
10	34.4%	42.0%	n.s.	**10/10**	11.6%	24.6%	*p*=0.05*
12	62.3%	56.8%	n.s.	**10/12**	45.9%	34.6%	n.s.
				12/12	36.8%	38.3%	

n.s.= non sigificant, X^2=6.01, df=2, *significant

Table 4. Neurocognitive scores of subjects carrying and not carrying the STin2.10 allele

	+ 10 allele		*- 10 allele*		*t test**
	Mean	*SD*	*Mean*	*SD*	*p*
N	42		27		
Age	51.2	9.8	50.3	11.1	0.7445
MADRS	30.6	10.7	29.7	11.5	0.7425
BDI	18.0	7.7	18.2	8.1	0.9171
TRAIL A	68.0	36.3	53.6	20.6	0.0651
TRAIL B	153.2	71.6	126.6	69.9	0.1330
STROOP 1	89.4	15.3	90.4	15.6	0.8073
STROOP 2	66.4	15.3	68.1	18.6	0.6818
STROOP 3	**38.1**	**12.4**	**44.7**	**12.5**	**0.0409**
RAVLT I-V	39.6	10.9	43.4	9.1	0.1292
RAVLT VI	7.1	3.3	8.6	2.8	0.0712
RAVLT VII	6.9	3.8	8.3	3.4	0.1299
ROFT A	32.1	4.2	33.6	2.6	0.0910
ROFT B	18.4	9.0	18.9	7.7	0.8115

*$p < 0.05$ significant

Table 5. Neurocognitive scores of subjects carrying and not carrying the STin2.12 allele

	+ 12 allele		*- 12 allele*		*t test**
	Mean	*SD*	*Mean*	*SD*	*p*
N	53		16		
Age	50.3	10.4	51.0	10.1	0.3903
MADRS	30.0	11.5	29.3	9.6	0.7541
BDI	18.1	8.4	17.2	6.4	0.8709
TRAIL A	60.0	29.9	62.2	33.8	0.2624
TRAIL B	140.3	75.1	141.7	48.4	0.5994
STROOP 1	88.6	16.7	95.8	6.6	0.2634
STROOP 2	66.4	17.4	74.1	10.3	0.5777
STROOP 3	41.4	13.3	37.8	9.6	0.3963
RAVLT I-V	**42.6**	**9.9**	**37.4**	**9.3**	**0.0292**
RAVLT VI	**8.3**	**3.0**	**6.5**	**3.1**	**0.0059**
RAVLT VII	**8.0**	**3.5**	**6.3**	**3.8**	**0.0322**
ROFT A	32.8	3.6	33.0	2.4	0.5279
ROFT B	19.2	8.2	16.0	9.4	0.2178

*$p < 0.05$ significant

Table 6. Results of visual reconstruction and visual recall tests

	Patients			*Controls*			*t-test (p)*		
	All N=96	*Male N=37*	*Female N=59*	*All N=52*	*Male N=20*	*Female N=32*	*Patients-controls*	*Depressed male-female*	*Controls male-female*
ROFT A	33.0±4.0	33.1±4.9	32.9±3.3	35.2±2.0	34.8±3.0	35.5±1.0	**0.0003**	0.8470	0.2569
ROFT B	19.2±7.8	22.1±6.8	17.3±8.0	22.9±8.8	23.1±8.4	22.9±9.1	**0.0101**	**0.0036**	0.9450

Table 7. Results of the Stroop test

	Patients			*Controls*			*t-test (p)*		
	All N=96	*Male N=37*	*Female N=59*	*All N=52*	*Male N=20*	*Female N=32*	*Patients-controls*	*Depressed male-female*	*Controls male-female*
STROOP 1	93.2±11.1	94.7±10.2	92.3±11.6	95.9±10.0	98.2±4.4	94.5±12.1	0.1702	0.3551	0.2262
STROOP 2	71.4±13..9	74.9±14.1	69.2±13.5	81.9±14.3	82.9±16.8	81.3±12.8	**0.0001**	0.0738	0.7039
STROOP 3	40.2±12.4	45.3±11.1	37.2±12.3	49.4±12.5	51.6±16.3	48.2±9.6	**0.0001**	**0.0036**	0.3681

CONCLUSION

Our results confirm the accepted surmise that neurocognitive impairment can be detected in depression. Neurocognitive deficits 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 (Hammar, 2003; Weiland-Fiedler, 2004; Clark, 2005; Bearden, 2001).

Remission and neurocognitive function are relatively independent of each other. (Kuny and Stassen, 1995). The brain activation is different in fMRI during cognitive interference test in euthymic bipolar patients and healthy controls (Strakowsky, 2005), demonstrating 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 depressed patients.

In the visual recall test there was no significant difference between depressed patients and controls. Our results 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 (Weiland-Fiedler, 2004). Neuropsychological function was assessed in the first four weeks of the current episode, but not during 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 (Gutierrez, 1998; de Lara, 2006).

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.

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 (Sarosi et al., 2008). It is well-known that healthy females perform better in verbal function (Kramer and Wells, 2004). and males perform better in visual function (Peters, 2005). Several studies report on the difference in the gender characteristics of brain activation patterns 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 (Hsu, 2008; Frings, 2006). This difference causes advantage in non-verbal functions in males. Neuroimaging assessments during the cognitive interference test (Stroop) show the hyperactivity of the rostral anterior cingular cortex in healthy controls, and the left dorsolateral prefrontal cortex in unipolar depressed patients (Ottowitz, 2002; Strakowsky, 2005; Wagner, 2006).

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.

Disclosure. This article is based on the doctoral theses of Andrea Sárosi. However, several colleagues participated in the experiments reported. The author wishes to acknowledge her tutor Prof. Gábor Faludi, Prof. Mária Sasvári-Székely, Anna Székely, Judit Kása and Gabriella Balogh for their help and participation in her research.

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Neurokogníció és pszichogenetikai vulnerábilitás depresszióban

A major depresszió klinikai tüneteit jellegzetes kognitív folyamatok kísérik. A szerotonin transzporter génjének egyik ismert polimorfizmusa a STin2 polimorfizmus, melynek depresszióra gyakorolt hatásáról keveset tudunk. Vizsgálatunk célja egyrészt a depressziósok és kontroll személyek kognitív teljesítményének összehasonlítása volt, mely alapján a betegség néhány vulnerábilitás markere meghatározható. Vizsgáltuk továbbá a STin2 polimorfizmus előfordulását major depresszióban, és felmértük e polimorfizmus kognitív teljesítményre kifejtett hatásait. Vizsgáltuk a neuropszichológiai jellemzők nemi különbségeit is. A depressziós csoport eredményei a kognitív funkciók többségében szignifikánsan rosszabbak voltak a kontrollcsoporténál, kivéve a tér-vizuális konstrukció próbát, ami a hippokampális folyamatok intaktságára utalhat depresszióban. A major depressziós csoportban a STin2 10/10 genotípus szignifikánsan gyakoribb volt, mint a kontrollcsoportban. Eredményeink szerint a szerotonin transzporter gén STin2.10 allél jelenléte és a STin2.12 allél hiánya a major depresszió kognitív diszfunkcióinak lehetséges endofenotípusaként értelmezhető. A neurokognitív funkciók nemi különbségeinek vizsgálatakor a depressziós nők szignifikánsan rosszabbul teljesítettek a vizuospaciális felidézés és a kognitív interferencia feladatokban. A depressziósok között észlelt nemi kognitív különbségek hátterében a hippokampusz funkció eltérő lateralizáltsága állhat, amit a képalkotó vizsgálatok is alátámasztanak.

Kulcsszavak: depresszió, neurokogníció, kognitív diszfunkció, vulnerábilitási marker, szerotonin transzporter, STin2 polimorfizmus, endofenotípus, nemi különbség