DOI:10.14753/SE.2012.1655

Association between the C(-1019)G functional polymorphism of the HTR1A gene and impulsivity and subthreshold depression

Doctoral dissertation

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Budapest
2011

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1. ABBREVIATIONS

5CSRTT = 5-choice serial reaction time task

5-HT = serotonin

5HTTLPR = serotonin transporter length polymorphic region

AcbC = nucleus accumbens core

ACC = anterior cingulate cortex

ACh = acetylcholine

ACTH = adrenocorticotropic hormone

ADHD = attention deficit hyperactivity disorder

ANOVA = analysis of variance

APA = American Psychiatric Association

BDNF = brain-derived neurotrophic factor

BIS-11 = Barratt Impulsiveness Scale

BLA = basolateral amygdala

CB1 = cannabinoid receptor 1

CI = confidence interval

C–I = compulsive–impulsive

CNS = central nervous system

COMT = catechol-O-methyl transferase

CPP = 3-(2-Carboxypiperazin-4-yl)propyl-1-phosphonic acid

DAT = dopamine transporter

DEAF-1 = deformed epidermal autoregulatory factor-1

DF = degree of freedom

DNA = deoxyribonucleic acid

DSM-IV = Diagnostic and Statistical Manual of Mental Disorders version IV

DLPFC = dorsolateral prefrontal cortex

DRD4 = dopamine receptor 4

GLS = generalized least squares

HAB = habenula

Hes5 = hairy and enhancer of split 5

HPC = hippocampus

ICDs = impulse control disorders

ICD-NOS = impulse control disorders not otherwise specified

IL = infralimbic cortex

IRS = Impulsivity Rating Scale

IVE-I = Impulsiveness subscale of the Eysenck Impulsiveness, Venturesomeness, and Empathy scale

KO = knock out

LOPFC = lateral orbital prefrontal cortex

MAO = monoamine oxidase

MAOA = monoamine oxidase A

MAOIs = monoamine oxidase inhibitors

MD = major depression

MDMA = 3,4-methylenedioxy-methamphetamine

MinD = minor depression

ML = maximum likelihood

MS = medial striatum

NAC = nucleus accumbens core region;

NAS = nucleus accumbens shell region

NEO-PI-R = Neuroticism-Extroversion-Openness Personality Inventory - revised

NMDA = N-Methyl-D-aspartate

NS = Novelty Seeking

NUDR = nuclear deformed epidermal autoregulatory factor

OCD = obsessive–compulsive disorder

OCSD = obsessive–compulsive spectrum disorders

OFC = orbitofrontal cortex

PET = positron emission tomography

PFC = prefrontal cortex

PL = prelimbic cortex

SE = standard error

SEM = structural equation modelling

SERT = serotonin transporter

SD = standard deviation

SNP = single nucleotid polymorphism

SSD = subsyndromal symptomatic depression

sgACC = subgenual anterior cingulate cortex

SSRIs = selective serotonin reuptake inhibitors

STAXI = State Trait Anger Expression Inventory

STN = subthalamic nucleus

TCI = Temperament and Character Inventory

TCAs = tricyclic antidepressants

TPH = tryptophan hydroxylase

TPH1 = tryptophan hydroxylase

TPH2 = tryptophan hydroxylase

TPQ = Tridimentional Personality Questionnaire

VNTR = variable number tandem repeats

WIN552122 = [(R)-(+)-[2,3-dihydro-5-methyl-3[(4-morpholinyl)methyl]pyrrolo[1,2,3-de]-1,4 benzoxazinyl]-(1-naphthalenyl)methanone mesylate salt]

ZSDS = Zung Self-Rating Depression Scale

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2. INTRODUCTION

Serotonin-1A (5-HT1A) receptors are known to play a role in impulsivity-related behaviour. The C(-1019)G functional polymorphism (rs6295) has been suggested to regulate the 5-HT1A receptor gene (HTR1A) expression in presynaptic raphe neurons, namely, increased receptor concentration and reduced neuronal firing could be associated with the G allele. Previous studies indicate that this polymorphism is associated with aggression, suicide, and several psychiatric disorders, yet its association with impulsivity has rarely been investigated. Furthermore, studies reported that dysfunction of the serotonin 1A receptor may play a role in the background of depression. Some authors suggested a direct relationship between depression and impulsivity. It was noted that there are phenotypic associations occurring in childhood and adolescence between constructs relating to impulsivity and depression and impulsivity shares similar biological background, both are have been shown to be related to decreased serotonin levels. Despite these associations, it remains unclear whether impulsivity is a predictor of the onset of depression in adulthood. Prior research on this issue has typically focused on the relationship between impulsivity and suicide in clinical populations or in children or adolescents with attention deficit hyperactivity disorder (ADHD) or conduct disorders. There have been only a few studies addressing the question of associations between impulsivity and depressive symptoms in subclinical depressive or non-clinical populations.

Our study is part of a 5-year research project called NewMood, which is short for New Molecules in Mood Disorders. It is a Europe-wide research study, a collaboration between 13 research groups in 10 EU countries. Research groups aimed to investigate the possible genetic and phenotypic background of mood disorders and also, to discover new mechanisms of effective drug treatment leading to the development of novel antidepressant therapies in animal models and human studies. Our human study group consisting of pharmacists, psychologists, physicians and biologists, collected data using paper questionnaires in collaboration with the group of Manchester, developing a questionnaire booklet together.

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In the present study, as part of the NewMood research, we investigated the relationship between impulsivity and depression and the C(-1019)G polymorphism of the HTR1A in a non-clinical population sample of 725 volunteers using the Impulsiveness subscale (IVE-I) of the Eysenck Impulsiveness, Venturesomeness, and Empathy scale, the Barratt Impulsiveness Scale (BIS-11) and the Zung Self-Rating Depression Scale (ZSDS). We studied the association between impulsivity and ZSDS scores below the level indicating major depression and the affect of the C(-1019)G polymorphism on this relationship using the structural equation model.

The biological and psychiatric background of impulsivity and depression is discussed in the following chapters.

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2.1 Neurobiology of impulsivity

2.1.1 Neuroanatomy of impulsivity

Impulsivity can be characterized as a personality trait, and it is an immediate response to thoughts or deeds without any consideration of the appropriateness or consequences. A growing body of data has indicated that impulsivity is heterogeneous: it consists of several distinct behavioural phenomena that are dissociable at the neuroanatomical as well as neuropharmacological levels (*1*).

Consistent with human imaging and brain damage data (*2*), prefrontal cortical, striatal and limbic brain regions have been found to play an important role in impulsivity in rodents.

Functional differences have been reported between subregions of the nucleus accumbens in modulating impulsivity, suggesting the involvement of the core and not shell portion of the nucleus accumbens in impulsive action (*3*). It is innervated by dopamine neurons that respond to errors in reward prediction in a manner appropriate for a teaching signal (*4*). Causal experimental studies have shown that lesions of the nucleus accumbens core (AcbC) produce impulsive choice, reducing rats' preference for large/delayed rewards, compared to small/immediate rewards (*5*), and AcbC lesions have also been found to impair performance on a task requiring rats to choose between an uncertain immediate reward and a certain delayed reward (*3*). Figure 1. shows the neuroanatomical regions in the brain involved in impulsive action, in inhibitory control processes and delay aversion.

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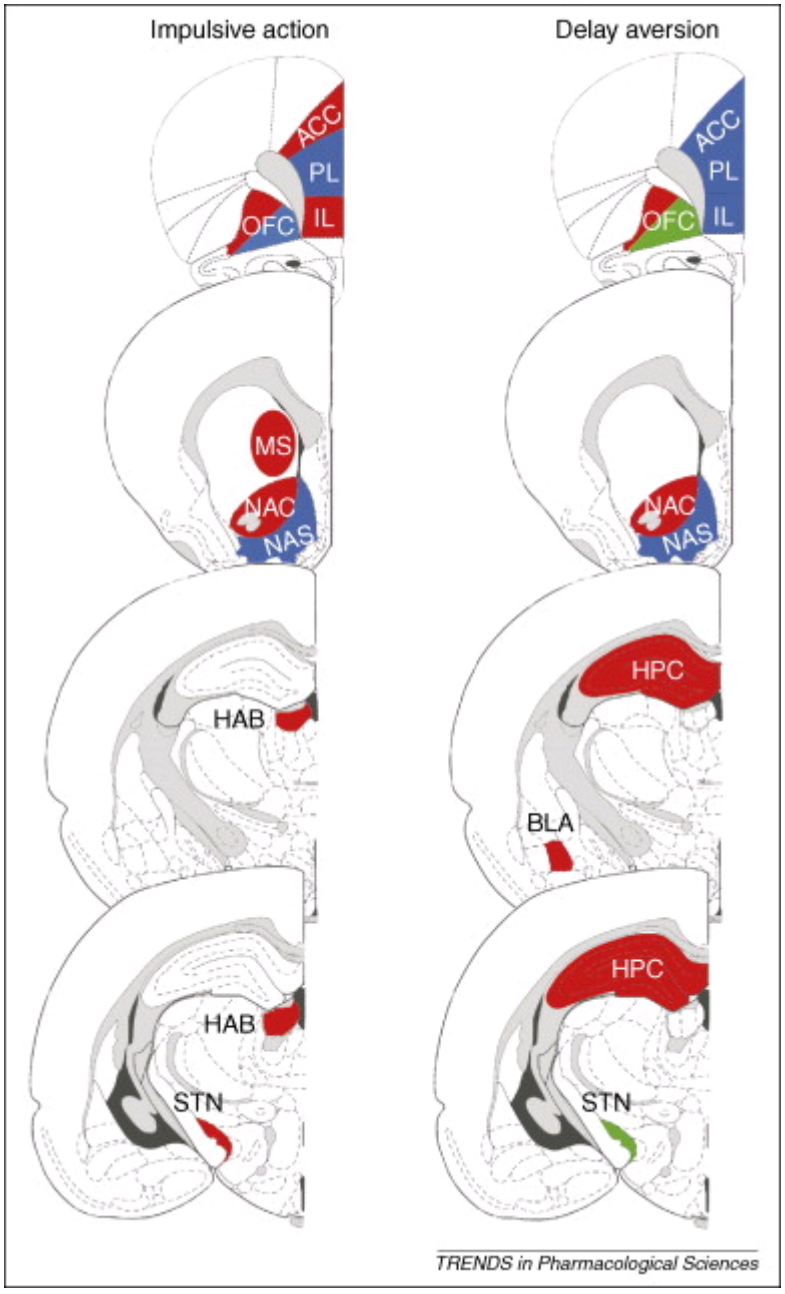
Figure 1. The neuroanatomical regions in the brain involved in impulsive action, in inhibitory control processes and delay aversion. Lesion studies demonstrated that there is considerable overlap in brain areas, including cortical and limbic regions, that modulate impulsive action and delay aversion in rodents. Red indicates that lesions of these regions increase impulsive action or delay aversion. Green indicates beneficial effects of lesions on impulsivity and in particular more self-controlled choice. Blue indicates that lesions of these brain regions did not affect impulsive action nor delay aversion; dark grey/black areas indicate ventricles in the brain, and light grey areas indicate fibre tracts in the brain. ACC, anterior cingulate cortex; BLA, basolateral amygdala; HAB, habenula; HPC, hippocampus; IL, infralimbic cortex; MS, medial striatum; NAC, nucleus accumbens core region; NAS, nucleus accumbens shell region; OFC, orbitofrontal cortex; PL, prelimbic cortex; STN, subthalamic nucleus. (*6*)



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The orbitofrontal cortex (OFC) is a region of the prefrontal cortex (PFC) that projects to the AcbC and is strongly implicated in the assessment of reward value. Choice between small, likely rewards and large, unlikely rewards increases cerebral blood flow in orbital and inferior PFC (*7*), with lesioned subjects deciding slowly and failing to choose the optimal, most likely outcome (*8*).

A role for limbic regions such as the habenula and hippocampus in impulsive action (*9*) has been more firmly established. The precise mechanisms by which these limbic structures affect impulsivity are not completely understood, although both regions project to striatal brain areas including the nucleus accumbens. The subthalamic nucleus (STN) is a component of the basal ganglia that receives projections both from the globus pallidus (pallidum) and the cerebral cortex (*10*). Lesions of the STN decreased impulsive choice in a task (*11*), a task in which OFC lesions had the same effect (*12*). There is good evidence that the hippocampus contributes to the representation of context and contextual conditioning is important in learning with delays. Lesions of the hippocampal formation have been shown to impair Pavlovian conditioning to a contextual conditioned stimulus in rats (*13*).

2.1.2 Neurochemical background of impulsivity

2.1.2.1 5-HT1A receptor

The 5-HT_{1A} receptor consists of a protein of 422 amino acids and it contains seven putative transmembrane domains and belongs to the G-protein-coupled receptor (GPCR) family (*14*). The intronless gene encoding the 5-HT_{1A} receptor is located on the human chromosome 5 at the locus 5q11.2-q13 (*15*). Studies show that the 5-HT_{1A} binding sites are especially abundant in the hippocampus, the lateral septum, the frontal and entorhinal cortex and the anterial raphe nuclei. Besides, the amygdala, the dorsal horn of the spinal cord, some thalamic and hypothalamic nuclei and the lateral part of the caude-putamen also express 5-HT1A receptors in a lower level (Figure 2.).

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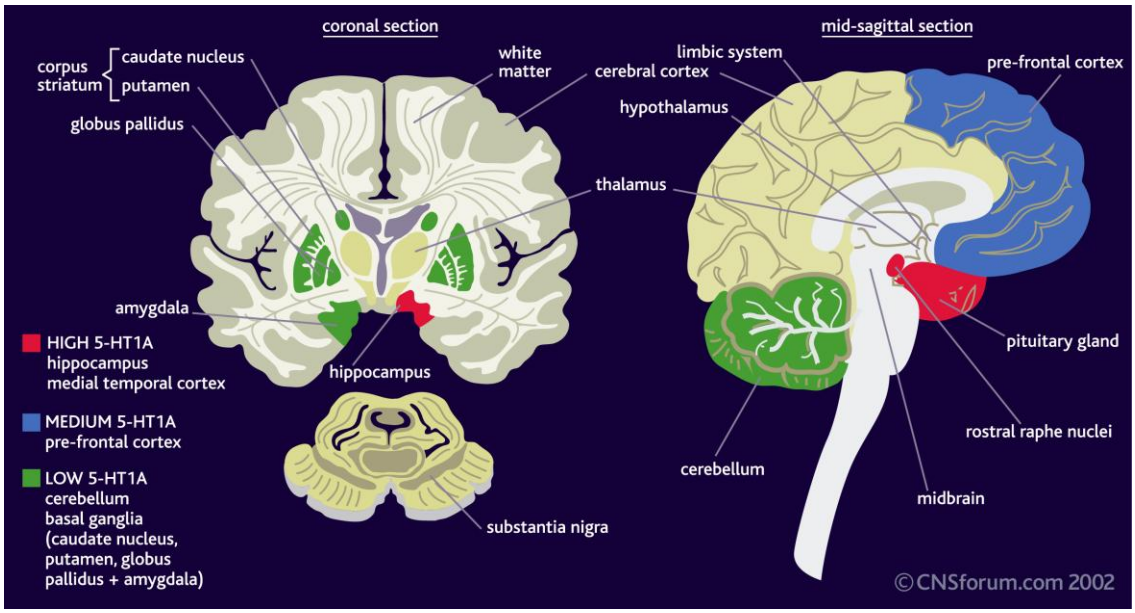
However, 5-HT_{1A} receptors hardly or not at all can be found in the cerebellum, the substantia nigra and in the globus pallidus (*16-18*).

Figure 2. Distribution of 5-HT_{1A} receptors.



5-HT_{1A} receptors are localized both on serotonergic neurons where they act as somato-dendritic autoreceptors and on the targets of serotonergic projections where they correspond to postsynaptic receptors (*17*), hence, different effects can be expected from their stimulation in the raphe versus other regions. Indeed, by acting at somato-dendritic autoreceptors, 5-HT agonists inhibit the electrical activity of serotonergic neurons reducing serotonergic neurotransmission. In contrast, at postsynaptic targets, 5-HT_{1A} agonists reproduce the effect of 5-HT which is released from serotonergic terminals therefore enhance 5-HT_{1A} receptor-dependent serotonergic neurotransmission (*19*).

The HTR_{1A} gene is located on the long arm of chromosome 5 (5q11.2-13) (*15*). The functional C(-1019)G polymorphism (also labeled as rs6295) is a common single nucleotid polymorphism (SNP) in the promoter region of the gene (*20*). The polymorphism is located within a 26 bp palindromic region, which binds the nuclear DEAF-1-related (NUDR) protein and Hes5; the G allele abolishes repression by NUDR, resulting in higher expression of HTR_{1A} enhancing the negative feedback inhibition of serotonergic raphe neurons exerted by HTR_{1A} autoreceptors and leading to lower serotonergic neurotransmission (*21*).

Previous studies indicate that the C(-1019)G polymorphism of the HTR_{1A} gene is associated with several psychiatric disorders including major depression (*21*) and anxiety disorders such as panic disorder with agoraphobia (*22*). It has also been found to be associated with suicide: Lemonde et al. (*21*) found an association between the G allele and completed suicide in an isolated population of French-Canadian origin and results from Sawiniec et al. (*23*) also indicated a significant role of the C(-1019)G polymorphism in the risk of suicide attempt. However, in the study of Serretti et al. (*24*), haplotype analysis in relation to suicidal behaviour did not reveal any significant association, although suicidal attempter females homozygous for the G allele scored significantly higher on the STAXI state anger scale. Studies investigating the possible association with suicide focused on both attempted and completed suicide, however suicidal behaviour is a more complex phenomenon. Besides its association with the serotonergic system (*25, 26*), suicide has also been linked to aggression and impulsivity (*27*); attempted suicides are related to impulsivity (*28*), while completed suicides to aggressiveness (*29*). Previously, both impulsivity and aggressiveness have also been associated with the serotonergic system (for a review, see Lee and Coccaro, 2001(*30*)).

Several studies have investigated a potential association between the C(-1019)G polymorphism and various personality traits; using the revised five-factor Personality Inventory (NEO-PI-R) and the Tridimensional Personality Questionnaire (TPQ), higher scores for Neuroticism and Harm Avoidance were found in carriers of the G allele compared with C allele carriers (*31*), although other studies did not find any significant association between neuroticism and this particular SNP (*32, 33*). Serretti et al. (*34*) failed to find any association between three SNPs in the HTR_{1A} gene or six SNPs in the HTR_{2C} gene and personality dimensions, measured by Cloninger's Temperament and Character Inventory (TCI).

2.1.2.2 Serotonergic system

The serotonergic system plays an important role in various physiological functions (*35, 36*), psychiatric disorders (e.g., anxiety disorders, depression, and

schizophrenia) (*37, 38*), and regulates complex functions related to cognition and emotions (*39*). At present, there are 14 different known serotonin receptors divided into 7 classes (*36*).

Serotonin (5-hydroxytryptamine, 5-HT) is among the oldest known biogenic amines (*40-43*). Serotonin is synthesised from the essential amino acid tryptophan, which is hydroxylated to 5-hydroxytryptophan (5-HTP) by tryptophan hydroxylase, and in a second step 5-HTP is decarboxylated to form 5-HT (*44*). The negative feedback created by stimulation of the 5-HT autoreceptor decreases further release of serotonin, while the serotonin transporter (SERT) removes serotonin from the synaptic cleft. SERT has been identified in the central nervous system (CNS), gastrointestinal tract, pulmonary and peripheral vasculature, and platelets (*45*).

Within the CNS, serotonin is synthesized and stored in presynaptic neurons. Serotonin is located in groups of cell bodies isolated to the pons and midbrain (*46*). The raphe nuclei represent the major nuclei with both ascending serotonergic fibers projecting to the forebrain and descending fibers that extend to the medulla and spinal cord. Furthermore, from the median raphe nuclei axons project to the limbic system, the hippocampus and the septum, and axons from the dorsal raphe nuclei provide innervation of the striatum and the thalamus (*46*). Serotonin synthesis outside the CNS is limited to enterochromaffin cells and to a lesser extent platelets, however, platelets are a major storage site for serotonin outside the CNS. About 90–95% of the body's serotonin is located in the periphery, mostly stored in platelets and enterochromaffin cells (*47*).

The serotonergic system plays an important role in various functions such as appetite (*48*), thermoregulation (*49*), sexual function (*50*), neuroendocrine regulation (*51*), motor activity (*52*), pain (*53*), memory and learning (*54*), sleep-wake cycle (*55*), aggression (*56*), mood (*57*), impulsivity (*58*), anxiety (*59*) and regulates complex functions related to cognition and emotions (*39*).

Previous animal and human research showed that serotonin is implicated in impulsivity (*60, 61*). Its interaction with other neurotransmitters, including dopamine, noradrenaline and glutamate, has been investigated as well.

Low brain serotonin level has been associated with increased impulsive choice in animals (*62*) and in humans (*63*), but contradictory findings have also been described

(*64, 65*). The role of 5-HT receptors, mainly 5-HT_1 and 5-HT_2 receptors, have been well studied in the regulation of impulsivity. These receptors can be located presynaptically on 5-HT neurons, where their activation inhibits the release of 5-HT. Thus, treatment with 5-HT_{1A} agonists would result in decreased 5-HT efflux (*66*). Selective 5-HT_{1B} receptor agonists and antagonists have been ineffective in altering impulsivity (*67*) while antagonists of the 5-HT_{2A} receptor have been shown to reduce impulsivity (*58, 68*).

In brain areas where postsynaptic 5-HT_{1A} receptors are located, such as the amygdala and frontal cortex, the density of 5-HT_{1A} receptors was found to be decreased in aggressive rats (*69*).

2.1.2.3 Dopaminergic system

The role of dopamine neurotransmission in impulsivity is quite well established. Psychostimulant drugs, such as amphetamine and methylphenidate has been successful in the treatment of attention deficit hyperactivity disorder (ADHD) (*70*), however psychostimulant drugs do not reduce all forms of impulsivity giving a showing its heterogeneous nature. Amphetamine has been found to enhance impulsive action in the 5-choice serial reaction time task (5CSRTT, more about the task see Robbins 2002 (*71*)), via the nucleus accumbens, because 6-hydroxydopamine lesions of the nucleus accumbens prevent the effect of amphetamine (*72*). In most studies, treatment with amphetamine has been found to reduce delay aversion (more about the task see Cardinal 2006 (*73*) in humans and rodents (*74, 75*), in contrast to the effects of amphetamine on impulsive action in the 5CSRTT, it is the orbitofrontal cortex that might play an important modulatory role in delay aversion (*76, 77*).

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2.1.2.4 Noradrenergic system

Noradrenaline neurotransmission also plays a role in impulsive action. Enhancing noradrenaline signaling decreases impulsive action, in the 5CSRTT and in the stop signal tasks, as well as in delay aversion via different mechanisms. In the 5CSRTT, this effect might be mediated through α1 or α2 adrenoceptors, which have been shown to be involved in impulsive action in this test (*78*). The α2 adrenoceptor agonist clonidine, which decreases noradrenaline release by stimulating presynaptic α2 autoreceptors, increased delay aversion (*75*). Furthermore, the effects of amphetamine in the stop signal task are mediated by increased noradrenaline neurotransmission (*79*, *80*).

2.1.2.5 Other neurotransmitter systems in the regulation of impulsivity

The nonselective N-Methyl-D-aspartate (NMDA) receptor antagonists 3-(2-Carboxypiperazin-4-yl)propyl-1-phosphonic acid (CPP) have been reported to increase impulsive action in the 5CSRTT (*81*) as well as delay aversion (*82*) suggesting the role of the glutamatergic system in impulsivity. Altered glutamate transmission in the medial prefrontal cortex has been associated with impulsive action as demonstrated by CPP infusions into these regions (*83*).

The cannabinoid system and particularly cannabinoid receptor 1 (CB1) receptors have been implicated in impulsivity. In a preclinical study the CB1 agonist WIN552122 [(R)-(+)-[2,3-dihydro-5-methyl-3[(4-morpholinyl)methyl]pyrrolo[1,2,3-de]-1,4 benzoxazinyl]-(1-naphthalenyl)methanone mesylate salt] was found to impair response inhibition in the stop signal task, whereas the CB1 antagonist rimonabant reduced impulsive action in the 5CSRTT but did not change delay aversion (*84*).

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2.1.3 Genetic background of impulsivity

The genetic background of impulsivity has long been investigated. Paaver et al. (*85*) reported that subjects with low platelet monoamine oxidase (MAO) activity carrying the s allele of the serotonin transporter length polymorphic region (5HTTLPR) showed a higher mean score of self-reported impulsivity as measured by BIS-11. Knockout mice lacking monoamine oxidase A (MAOA) differed from wild types by increased aggression (*69*). Of the 14 different known subtypes of serotonin receptors, the 5-HT_{1A} and 5-HT_{1B} receptor genes have been investigated more thoroughly. Enhanced aggression was revealed in 5-HT_{1B} receptor knockout mice (*86*). At the same time 5-HT_{1A} receptor knockout mice showed anxiety-related behaviour (*87*) rather than enhanced aggression (*88*). In contrast, low aggression and high social anxiety parallel with rapid desensitization of 5-HT_{1A} receptors during chronic selective serotonin reuptake inhibitor (SSRI) treatment were found in Fawn- Hooded rats compared to other rat strains (*89*, *90*).

Nomura et al. (*91*) investigated the relationship between a 5-HT_{2A} receptor gene polymorphism and impulsive behaviour in healthy subjects by using a behavioural task (go/no-go task) and found that the A-1438A polymorphism of this gene is possibly involved in impulsive behaviour.

There are certain gene polymorphisms within the dopaminergic system that may influence impulsivity including polymorphisms of the genes coding for the D4 dopamine receptor (DRD4), the dopamine transporter (DAT), and the catechol-o-methyltransferase enzyme (COMT).

The D4 receptor is expressed in the cerebral cortex, amygdala, hypothalamus, hippocampus, pituitary, and basal ganglia (*92*). The D4 receptor gene expression in the human brain is most abundant in the prefrontal cortex and low in the striatum (*93*, *94*). The gene coding the D4 receptor contains a variable number tandem repeats (VNTR) polymorphism that comes in a number of variants, ranging from two to ten repeats, (*92*).

Positive association has been reported between novelty seeking and the presence of the 7-repeat allele (*95, 96*), however contradictory results can be found too due to methodological differences, small samples and selection of trait questionnaires (*97*). The DRD4 polymorphism is also associated with ADHD which is characterized by high impulsivity; Faraone et al. found a small but significant association between the 7-repeat allele of the DRD4 and ADHD (*98*).

The DAT is a protein that plays a role in dopaminergic neurotransmission and it is responsible for removing dopamine from the extracellular space (*99*). The DAT contains a VNTR polymorphism, resulting in variants that range from 3- to 13-repeats (*99*). The striatum plays a critical role in impulsivity, such as behavioural inhibition (*100, 101*). Excessive amounts of the DAT could lead to an overly efficient reuptake of dopamine, reducing extracellular dopamine level. Therefore, studies suggest an increase in expression of the DAT in individuals with the 10-repeat variant, and that the 10-repeat variant can be associated with impaired inhibitory control (*102*).

The role of COMT in regulating dopamine in the frontal cortex is important, because the frontal cortex lacks the DAT (*103*), leaving dopaminergic disposal to COMT. The COMT gene contains a functional SNP, which results in the substitution of the amino acid methionine (met) for valine (val) of the val enzyme (*104*). The met variant (associated with low enzymatic activity) results in high levels of extrasynaptic dopamine, whereas the val variant (associated with high enzymatic activity) results in low levels of extrasynaptic dopamine (*103-105*). The COMT polymorphism has been associated with with novelty seeking (*106, 107*), with aggressive behaviour (*108-111*), and with ADHD (*112, 113*).

2.2 Impulsivity in psychiatry

Impulsivity is a heterogeneous behavioural phenomenon that has various definitions (Table 1), the main element being that impulsivity is a human behaviour without adequate thought; the tendency to act without taking into consideration the

consequences of action, or a general predisposition toward rapid, unplanned reactions to internal or external stimuli without regard to the possible negative consequences of these reactions (*1*).

In everyday life we all engage from time to time in impulsive acts, such as saying out critical comments without thinking, or buying expensive items on the spur of the moment. It plays a role in normal behaviour, as well as, in a pathological form of behaviour. Although impulsivity can be present in any individual with or without a DSM-IV axis I or II diagnosis, it is more likely to be present in individuals with certain psychiatric disorders. The association between these disorders and impulsivity is at least partly due to the manner in which these disorders have been conceptualized, with a lack of behavioural inhibition being an element of all of these disorders. Impulsivity may be related to an underlying mechanism of behavioural inhibition (*114*).

In the Diagnostic and Statistical Manual of Mental Disorders version IV (DSM-IV) several neuropsychiatric disorders are either classified as impulse control conditions or encompass impulsive symptoms in the diagnostic criteria. These extreme pathological manifestations of impulsivity impair quality of life and everyday functioning, and as such represent important targets for treatment intervention (*115*).

Impulse control disorders, characterized by an impaired ability to resist impulses to engage in self-destructive behaviour, have been categorized in DSM-IV. These disorders include pathological gambling (persistent and maladaptive pattern of gambling), kleptomania (involves the failure to resist impulses to steal things), intermitted explosive disorder (frequent and often unpredictable episodes of extreme anger or physical outbursts), trichotillomania (recurrent pulling out of one's own hair which results in significant hair loss), pyromania (involves deliberate and purposeful fire setting on at least two occasions) and impulse control disorder not otherwise specified (*116*). Researchers have suggested that the impulse control disorders (ICDs) might be a part of an obsessive–compulsive spectrum based on their clinical characteristics, familial transmission, and response to pharmacological and psychosocial treatment (*117, 118*). Two important changes are considered in DSM-V: separating obsessive–compulsive disorder (OCD) from the anxiety disorders and placing it in an autonomous category—the obsessive–compulsive spectrum disorders (OCSD); and

creating several new autonomous disorders from those currently belong to ICD's not otherwise specified (ICD-NOS) (*116*) including four new impulsive disorders, namely compulsive–impulsive (C–I) internet usage disorder, C–I sexual behaviours, C–I skin picking and C–I shopping. They are called compulsive–impulsive disorders due to their impulsive features and the compulsive drive that causes the behaviours to persist over time.

Impulse control disorders are treated with medication, psychotherapy, behaviour modification, anger and stress management. If these disorders are occurring in conjunction with another condition, such as ADHD, medication and therapy for that condition often helps alleviate the impulse control disorder. Depression and anxiety are often underlying factor in some impulse control disorders, therefore, treatment with antidepressants and anxiolytics may be helpful. Long-term counseling, support groups is usually necessary as well (*119*).

Impulsivity is one of the DSM-IV diagnostic criteria for *borderline personality disorder* as are affective instability and identity disturbance (*120*). The study of Dougherty et al. (*121*) supported a higher level of impulsivity in patients with borderline personality disorder using questionnaire and laboratory measures. Several studies have found a relationship between suicidality and impulsivity in patients with borderline personality disorder. In the study of Soloff et al. (*122*), patients with borderline personality disorder were compared to patients with major depression alone on measures of depressed mood, hopelessness, impulsive aggression, and suicidal behaviour. A higher level of impulsive aggression or hopelessness or a diagnosis of borderline personality disorder predicted a greater number of suicide attempts. Similarly, in a previous study by Soloff and colleagues (*123*), borderline personality disorder patients with a history of suicide attempts had more impulsive actions, antisocial personality disorder comorbidity, and depression than those without a history of suicide attempts.

Psychotherapy is necessary for individuals with borderline personality disorder. The treatment framework includes discussion and clarification of the goals of treatment and the expected roles of the patient and therapist in achieving these goals. Treatment goals such as symptom reduction, improved relationships, and ability to

maintain constancy at work should be made explicit. Psychodynamic therapy, dialectical behaviour therapy, and psychoeducational approaches are all helpful in working with patients with borderline personality disorder. Common to all successful therapies is the need for a strong therapeutic alliance (*124*).

Studies measuring impulsivity in substance-dependent individuals have also supported a link between impulsivity and *substance abuse*. Most studies that use questionnaire measures of impulsivity find higher levels of impulsivity in substance-dependent individuals than in healthy comparison subjects (*125, 126*). Medication behavioural therapy and support groups especially when combined, are important elements of an overall therapeutic process that often begins with detoxification, followed by treatment and relapse prevention (*127*).

Studies that have used human behavioural laboratory tasks to measure impulsivity have found high levels of impulsivity in *ADHD and conduct disorder*. Treatments include medication, various types of psychotherapy, education or training, or a combination of treatments. Evidences suggest that this increase in impulsivity may be related to dopamine function, which has an impact on treatment of these disorders. These evidences in humans, supporting a role for dopamine has come from treatment studies in which psychostimulants are used to treat ADHD and conduct disorder. Psychostimulants are dopamine-releasing agents, although they also lead to increases in the levels of other neurotransmitters, including serotonin and noradrenalin (*128*). Moreover, genetic studies found a relationship between dopamine transporter and D4 receptor alleles and ADHD (*129, 130*) and findings indicate increased activity of dopamine-synthesizing enzymes in brains of children with ADHD (*131*).

Antisocial personality disorder is defined in DSM-IV as “a consistent pattern of disregard for and violation of the rights of other occurring since age 15”; one of the possible criteria for the disorder is “impulsivity or failure to plan ahead”. It is likely that individuals with antisocial personality disorder, as categorized by DSM-IV, vary in impulsivity. Barratt et al. (*132*) studied aggression among subjects who met DSM-IV criteria for antisocial personality disorder. Responses to a structured interview were used to classify subjects into two groups on the basis of whether they committed impulsive aggressive acts or premeditated aggressive acts, the remainder had a mixture

of impulsive and premeditated aggressive acts. People with antisocial personality disorder often lack the motivation to improve and are notoriously poor self-observers. Antisocials who seek care do so for problems such as marital discord, alcohol or drug abuse or suicidal thoughts. Psychotherapy for people with antisocial personality disorder should focus on helping the individual understand the nature and consequences of his disorder so he can be helped to control his behaviour. The treatment and management of the symptoms and behaviours associated with antisocial personality disorder, such as impulsivity and aggression is also needed (*133*).

Personality traits associated with impulsivity normally decrease during emerging and young adulthood. For example, a study has found that problem alcohol use in a 18-to-25-years-of-age group exhibited the largest declines in impulsivity as well as the sharpest decreases in alcohol consumption suggesting that impulsivity can be viewed as a dynamic construct and developmental covariate of alcohol involvement (*134*). Risk-taking behaviour (n=177; ages 17–73) as one component of the general concept of impulsivity decreased with age, demonstrated by performance on a computer based gambling task (*135*). Furthermore in children with ADHD, from seven to ten years of age, attention increased and a decrease in impulsivity, response time, and its variability were revealed (*136*).

Table 1. Definitions of impulsivity. *APA* American Psychiatric Association, *BIS* Barratt Impulsiveness Scale, *DSM -IV* Diagnostic and Statistical Manual of Mental Disorders (4th ed) *IRS* Impulsivity Rating Scale

Dickman (*137*)	Dysfunctional impulsivity	The tendency to act with less forethought than most people of equal ability when this tendency is source of difficulty
	Functional impulsivity	The tendency to act with relatively little forethought when such a style is optimal
Dickman (*138*)	Attentional "Reflection-impulsivity"	Insufficient focusing of attention leads to impulsivity As measured by the matching familiar figures task (Kagan 1966)
	Disinhibition	Failure to withhold responses often leading to omission of reward (Newman et al. 1985)
Buss and Plomin (*139*)	Inhibitory control	„I have trouble controlling my impulses, usually I can't stand waiting"
	Decision time	„I often say the first thing that comes into my head, or act on the spur of the moment"
	Lack of persistence	„I tend to give up easily, I tend to hop from interest to interest quickly"
	Boredom/sensation seeking	„I generally seek new and exciting experiences and sensations, I get bored easily"
Eysenck (*140*)	Impulsiveness	Unconscious risk taking
	Venturesomeness	Conscious sensation seeking
BIS-11 (*141*)	Motor	Acting without thinking
	Cognitive	Making quick cognitive decisions
	Non-planning	Present orientation or lack of "futuring"
TCI (*142*)	Novelty seeking	„Acts immediately on momentary whims"
	Harm avoidance	„Carefree lack of inhibition even when the situation calls for attention"
	Reward dependence	„Lack of persistent ambition for delayed rewards"
Karolinska Scales of Personality (*143*)	Impulsiveness	„I have a tendency to act on the spur of the moment"
	Irritability	Irritable, lacking in patience
IRS (*144*)	"Self-control"	In normals weighting irritability, aggressivity and control of responses
	Time needed for decision	In normals weighting time needed for decision and capacity for delay
DSM IV (*116*) Substance abuse disorders		„Persistent desire or unsuccessful efforts to cut down or control substance abuse"
DSM IV (*116*) Attention deficit/ hyperactivity disorder	Inattention	„Often has difficulty in sustaining attention in tasks or play activities"
	Hyperactivity	„Often leaves seat in classroom or situations in which remaining seated is expected"
	Impulsivity	„Often blurts answers before questions have been completed"
DSM IV (*116*) Mania	Criterion 7	Excessive involvement in pleasurable activities that have a high potential for painful consequences
DSM IV (*116*) Borderline personality disorder	Criterion 4	Impulsivity in at least two areas that are potentially self-damaging

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2.3 Neurobiology of depression

2.3.1 Neuroanatomy of depression

Mood disorders such as major depression and bipolar disorders are the most common psychiatric disorders in modern society. About 16% of the population is estimated to be affected by major depression one or more times during their life time, respectively (*145*). Most of the major symptoms of depression observed today were recognized in ancient times. The term melancholia (which means black bile in Greek) was first used by Hippocrates around 400 B.C. (*146*). Major depression is a diagnostic category within the mood disorders, which also include dysthymia, cyclothymia, minor depression and bipolar disorder (DSM-IV).

Neuroimaging studies have demonstrated the role of several brain areas in mediating the symptoms of depression, including the prefrontal cortex, anterior cingulate cortex**,** hippocampus, amygdala, insular cortex, striatum and thalamus.

Subregions of the prefrontal cortex most often implicated in depression are the ventromedial prefrontal cortex (VMPFC), the lateral orbital prefrontal cortex (LOPFC) and the dorsolateral prefrontal cortex (DLPFC). VMPFC has rich reciprocal connections with limbic formations and the hypothalamus (*147*) and also modulates amygdala and hippocampal activity through complex feedback mechanisms (*148*). Increased VMPFC activity in major depression (MD) has been associated with ruminations and intensity of negative affect (*149*). The LOPFC have a major role in the regulation of emotion and cognitive reappraisal (*150*) but it is also involved in involved suppressing maladaptive and perseverative emotional responses (*151*). Significant reduction has been found in LOPFC gray matter volume of MD patients compared with healthy subjects (*152*). Decreased activity in DLPFC contributing to the compromised working memory, impaired sustained attention and executive dysfunction has been seen in the disorder (*153*).

The subgenual anterior cingulate cortex (sgACC) has a role in assessing the salience of emotional and motivational information and making necessary adjustments

in behaviour. It is also involved in modulation of sympathetic and neuroendocrine responses. Functional imaging studies suggest increased metabolism in this area in depressed patients (*154*). Studies have noted significantly decreased volume of sgACC in MD subjects that can explain the disturbances of motivation, limbic regulation, and neuroendocrine function, commonly seen in patients with MD (*155*).

The hippocampus plays an important role in mood modulation and memory formation (*156*). Frodl et al. found a significant decrease over a three-year period in hippocampal gray matter volume in MD patients compared to healthy controls. Successful treatment had a protective effect, given that remitted patients had a significantly greater hippocampal density than non-remitted ones (*157*).

The amygdala plays a role in conditioned fear (*158*) and emotional regulation and it was noted that patients with MD respond to angry and fearful faces with increased amygdala activity (*159*). Neuroimaging studies suggest that functional abnormalities of the amygdala may contribute to depressive symptom development and that pathophysiological processes inherent to depression may damage this brain structure. Functional neuroimaging studies have found increased activity in the amygdala of depressed patients (*160*).

The insula plays an essential role in sensory-affective integration that creates a bodily sense of self and it is also involved in modulating the influence of sensory and emotional distractors (*161*). MD patients appear to have decreased activity of insula, which can be improved with antidepressant treatment (*162*).

The hypothalamus is known to mediate several neuroendocrine and neurovegetative functions. Studies suggest that dysfunction of orexinergic neurons may be involved in the pathology of depression. Orexin-producing neurons are specifically localized in the lateral hypothalamic area and in the posterior hypothalamus (*163, 164*). Decrease in orexin-A levels has been reported to be associated with depression (*165, 166*).

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2.3.2 Neurochemistry of depression

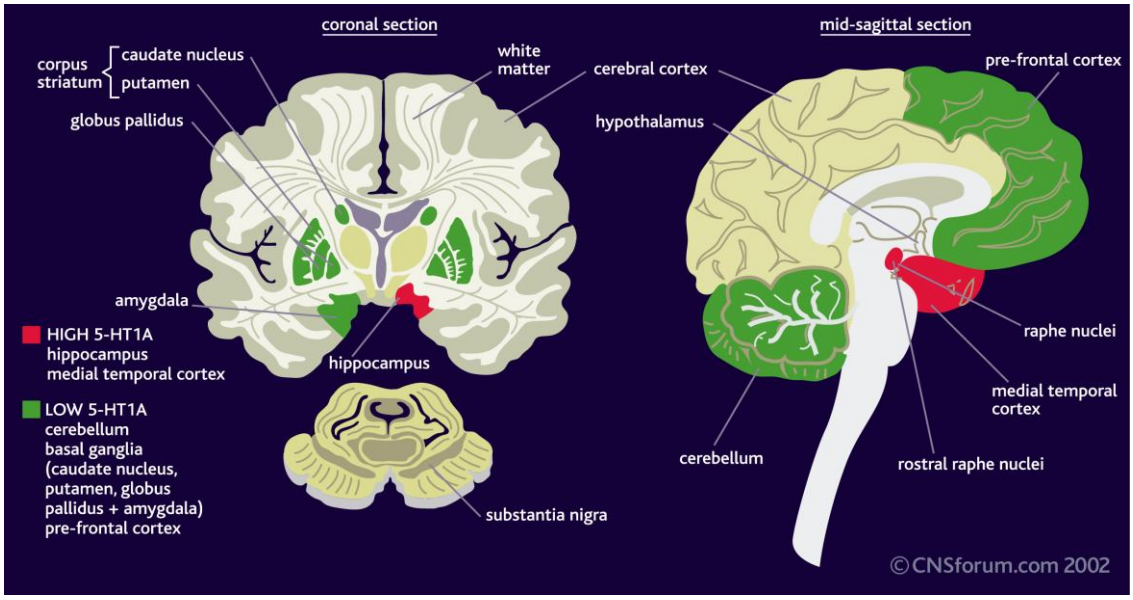
The monoamine hypothesis of depression, that depression is caused by decreased monoamine function in the brain, originated from early clinical researches (*167, 168*). Two compounds, namely iproniazide and imipramine, had potent antidepressant effects in humans by enhancing serotonin and noradrenalin transmission. This view was supported by the pharmacological action of both tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs), able to acutely increase synaptic levels of monoamines, and by drugs, such as reserpine, to induce depression (*169*). Rapid dietary depletion of the precursor of serotonin synthesis, tryptophan, caused a transient return of depression in 67% of patients who have had a therapeutic antidepressant response, underlying that serotonin has a role in the background of depression (*170*). Although the monoaminergic hypothesis does not provide a complete explanation for the pathophysiology of depression, investigating the role of serotonin and noradrenalin in the treatment of depression is still in the centre of attention.

Antidepressant drugs modulate monoamine neurotransmission through the inhibition of the serotonin transporter, thus increasing synaptic levels of serotonin (SSRIs), although their therapeutic effects need as long as 6 to 8 weeks to develop, and each drug is efficacious in only 60–70% of patients (*171*). Inhibitors of both serotonin and noradrenaline (SNRI) are also in use (*172*). Both SSRIs and SNRIs produce side effects due to an increase in noradrenalin and serotonin turnover which effects multiple noradrenalin and serotonin receptors including 5-HT2 and 5-HT3 receptors. Thus inhibitors of the serotonin reuptake that block $5HT_2$ receptors (SARI) at the same time can produce less side effects (*173*). Other drugs such as mirtazapine (NaSSA) that act by increasing both serotonergic and noradrenergic neurotransmission by blocking central α_2 auto- and heteroreceptors as well as $5HT_2$ and $5HT_3$ receptors are also in use (*174*) while bupropion acts through the inhibition of dopamine and noradrenaline reuptake (*173*).

In major depression the density of 5-HT_{1A} receptors is altered compared with the normal brain (Figure 3.). The 5-HT_{1A} receptor density is increased in the hippocampus

and medial temporal cortex, while the density of these receptors is reduced in the cerebellum, basal ganglia and prefrontal cortex (*175*).

Figure 3. The density of 5-HT$_{1A}$ receptors in depression.



Other neurotransmitters also play a role in depression. Hamner et al. (*176*) found that dopaminergic dysregulation in depression is responsible for anhedonia, loss of motivation, and psychomotor slowdown.

Cholinergic systems appear to be associated with depression as well. Acetylcholine (ACh) plays a significant role in mediating neuroendocrine, emotional, and physiological responses to stress (*177*). Central ACh turnover is increased following stress (*178*) and ACh facilitates the release of several stress-sensitive neurohormones and peptides including corticosterone, adrenocorticotropin (ACTH), and corticotropin-releasing factor (CRF) (*179*) suggesting an interaction between cholinergic and monoaminergic systems in the regulation of mood.

Glutamate is the major mediator of excitatory synaptic transmission in the brain (*180*). Glutamatergic abnormalities have been reported in plasma (*181*), serum (*182*) cerebrospinal fluid (*183*), and brain tissue (*184*) of subjects affected by mood disorders.

DOI:10.14753/SE.2012.1655

2.3.3. Neurotrophic factors associated with depression

Brain-derived neurotrophic factor (BDNF) was found to play a major role not only in the birth, survival and maturation of brain cells during development but also in cell growth and in allowing changes in the synapses between neurons (synaptic plasticity) throughout life. BDNF activates DNA-binding factors that stimulate gene transcription. In the raphe nuclei located in the brain stem, BDNF stimulates transcription of genes involved in serotonin function, such as tryptophan hydroxylase and the serotonin transporter (*185*). A polymorphism in the gene that codes for BDNF produces alleles called "Val" and "Met." Studies suggest that having the Met allele, having the short allele of the serotonin transporter and psychosocial stress, increases vulnerability to depression more than having the short allele of the serotonin transporter and psychosocial stress alone (*186*).

Further evidences supporting the role of BDNF in the pathophysiology of depression come from postmortem studies, which have found low levels of BDNF in the hippocampus and prefrontal cortex of depressed patients (*187, 188*).

There is also evidence that antidepressants increase hippocampal BDNF levels in humans (*189*) and this antidepressant-induced upregulation of BDNF could help repair some stress-induced damage to hippocampal neurons and protect vulnerable neurons from further damage (*190*).

2.3.4 Neuroendocrine system

Psychosocial stress can influence multiple neurobiological systems relevant to major depressive disorder. Stress may activate can activate the hypothalamic–pituitary–adrenal axis by stimulating local synthesis and release of corticotropinreleasing factor

(*191*) in addition it also activate this axis by releasing corticotropin-releasing factor from neurons in other regions of the brain, including the amygdala (*192*). These neurons may also contribute to activation of the serotonergic and noradrenergic systems (*193, 194*).

Dysregulation of the hypothalamic and extrahypothalamic corticotropin-releasing factor systems may gives an explanation why patients with major depressive disorder often have high levels of corticotropin-releasing factor and elevated levels of noradrenaline in their blood plasma and cerebrospinal fluid, and why they exaggerated stress reactions. Bradley et al (*195*) suggests that the impact of childhood abuse on a person's vulnerability for depression may be moderated by polymorphisms in the corticotropin-releasing factor type 1 receptor gene.

2.3.5 Genetics of depression

Depression is a complex phenomenon with many genes possibly involved. Researchers have not identified a single gene or a series of genes that cause depression, rather, certain variations in genes, called polymorphisms, may increase risk for depression. Genes can predispose individuals to major depressive disorder in many ways (*196*). Among the many genes that have been identified to play a role in the background of the disorder, studies have most consistently supported a role for polymorphisms in genes that regulate the serotonin transporter promoter locus (5HTTPR), catechol-o-methyl transferase (COMT), monoamine oxidase (MAO), brain-derived neurotrophic factor (BDNF) and glutamate receptors.

The serotonin transporter gene is one of the most studied genetic polymorphisms in major depressive disorder. This gene contains a polymorphism (5-HTTLPR) that gives rise to 2 different alleles, the long and short one. People usually have 2 copies of each gene in their deoxyribonucleic acid (DNA); therefore, a person can be homozygous for the long allele, homozygous for the short allele or heterozygous. The short allele slows down the synthesis of the serotonin transporter. This is thought to

reduce the speed with which serotonin neurons can adapt to changes in their stimulation (*197*). Several studies found association between the 5HTTLPR and major depression mainly in interaction with stressful life events (*198-200*).

Studies reported an association between the Val/Val genotype of the COMT enzyme and early onset major depressive disorder (*104, 201*) suggesting the involvement of this genotype in the background of depression.

Tryptophan hydroxylase (TPH) is the enzyme involved in the biosynthesis of serotonin (*202*). Two genes have been discovered which encode for the TPH isoforms (TPH1 and TPH2). Zill et al (*203*) reported that MD was associated with 10 SNP haplotypes in TPH2 in 300 MD patients and 265 control subjects.

Brain-derived neurotrophic factor (BDNF) is a neuroprotective protein, and reduced serum BDNF was reported in MD (*204*). The activity of genes known to modulate neurotrophic factors, neuroplasticity and neurogenesis may be compromised in MD patients (*205*). The val66met allele confers reduced BDNF functioning and has been associated with structural brain changes common in MD (*206*).

Depression aggregates in families. Family studies observed an increase in the risk of developing major depressive disorder in the relatives of individuals with major depressive disorder (*207-210*). Twin studies consistently support genetic effects in the development of depression as well (*211, 212*). Expression of major depression's heritability is also influenced by the family environment and "parental coldness" was found to be associated with a 38% increased risk for developing this disease (*213*).

The lifetime prevalence of major depression is at least 10%, with the risk in women twice that in men (*214, 215*). Epidemiologic studies show that approximately 40%–50% of the risk for depression is genetic (*216, 217*) so vulnerability to depression is only partly genetic, with nongenetic factors also being important such as stress and emotional trauma or viral (e.g., Borna virus) infections (*146, 216*).

DOI:10.14753/SE.2012.1655

2.4 Clinical and subclinical manifestations of depression

2.4.1 Major depression

Major depression, a common (*218, 219*) and recurrent disorder (*220*), is associated with considerable morbidity (*221*) and excess mortality (*222*). Major depression has been projected to become the second leading cause of disability worldwide by 2020 (*223*). Moreover, major depression is of increasing importance in clinical psychiatry (*224*).

Studies investigated that depressive symptoms are common in the Hungarian population as well. In a study Szádóczky et al. reported the lifetime rate for major depression in the Hungarian population was 15.1%, which was similar to the data from the Western countries (*225*). According to earlier studies, 24%, 31% and 27.3% of the Hungarian population complained of mild depressive symptoms in 1988, 1995 and 2002, respectively (*226*).

Kopp et al. reported that 30.6% of the Hungarian adult population had complained of depressive symptoms; and the rate of severe depression was 7% (*227*). Even though our knowledge about the basis and treatment of depression increased, similar results were established in 2002, 27.3% of the Hungarian population suffered from depressive symptom; in which 7.3% reported severe depressive symptoms (*228*).

According to the DSM-IV (*116*), a person who suffers from major depressive disorder must either have a depressed mood or a loss of interest or pleasure in daily activities consistently for at least a two week period. This mood must represent a change from the person's normal mood; social, occupational, educational or other important functioning must also be negatively impaired by the change in mood. A depressed mood caused by substances (such as drugs, alcohol, medications) or which is part of a general medical condition is not considered to be major depressive disorder. Major depressive disorder cannot be diagnosed if a person has a history of manic, hypomanic, or mixed episodes or if the depressed mood is better accounted for by schizoaffective disorder and is not superimposed on schizophrenia, schizophreniform disorder, delusional disorder or psychotic disorder. Further, the symptoms are not better accounted for by

DOI:10.14753/SE.2012.1655

bereavement (i.e., after the loss of a loved one) and the symptoms persist for longer than two months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either depressed mood or loss of interest or pleasure:

(1) depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful). Note: In children and adolescents, can be irritable mood.

(2) markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)

(3) significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. Note: In children, consider failure to make expected weight gains.

(4) insomnia or hypersomnia nearly every day

(5) psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)

(6) fatigue or loss of energy nearly every day

(7) feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)

(8) diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)

(9) recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

Major depression is a multifactorial disorder that is influenced by several risk factors. Epidemiologic data indicate that gender and age are two independent risk factors for the development of MD. Lifetime episodes of MD have high heritability, and MD is 1.5 to 3 times more common among first-degree biological relatives of people with this disorder than in the general population (*229*). Socioeconomic status (e.g., income and education), and marital status, ethnicity, urbanicity, and geographic region also affects mental health (*219*). Kessler et al. (*230*) noted that adult gender-role stresses contribute to the greater risk of adult-onset depression in women.

Childhood sexual abuse is an important early stressor that can predispose individuals to adult-onset depression, just like other types of childhood trauma, such as parental loss, poor parenting, parental drinking, mental illness, and family violence (*231*).

Kendler et al. (*232*) found that recent stressful events can be the single most powerful risk factor for 1-year prevalence of MD, followed by genetic factors, previous history of MD, and temperament. Furthermore, the subjective interpretation of a situation depends on the early environmental influences on development, both in respect to the development of the brain structures and psychological coping abilities. The "social stress model" of depression can be characterised with an early life chronic stress situation which is the result of the disruption of mother–infant or peer bonding, which seems to resemble human depression or vulnerability to depression (*233*). Learned helplessness is a chronic stress situation, when feeling of total lack of control makes the avoidance of an emotionally negative situation impossible. In such a state, the hippocampus is affected by the long-lasting elevations of circulating corticosteroids resulting from uncontrollable stress. Severe stress for a long period causes damage in hippocampal pyramidal neurons, mainly in the CA3 and CA4 region and reductions in the length and arborization of their dendrites. In connection with the physiological consequences of chronic stress the feeling of lack of control has central importance (*234*).

Psychotherapy is necessary for individuals suffering from depression. Interpersonal therapy is one of the most promising types of psychotherapies. It is a short-term psychotherapy, normally consisting of 12 to 16 weekly sessions. It was developed specifically for the treatment of major depression, and focuses on correcting current social dysfunction (*235*).

Cognitive behavioural therapy is also widely used in the treatment of depression. The cognitive behavioural theory of depression states that the patient's self-rejection and self-criticism causes major depression. This therapy seeks to correct these negative thoughts or dysfunctional attitudes in order to overcome the patient's pessimism and hopelessness and tries to break the depressed patient's vicious cycle of increased negative thinking leading to increased social isolation which further increases the negative thinking (*236*).

Psychoanalytic psychotherapy for major depression usually continues with one or more weekly visits for several years. The psychoanalytic approach to treating major depression focuses on hypothesized unconscious phenomena, such as defense mechanisms or internal conflicts and it focuses on the patient's past analyzing the historical reasons why the patient has "turned anger inwards against the self" in becoming depressed. A modified form of this technique is the short-term psychodynamic psychotherapy, that was scientifically proven effective (*237*).

Family therapy can be a crucial and effective modality in the treatment of mood disorders in cases when the depression appears to be seriously jeopardizing the patient's marriage and family functioning. Family therapy examines the role of the depressed member in the psychological well-being of the family and it also examines the role of the entire family in the maintenance of the depression (*238*).

2.4.2 Subthreshold depression

Depression can best be conceptualized within a continuum from normality to full blown depression (*239, 240*). According to a 2009 research (*241*), subthreshold

depression is associated with functional impairment. This research showed that functional impairment becomes apparent early on the continuum.

Subthreshold depression is generally defined to represent patients who suffer from depressive symptoms, in which the number, duration, or quality of symptoms do not meet the DSM criteria necessary for a diagnosis of major depression (*242*). This category includes patients who complain of depressive symptoms, but do not complain of depressed mood or anhedonia. Therefore, they lack a necessary criterion for all DSM-IV depressive categories. Judd et al. (*243*) labeled the cluster as subsyndromal symptomatic depression (SSD). Depressive symptoms in SSD can either be operationalized as scoring above a cut-off score of a self-rating depression scale or meeting the criteria of minor depression (*244*).

It has been known since Kraepelin, that fluctuating affective manifestations occur prior and after major affective episodes. Paskind noted relatively minor affective symptoms which recurred on a cyclical basis, as well as neurovegetative symptoms such as anergia, headaches, insomnia, sexual disturbances, gastro-intestinal disturbances, palpitations, and anxiety symptoms (*245*).

SSD shares four out of the five most common symptoms of MD and minor depression (MinD): insomnia, tiredness, frequent thoughts of death, and decrease in concentration (*243*). The risk of suicide is significantly higher in patients with SSD as compared to normal subjects (*246*), but lower than in MD and MinD. SSD has greater prevalence than MinD of significant weight gain, slowed thinking, and hypersomnia, however, decreased prevalence of poor appetite compared with MinD. After clinical researchers started to study and identify the features of subthreshold depressive states, three additional categories were added to the DSM as subthreshold forms of major depression: dysthymia, minor depression and recurrent brief depression. *Dysthymic disorder* is characterised by a reduced number of symptoms showing a minimal duration of 2 years. *Minor depression* is diagnosed in patients who have more than two, but less than five, symptoms of depression for at least 2 weeks duration. *Recurrent brief depression* is diagnosed in patients who suffer from recurrent episodes of depressive symptoms that are identical to major depressive episodes in number and quality of symptoms but do not meet the 2-week duration requirement. The episodes recur at least once per month for a period of one year.

Despite the addition of the three newly identified subthreshold categories, approximately two-thirds to three-fourths of patients with subthreshold depression continued to present with depressive symptoms, causing significant psychosocial impairment, but which still did not satisfy any DSM-IV diagnosis (*243, 246*). Generally, these patients failed to complain of anhedonia and depressed mood, the necessary criterion for all DMS-IV categories of depression (*243, 246*).

The cluster of symptoms that failed to meet the previously established DSM-IV criteria was labeled as SSD (*243*). SSD was defined by at least two or more current depressive symptoms, present every day for most or all of the time, at least 2 weeks in duration and it is associated with social dysfunction, in persons not meeting the criteria for minor depression, dysthymia or major depression (*243*). Subthreshold depression is often characterized by somatic symptoms such as insomnia, morning hypersomnia, fatigue, headache, abdominal pain, hyperventilation, palpitations, erectile failure (*247*).

There are two types of SSD categories:

a) *subsyndromal depressive disorder with mood disturbance* which has a one year prevalence of 3.4%
b) *subsyndromal depressive disorder without mood disturbance* which has a remarkably high prevalence in the population, one year prevalence is 8.4%, two thirds (63.4%) of whom are women (*243*).

Despite the fact that subthreshold depression causes social dysfunction, work impairment as well as suffering and effects a high portion of the population, its biological background has not been extensively studied so far. Gonda et al. (*248*) found an association between the s allele of the 5HTTLPR gene and subthreshold depression suggesting that subclinical forms of depression are a part of the same continuum as other, DSM-IV defined affective disorders which have also been found to be related to this polymorphism (*249, 250*).

DOI:10.14753/SE.2012.1655

3. OBJECTIVES

The aim of the present study was to test the hypothesis of the involvement of the C(-1019)G polymorphism in impulsivity related behaviour and subthreshold depression. Furthermore, we aimed to investigate the relationship between impulsivity and subthreshold depression and the effect of genotype on the relationship between impulsivity and subthreshold depression. The aims of our study were:

1. Previous studies indicate that the C(-1019)G functional polymorphism of the HTR1A gene is associated with aggression, suicide, depression and several psychiatric disorders**.** Is there any relationship between the C(-1019)G functional polymorphism and impulsivity?
2. Since it is well known that the C(-1019)G polymorphism is related to major depression, is subthreshold depression also associated with the C(-1019)G functional polymorphism?
3. Impulsivity is known to be associated with depression but the nature of this relationship is not elucidated. Is there a relationship also between impulsivity and subthreshold depression and which facets of impulsivity play a role this relationship?
4. Does genotype (subjects with the GG genotype compared to subjects with the GC or CC genotype) affect the relationship between impulsivity and subthreshold depression?

DOI:10.14753/SE.2012.1655

4. MATERIALS AND METHODS

4.1. Subjects

Eight hundred fifty-one unrelated Hungarian volunteers were recruited for the study. Subjects whose DNA sample were not successfully genotyped and subjects with missing questionnaire data were excluded from all statistical tests. Finally 725 subjects remained, 596 women and 129 men. The participants were aged 18–60 years; the mean age was 30.26±10.601 years. Participants were recruited from general practices, universities, and a community-based population. The inclusion of subjects was independent of any positive psychiatric anamnesis. Each subject was given an oral and written summary of the aims and procedures of the project and gave formal written consent before entering the study. All subjects were Hungarian and of Caucasian origin. The study protocol was approved by the Central Ethics Committee in charge of genetic studies with human subjects.

4.2. Procedures and Measures

4.2.1. Background information

Background information was obtained from all participants. The background questionnaire was adapted from the version developed by the Epidemiology Unit at the University of Manchester. The self-rating questionnaire consisted of 22 items and collected detailed information about socioeconomic background, and medical history including personal and family psychiatric history.

DOI:10.14753/SE.2012.1655

4.2.2. IVE-I and BIS-11

Impulsivity was measured by two questionnaires: the Impulsiveness subscale of the Eysenck Impulsiveness, Venturesomeness, and Empathy scale (IVE-I) (*251*) and the Barratt Impulsiveness Scale (BIS-11) (*252*).

The Eysenck IVE scale consists of 54 true/false items and contains 3 unidimensional subscales: Impulsiveness, Venturesomeness, and an Empathy scale. In our study we only used the Impulsiveness subscale (IVE-I), which contains 19 items (e.g., ‘‘Do you often do things on the spur of the moment?’’). The total score is the sum of the points; a high score indicates a high level of impulsivity.

The most recent version of BIS-11 (*252*) consists of 30 items asking about impulsivity-related behaviours and cognitions. According to Barratt’s most recent proposal (*141*) that there are three subtraits (measured by three subscales) which are Motor Impulsiveness (e.g., ‘‘I do things without thinking,’’ 11 items), Cognitive Impulsiveness (e.g., ‘‘I don’t pay attention,’’ 8 items), and Nonplanning Impulsiveness (e.g., ‘‘I plan tasks carefully,’’ inverted item, 11 items). The BIS total score is the sum of the three scales. Each item is measured on a 4-point scale, 4 indicates the most impulsive response. The total score is the sum of the points.

4.2.3. Zung Self-Rating Depression Scale

Subjects completed the standardised Hungarian version of the Zung Self-Rating Depression Scale (*253*, *254*). The Zung Self-Rating Depression Scale is a 20-item short self-administered test and its items cover affective, psychological and somatic features of depression. Each question is scored on a scale of 1 through 4 ("a little of the time," "some of the time," "good part of the time," "most of the time"). Non-depressed individuals typically score less than 40, while 40 to 80 cover various grades of depressive symptomatology (*255*). Between 40-47 points individuals show mild

depressive symptoms and above 48 points moderate and severe depressive symptoms can be observed (*255, 256*).

The main reason we have chosen the Zung Self-Rating Depression Scale (ZSDS) was that it contains more items relating to the vegetative and physical aspects of depression than other self-rating depression scales.

4.2.4. Genotyping

Buccal mucosa samples were collected from each subject, and genomic DNA was extracted according to a protocol previously described (*257*). DNA quality and quantity were determined with NanoDrop B-100 spectrophotometer, and all samples were diluted to a DNA concentration of 20 ng/ml. The SNP rs6295 was genotyped at the Centre for Integrated Genomic Medical Research at the University of Manchester using Sequenom MassARRAY technology (Sequenom, San Diego, CA). The iPLEX assay, based on post-PCR single base primer extension, was performed according to manufacturer's instructions. Forward (5-GTCAGTCTCCCAATTATTGC-3), reverse (5-CGAGAACGGAGGTAGCTTTT-3), and extension (5-AGACCGAGTGTGTCTTC-3) primers were designed using the Assay Design 3.0 software of Sequenom. The iPLEX reaction products were dispensed onto a 384-well SpectroChip (Sequenom), processed and analyzed in a Compact Mass Spectrometer by MassARRAY Workstation 3.3 software (Sequenom).

4.3. Statistical methods

4.3.1. Genetic association analysis

Statistical Analysis Haploview 4.0 software was used for computing Hardy–Weinberg equilibrium and minimal allele frequency (*258, 259*). Association tests were performed by means of analysis of variance (ANOVA) with the rs6295 SNP (GG vs.

GC vs. CC) as an independent variable and IVE-I and BIS-11 scales entered as dependent variables. Tukey HSD post-hoc test was used for multiple comparisons. Age and gender were included in the ANOVA model as covariates. Statistical analyses were carried out using SPSS 15.0 (SPSS Inc., Chicago, IL). $P<0.05$ was accepted as level of significance. Results are presented as mean±standard error (SE). For power calculations we used G*Power 3 (*260*).

4.3.2. Structural Equation Modeling

Structural equation models (*261, 262*) refer to general statistical procedures for multiequation systems that allow modeling linear relationships between continuous latent variables (also called "factors" or "unmeasured variables") and observed variables. A full structural equation model also includes the links between the latent variables and their observed measures.

Latent variables are theoretical constructs that cannot be observed directly. Examples of latent variables in psychology are self-concept and motivation. In psychology the typical observed variables are observation scores representing some physical task or activity or coded responses to interview questions. These measured scores are termed observed or manifest variables.

Additionally there might be other variables called exogenous latent or background variables. Exogenous latent variables are synonymous with independent variables; they "cause" fluctuations in the values of other latent variables in the model. Typical background variables are gender, age, and socioeconomic status.

The resulting statistical models provide an efficient and convenient way of describing the latent structure underlying a set of observed variables. Expressed either diagrammatically or mathematically via a set of equations, such models explain how the observed and latent variables are related to each-other. The hypothesized model then can be tested statistically in a simultaneous analysis of the entire system of variables to determine the extent to which it is consistent with the data. If goodness-of-fit is

DOI:10.14753/SE.2012.1655

adequate, the model argues for the plausibility of postulated relations among variables; if it is inadequate, the tenability of such relations is rejected.

Structural equation model (SEM) building includes several steps. These steps are:

(i) Model specification. The first step is to specify the hypothesized relation among all latent and observed variables. Typically, a researcher postulates a statistical model based on his or her knowledge of the related theory.

(ii) Model identification. Model identification concerns to the question whether it is possible to determine uniquely the parameters of a model from the means, variances, and covariances of the observed variables. Widely used are empirical checks on model identification that are based on whether the information matrix of the model parameters from a maximum likelihood solution is nonsingular. Models for which there are an infinite number of possible parameter estimate values are said to be underidentified. Singularity suggests that the model is underidentified.

Models in which there is only one possible solution for each parameter estimate are said to be just-identified. Finally, models that have more than one possible solution for each parameter estimate is considered overidentified. Typically, most people who use SEM prefer to work with models that are overidentified. An overidentified model has positive degrees of freedom and may not fit as well as a model that is just identified. When an overidentified model does fit well, then the researcher typically considers the model to be an adequate fit for the data.

(iii) Estimation of the parameters. Typically, either maximum likelihood (ML) or normal theory generalized least squares (GLS) estimation is used; both demand that the data be continuous and multivariate normal.

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(iv) Checking of the plausibility of the model. Once the model is estimated then attention turns to assessing its goodness of fit. Goodness of fit refers to summary measures of how well the model as a whole corresponds to the data. The most widely used measure of overall fit is based upon the chi-square distribution. If the distributional assumptions of the test are satisfied, a significant value of the test statistic suggests that the model is misspecified.

(v)- If any of steps (ii)-(iv) fails then the model has to be respecified (step i) and another try has to be made to get a model which is scientifically solid and statistically plausible (step iv).

Working with AMOS

We used AMOS (ver 18, SPSS Inc.) for SEM analysis. Amos gives a convenient graphical user interface to the whole SEM modeling process. Structural equation models are schematically portrayed using particular configurations of four geometric symbols—a circle (or ellipse), a square (or rectangle), a single-headed arrow, and a double-headed arrow. By convention, circles (or ellipses) represent unobserved latent factors, squares (or rectangles) represent observed variables, single-headed arrows (›) represent the impact of one variable on another, and double-headed arrows (-) represent covariances or correlations between pairs of variables. Figure 4 is a snapshot of the AMOS interface during the work.

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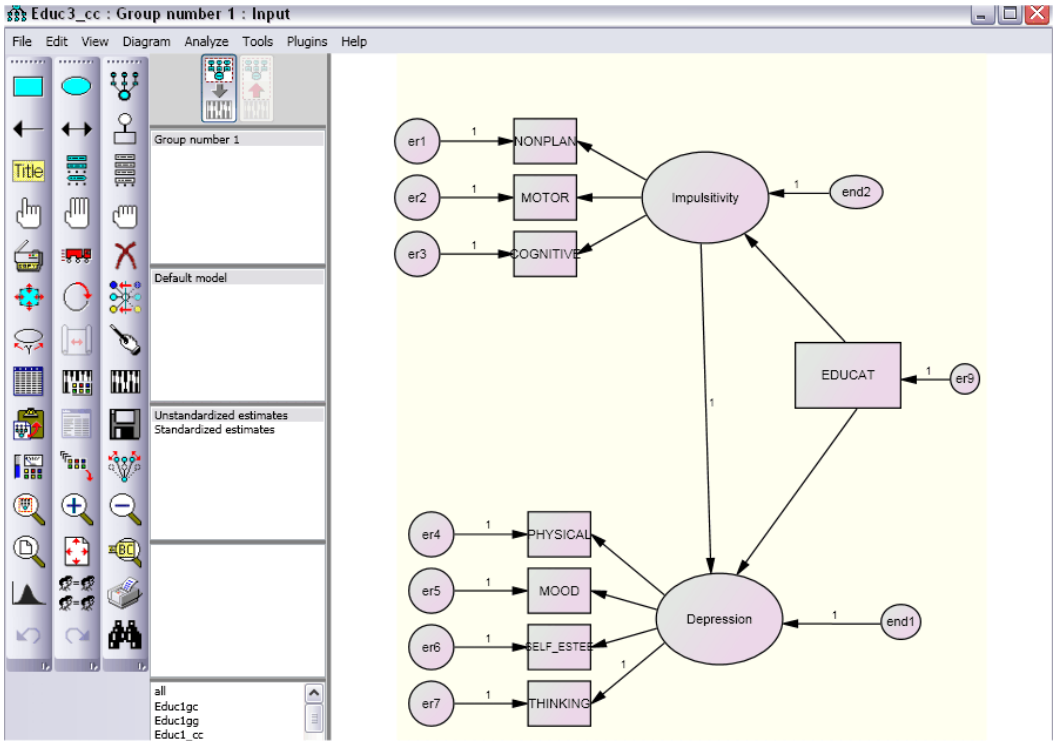
Figure 4. Graphical User Interface of AMOS.



Modeling is a simple and straightforward point-click and drag process with AMOS. The first step is importing the observed variables in the program. In the second step they are connected with each other or with the supposed latent variables. Figure 4 shows a full latent model because the latent variables (represented by the big ellipsoids) are connected as well. The small circles representing the inherent error part of the model. After the model is drawn the user click on the Analyze menu all analysis are done automatically.

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Interpretation of the results

The output of AMOS is extensive and detailed. The most important parameters from my perspective were:

- **Model plausibility.** AMOS gives this parameter under the heading "Notes for Model." It is based upon Chi-square statistics and (contrary to conventional statistical hypothesis test) the model is better if p is higher. If p is less than 0.05 then the model is not plausible.

- **Standardized regression coefficients.** Variables are standardized by subtracting the mean from the variables and then dividing them by the standard deviation. This yields the standardized regression coefficients which show the change in the dependent variable measured in standard deviations. The change shown indicates what would happen if the independent variable is subject to a similar change of one standard deviation. A standardized regression coefficient thus indicates the expected difference on Y in standard deviation units, given an increase on X of one full standard deviation. Unlike the unstandardized regression coefficient B, the value of the standardized regression coefficient (rXY) is unaffected by the scale of either X or Y. For two standardized variables, the correlation coefficient between them is the standardized regression coefficient. In multiple correlation setting the standardized regression coefficients are also called beta weights or standardized regression weights. In this case standardized regression weights are analogous to partial correlations but not to correlations.

- **Confidence intervals the estimated standardized regression coefficients.** They were estimated by bootstrapping. If the 90% confidence interval did not cross zero then corresponding effect was considered statistically significant at p = 0.05 level.

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5. RESULTS

The demographic characteristics of the study population are shown in Table 2. There was no significant deviation from the Hardy–Weinberg equilibrium (P=0.655), and minimal allele frequency of rs6295 polymorphism was more than 5%. Frequencies of the GG, GC, and the CC genotypes were 27% (n=193), 51% (n=368), and 22% (n=163), respectively. Frequencies of the G and C alleles were 52% (n=754) and 48% (n=694), respectively.

Table 2. Demographic characteristics

Sociodemographic data (self-reported)	**N (%)**
Total	725 (100 %)
Female	596 (82.2 %)
Male	129 (17.8 %)
Mean age ± SD	30.26 ± 10.601
Education	
No qualification	4 (0.6 %)
Technical School	55 (7.6 %)
High School	552 (76.1 %)
Degree	187 (25.8 %)
Marital Status	
Single	367 (50.6 %)
Married	228 (31.4 %)
Couple	70 (9.7 %)
Divorced	37 (5.1 %)
Separated	13 (1.8 %)
Widowed	5 (0.7 %)
Personal history (anamnesis)	
Anxiety/panic/phobia	147 (20.3%)
Suicide attempt	33 (4.6%)
Manic episode/manic depression/bipolar disorder	10 (1.4%)
Depression	147 (20.3%)
Obsessive-compulsive disorder	15 (2.1%)
Psychotic episode/schizophrenia	4 (0.6%)
Eating disorders	46 (6.3%)
Drug or alcohol problem	16(2.2%)

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5.1. The association of IVE-I and BIS-11 Scales with genotypes

Using the IVE-I scale, there were significant differences (P=0.014) in the test scores between the three genotype groups (Table 3). Test results (Fig. 5), indicate that subjects with the GG genotype show significantly higher impulsivity, and with no overlap at 95% confidence, compared to CC subjects; the scores for the GC heterozygotes lying approximately midway. A very similar pattern with significant difference (P=0.008) was observed using the BIS total scores (Fig. 6a); subjects with the GG genotype show significantly higher impulsivity, and with no overlap at 95% confidence, compared to CC subjects; the scores for the GC heterozygotes lying approximately midway. On the Motor Impulsiveness subscale of BIS-11 (Fig. 6b), the GC subjects behaved like CC individuals, with a significant difference (P=0.021) between the GC and the GG genotypes; whereas on the Cognitive Impulsiveness subscale (Fig. 6c), GC subjects behaved more like GG individuals, with significant differences (P=0.002) between each of these two groups and the CC homozygotes; however, there was no significant difference (P=0.520) between the different genotype groups in the Nonplanning Impulsiveness subscale (Fig. 6d). Post-hoc analysis revealed that the study had 0.958 power to detect 0.15 effect size (Table 3).

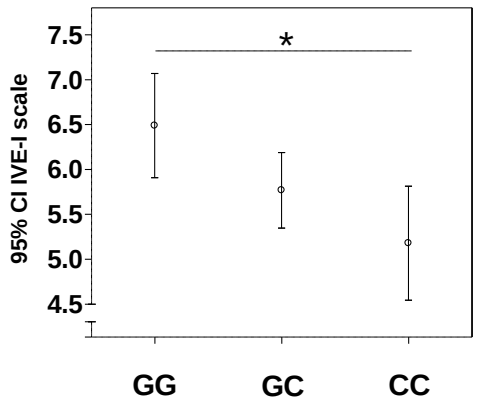
Although age and gender were included in the ANOVA model as covariates, separate analyses of males and females were also performed. These analyses revealed that on the IVE-I scale, genotype had significant effect in both groups (males: P=0.017, females: P=0.005). On the Motor and the Cognitive Impulsiveness subscales of the BIS-11, the effect of genotype remained significant only among females (P=0.016 and P=0.006) but not among males P=0.09 and P=0.23). Because the ratio of females to males was higher than 4 in our study group, we attribute the lack of significance in males due to the smaller sample size in the latter case. Indeed, the general patterns were the same for both groups and subjects carrying GG genotypes had the highest impulsiveness scores in all comparisons.

DOI:10.14753/SE.2012.1655

Table 3. Analysis of variance table for the Barratt Impulsiveness Scale (BIS-11) and the Impulsiveness Subscale (IVE-I) of the Eysenck Impulsiveness, Venturesomeness and Empathy Scale associated with genotypes GG, GC and CC

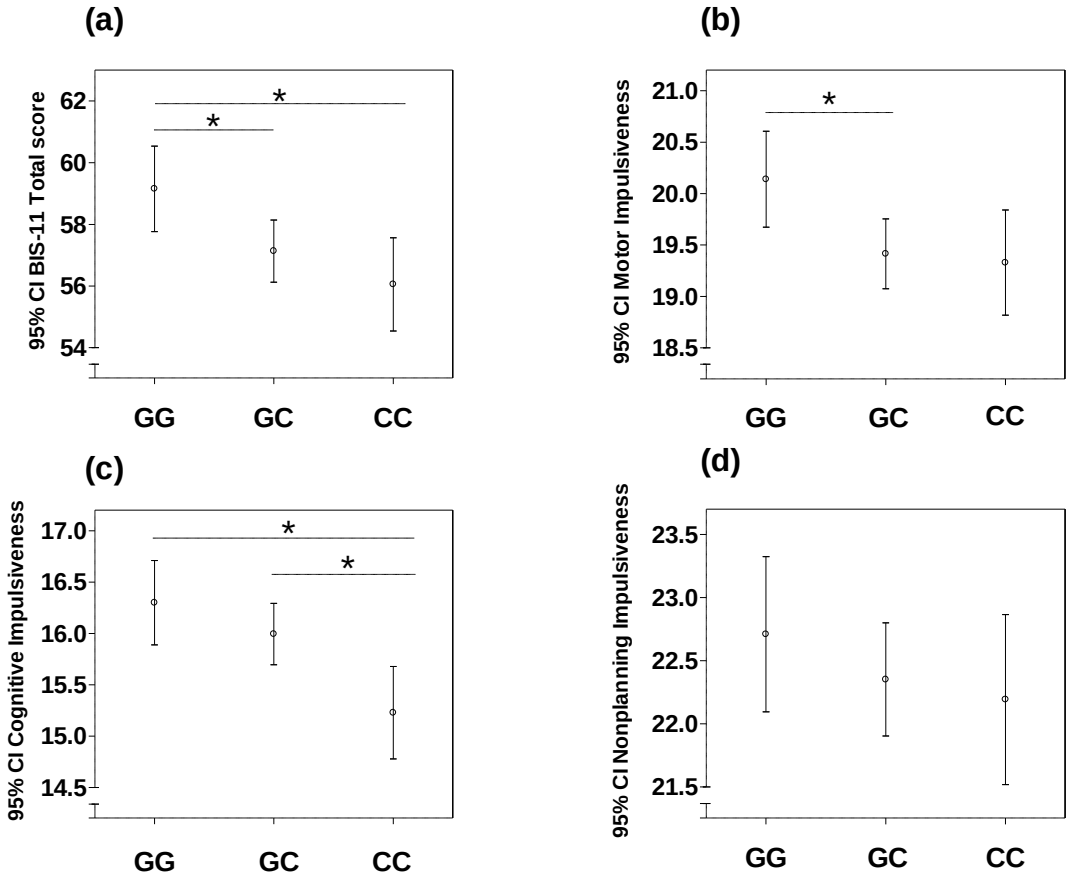
BIS-11 and IVE-I scales	GG			GC			CC			df	F	p-value	Observed power
	n	Mean	S.E.	n	Mean	S.E.	n	Mean	S.E.				
BIS total	193	59,18	0,698	368	57,09	0,505	163	56,11	0,759	2, 719	4,862	**0.008**	0.98
BIS motor	193	20,15	0,236	364	19,40	0,171	161	19,34	0,258	2, 713	3,886	**0.021**	0.88
BIS cognitive	193	16,31	0,204	364	15,97	0,148	161	15,25	0,223	2, 713	6,337	**0.002**	0.99
BIS nonplanning	193	22,70	0,313	364	22,34	0,228	161	22,21	0,343	2, 713	0,654	0.520	0.29
IVE-I	192	6,47	0,291	368	5,75	0,210	161	5,228	0,318	2, 716	4,302	**0.014**	0.97

Figure 5. Comparison of GG, GC, and CC genotypes for the IVE-I scale. Error bars show 95% confidence interval. *P<0.05 post-hoc Tukey's HSD test.



DOI:10.14753/SE.2012.1655

Figure 6. Comparison of GG, GC, and CC genotypes for the Barratt Impulsiveness scale (BIS-11). Error bars show 95% confidence interval. (a) BIS-11 total score, (b) BIS-11 Motor Impulsiveness, (c) BIS-11 Cognitive Impulsiveness, and (d) BIS-11 Nonplanning Impulsiveness. *P<0.05 post-hoc Tukey's HSD test.



DOI:10.14753/SE.2012.1655

5.2. The association of the Zung Self-rating Depression Scale scores with genotype

686 subjects (123 male and 570 female) who had Zung Self-Rating Depression Scale scores below the level indicating depression (48 points) remained in the statistical analysis. We found no significant difference (P=0.94) between the three genotype groups and ZSDS total scores (Table 4). 258 (37%) subjects scored between 40-48 points indicating subthreshold depressive symptoms.

Table 4. Analysis of variance table for the Zung Self-Rating Depression Scale (ZSDS) associated with genotypes GG, GC and CC

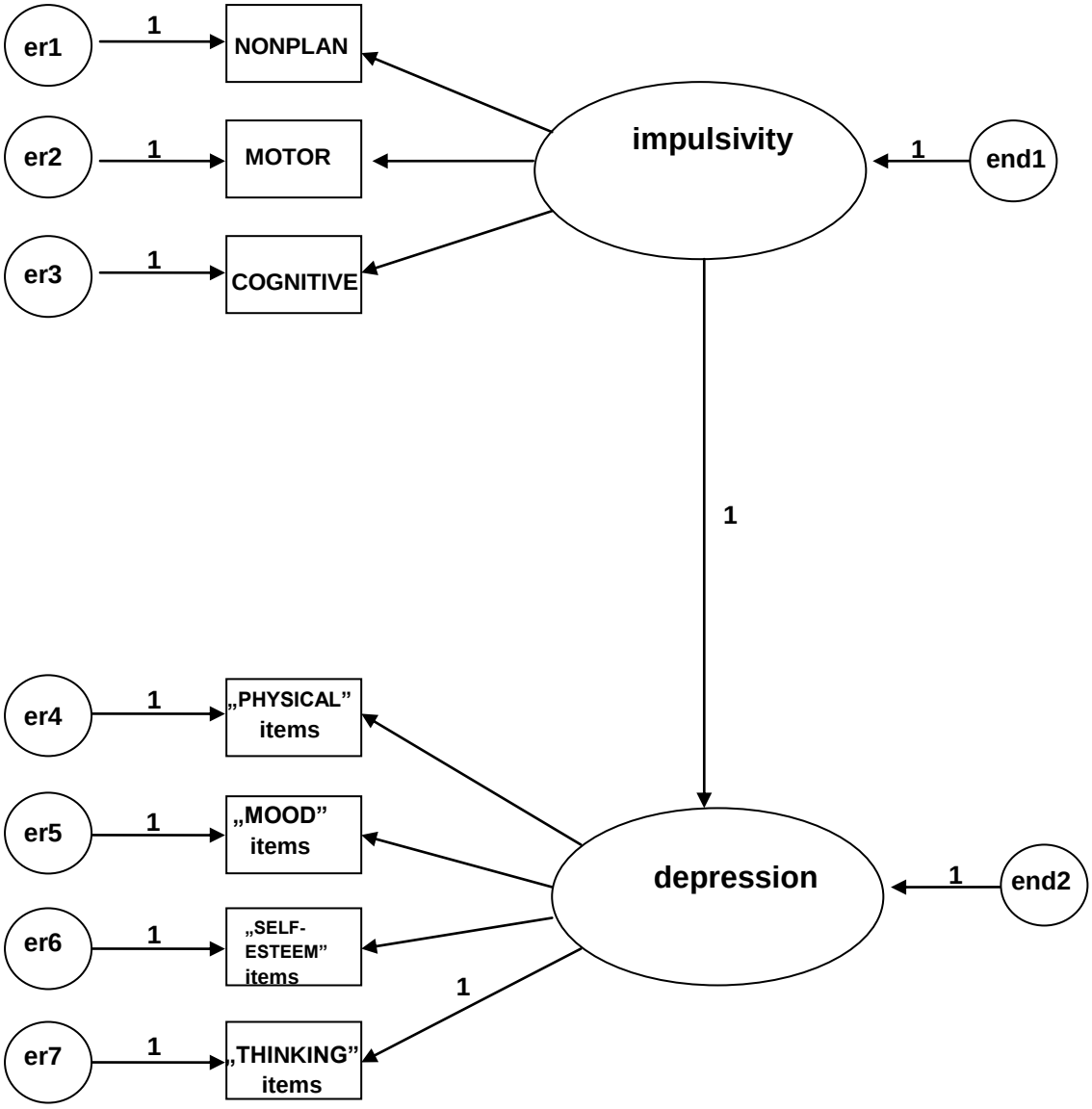
ZSDS	GG			GC			CC			df	F	p-value
	n	Mean	S.E.	n	Mean	S.E.	n	Mean	S.E.			
ZSDS Total score	186	38,83	0,342	349	37,95	0,249	151	38,54	0,379	2, 686	2,370	**0.094**

5.3. The association between impulsivity and subthreshold depression and the effect of genotype on the relationship between impulsivity and subthreshold depression

We analysed the latent structural relationship between impulsivity and Zung scores below 48 points (as previously described in our study) by structural equation modelling (SEM). Figure 7 shows the general model.

DOI:10.14753/SE.2012.1655

Figure 7. General SEM model.
The relationship between impulsitivity and depression is represented by a path diagram where single-headed arrows indicate causal relationships, and double-headed arrows represent correlations. By convention, observed variables are shown as squares and latent variables are shown as circles. Variables er1-er7 and end1-end2 are representing the model discrepancy error. Nonplan=Nonplanning Impulsiveness subscale, Motor=Motor Impulsiveness subscale, Cognitive=Cognitive Impulsiveness subscale.



DOI:10.14753/SE.2012.1655

The preliminary model was the simplest model concerning measurement, and the main association to be analysed was the relationship between the two latent variables (impulsivity and depression). Our strategy was to investigate the whole model as the first step, and then in the next step we divided our sample according to genotype (*263*) to subjects carrying the CC, GG and GG genotype.

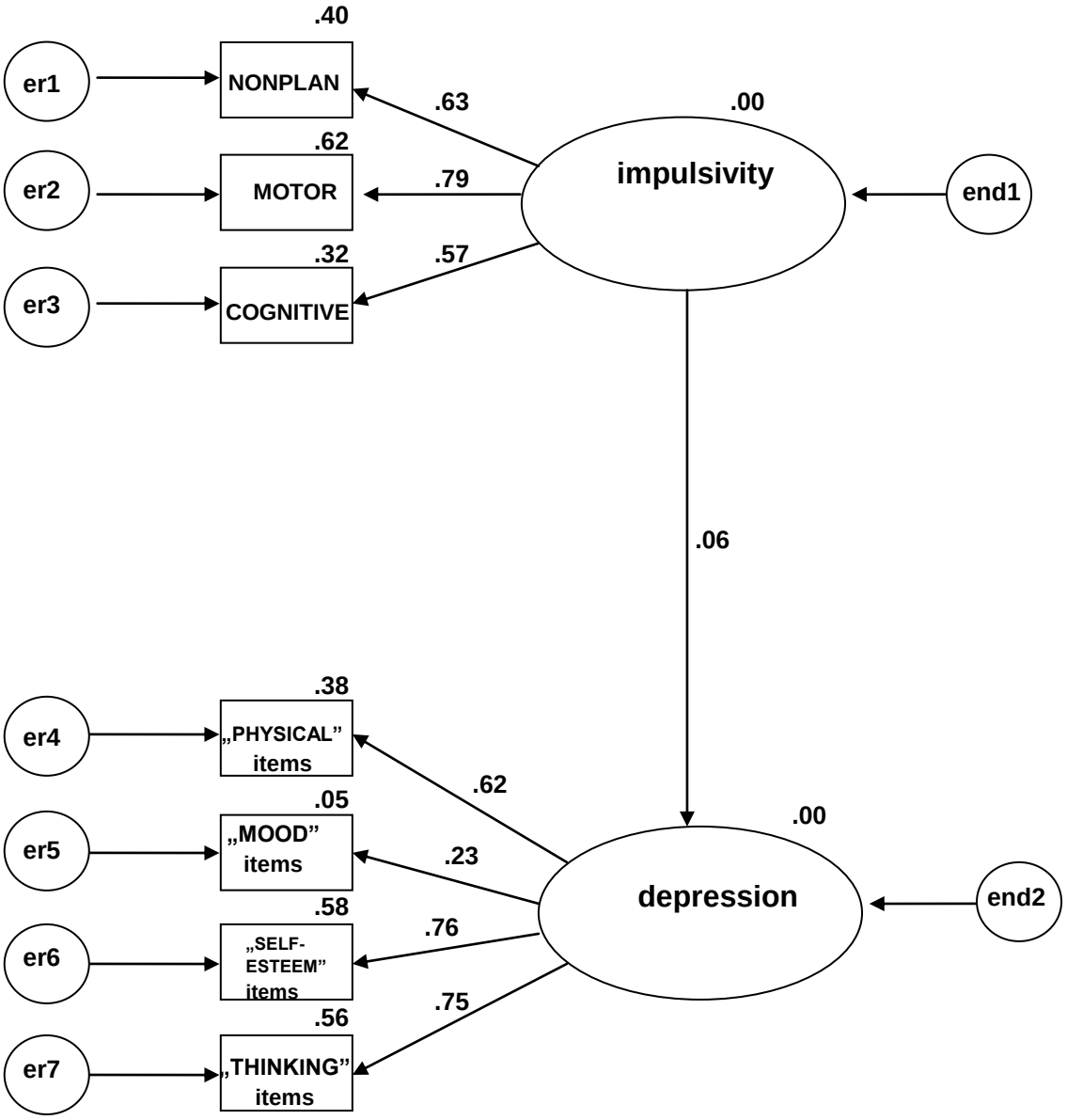
5.3.1. Model for the whole study cohort: association between the BIS-11 and the ZSDS

Figure 8 shows the model for the whole study cohort. Numbers on the arrows indicate standardised regression coefficients. The standardised regression coefficients between latent and observed variables can also be interpreted as correlation coefficients. Accordingly, the numbers on the rectangles show the explained part of the total variance

In overall the model is plausible (Chi-square = 17.576, DF=13, p=0.174) because the p value is much larger than 0.05.

DOI:10.14753/SE.2012.1655

Figure 8. The relationship between impulsivity and depression is represented by a path diagram where single-headed arrows indicate causal relationships, and double-headed arrows represent correlations. By convention, observed variables are shown as squares and latent variables are shown as circles. Variables er1-er7 and end1-end2 are representing the model discrepancy error. Nonplan=Nonplanning Impulsiveness subscale, Motor=Motor Impulsiveness subscale, Cognitive=Cognitive Impulsiveness subscale.



DOI:10.14753/SE.2012.1655

Though the model is plausible but it does not mean that some of the relationships depicted in Figure 8 are really existing, statistically significant relationships. Therefore, we computed the 90% confidence intervals of the corresponding parameters. Results are summarized in Table 5.

Table 5 shows the standardized regression coefficients the corresponding bootstrap confidence intervals. Based on the confidence intervals the relationship between impulsivity and depression can be considered significant because the corresponding 90% confidence interval does not cross zero. This confidence interval-based, reasoning corresponds to a one-sided test at 0.05 level. In classical two-sided hypothesis setting the alpha error is 0.054 which is at the border of being significant. The estimated standardized coefficient between impulsivity and depression is 0.064 meaning that about 6.4% percent of the total variability can be attributed to differences in impulsivity. All other connection between the observed and latent variables are highly significant which support the content validity of the applied scales. Still it is noteworthy to observe that there are significant differences among the strengths of association of sub-scales to latent variables they measure. For example, the association between depression (as latent variable) and self-esteem (as an observed variable) is much stronger then association between depression and mood because he corresponding correlations are 0.762 and 0.223 respectively.

DOI:10.14753/SE.2012.1655

Table 5. Correlation coefficients and 90% bootstrap confidence intervals (percentile method) for the structural equation model for the whole study cohort

Parameter			Estimate	Lower	Upper	P
Depression	<---	Impulsivity	.064	.021	.119	.053
COGNITIVE	<---	Impulsivity	.569	.514	.621	.011
MOTOR	<---	Impulsivity	.785	.734	.860	.007
NONPLAN	<---	Impulsivity	.630	.561	.687	.012
THINKING	<---	Depression	.746	.694	.793	.012
SELF ESTEEM	<---	Depression	.762	.710	.805	.010
MOOD	<---	Depression	.226	.168	.291	.012
PHYSICAL	<---	Depression	.616	.573	.670	.005

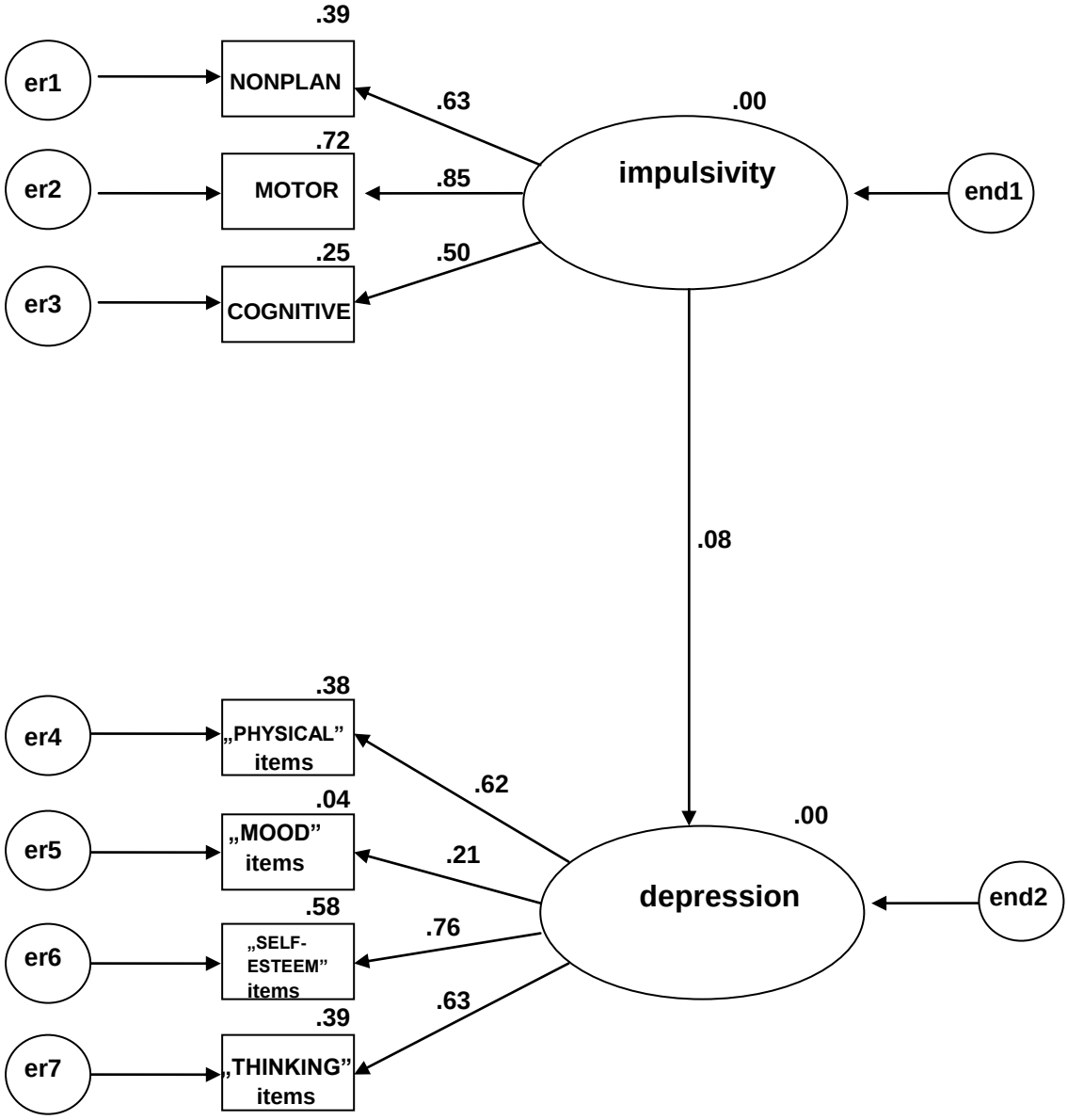
In the next step we analysed our data separately for subjects carrying the CC, GG and GC genotype.

5.3.2. SEM statistics for the CC group

Figure 9, 10, 11 shows the model for the CC, GG and GC genotype groups, respectively. Table 6, 7, 8 shows the standardized regression weights and confidence intervals for the SEM for the CC, GG and GC genotype groups, respectively.

DOI:10.14753/SE.2012.1655

Figure 9. Model for the CC group.
By convention, observed variables are shown as squares and latent variables are shown as circles. Variables er1-er7 and end1-end2 are representing the model discrepancy error. Nonplan=Nonplanning Impulsiveness subscale, Motor=Motor Impulsiveness subscale, Cognitive=Cognitive Impulsiveness subscale.



DOI:10.14753/SE.2012.1655

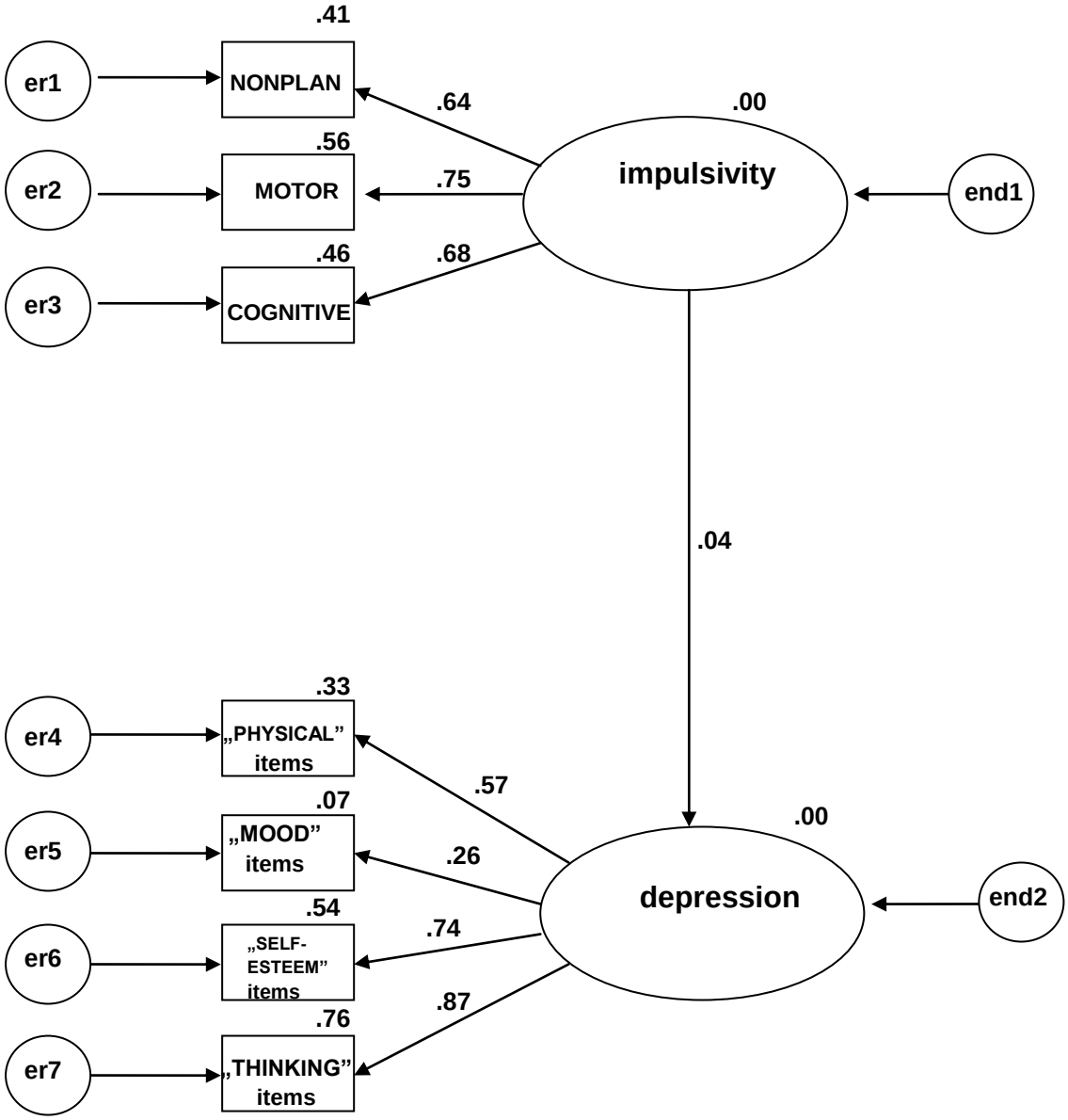
Table 6. Correlation coefficients and confidence intervals for the structural equation model for the CC group

Parameter			Estimate	Lower	Upper	P
Depression	<---	Impulsivity	.080	.031	.316	.010
COGNITIVE	<---	Impulsivity	.498	.360	.632	.010
MOTOR	<---	Impulsivity	.846	.679	.992	.010
NONPLAN	<---	Impulsivity	.626	.500	.783	.010
THINKING	<---	Depression	.628	.446	.728	.010
SELF ESTEEM	<---	Depression	.761	.672	.985	.010
MOOD	<---	Depression	.212	.066	.365	.029
PHYSICAL	<---	Depression	.619	.426	.728	.010

DOI:10.14753/SE.2012.1655

5.3.3. SEM statistics for the GG group

Figure 10. Model for the GG group.
By convention, observed variables are shown as squares and latent variables are shown as circles. Variables er1-er7 and end1-end2 are representing the model discrepancy error. Nonplan=Nonplanning Impulsiveness subscale, Motor=Motor Impulsiveness subscale, Cognitive=Cognitive Impulsiveness subscale.



DOI:10.14753/SE.2012.1655

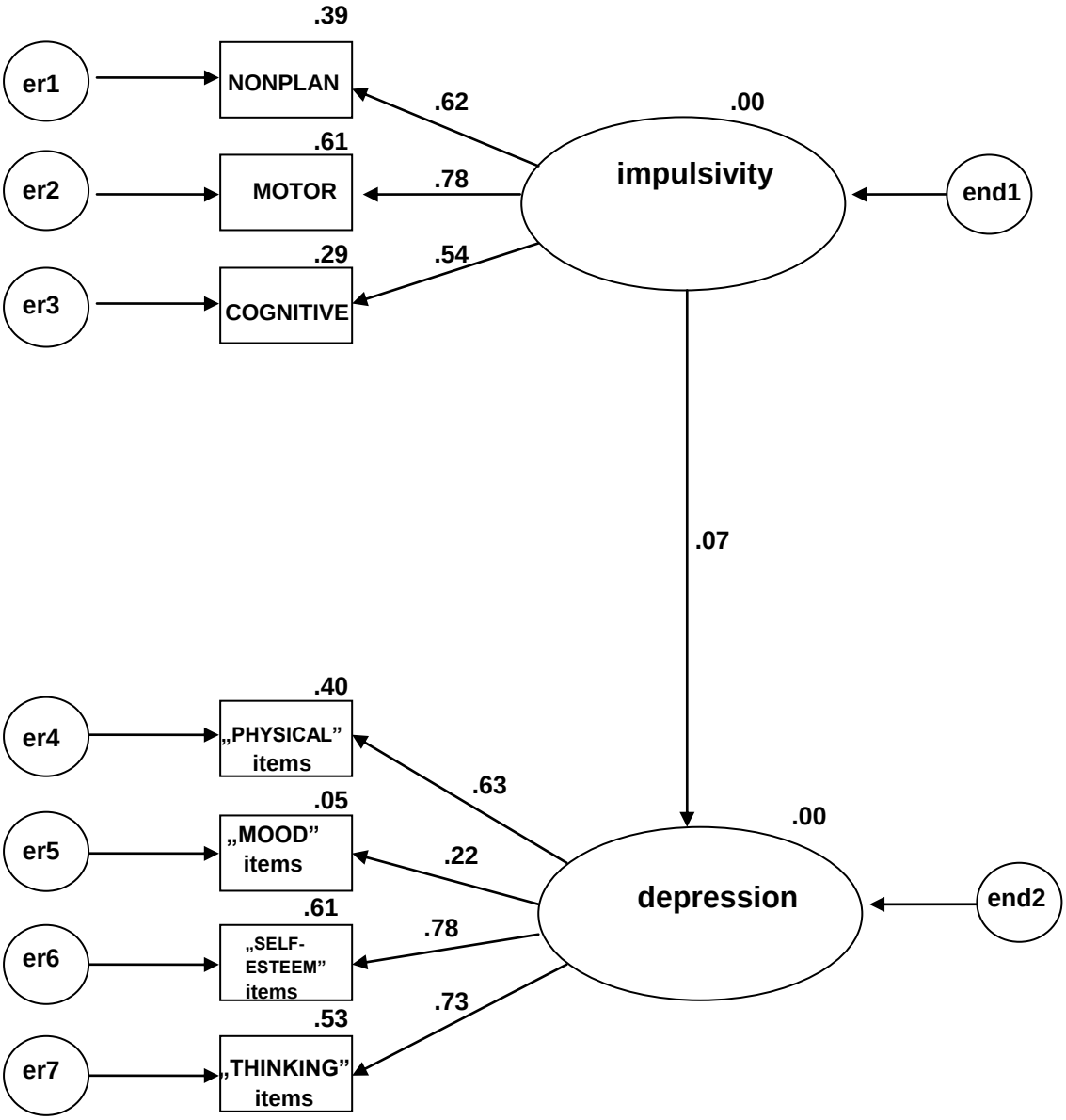
Table 7. Correlation coefficients and confidence intervals for the structural equation model for the GG group

Parameter			Estimate	Lower	Upper	P
Depression	<---	Impulsivity	.037	.020	.212	.010
COGNITIVE	<---	Impulsivity	.681	.570	.796	.010
MOTOR	<---	Impulsivity	.751	.644	.859	.010
NONPLAN	<---	Impulsivity	.638	.529	.723	.010
THINKING	<---	Depression	.870	.779	.956	.010
SELF ESTEEM	<---	Depression	.736	.645	.813	.010
MOOD	<---	Depression	.264	.131	.385	.010
PHYSICAL	<---	Depression	.574	.455	.653	.010

DOI:10.14753/SE.2012.1655

5.3.4. SEM statistics for the GC group

Figure 11. Model for the GC group.
By convention, observed variables are shown as squares and latent variables are shown as circles. Variables er1-er7 and end1-end2 are representing the model discrepancy error. Nonplan=Nonplanning Impulsiveness subscale, Motor=Motor Impulsiveness subscale, Cognitive=Cognitive Impulsiveness subscale.



DOI:10.14753/SE.2012.1655

Table 8. Correlation coefficients and confidence intervals for the structural equation model for the GC group

Parameter			Estimate	Lower	Upper	P
Depression	<---	Impulsivity	.068	.030	.202	.010
COGNITIVE	<---	Impulsivity	.542	.446	.626	.010
MOTOR	<---	Impulsivity	.780	.695	.890	.010
NONPLAN	<---	Impulsivity	.625	.520	.706	.010
THINKING	<---	Depression	.729	.645	.794	.010
SELF ESTEEM	<---	Depression	.779	.714	.847	.010
MOOD	<---	Depression	.216	.123	.325	.010
PHYSICAL	<---	Depression	.634	.550	.697	.010

As Table 6, 7 and 8 show there is a clear trend can be observed between genotype and impulsivity ->depression beta weights. The association is the weakest in the GG group (0.037), strongest is the CC group (0.08) and as expected the GC group occupies the middle position (0.068). The regression coefficients were significant in case of all three groups, indicating that the studied genotype does not influence the association between the ZSDS scores and impulsivity.

DOI:10.14753/SE.2012.1655

6. DISCUSSION

6.1. The C(-1019)G functional polymorphism of the HTR1A gene and impulsivity

We found a significant association between the C(-1019)G functional polymorphism of the HTR_{1A} gene and impulsivity. Subjects with the GG genotype scored significantly higher on the IVE-I, and on the Motor Impulsiveness and Cognitive Impulsiveness subscales but not on the Nonplanning Impulsiveness subscale of BIS-11 compared to subjects with the GC or CC genotypes.

Impulsivity is a multifaceted trait, and there are several scales developed to measure impulsivity based on slightly different theoretical concepts. We used two of these scales in our study to be able to analyse impulsivity in a more complex and global way. The Barratt Impulsiveness Scale contains three subscales describing three different components of impulsivity: motor impulsiveness is a tendency to act without thinking; cognitive impulsiveness is involved in making quick cognitive decisions; nonplanning impulsivity refers to a lack of sense of the future. Barratt defined impulsivity as a personality trait, and linked it to Eysenck's extraversion and sensation seeking personality traits. The questionnaire originally measured impulsivity as a unidimensional personality trait, the three dimensions were characterised only later (*252*).

Previous animal and human research showed that serotonin is implicated in impulsivity (*60, 61*), for example, low brain serotonin level has been associated with increased impulsive choice in animals (*62*) and in humans (*63*), but contradictory findings have also been described (*64, 65*). The role of 5-HT receptors, mainly 5-HT1 and 5-HT2 receptors, have been well studied in the regulation of impulsivity. Agonists that act on 5-HT1A receptors decrease impulsive behaviour (*264*). In brain areas where post-synaptic 5-HT1A receptors are located, such as the amygdala and frontal cortex, the density of 5-HT1A receptors was found to be decreased in aggressive rats (*69*).

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The role of 5-HT receptors, mainly 5-HT_1 and 5-HT_2 receptors, have been well studied in the regulation of impulsivity. Agonists that act on 5-HT_{1A} receptors decrease impulsive behaviour (*264*). In brain areas where postsynaptic 5-HT_{1A} receptors are located, such as the amygdala and frontal cortex, the density of 5-HT_{1A} receptors was found to be decreased in aggressive rats (*69*).

It has been suggested that the C(-1019)G polymorphism regulates the HTR_{1A} gene expression through altered control of the promoter in presynaptic raphe neurons. The polymorphism is located in a 26-bp palindrome region recognized by the transcription factors DEAF-1 and Hes5 that bind efficiently to the C allele, but not to the G allele. Thus the 5-HT_{1A} receptor function is altered by this polymorphism – the G allele leading to reduced serotonergic neurotransmission due to impaired binding of the DEAF-1-related (NUDR) repressor protein (*21*). Impulsive behaviour has been suggested to occur due to a dysfunction of the serotonergic neurotransmission. Walderhaug et al (*265*) reported that impulsive behaviour increased after acute tryptophan depletion causing a decrease in 5-HT neurotransmission in healthy individuals. Another study investigating the effects of Ecstasy (3,4-methylenedioxy-methamphetamine, MDMA) found a long-term reduction in 5-HT level and increased impulsivity measured by IVE in Ecstasy users compared to non-users (*266*). These findings support earlier evidence that elevated levels of impulsivity are associated with reduced serotonergic function. Our findings support the involvement of a genetic polymorphism of the 5-HT_{1A} receptor in the regulation of impulsive behaviour.

Lemonde et al. (*21*) reported an association of the G allele of the C(-1019)G polymorphism with completed suicide but not with suicidality among depressed patients. In the study of Serretti et al. (*24*) the G allele and STAXI state anger scale showed an association with suicide attempt in females, supporting previous reports that 5-HT_{1A} receptor plays an important role in aggression. Data of Sawiniec et al. (*23*) also support the hypothesis that the G allele of the C(-1019)G polymorphism is a biological risk factor of suicide attempt, while Wasserman et al. (*26*) found that this polymorphism is not associated with suicide attempts generally and pointed out that this discrepancy in the literature is due to suicidal behaviour being a complex phenomenon.

Strobel et al. (*31*) examined anxiety- and depression-related personality traits using the NEO-PI-R and the TPQ questionnaires in a German cohort of 284 students. They found association between the G allele and Neuroticism (NEO-PI-R) and Harm Avoidance scales (TPQ). However, other studies failed to detect significant association of this polymorphism with neuroticism (*32, 33*), although subsequent analyses showed no significant association with the C(-1019)G polymorphism and Impulsiveness as one of the subscales of the Neuroticism scale (*31*). Serretti et al. (*34*) investigated the association between HTR_{1A} and HTR_{2C} SNPs and personality traits, measured by the TCI, in a sample of suicide patients and healthy volunteers. According to their results, SNPs – including rs6295 – and haplotypes were not associated with any personality dimensions including Novelty Seeking (NS) that contains an Impulsivity subscale, too. The Impulsivity subscale of NS was, however, not analysed separately.

The TPQ, TCI and NEO-PI-R provide a broad characterization of personality traits. By contrast, the BIS-11 and other impulsivity-related questionnaires focus on one personality trait in detail (*267*). The different construct of impulsivity measured by the personality inventories and specific impulsivity questionnaires may provide an explanation for the different results. The Temperament and Character Inventory was designed to measure four temperament and three character dimensions. One of the temperament dimensions is the above mentioned Novelty Seeking. The NS scale was designed to measure exploratory, impulsive and extravagant behaviour, and has been related to the dopamine system by Cloninger (*268*), while the BIS-11 provides an integrated measure of impulsivity. Impulsivity can be viewed as having multiple dimensions, rather than being measured as a unidimensional, single or narrow component (*269*).

Studies investigating the possible association of C(-1019)G and aggression focused on suicide attempters and completers. Impulsivity is a risk factor of suicide and we found a significant association between the impulsivity scales and C(-1019)G, suggesting that 5-HT_{1A} receptor function may be one of the biological predispositions to suicidality. Impulsivity is not the main risk factor of suicidal behaviour, however this trait has been consistently found to characterize suicide attempters (*270*).

DOI:10.14753/SE.2012.1655

In our study we found a significant association between C(-1019)G, and the Impulsiveness subscale of the Eysenck IVE Scale, and also the Motor and Cognitive Impulsiveness subscales but not the Nonplanning Impulsiveness subscale of the BIS-11. Our results thus indicate a profound relationship between this polymorphism and impulsivity, as indicated by the significant relationship we found in case of two different scales. Furthermore, our result of no significant association between nonplanning impulsivity and the C(-1019)G polymorphism indicates that this relationship is valid only for the basic and elementary manifestations of impulsivity-related behaviour but not for nonplanning impulsivity which incorporates more complex and higher mental processes. Other genes regulating these processes are likely to play an important role in the background of nonplanning impulsiveness.

6.2. The C(-1019)G functional polymorphism of the HTR1A gene and subthreshold depression

There have been only a few studies examining the possible biological and genetic background of subthreshold depression, although subthreshold depression causes subjective suffering, social and work impairment. In the present study we found no significant association between the C(-1019)G functional polymorphism of the HTR_{1A} gene and the ZSDS scores below the level indicating depression. Previously, subthreshold depression was associated with the s allele of the serotonin transporter gene (5HTTLPR) in a psychiatrically healthy population (*248*).

Studies indicate that dysfunction of the serotonin 1A receptor (5-HT1A) may play a role in the background of depression.

Long-term treatment with 5-HT1A receptor agonists such as buspirone have been reported to exert modest antidepressant and anxiolytic effects in both animal and human studies, possibly through their desensitizing effects on 5-HT1A autoreceptors and their activation of post-synaptic receptors (*66, 271*).

Positron emission tomography (PET) studies reported a wide-spread reduction (frontal, temporal and limbic cortices) in 5-HT1A receptor binding in individuals with major depressive disorder (*272*, *273*) and a follow-up study indicated that this effect holds true for remitted patients (*274*). Congruent with the PET imaging data, SERT KO mice have also been reported to display a reduced density of 5-HT1A receptors in the hypothalamus, amygdala and dorsal raphe nucleus (*275*).

Genetic studies showed that the C(-1019)G polymorphism of the HTR_{1A} gene (rs6295) is associated with several psychiatric disorders including major depression (*21*). The rs6295 G allele both decreases postsynaptic 5-HT1A receptor expression, and increases the risk of developing MD, is consistent with pharmacological (*276*), postmortem (*277*), PET (*278*) data suggesting impaired serotonergic signaling at the postsynaptic 5-HT1A receptor. The association of the 5-HT1A G(-1019) allele and the G/G genotype with major depression has been replicated by others (*278-281*), however, some studies have not observed association of the G(-1019) allele with depression (*282*, *283*). This discrepancy may be due in part to the frequency of the risk allele in the population studied. For example, in the study of Lemonde et. al. (*21*) the G/G genotype was 5% of control subjects, and 17% of suicides, a threefold odds ratio while in other Caucasian populations the frequency of the G/G genotype is 25%, and hence the odds ratios are decreased and much larger populations are needed to observe the association, which may introduce increased variability in phenotype.

Francois et al. (*284*) suggested that one strategy to overcome the high frequency of the G/G genotype is to examine discrete subsets of depression. For example, in the study of Kraus et al. (*280*) interferon-alpha induced depression has been associated with the G/G genotype, while an association with major depression has not been reported. Another possible strategy to enhance the power of associations with the rs6295 polymorphism is to examine genetic epistasis among multiple functional risk alleles. For example, risk alleles of the 5-HTT and 5-HT1A receptor genes have in combination been associated with reduced response to antidepressants (*285*). Association has also been observed between HTR1A rs6295 and COMT or BDNF (Val66Met) risk alleles with panic disorder or major depression, (*279*, *286*), and gene–gene interactions may explain why some studies did not observe association with 5-HT1A G(-1019) allele

alone. Thus, ethnic, disease and genetic heterogeneity among subjects may obscure associations of mental illness with common polymorphisms.

6.3 The latent relationship between impulsivity and subthreshold depression, and the effect of genotype on this relationship

First we investigated the relationship between genotype and impulsivity (*263*). There was a significant association between the motor and cognitive impulsiveness subscales of the BIS-11 and the C(-1019)G polymorphism. There was, however, no significant association between this polymorphism and the ZSDS, as mentioned previously in this study.

In the next step we investigated the relationship between impulsivity and ZSDS scores below the level indicating clinical depression and the influence of genotype on this relationship.

Standardised regression coefficients concerning the relationship between impulsivity and depression for GG, GC and CC genotype were 0.037, 0.068 and 0.08 respectively. These regression coefficients were significant in case of all three groups, indicating that the studied genotype does not influence the association between the ZSDS scores and impulsivity.

Subthreshold depression, as measured in our general sample by the ZSDS is significantly associated with impulsivity however this association is weak. The mood items of the ZSDS have a smaller influence on subthreshold depression, which is in line with previous studies reporting that in case of subthreshold depression mood symptoms are often absent (*287*).

There have been several previous studies suggesting a relationship between depression and impulsivity.

There are phenotypic associations occurring in childhood and adolescence between constructs relating to impulsivity and depression. Brodsky et. al. (*288*) reported an association of childhood trauma and impulsivity with suicidal behaviour and major

depression in adulthood. Cataldo et. al. (*289*) found that depressed children and adolescents were rated by their parents as significantly more impulsive or restless than controls.

There is also association between depression and impulse control disorders (ICDs). Impulse control disorders (ICDs) are characterized by the repetitive occurrence of impulsive behaviour (*290*). The association between ICDs and depression is frequent; 72% of pathological gamblers have experienced at least one episode of major depression, and 52% have recurrent major affective episodes (*291, 292*). Severity of depression is positively correlated to severity of pathological gambling (*293*). Studies revealed that there is also association between depression and kleptomania (*294*) and trichotillomania (*295*).

Research reports found associations between impulsivity and suicide within depressed adults, however, most of studies on impulsivity and depression in adults focused on the effect of impulsivity on suicidality of depressed patients (*296, 297*). Elovainio *et al.* (*298*), in a prospective study with a 4-year follow-up, showed that some subtraits of Cloninger's psychobiological model of personality, e.g. impulsivity, shyness with strangers, fatigability, sentimentality and persistence were associated with an increased risk of depressive symptoms independently of a variety of other risk factors for depression.

Assessment of biochemistry provides further evidence of an association between impulsivity and depression. Both depression and impulsivity have been shown to be related to decreased serotonin levels (*299-301*).

Although there have been several studies reporting association between impulsivity and depression, these studies focused on mainly psychiatric samples. Granö et. al (*302*) investigated the association between impulsivity and incidence of newly diagnosed depression in a working population and found that impulsivity was predictive of an increased likelihood of newly diagnosed depression among hospital employees who were free from diagnosed depression at study entry. The odds for newly diagnosed depression were 1.7 times higher for impulsive individuals than for their non-impulsive counterparts. Their data were based on self-reports and mainly female, ethnically Northern European hospital employees but it was the first study investigating the association between impulsivity and depression in a non-clinical population.

Earlier studies show that impulsivity could be a component of the depressive state itself. Corruble et al. for example, have characterized impulsivity in subjects with major depressive episodes. Using the BIS and other questionnaires, this group described increased attentional, behavioural, and nonplanning impulsivity in subjects experiencing depressive episodes (*303*). Among non-bipolar subjects with methamphetamine abuse, Beck depression scale scores were increased in the subjects with high impulsivity (*304*). Swann et al. (*305*) reported that BIS scores correlated most strongly with hopelessness and anhedonia among depressed subjects, rather than subjective depression.

Subthreshold depression patients have a high risk of developing major depression, more than 25% of the subthreshold patients develop major depression over a period of 2 years (*306, 307*). Judd et al (*243*) reported that the most common SSD symptoms are insomnia (44.7%), feeling tired out all the time (42.1%), recurrent thoughts of death (31.0%), trouble concentrating (22.7%), significant weight gain (18.5%), slowed thinking (15.1%), and hypersomnia (15.1%). People with subthreshold depression report more health service use (*308*), need for public assistance (*243*), more limitations in role work function (*309*), increased physical limitations (*306, 309*), increased job absenteeism (*308*), increased bed days (*309*), increased social irritability and household strain (*309*) and it has been found to be associated with large-scale economic costs because of disability days (*310*). Females significantly more frequently present with SSD than males (*243*).

Furthermore, in our study, impulsivity measured by the BIS-11 is determined by the Motor Impulsiveness subscale in 62%. Impulsivity may have a central role in the clinical biology of affective disorders. It appears clearly to be related to mania (*311*) and because of its relationship to suicidal behaviour, relationships between impulsivity and depression have also been studied (*312, 313*).

Studies suggest that depression or hopelessness can interact with impulsivity to result in risk for suicide (*312-314*), however, hopelessness or anhedonia may be more directly related to suicidality than depressed mood is (*315*). A fourteen-year prospective study found that nearly lethal suicide attempts and completed suicide were associated with impulsivity, substance abuse, previous attempts, and a mixed clinical presentation, with trait impulsivity predicting suicide even more than 12 months later (*316*). Furthermore, in major depressive disorder, impulsive aggression was associated with greater risk for completed suicide (*317*). Depressive episodes with concomitant manic

DOI:10.14753/SE.2012.1655

symptoms could represent a combination of depression and impulsivity. This combination is potentially dangerous in terms of risk for violence, substance abuse, or suicide (*296, 297*). The risk of suicide is significantly higher in patients with SSD compared to normal subjects, but lower than in major depression or minor depression (*243*). Subthreshold depression patients have a relatively high risk of developing major depression, thus recognizing subthreshold depressive symptoms is important in the prevention of major depression.

7. CONCLUSIONS

In the present study we investigated the involvement of the C(-1019)G polymorphism in impulsivity related behaviour and subthreshold depression. Furthermore, we investigated the relationship between impulsivity and subthreshold depression and the effect of genotype on the relationship between impulsivity and subthreshold depression.

- We found a significant association between the C(-1019)G polymorphism, and the Impulsiveness subscale of the Eysenck IVE Scale, and also the Motor and Cognitive Impulsiveness subscales but not the Nonplanning Impulsiveness subscale of the BIS-11 in a non-clinical population. Subjects with the GG genotype are significantly more impulsive compared to subjects with the GC or CC genotypes. Our results suggest the involvement of the HTR1A gene in the continuum phenotype of impulsivity.
- The majority of work that has been done in this area has focused on impulsive aggression. This focus is partly the result of the fact that aggressive acts are more easily measured than other aspects of impulsivity. Repeatable measures of impulsivity that capture the core aspects of this behaviour are needed.

- Impulsivity is a key factor in so many disorders and an important factor in treatment, but the biological and psychological research is limited by current diagnostic categories and that a dimensional approach may be more appropriate than the categorical approach used in psychiatric diagnosis and treatment.

- In the present study we found no significant association between the C(-1019)G functional polymorphism of the HTR_{1A} gene and the ZSDS scores below the level indicating depression.

- The ZSDS scores below the level indicating major depression is significantly associated with impulsivity in a non-clinical population suggesting that high impulsivity could be a risk factor for depression in healthy adults.

- The mood items of the ZSDS have a smaller influence on subthreshold depression, which is in line with previous studies reporting that in case of subthreshold depression mood symptoms are often absent.

- Impulsivity measured by the BIS-11 is determined by the Motor Impulsiveness subscale in 62%.

- There is a statistically significant connection between impulsivity and depression as latent variables. This connection seems to be influenced by the polymorphism of HTR_{1A} gen however we could not demonstrate that this polymorphism effect is statistically significant. Standardised regression coefficients concerning the relationship between impulsivity and depression for GG, GC and CC genotype were 0.037, 0.068 and 0.08 respectively. These regression coefficients were significant in case of all three groups, suggesting some influence on the association between impulsivity and depression.

- From a clinical point of view, recognizing subthreshold depression is important as subthreshold depression causes considerable psychological suffering, thus treatment is necessary. The goal of this treatment is to reduce depressive symptomatology and to improve quality of life.

- Another reason why subthreshold depression is important from a clinical viewpoint is the increased risk of developing major depression and an increased risk of suicide.

DOI:10.14753/SE.2012.1655

8. SUMMARY

8.1 Summary

Serotonin-1A (5-HT1A) receptors are known to play a role in impulsivity-related behaviour and depression as well. The C(-1019)G functional polymorphism has been suggested to regulate the 5-HT1A receptor gene (HTR1A) expression in presynaptic raphe neurons. Previous studies indicate that this polymorphism is associated with aggression, suicide, and several psychiatric disorders, yet its association with impulsivity has rarely been investigated. Furthermore, studies reported that dysfunction of the serotonin 1A receptor may play a role in the background of depression but its association with subclinical forms of depression has not been investigated yet. Some authors suggested a direct relationship between depression and impulsivity.

The aim of the present study was to test the hypothesis of the involvement of the C(-1019)G polymorphism in impulsivity related behaviour and subthreshold depression in a non-clinical population of 725 subjects. Furthermore, we aimed to investigate the relationship between impulsivity and subthreshold depression and the effect of genotype on the relationship between impulsivity and subthreshold depression.

We found a significant association between the C(-1019)G polymorphism, and the Impulsiveness subscale of the Eysenck IVE Scale, and also the Motor and Cognitive Impulsiveness subscales but not the Nonplanning Impulsiveness subscale of the BIS-11. Subjects with the GG genotype are significantly more impulsive compared to subjects with the GC or CC genotypes, our results suggest the involvement of the HTR1A gene in the continuum phenotype of impulsivity. We found no significant association between the C(-1019)G functional polymorphism of the HTR_{1A} gene and subthreshold depression.

There is a statistically significant connection between impulsivity and depression. This connection seems to be influenced by the polymorphism of the HTR_{1A}

gene however we could not demonstrate that this polymorphism effect is statistically significant.

Subthreshold depression (SSD) patients have a high risk of developing major depression, more than 25% of the subthreshold patients develop major depression over a period of 2 years. The risk of suicide is significantly higher in patients with SSD compared to normal subjects, but lower than in major depression or minor depression.

Overall, our study suggest the involvement of the C(-1019)G polymorphism in the background of impulsivity-related behaviour. Furthermore, the association between impulsivity and subthreshold depression suggest that in a non-clinical population impulsivity could be a risk factor for depression in healthy adults.

8.2 Összefoglalás

A szerotonin-1A (5-HT_{1A}) receptorok szerepet játszanak az impulzivitás illetve a depresszió biokémiai hátterében. A C(-1019)G funkcionális polimorfizmus (rs6295) szabályozza az 5-HT1A receptor gén (HTR1A) expresszióját a preszinaptikus raphe neuronokon. Tanulmányokban leírták, hogy kapcsolat van a C(-1019)G polimorfizmus és az agresszió, öngyilkosság, major depresszió s számos pszichiátriai betegség között, de kapcsolatát az impulzivitással csak keveset, a depresszió szubklinikus formáival pedig egyáltalán nem vizsgálták. Továbbá számos kutatás szól a major depresszió és az impulzív viselkedés összefüggéseiről.

Kutatásunk célja a C(-1019)G funkcionális polimorfizmus és az impulzivitás, valamint a szubklinikus depresszió kapcsolatának vizsgálata egy 725 fős átlag populáción. Továbbá vizsgáltuk az impulzív viselkedés és a szubklinikus depresszió kapcsolatát, s a genotípus hatását erre a kapcsolatra.

Szignifikáns összefüggést találtunk a C(-1019)G polimorfizmus és az IVE-I skála valamint a BIS-11 skála Motoros és Kognitív Impulzivitás alskálája között, de a polimorfizmus és a Tervezés hiánya alskála között nem volt szignifikáns összefüggés. A GG genotípust hordozók szignifikánsan impulzívabbak, mint a CC és GC hordozók. Eredményeink szerint a vizsgált polimorfizmus szerepet játszik az impulzív viselkedés

DOI:10.14753/SE.2012.1655

biológiai hátterében. Vizsgálataink során nem találtunk szignifikáns összefüggést a C(-1019)G polimorfizmus és szubklinikus depresszió között.

A két látens változó, az impulzivitás és depresszió között statisztikailag szignifikáns a kapcsolat. Erre a kapcsolatra hatással van a HTR1A gén polimorfizmus, viszont számottevő különbség nincs a genotípus csoportok között.

Annak kockázata, hogy a szubklinikus depresszióból major depresszió alakul ki elég nagy, mintegy 25%-uk major depresszióssá válik 2 éven belül. Az öngyilkossági kísérletek veszélye szubklinikus depresszióban pedig nagyobb, mint egészségeseknél vagy minor depresszióban.

Összességében eredményeink rámutatnak, hogy a C(-1019)G polimorfizmus szerepet játszik az impulzív viselkedés hátterében. Továbbá, a szubklinikus depresszió és az impulzivitás közti szignifikáns kapcsolat jelezheti, hogy átlagpopulációban a depresszió kialakulásának rizikófaktora lehet az impulzív viselkedés.

DOI:10.14753/SE.2012.1655

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DOI:10.14753/SE.2012.1655

10. PUBLICATIONS

10.1Publications relevant to the dissertation

1. Benko, A., Lazary, J., Molnar, E., Gonda, X., Tothfalusi, L., Pap, D., Mirnics, Z., Kurimay, T., Chase, D., Juhasz, G., Anderson, I. M., Deakin, J. F., and Bagdy, G. (2010) Significant association between the C(-1019)G functional polymorphism of the HTR1A gene and impulsivity, *Am J Med Genet B Neuropsychiatr Genet 153B*, 592-599.

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10.2 Other publications

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10.3 Book chapters

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12. Juhász Péter, Benkő Anita: Interjúk az ecstasy hatásáról. In: (Bagdy Gy. Szerk) Amit az ecstasyról tudni kell. Budapest. *Akadémia Kiadó.* 2006

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DOI:10.14753/SE.2012.1655

11. ACKNOWLEDGEMENT

I would like to express my gratitude to all those people who helped me in my PhD research, without whom my dissertation could not have been carried out.

First of all I would like to thank my supervisor Prof. Dr. György Bagdy (Department of Pharmacodynamics, Semmelweis University), for his professional guidance, support and humanity through the past 8 years, since we have started to work together during my university years and then our research work continued.

For his supervision, guidance and advices is all the statistical work I would like to thank Dr. László Tóthfalusi (Department of Pharmacodynamics, Semmelweis University).

I would like to thank Dr. Xenia Gonda (Department of Clinical and Theoretical Mental Health, Semmelweis University) for her professional advice and encouragement even during the difficult moments of my research work.

I am thankful to all my colleagues in the Laboratory of Semmelweis University, Dr. Judit Lazáry, Eszter Molnár, Rómeó Andó, Dorottya Pap, Tamás Kitka, Zita Kátai for their friendship and support at all times. Special thanks to Dr. Gabriella Juhász (Manchester University) for her help and collaboration.

Special thanks to Edit Módosné Ányok for her help at the very beginning in the National Institute of Psychiatry and Neurology and to my dear past colleges for their friendship and support: Zsuzsa Egonné Anheuer and Nóra Nagyné.

I would like to thank all the volunteers for their participation in our study.

Last but not least I would like to thank my family, friends and workmates for their love, patience and support day by day.

These studies were supported by the Sixth Framework Programme of the EU, LSHM-CT-2004-503474 and the PhD Fellowship Program of the Semmelweis University, Ministry of Culture and Education, Hungary.

DOI:10.14753/SE.2012.1655

12. APPENDIX