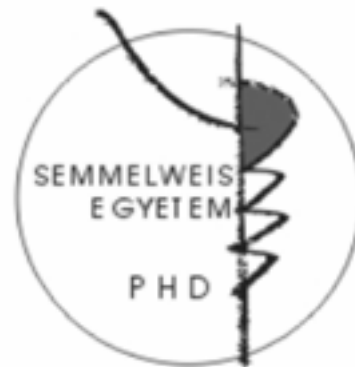


The effect of the COMT gene and impulsivity, rumination, and their role in the development of depression.

Thesis

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Introduction

Depression

Depression affects about 350 million people worldwide, and this is the third leading cause of disability in developed countries. It is predicted that it will be the first cause of disease burden by 2030 according to the latest survey by the World Health Organization. Depression has been characterized by specific cognitive changes that appear in parallel with depressive symptoms and alter the thought style of depressed patients towards negative ideas about themselves and about their future, eventually leading to impairment in all areas of their lives. The cognitive symptoms also include reduced concentration and problem-solving skills. These symptoms typically develop by functional changes in the information processing brain areas including the prefrontal cortex (PFC) and the hippocampus. Damages of these regions lead to alteration in psychomotor speed, working memory, selective attention, cognitive flexibility, executive functions, and complex problem solving.

According to the psycho-neuro-biological model of depression, the mental health is dependent on the psychological, neurological and biological events that arise throughout the development and the additive results of these events will also determine the physical health and personality of an individual. Brain development is influenced by interaction of genetic and environmental effects, activity-dependent neuronal plasticity, and the time windows when protective or risk factors exert their effects. Mental models based on early experiences allow the anticipation of the future, contributing to social learning. Due to the sequential maturation of the PFC the early pathologies remain hidden until adolescence, when the PFC takes control over the predominantly amygdala-directed emotional regulation.

Dopamine (DA) plays an important role in mood regulation, such as control of emotions, behaviour, and cognition. Several studies have shown that changes in DA level in the PFC are associated with cognitive alterations in psychiatric disorders. Most importantly the impairment of the top-down frontal cortical control leads to the overactivation of subcortical limbic areas.

COMT gene

In the PFC, the catechol-O-methyltransferase (COMT) enzyme is the rate limiting factor in eliminating DA from the synaptic cleft. The most studied COMT gene polymorphism is a Valine to Methionine substitution (rs4680), which affects the thermostability of the produced protein. The Valine-containing protein is stable thus 3 to 4

times more efficient in the DA catabolism than the Methionine-containing enzyme version. The combination of the Valine and Methionine coding alleles in the rs4680 polymorphisms of the COMT gene determines three activity levels: low, medium, and high. It is assumed that the homozygous Valine carriers have the highest COMT activity, leading to relative DA deficiency in the PFC, while the homozygous Methionine carriers have the lowest COMT activity, thus the highest DA level in the PFC.

The PFC organises and coordinates the various regions of the brain that are involved in information processing and cognitive function. The two important components of the adequate cognitive function are flexibility and rigidity. Both cognitive styles are required for optimal adaptive thinking. Cognitive flexibility ensures that we can adapt to new information in a constantly changing environment. Cognitive rigidity is required to consider the specific situations and summarize life experiences. Due to the fact that the COMT gene determines the DA level in the PFC, variants of the COMT gene indirectly control cognitive abilities through the PFC function. If the DA level is very low the cognition became too rigid, but too high DA level causes uncontrollable switches in the cognitive styles. As the COMT gene one of the main factors that determines the function of the PFC, it is plausible that it has a role in the altered information processing in mood disorders, as well.

Impulsivity

The most widely accepted definition of impulsivity is that impulsive individuals act of the heat of the moment without considering the consequences. Impulsivity partially originated from the dysfunction of the PFC, which is the main regulator of executive function. If the PFC is not working properly, the integrated inhibitory function is impaired. Impulsivity may be due to poor inhibition control, low-attention, or a series of bad decisions. The heritability of impulsivity indicates its genetic background. The dopaminergic system plays an important role in the development of impulsivity partially through the PFC, hence investigating the COMT gene is relevant. Variations in the dopaminergic genes alter the structural and functional connectivity of the frontostriatal system, causing individual differences in behavioral inhibition. The effect of impulsivity in depression has not been studied intensively yet, despite psychological, biological and morphological data which warrant further examinations.

Rumination

The unpleasant and distressing automatic thoughts are present in the everyday life of depressed patients, from which they can not escape. Their cognitive style are dominated by inflexibility, excessive rigidity, negative self monitoring, recurrent negative and intrusive thoughts. This kind of distortion of executive function can lead to development of depression. The PFC plays an important role in rumination by constantly re-evaluating emotionally significant events and thus allocating alternative meaning to them. The ruminating people typically waste too many (negative) thoughts on themselves, so there is not enough attention for problem solving. In depression, the top-down frontal cortical control is impaired, and a negative emotional bias is characteristic especially in case of self-relevant information. This is based on altered connectivity between those brain regions, such as the PFC and subcortical limbic areas, which are involved in conflict monitoring and attentional control. In depression, the regulatory function of the frontal cortical areas are impaired, thus the attentional and emotional control disturbed, characterised by amygdala overactivity. The dominance of the subcortical limbic areas eventually leads to maladjusted emotional life. In summary, the ruminative thinking style is based on the weaknesses of cognitive control and not purely on negative patterns in working memory.

Aims

Our aim was to investigate the impact of COMT gene on impulsivity and rumination as a possible intermediate phenotypes in Hungarian and English population cohorts. Another objective was to determine whether impulsivity and rumination as intermediate phenotypes affects the susceptibility to depression. In the literature the connection between COMT gene and depression nor or little studied, however, a number of psychological and biological data would justify the exploration of the possible link, that can contribute to a better understanding of predisposition to depression. The most studied functional polymorphism in COMT gene is a Val158Met substitution (rs4680). However, the results are contradictory in many cases, so in our analyses we used three other tagging SNP-s to cover the whole COMT gene and investigated its relationship with depression and related intermediate phenotypes. To better understand the effect of COMT variants on vulnerability to depression, we used different measure of cognitive function. In our analysis we investigated different allele variants of COMT gene polymorphisms. Rumination, as an intermediate phenotype, is an important cognitive risk factor for depression, thus our further aim was to examine the relationship

between rumination and COMT gene. Furthermore we were investigated the combined effect of impulsivity and rumination on depression.

In our studies we aimed to investigate the following hypotheses in a large Hungarian and English population cohort

A. What is the role of impulsivity and the COMT gene in the development of depression?

1. Are the COMT gene haplotypes associated with impulsivity?
2. Does the COMT gene exert its effect on depression directly or indirectly, through impulsivity?
3. Does the PFC play a role in the development of depression through the measured impulsivity, or independently through other cognitive factors?
4. What is the role of impulsivity in the development of depression?

B. Does the COMT gene play a role in the development of rumination?

1. Is there any association between the COMT gene and the ruminative phenotype representing rigid cognition?

C. What kind of complex relationship exists between rumination, impulsivity and depression?

1. Does rumination or impulsivity convey the effect of childhood and adulthood threatening life events to depression?
2. Rumination or impulsivity represents the stronger phenotypic risk factor?
3. In what way and how can the co-occurrence of impulsivity and rumination increase the risk of depression?
4. What is the complex relationship between the phenotypes listed above (Structural equation modeling, SEM)?

Methods

Subjects

In this thesis three studies were presented. In our studies male and female volunteers aged 18-60 years were involved from Budapest and Manchester. To ensure genetic homogeneity participants of Caucasian origin were included in the analyses. Subjects with hypomanic episodes, obsessive-compulsive and psychotic symptoms or with non-Caucasian origin were excluded from the study. In Manchester, the study was designed to carry out two levels. In the second level the subjects were invited for a face-to-face diagnostic interview and psychological testing session. The second and third study was single stage.

Populations involved in the studies, as well as questionnaires and statistics used in the summary table

	1. STUDY			2. STUDY		3. STUDY
	Manchester	Budapest	Interviewed population (Manchester)	Budapest	Manchester	
<i>Number</i>	1267	942	207	939	1267	2588
<i>Woman</i>	70%	71%	69%	71%	70%	30%
<i>Man</i>	30%	29%	31%	29%	30%	70%
<i>Age</i>	34±0,3	31±0,3	32±0,7	31,7±10,4	33,7±10,2	32,8±10,5
QUESTIONNAIRES						
<i>Impulsivity</i>	IVE		NEO-PI-R neur/imp	--		IVE
<i>Rumination</i>				RRS		RRS
<i>Neuroticism</i>	BFI		NEO-PI-R neur.	--	--	BFI
<i>Currend depression</i>	BSI depr.		MADRS	--	--	BSI depr.
<i>Lifetime depression</i>	BGR		SCID	--	--	BGR
<i>Childhood trauma</i>	--		--	--	--	CTQ
<i>Adulthood trauma</i>	--		--	--	--	TLE
<i>Anxiety</i>	--		--	--	--	BSI anx.
<i>Cognitive test</i>	--		SOC	--	--	--
<i>Genetic</i>		VAN			VAN	--
STATISTICS						
<i>Haplotype-phenotype association</i>	Association study (PLINK)			SPSS 15.0		SPSS 15.0
<i>Models</i>	SEM			--		SEM

BFI (BigFive, neurotics subscale)
 BGR (Background Questionnaire)
 BSI anx. (Brief Symptom Inventory anxiety subscale)
 BSI depr. (Brief Symptom Inventory depression subscale)
 CTQ (Childhood Trauma Questionnaire)
 IVE (Eysenck Impulsivity Questionnaire)
 NEO-PI-R neur/imp (NEO-PI-R neuroticism-impulsivity subscale)

NEO-PI-R neur. (NEO-PI-R neuroticism subscale)
 MADRS (Montgomery Asberg Depression Rating Scale)
 RRS (Rumination Response Scale)
 SCID (Structural Clinical Interview for DSM-IV)
 SEM (Structural Equation Modelling)
 SOC (Stocking of Cambridge)
 TLE (Threatening Life Events)

Results

In summary, our study demonstrated a significant association between the COMT gene haplotypes and impulsivity, in two independent populations. According to our results, the polymorphisms of COMT gene influence cognitive performance, and thus impulsivity, eventually leading to increased vulnerability to depression. Based on these results impulsivity is a possible intermediate phenotype of depression. In the Budapest cohort we found significant association between COMT gene polymorphisms and depression. In the next study the COMT gene showed significant association with rumination, also in the Budapest sample. The investigation of the complex relationship between impulsivity, rumination and depression demonstrated that subjects characterized by high rumination and high impulsivity have the highest risk of developing depression. Our genetic and phenotypic analyses serve as a basis of a complex model, in which impulsivity and rumination as a possible intermediate phenotypes may play a role in the development of depression.

Our main results and the conclusions can be summarized in the following brief points:

1. There is a relationship between the COMT gene variants and impulsivity, which effect has been replicated in our two independent populations.
2. A significant association was found between depressive symptoms and the tested haplotypes, which was predominant in healthy individuals. It is assumed that in previously depressed subjects this effect is masked by other mechanisms (e.g. negative emotional and attentional bias), which alter the function of the PFC.
3. We set up a model examining the complex relationship between impulsivity, depression and the COMT gene. Based on these results the COMT gene has a direct effect on depression, and an indirect effect through impulsivity and neuroticism. Impulsivity also showed independent direct effect on depression scores.
4. We completed the above model with cognitive measures and proved that the COMT gene is a risk factor for depression not only via impulsivity but via other cognitive mechanisms.
5. To our knowledge, this is the first study to demonstrate significant association between the COMT gene haplotypes and rumination in large population cohorts.

6. Our data suggest that T,A,A(M),C, and T,G,G(V),C haplotype carriers have lower scores on impulsivity, and higher scores on rumination scale despite they carrying different alleles at the rs4680 functional polymorphism. Our results provide further evidence that the Val158Met polymorphism (rs4680) does not determine the function of the COMT gene itself, so the investigation of tagging SNPs that cover the whole gene are required to understand its relationship with complex phenotypes.
7. Based on our phenotype experiments impulsivity is a risk factor for depression and plays a role in the depressogenic effect of childhood adversity and adult negative life events, but this effect is weaker than the effect of rumination.
8. The most vulnerable phenotypes for depression characterised by high level of impulsivity and rumination. Interestingly, this phenotype combination is frequent, nearly 25 % in our studied populations. The high risk for depression in this subgroup may be explained by maladaptive rumination for stress, which by increasing the distress may eventually lead to impulsive behaviour as a result of the weakened emotional and behavioral control.

Summary

According to the WHO, depression will be the first cause of disability by 2030 causing serious burden for individuals and financial loss to society. Therefore, to better understand the underlying mechanisms of depression it is necessary to perform large scale studies, which simultaneously take into account the biological and psychological risk factors of depression and investigate their complex relationship. Using this approach, we investigated the effect of the COMT gene haplotypes on impulsivity, depression and rumination in two large population cohorts, and modelled the complex relationships between these phenotypes. We confirmed that impulsivity, representing a too flexible cognition, can be a risk factor for depression. Furthermore, the COMT gene showed significant association with impulsivity and depression scores. In addition, we demonstrated that the COMT gene also associated with rumination, which represents a too rigid cognition. These results indicate that optimal cognitive stability improve performance in everyday life, while too flexible or rigid forms of cognition, like impulsivity and rumination are risk factors for depression. According to our expectations, those COMT haplotypes that were risk factors for rumination proved to be protective for impulsivity and vice versa, so we demonstrated opposite effects of COMT haplotypes on impulsivity and rumination. However, at phenotypic level high rumination and impulsivity can occur together creating the most vulnerable group in terms of developing depression. This phenomenon can be explained by the multifactorial origin of our studied phenotypes. According to this observation, genetic effects can be better discovered at intermediate phenotype level, while at the diagnosis level it is difficult to determine biological and genetic risk factors. Thus our results further emphasise that it is necessary and essential to use intermediate phenotypes in depression to identify genetic risk factors and useful biomarkers for this devastating disorder.

Publication list

Publications relevant to the dissertation

Pap D, Gonda X, Molnar E, Lazary J, Benko A, Downey D, Thomas E, Chase D, Toth ZG, Mekli K, Platt H, Payton A, Elliott R, Anderson IM, Deakin JF, Bagdy G, Juhasz G.

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