DISSERTATIONES PSYCHOLOGICAE UNIVERSITATIS TARTUENSIS
22

DISSERTATIONES PSYCHOLOGICAE UNIVERSITATIS TARTUENSIS
22

TYPES OF IMPULSIVITY, THEIR BEHAVIOURAL EXPRESSION, AND ASSOCIATION WITH THE MARKERS OF VULNERABILITY OF SEROTONIN SYSTEM

MARIKA PAAVER

TARTU UNIVERSITY
PRESS

Department of Psychology, University of Tartu, Estonia

Dissertation is accepted for the commencement of the degree of Doctor of Philosophy (in Psychology) on June 4, 2007, by the Doctoral Committee of the Department of Psychology, University of Tartu

Supervisor: Jaanus Harro, PhD, MD, Professor
University of Tartu, Estonia

Opponent: Petra Netter, PhD, MD, Professor
University of Giessen, Germany

Commencement: July 5, 2007

ISSN 1024–3921
ISBN 978–9949–11–634–8 (trükis)
ISBN 978–9949–11–635–5 (PDF)

Tartu Ülikooli Kirjastus
www.tyk.ee
Tellimus nr. 226

CONTENTS

LIST OF PAPERS

I Eensoo, D., Paaver, M., Pulver, A., Harro, M., & Harro, J. (2004) Low platelet MAO activity, high dysfunctional impulsivity and antisocial behaviour: evidence from drunk drivers. *Psychopharmacology* 172, 356–359.

II Eensoo, D., Paaver, M., Harro, M., & Harro, J. (2005). Predicting drunk driving: contribution of alcohol use and related problems, traffic behaviour, personality and platelet monoamine oxidase (MAO) activity. *Alcohol and Alcoholism* 40, 140–146.

III Paaver, M., Eensoo, D., Pulver, A., & Harro, J. (2006) Adaptive and maladaptive impulsivity, platelet monoamine oxidase (MAO) activity and risk-admitting in different types of risky drivers. *Psychopharmacology* 186, 32–40

IV Paaver, M., Nordquist, N., Parik, J., Harro, M., Oreland, L., & Harro, J. (2007) Platelet MAO activity and the 5-HTT gene promoter polymorphism are associated with impulsivity and cognitive style in visual information processing. (resubmitted to *Psychopharmacology*)

V Paaver, M., Kurrikoff, T., Nordquist, N., Oreland, L., & Harro, J. The effect of 5-HTT gene promoter polymorphism on impulsivity depends on family relations in girls. (submitted to *Neuroscience Letters*)

ABBREVIATIONS

ADHD	– attention deficit hyperactivity disorder
ANOVA	– analysis of variance
ANCOVA	– covariate analysis of variance
AMIS	– Adaptive and Maladaptive Impulsivity Scale
BIS-11	– Barratt Impulsiveness Scale, 11th version
CI	– confidence interval
CNS	– central nervous system
CSF	– cerebrospinal fluid
DAD	– driving after drinking
DII	– Dickman Impulsivity Inventory
DSM-IV-R	– diagnostic and statistical manual of mental disorders, 4^{th} edition
DWI	– driving while intoxicated
EDTA	– ethylenediamine tetraacetic acid
EPI	– Eysenck Personality Inventory
fMRI	– functional magnetic resonance imaging
KSP	– Karolinska Scales of Personality
I-score	– the score of impulsiveness in the Visual Comparison Test
I_7	– Eysenck Impulsivity Inventory
MANOVA	– multiple analysis of variance
MAO	– monoamine oxidase
MFFT	– Matching Familiar Figures Test
NEO-PI	– Neuroticism Extraversion Openness Personality Inventory
OR	– odds ratio
PCR	– polymerase chain reaction
PET	– positron emission tomography
SD	– standard deviation
SEM	– standard error of the mean
SPM	– Standard Progressive Matrices
SSRI	– selective serotonin reuptake inhibitor
UPPS	– impulsivity scale measuring Urgency, Premeditation, Perseverance and Sensation-Seeking
VCT	– Visual Comparison Test
5-HIAA	– 5-hydroxyindoleacetic acid
5-HT	– 5-hydroxytryptamine, serotonin
5-HTT	– serotonin transporter
5-HTTLPR	– serotonin transporter linked polymorphic region
β-PEA	– β-phenylethylamine

1. INTRODUCTION AND REVIEW OF LITERATURE

1.1. The types of impulsivity, and their expression in behaviour

1.1.1. Impulsivity as a multidimensional construct: the interdisciplinary view

A typical definition of impulsiveness is something like "a predisposition toward rapid, unplanned reactions to internal or external stimuli without regard to the negative consequences of these reactions to the impulsive individual or others" (Moeller et al. 2001). Impulsive person is described as a happy-go-lucky; a doer, not a thinker; likes to take chances; restless when required to sit still; has problems concentrating on one thing (Barratt 1993), has a diminished ability to delay gratification, does not plan ahead, is susceptible to boredom, a hedonist, and is present-oriented (Petry 2001). Impulsivity is more or less related to other terms like disinhibition, self-control, conscientiousness, constraint, non-planning, sensation seeking, novelty seeking, excitement seeking, venturesomeness, and boredom susceptibility. Apparently these definitions and descriptions include more than one quality and it has occurred that the different measures of impulsivity have emphasized the different aspects of impulsivity — focusing either on the behavioural (engaging in risky and health-compromising behaviours, changing jobs or partners etc.), cognitive (speed and style of information processing, e.g., holistic versus analytic), motivational (e.g., preference for smaller immediate rewards, inability to tolerate boredom), affective (difficulties in emotion regulation) or social (lower competence in social situations, where self-restraint is needed) aspects of the impulsive way of reacting to the world.

Several personality trait inventories have tried to classify impulsivity under wider dimensions like neuroticism (Costa & McCrae 1989); however, other dimensions of personality in NEO Personality Inventory also include components of impulsivity (e.g., the dimensions of extraversion and conscientiousness). In the earlier version of Eysenck Personality Inventory (EPI) impulsivity was included under the dimension of extraversion, however in the later version of EPI it was reorganized under the dimension of psychoticism (Eysenck 1993). The difficulties in compressing impulsivity under a single personality domain may have different reasons, addressed below in this thesis.

The disciplines dealing with impulsivity (trait psychology, cognitive psychology, psychiatry, psychopharmacology) have different purposes, concepts and tests for measuring impulsivity, and in earlier studies it used to be common not to cite each other's work or compare the used measures of impulsivity (Evenden 1999). The conceptualization in trait psychology was described in previous paragraphs. The psychiatric classifications delimit impulsivity as a disorder (in

case of impulse control disorders like gambling or compulsive fire setting), a symptom of a disorder (in case of attention deficit hyperactivity disorder or borderline personality disorder) or a symptom of a state (e.g., impulsive spending in the manic state) (DSM IV-R, Moeller et al. 2001, Barratt 2005). Psychopharmacological studies, which measure the effects of drugs on impulsive behaviour, conceptualize impulsivity through reaction time, ability to inhibit reaction in response to conflicting stimuli (Fillmore 2003) and tendency to choose smaller immediate reward in favour of delayed bigger reward. These concepts used in psychopharmacological studies are based on both behaviouristic view on impulsivity dealing with the discounting of values over time (Rachlin 2000, Mischel et al. 1989, Ainslie 1975), and on the cognitive view at impulsivity as a fast and error-prone, holistic information processing style (Dickman 1985).

If categorising personality traits though lexical approach leads to inconsistent results, as it has happened in case of impulsivity, it may be of use to start the definition from the other end. It has been rather common to study the psychobiology of personality through finding correlates for a trait predefined, but instead, it can be started from finding a certain biological function and define the traits according to individual differences in this function (Barratt 1993, Kas et al. 2007). The biological, behavioural, cognitive and social/ environmental aspects need to be considered for describing the impulsiveness of a person (Barratt & Slaughter 1998). One emphasis in current research of impulsivity is bringing together different measures of impulsivity with psychopharmacological and brain imaging data in case of impulsive behaviour. The knowledge about whether different types of impulsivity have a common, partly common or diverse biological background may help to conceptualize these types better.

1.1.2. Types of impulsivity

1.1.2.1. Self-reported measures

Recent studies have tried to clarify the types of impulsivity by including the items of all well-known scales of impulsivity into common factor analysis. By factor-analysing impulsivity-related items in NEO-PI and all items in nine well-known impulsivity inventories (BIS, I_7, DII and others) Whiteside & Lynam (2001) created of a new inventory (UPPS) measuring four types of impulsivity: Urgency, Lack of Premeditation, Lack of Perseverance, and Sensation Seeking. Miller et al. (2004) and Flory et al. (2006) have conducted similar factor-analytic studies on more narrow sets of impulsivity inventories and both extracted three components of impulsivity. The three components of impulsivity discovered in the first study by Miller et al. (2004) were called Non-Planning/ Dysfunctional, Functional Venturesomeness and Drive/Reward Responsiveness.

The three components of impulsivity in the study by Flory et al. (2006) were called Thrill Seeking, Nonplanning, and Disinhibited Behavior.

1.1.2.2. The types of performance measures of impulsivity

There are several performance tasks more or less in touch with impulsive cognitive style: tasks measuring delay of reward or delay of gratification (Rachlin 2000, Ainslie 1975, Michel 1989), speed-accuracy trade-off (like Matching Familiar Figures Test, MFFT) (Kagan 1964; Dickman 1988), disinhibition or commission errors in stop-signal or Go/No-go paradigm (Fillmore 2003), measures for executive control, attention switching and planning (Trail-Making tasks, Porteus Mazes Q score), and time perception (de Wit et al. 2002). The speed-accuracy trade-off performance tests are most commonly used for measuring impulsivity in children in the educational psychology paradigm (Fink & McGown 1993), while in psychopharmacological studies in humans, Go/ No-go or delay of reward tasks are often used. In animal studies, in addition to Go/No-go and delay of reward measures, there are procedures like differential reinforcement of fixed consecutive time intervals, unreliable visual discrimination, premature responding, timing, motor impulsivity, etc.) (Evenden 1999). Similarly to self-reported measures, the results in different performance tests do not correlate with each other well (Reynolds et al. 2006, Olson 1989, Helmers et al. 1995). The comparative analyses have identified two broad distinct categories: reward-delay models, and rapid-response models (Swann et al. 2002, Reynolds et al. 2006, Dom et al. 2007).

1.1.2.3. The link between self-reported and performance measures of impulsivity

The correlation between self-reported and performance measures of impulsivity is in several studies quite low or absent (Reynolds et al. 2006, Helmers et al. 1995). Even though impulsive individuals claim to act with less forethought, they often respond more slowly in experimental tasks than non-impulsive individuals (e.g. Dickman 1985). Helmers et al. (1995) have demonstrated lack of correlation of several laboratory tests with all of the used impulsivity measures but State Sensation Seeking (described as carefreeness, enthusiasm, adventurousness) after controlling for general cognitive abilities.

The reason for these inconsistencies between the self-reported and performance measures of impulsivity may have been as follows: 1) the conceptualization of the types of impulsivity has different routes and no attempt has been made to unify the self-reported and performance measures of impulsivities conceptually (Evenden 1999, Helmers et al. 1995) 2) cognitive style is confounded by ability (Helmers et al. 1995) 3) impulsive people may lack insight of their own impulsivity and thus their self-reported measures may not be reliable (Bütz & Austin 1993) 4) people may have a bias for socially desirable answering in their estimation of their impulsivity, as impulsivity is generally

considered a maladaptive and socially undesirable trait, and 5) some performance measures may lack the affective or social stimuli that are important triggers for some types of impulsive behaviour (Shoda et al. 1990). In fact, the low correlation between the self-reported and laboratory measures of impulsivity is partly natural, as the cognitive aspect of impulsivity is hard to measure via self-reported measures (Barratt 1993). Measuring the cognitive side of impulsiveness by relying only on self-reported questionnaires would be similar to trying to measure intelligence only with self-reported items like "I am a clever person". Thus, studies addressing the psychobiology of impulsivity or expression of impulsivity in real-life behaviour should use both ways of measuring impulsivity.

Somewhat better correlation has been demonstrated between laboratory measures of impulsivity and the teacher- or parent-reported impulsivity (Olson et al. 1999). Also, some success has been made comparing the performance measures with conceptually appropriate self-reported measures, e.g. BIS scores have been shown to correlate with impulsive responding in tasks measuring disinhibition (Spinella 2004, Christodoulou et al. 2006, Swann et al. 2002).

1.1.3. The etiology of impulsive behaviour

1.1.3.1. Affective and cognitive path to impulsive behaviour

Impulsive temperament may lead to risky behaviour through affective, cognitive or social mediators (Hoyle 2000). A person may behave impulsively (quickly, abrubtly) mainly because of mainly cognitive reasons: 1) due to lack of ability to think about the possible consequences (theoretically a component of dysfunctional impulsivity, lack of premeditation, thoughtlessness, non-planning), 2) because the situation demands the quick decision or engaging in an activity involving risk (theoretically a component of functional impulsivity, venturesomeness, fast decision-making), or 3) he does not bother to think about the possible consequences (theoretically a component of thoughtlessness, dysfunctional impulsivity, boredom susceptibility, lack of perseverance, low conscientiousness). As a different possibility, a person may engage in impulsive activity because of mainly affective reasons 1) because the urge or expectancy for achieving positive affect from risk interferes thinking about consequences (theoretically a component of sensation seeking, approach, drive, venturesomeness, functional impulsivity) 2) because negative or positive affects cause the impaired ability to rationally analyse situation and impulsive reacting (theoretically a component of urgency, disinhibition).

It is proposed herewith that it may be of use to differentiate the affective and cognitive components when studying the association of impulsive predisposition with real-life behaviour. In fact, the impulsivity scale by Barratt (BIS-11, Patton et al. 1995) is constructed with an aim to eliminate the affective or

anxiety-related component of impulsivity (Barratt 1993), while other measures do contain the component of affect regulation (e.g., the measures of impulsive aggression, impulsive sensation seeking, impulsivity in case of borderline personality disorder or impulsivity under the facet of neuroticism in NEO Personality Inventory). Still, measuring cognitive component of impulsivity purely by self-reported measures may still be difficult (Barratt et al. 2005) and performance tests may provide more valid data. The affective and cognitive components of impulsivity may both lead to impulsive behaviour, but they may not be necessarily interrelated.

1.1.3.2. Cognitive abilities and impulsive behaviour

Accompanying traits, situational pressures or cognitive abilities may moderate the expression of impulsivity in behaviour: they may either enhance the expression of impulsivity in behaviour or protect from it (Hoyle 2000). Wright and Mischel (1987) have proposed that impulsive temperament is behaviourally expressed mostly in situations which presuppose social, self-regulatory or cognitive competencies that the subjects lack. Young et al. (2007) demonstrated that in persons with biological predisposition for impulsivity (the 7-repeat allele of dopamine D4 receptor 48-basepair-repeat polymorphism, DRD4) impulsive behaviour did not depend on cognitive abilities, while in the subjects with no biological predisposition, impulsive behaviour was associated with lower cognitive abilities. Thus, cognitive abilities may have a bigger role in impulsive and risky behaviour, when there is no biological predisposition for impulsive behaviour.

Reflection-impulsivity measured by MFFT is associated with lower intelligence (Milich & Kramer 1984, Brannigan et al. 1980), especially in attention-concentration and visual organization domains of intelligence inventories (Brannigan et al. 1980). The studies which have controlled for cognitive abilities have still demonstrated the independent effect of disinhibition on responding (Kindlon et al. 1995, Dickman 1985). Impulsive responding in performance tests contains a component of general ability as well as inhibitory processes or executive functions (Amador-Campus & Kircher-Nebot 2001, Dickman 1985) and these two have also a weak correlation (Vigil-Colet & Morales-Vives 2005). Impulsive children get lower grades at school, but the causal path for this is not clear: impulsiveness may influence learning process through reduction in attention span, it may have the same core component with learning disabilities, and it may also be a consequence to the frustration because of learning difficulties (Fink & McGown 1993).

In general, to differentiate between the preferred style and ability in studies observing impulsive behaviour, cognitive abilities should be controlled for.

1.1.3.3. Risk acknowledgement and impulsive behaviour

Eysenck S.G.B. (1993) explains the concepts of impulsiveness and venturesomeness in I_7 through the analogy of drivers, whose behavioural outcome may look similar (risk-taking in traffic), but has a different etiology. A driver scoring high on impulsiveness never considers the danger he might be exposing himself to and is genuinely surprised when an accident occurs, while a driver scoring high on venturesomeness considers the position carefully and decides to take the risk hoping to get the excitement from the "near miss". Whether this holds true for risky drivers scoring high on different types of impulsivity could be controlled through grouping risk-taking subjects according to their risk acknowledgement. Sensation seekers are shown to have lower risk perception when driving (Jonah 1997), similarly impulsive individuals are described as acting without reflecting over the risk or possible consequences (Barratt 1993, Whiteside & Lynam 2001, Eysenck S.G.B. 1993). Studies have shown that many young people engaging in risky health behaviours do not actually intend to do so, which may reflect their lower risk perception in the situation (Gibbons et al. 2006). A study by Ryb et al. (2006) found that low risk perception and trait impulsivity were at least partly independently associated with risky behaviours. It is clear that the acknowledgement of risks is important moderator of risky behaviour, but it is not fully clear how does it interact with the different types of impulsiveness of person.

1.1.4. Family relations and impulsivity

The development of impulsivity has been shown to depend on parenting styles, for example Olson et al. (1990) found in a 6-year longitudinal study that a responsive, cognitively stimulating parent-toddler interactions in the 2nd year predicted later measures of cognitive non-impulsivity and ability to delay gratification. Straus & Mouradian (1998) found that corporal punishments such as spanking or slapping a child for purposes of correcting misbehavior were associated with impulsiveness by the child. It is however possible that parenting styles also depend on pre-existing child's temperament (McGue & Bouchard 1998). There are some studies which have controlled for the effect of pre-existing child's temperament, e.g. in a sample of lower socioeconomic status families, maternal insensitivity and over-stimulating or non-responsive physical intimacy during infancy predicted both distractible and hyperactive child behavior at follow-up, even with the effects of early child temperament controlled (Carlson et al. 1995).

1.1.5. Adaptiveness of impulsivity

While majority of studies in the field of psychiatry and psychopharmacology define impulsivity as a dysfunctional feature, the current approach in personality psychology consistently refers to both maladaptive and adaptive side of impulsivity. Dickman (1990) has first explicitly brought out that impulsivity may be adaptive in certain circumstances, where fast responding is more important than accuracy. Functional impulsives appear to act with little forethought because they have been rewarded for such behaviour. They are described as lively, adventurous, are willing to take risks and such characteristics appear to compensate for their error-proneness. His idea that impulsivity may be functional was partly derived from laboratory studies, which showed that impulsive individuals had indeed an advantage in neuropsychological tests, and they even responded more accurately compared to non-impulsive subjects, when the time given for responding was very short (Dickman 1985) and they did not pay with significantly more errors, but were faster in case of very simple tasks (Dickman 1993). With further analysis, it was clear that impulsive individuals could be divided into two groups: those having an advantage in certain task condition and those who still remained non-accurate in responding, despite the task condition. Thus, Dickman developed a scale measuring "functional impulsivity", which is defined by deciding quickly in situations where this style is optimal and grasping the moment. Brunas-Wagstaff et al. (1995) have demonstrated that functional impulsivity correlates positively with psychoticism and negatively with neuroticism, while both functional and dysfunctional impulsivity are positively correlated with extraversion (measured by EPI). Smillie and Jackson (2006) have demonstrated a conceptual similarity between functional impulsivity and reward reactivity, as detailed in reinforcement sensitivity theory (Corr 2006), and showed the negative correlation of functional impulsivity with neuroticism and positive correlation with extraversion.

There are still several unanswered questions about functional impulsivity: First, what unites it with dysfunctional impulsivity? Is the psychobiological background of adaptive and maladaptive types of impulsivity similar or different? And if it is similar, how do some individuals learn to express their basic impulsive tendency adaptively, while others go for deviant behaviour, criminality and substance abuse. In this case, what moderates the development of impulsivity into adaptive as opposed to maladaptive expression — is it choosing appropriate environments (e.g. professions), social support, higher intelligence or co-occurring adaptive personality traits? Functional impulsivity is still not sufficiently validated through behavioural observations, prediction of behavioural outcomes and the power of differentiating certain groups of people from others. There is also a debate over calling this type of impulsivity differently, i.e. spontaneousness, Fast Decision-Making or something else, because having

two separate constructs with a similar name may add further confusion to the area (Eysenck 1993).

Dickman (1990) managed to demonstrate that subjects with functional impulsivity gave more correct answers in a given time period in a simple task of visual comparison. However, he did not find any association of dysfunctional impulsivity with speed and accuracy of responding. As to the link between functional impulsivity and performance impulsivity, in some studies functional impulsivity was correlated to speed of responding (Brunas-Wagstaff et al. 1996, Brunas-Wagstaff et al. 1994, Reeve 2007), but other studies failed to show association between functional impulsivity and reaction time or number of errors (Vigil-Colet & Codorniu-Raga 2004). Dysfunctional impulsivity has been shown to correlate with the number of mistakes in tasks with conflictual signals (Brunas-Wagstaff et al. 1996, Brunas-Wagstaff et al. 1994). While some studies have shown faster responding in case of dysfunctional impulsivity as well (Vigil-Colet & Codorniu-Raga 2004), this correlation was not present in the study by Brunas-Wagstaff et al. (1994).

1.1.6. Ecological validity of the types of impulsivity

1.1.6.1. Impulsivity in different populations

One line of research on impulsivity deals with the issue how well do self-reported and performance measures of impulsivity predict the actual behaviour, psychopathology, and deviant behaviour, which is of a huge benefit for the applied fields of forensic, educational, clinical and military psychology.

The UPPS scales developed by Whiteside & Lynam (2001) accounted for 7% of the variance of gambling (which is classified under impulse control disorders in DSM IV-R), and reached to the explanatory value of 64% in case of borderline personality disorder (Whiteside et al. 2005). The UPPS scales were also significantly related to several externalizing problems, and Lack of Premeditation was the best predictor of ADHD symptoms, conduct disorder, substance abuse and risky sex, while Urgency predicted borderline symptoms and eating disorder. BIS has been shown to differentiate well between juvenile delinquents and controls (Barratt 1993).

The studies trying to ecologically validate the performance measures of impulsivity have shown moderate discriminant validity for predicting ADHD when using either stop-signal or delay of reward task, but excellent discriminant validity when both tasks were considered (Solanto et al. 2001). Pathological gamblers were less effective in delay of reward task (Petry & Casarella 1999). The MFFT measuring preference for speed over accuracy predicted juvenile delinquency (Barratt 1993), social aggression (Bernfeld & Peters 1986), and lower accuracy in MFFT was demonstrated in MDMA users (Morgan 1998). Higher reflection impulsivity in current as well as former substance abusers was

demonstrated by Clark et al. (2006). Measures of inhibitory control and insensitivity to punishment discriminated well the behaviourally disordered children from controls (Kindlon et al. 2001). However, attention shifting and planning measures like Trail Making and Porteus Mazes Q score did not differentiate the impulsive patients from controls (O´Keefe 1975). Lower delay of gratification predicted lower social competence (Olson 1989).

Less validation has been carried out on normal populations and putting focus on the adaptive side of impulsivity. It is natural that a lot of research in clinical psychology focuses on problem-behaviours instead of positive emotions or adaptive traits (Eysenck 1993). However, it may also be useful to measure the potentially adaptive traits as resources of an individual. If one has high scores on disinhibition and is therefore at high risk for substance abuse, gambling, borderline personality disorder or bulimia nervosa, does he or she also have a potential for using his impulsive tendency adaptively? Still, identifying the measurable behaviours and specific samples for ecological validation of functional impulsivity is more difficult than in case of maladaptive types of impulsivity. For the latter, a variety of data exists represented by the special samples of violent criminals, psychiatric patients with impulse control problems, children with ADHD or conduct disorder who behave impulsively. The potential samples for validating the functional impulsivity/venturesomeness may be e.g., well-adjusted, highly coping subjects, with no psychopathology, who have high education and income, but can be characterised as impulsive or who have to take risks and decide fast with minimal information — investment bankers, directors of large enterprises, doctors in emergency medicine, pilots.

1.1.6.2 Impulsivity and risky driving

Impulsivity (and its variations like low constraint, low self-control and sensation-seeking) is one of the most exclusively studied traits in connection with alcohol- and non-alcohol-related reckless driving (Dahlen et al. 2005, Caspi et al., 1997; Torgersen & Vollrath 2006). In an article reviewing 40 studies on sensation seeking and risky driving, Jonah (1997) concluded that most studies demonstrated the association of sensation seeking with drunk driving and also with other risky driving behaviours. Sensation seekers also perceived risk worse in these studies (Jonah 1997), but again, the age factor was not controlled for. Thrill and Adventure Seeking subscale under SSS together with impulsivity predicted risky driving the best (Wilson & Jonah 1988). Predicting different types of risky behaviours through personality types rather than traits has shown higher explanatory power (Torgersen & Vollrath 2006).

Risky driving may include drunk driving, dangerous maneuvers, violations of speed-limits, not using safety belts etc. Some of the earlier studies comparing drunk drivers and high-risk drivers with multiple non-alcohol-related traffic violations have concluded that these two groups are different subgroups of people with risky driving habits (Donovan et al. 1985; Wilson 1992). Drunk

drivers and high-risk drivers differ regarding other traffic behaviour habits and in socio-economic terms (Golias & Karlaftis 2002). Regarding personality, they have been found to be similar in traits like emotional adjustment, externality and sensation seeking, while high-risk drivers were more deviant on the scale of driving attitudes (Donovan et al. 1985). However, Wilson (1992) attempting to replicate this study, stated that while drunk drivers and high-risk drivers both scored higher than controls on sensation seeking, drunk drivers were simply more deviant on those features, and that some of the characteristics of high-risk drivers in the study by Donovan et al. (1985) may have been exaggerated due to confounding by age. However, exceeding speed limits and violating traffic rules might be more strongly associated with acknowledged and intentional risk-taking, while alcohol-related traffic offences are associated with risk-taking in impaired state, where the control over one's behaviour is distorted.

Driving while impaired (DWI) or drinking and driving is a behaviour that combines different risks to one's health, life and finances — the risks involved in alcohol abuse, possible traffic accident, law breaking and penalties. Wilson (1991) has shown that there are maladjusted as well as well-adjusted risk-takers, out of whom the first type scores higher on thrill-seeking and low responsibility, while the second type does not differ from controls by personality or life-style. McMillen et al. (1992) have studied drunk drivers caught after accident or other violation, and shown that these are deviant by several personality features, while those, whose only violation is driving while impaired, were similar to controls. Comparing the personality traits of arrested drunk drivers and drunk drivers who had never been arrested, McMillen (1991) found the former to be deviant on several personality markers, while the non-arrested drivers did not differ from controls. Thus the ability to avoid being caught by the police may be one feature differentiating impulsive from non-impulsive drivers.

1.2. Serotonin system and impulsivity

1.2.1. Impulsive behaviour and low activity of the serotonin system

The ascending serotonergic system originating from raphé nuclei and innervating amygdala, hippocampus, hypothalamus and frontal orbital cortex may be the system connected with self-control and capacity for delay. The association of impulsive behaviour with a low capacity of the serotonergic system has been demonstrated in both rodents (Evenden 1999) and primates (Fairbanks et al. 2001). Human studies linking impulsiveness to the serotonergic system have demonstrated lower levels of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) in the cerebrospinal fluid (CSF) of violent criminals (Nelson 2005) and impulsive suicide committers (Brown et al. 1982). Linnoila (1983)

demonstrated that CSF 5-HIAA was reduced only in individuals whose aggression was impulsive, rather than those in whom it was premeditated. Association of lower serotonin transporter (5-HTT) density or 5-HT reuptake and impulsiveness (BIS whole score) in women with bulimia nervosa was demonstrated by Steiger et al. (2001).

Impulsive behaviour associated with lowered 5-HT function is often comorbid with alcohol abuse and pre-existing lower serotonergic function may lead to alcohol abuse and impulsive behaviour, while chronic ethanol intoxication may potentiate the impulsive tendencies (leMarquand et al. 1993, Johnson 1993). The findings of Schmidt et al. (1997) indicate that the alterations of the central serotonin system may occur as predisposing factors for alcoholism in individuals with anti-social traits. As to impulsivity in substance abusers, nicotine exposure in adolescents may impair 5-HT projections and thus smoking may further modify the progression of alcoholism and impulsivity due to serotonin system's lowered function (Xu et al. 2001, Schmidt et al. 1997).

Reduced serotonergic reactivity to challenge by clomipramine has been demonstrated in impulsive gamblers (Lopez-Ibor et al. 1985). Measures of cortisol and prolactin in response to administration of serotonergic agonists or selective serotonin reuptake inhibitors (SSRIs) reflect the reactivity of serotonin system; and subjects scoring high in experience seeking or disinhibition subscales of Sensation Seeking Scale (SSS) were shown to have blunted responses to this type of serotonergic challenges (Netter et al. 1996). Also in response to 5-HT agonists the prolactin release was lower in subjects scoring high on BIS (Depue 1995) or venturesomeness (Weijers et al. 2001).

An increase in impulsivity with decreasing the serotonergic function by tryptophan (the precursor of serotonin) depletion has been found in Go/No-go tasks (Murphy et al. 2002, Walderhaug et al. 2002) and decrease in impulsivity by acute release of serotonin by d,l-fenfluramine (Cherek and Lane 1999). Still in some studies no effect of serotonergic manipulations on disinhibition in neuropsychological tests was found (Chamberlain and Sahakian 2007), and serotonergic manipulations seem to have less effect on the delay of gratification (Anderson et al. 2003).

Animal models of impulsivity have demonstrated association of behavioural inhibition and novelty-seeking to serotonergic system, namely the decrease in serotonergic functioning has led to attenuation of suppression of novelty-induced behaviour, while serotonin enhancing drugs have led to enhancement of punishment-induced inhibition (Soubrié, 1986). Soubrié (1986) concluded that serotonergic neurones are brought into play when ever behavioural inhibition is required or an overt conflict emerges between making (Go) and refraining (No-go). A decrease in serotonergic transmission renders animals less able to adopt passive or waiting attitudes.

Most of the studies addressing the association of serotonergic function with impulsivity are 1) carried out on special populations like subjects with psychiat-

ric disorders, substance abuse or criminal behaviour (Manuck 2005) 2) do not differentiate the types of impulsivity or conceptualise the impulsivity they measured and 3) concentrate either on self-reported or performance measure of impulsivity. These may also be reasons why serotonergic manipulations have different and sometimes opposite effects on the performance in different impulsiveness models of rodents as well as in humans (Evenden 1999).

1.2.2. Platelet monoamine oxidase (MAO)

1.2.2.1. Platelet MAO activity as a peripheral marker of central serotonergic function

Monoamine oxidase is an integral protein of outer mitochondrial membranes (Schnaitman et al. 1967) and it occurs as two subtypes, MAO-A and MAO-B, which are important in catalyzing the oxidative deamination of many exogenous and endogenous monoamines including trace amines such as phenylethylamine (PEA). Only MAO-B isoensyme is found in platelets and while it has the same amino acid sequence as MAO-B in brain (Chen et al. 1993), no correlation between platelet and brain MAO-B exists (Winblad et al. 1979). The platelet has been considered as a model for studying central serotonergic functioning, because there are multiple biochemical and pharmacological similarities existing between blood platelets and 5-HT-containing neurons of the central nervous system referring to common genetic control (Pletcher 1987, Da Prada et al. 1988).

Platelet MAO activity is a peripheral marker for the activity of the central serotonin system due to a common genetic control (Oreland, 2004) that could occur via common gene promoter sequences and co-regulation of platelet MAO and monoamine transmitter genes. The ability of the platelet MAO activity to predict central serotonergic activity is confirmed by the finding that there is a strong correlation between cerebrospinal fluid levels of the serotonin metabolite 5-HIAA and platelet MAO activity (Fahlke et al. 2002). The catalytic activity of platelet MAO is under strong genetic control: studies have shown heritability factor of about 0.75 for both males and females (Oxenstierna et al. 1986, Pedersen 1993). Platelet MAO activity has been reported to be on average 10–27% higher in adult females than in males (Coccini et al. 2005).

1.2.2.2. Platelet MAO activity, deviant behaviour and impulsivity

Low platelet MAO activity is proposed to be a marker of several behavioural and psychiatric problems, including impulsive behavioural tendencies, vulnerability to alcohol abuse and antisocial behaviour (Oreland 2004). Low platelet MAO activity has been demonstrated in children with attention deficit hyperactivity disorder (ADHD) (Shekim et al. 1986), violent criminals (Eklund

et al. 2005), former juvenile deliquents who were registered for crime as adults (Alm et al. 1996), and patients with suicidal history (Simonsson et al. 1991). In general, low platelet MAO activity is associated with personality traits that increase the vulnerability to several psychiatric disorders and maladaptive behaviours such as drug abuse and social maladjustment (Buchsbaum et al. 1976).

Some studies focusing on the association of performance measures of impulsivity with platelet MAO activity have found its significant correlation with response time in computerized tests (af Klinteberg et al. 1987, af Klinteberg et al. 1990), and male subjects with low MAO activity had difficulties with inhibiting response, and they also reacted faster to novel stimuli (af Klinteberg et al. 1987). Low MAO activity was associated with more impulsive performance in MFFT (Shekim et al. 1986) and the number of failed inhibitions in a task with conflictual signals for pressing the button and canceling this (af Klinteberg et al. 1990).

1.2.2.3. Alcohol consumption, impulsivity and platelet MAO

Many studies declaring higher impulsivity, monotony avoidance and sensation seeking in subjects with low MAO activity have been carried out in subjects abusing drugs or alcohol (Longato-Stadler et al. 2002; von Knorring et al. 1984). Zuckerman & Kuhlman (2000) have suggested that the relation between impulsiveness and substance abuse is mediated by a common biological mechanism responsible for both drug abuse and sensation seeking. Even primate studies link low platelet MAO activity with excessive alcohol consumption and co-occurring low social dominance (Fahlke et al. 2002). As problem behaviours like smoking, alcohol abuse and risky behaviours tend to covary (Caspi et al. 1997, Zuckerman 2005), it is not clear, whether platelet MAO activity would be associated with each of these tendencies separately. For example, an association of low platelet MAO activity was found with type II alcoholism (which starts in the earlier age and is associated with antisocial behaviour), while the platelet MAO was similar to controls in type I alcoholics (von Knorring & Oreland 1996). It has also been shown that the risk for substance abuse, social maladjustment and less socially acceptable forms of sensation seeking in subjects with low MAO activity depend partly on cognitive abilities (von Knorring et al. 1984).

1.2.2.4. The confounding effect of smoking in the studies addressing platelet MAO and behaviour

Smokers have lower MAO activity than non-smokers, and ex-smokers have similar MAO activity to that of the non-smokers (Norman et al. 1987; Oreland et al. 1981). Researchers for long tended to give the interpretation that individuals with low MAO activity are more prone to start smoking and less prone to quit smoking. However, more recently it has been shown that some components in cigarette smoke directly inhibit MAO activity (for a review, see Fowler, 2003). Whitfield et al. (2000) have demonstrated that smoking reduced MAO

activity in a dose-related manner. As in the groups where the association of impulsivity and low platelet MAO activity has been found (criminals, children with deviant behaviour disorders, alcoholics, etc.), the frequency of smoking is higher than in general population, and as impulsivity is itself strongly associated with smoking, smoking is one potential confounder. When accounting for smoking, several studies failed to confirm the relationship of impulsive behaviour or alcohol abuse with lower platelet MAO activity (Ward et al. 1987; Kiive et al. 2002, Whitfield 2000, Anthenelli et al. 1998). Other researchers have still claimed that the effect of MAO on alcoholism and personality cannot be fully explained as an artifact of smoking (Oreland et al. 2002).

Some studies have shown the connection of high MAO activity to disruptive behaviour in boys (Stoff et al. 1989), in less than 12 years old sons of substance abusing fathers (Gabel et al. 1994), and higher likelihood for psychiatric disorders in children (Young et al. 1980). These associations appeared especially among children or adolescents, and this may be due to lower prevalence of smoking in this age-group. In the study by Kirk et al.(2001), the positive association between MAO activity and neuroticism was strengthened when adjusting for the effect of smoking. There are also findings showing a link of high MAO activity with higher anxiety in a male community sample (Irving et al. 1989), higher muscular tension and suspicion in normal male subjects (Scalling et al. 1987), and performance in neuropsychological tests (af Klinteberg et al. 1987). Several items of I_7 were shown to be associated with MAO activity either lower or higher than average (Schalling et al. 1988). Although the Narrow Impulsiveness in I_7 was negatively correlated with platelet MAO activity, there was no statistically significant association between platelet MAO activity and venturesomeness, and the tendency was even towards higher venturesomeness in case of high MAO activity (Schalling et al. 1988). Similarly with impulsivity, the association between platelet MAO activity and anxiety shows a tendency for non-linearity (Schalling et al. 1987) — e.g., subjects with high MAO activity being the most anxious and subjects with low MAO activity being slightly less anxious, however, more anxious compared to subjects with medium MAO activity (Irving et al. 1989). Furthermore, Harro et al. (2004) have demonstrated that lower as well as higher than medium platelet MAO considerably increases the probability of becoming a regular smoker. Thus, accounting for the possible confounding effect of smoking is necessary; however, it is extremely difficult due to this specific non-linear relationship between these two variables.

In general, low platelet MAO activity has been related to self-report-, performance- as well as behavioural measures of impulsivity. There is still a lack of studies of the self-reported measures of impulsivity and platelet MAO activity in normal populations, and the association of platelet MAO activity with adaptive impulsivity types. Also, in majority of studies smoking has not been controlled for.

1.2.3. 5-HT transporter promoter region polymorphism (5-HTTLPR)

1.2.3.1. 5-HTTLPR and serotonergic functioning

The promoter region of the serotonin transporter gene contains a 44-base-pair insertion/deletion polymorphism that is located ~1 kb upstream of the transcription initiation site and influences the expression of this locus at the transcriptional level. The long (L) allele of the 5-HTT gene has a more efficient promoter than the short allele and the cells expressing two L alleles (LL genotype) produce more 5-HTT mRNA and take up more serotonin from the medium than LS or SS genotype cells (Lesch et al. 1996).

1.2.3.2. 5-HTTLPR, vulnerability to psychopathology and impulsivity

There is a substantial knowledge that 5-HTTLPR S allele leads to higher likelihood of depression, anxiety-related characteristics and other affective dysfunctions (Lesch et al. 1996, Ebstein 2006), and lower response to anti-depressant treatment with serotonin reuptake inhibitors (Smeraldi et al. 1999). Higher prevalence of the S allele in impulsive suicide attempters has been demonstrated (Li & He 2007). Also, some evidence exists for the higher prevalence of the S allele in substance abusers — e.g., violent type 2 alcoholics (Hallikainen et al. 1999) and aggressive heroin-addicts (Gerra et al. 2004). An influence of S allele carrying on aggressiveness in children has also been demonstrated (Haberstick et al. 2006). Higher prevalence of S allele carriers has been found in case of antidepressant-induced mania, which is associated with impulsiveness (Masoliver et al. 2006). Wendland et al. (2006) have demonstrated that the 5-HTT gene is polymorphic in the more aggressive and intolerant species of macaques living in hierarchical societies, while it is monomorphic in more social and conciliatory species with less hierarchical societies. The association of 5-HTTLPR S allele with avoidance- as well as aggression related traits have been confirmed in a meta-analysis by Munafo et al. (2003). Still, no effect of S allele on impulsive responding in a laboratory task of disinhibition (Clark et al. 2005) and Go/No-go task (Fallgatter et al. 1999) has been found. While S allele in normal populations has been associated with neuroticism (Schinka et al. 2004), less is known for the association of the S allele with impulsive personality dimension in normal population.

1.2.3.3. 5-HTTLPR X environment interaction in the development of serotonin system

The impact of 5-HTTLPR genotype on depressive symptoms is shown to depend on environmental stressors. Depressive symptoms only appeared among these S allele carriers, who suffered from stressful life events in the early age (Caspi et al. 2003), and hostile family environment (Kaufman et al. 2006, Tay-

lor et al. 2006). Furthermore, development of a less efficient serotonergic system was demonstrated among those 5-HTTLPR S allele carriers who had adverse events in the early age (Lesch & Gutknecht 2005) or low socio-economic background (Manuck et al. 2004). Similar gene x environment interaction has been shown in rhesus monkeys — in a sample of mother-reared rhesus monkeys, the rh5-HTTLPR LS and the SS genotypes were associated with lower CSF 5-HIAA and higher aggressive behavior during alcohol intoxication (Bennett et al. 2004). Also in a smaller sample of rhesus monkeys, who had been separated from their mothers after birth and reared with their peers, the brainstem 5-HTT imaging correlated negatively with both sensitivity to alcohol intoxication and 5-HIAA concentrations in the cerebrospinal fluid (CSF), and was positively correlated to lifetime ratings of aggressive behaviors (Heinz et al. 1998).

2. AIMS OF THE STUDY

The biological, behavioural, cognitive and social/environmental aspects need to be considered for describing the impulsiveness of a person (Barratt & Slaughter 1998).

The aim of the current thesis was to explore the endophenotypes of different types of impulsivity through the measures of real-life behaviour, preferred style of information processing, and association with family relations, using the markers of central serotonergic functioning.

The specific objectives were formulated as follows:

1. to study the types of impulsivity in drivers caught by the police with alcohol-related and non-alcohol-related driving violations
2. to characterize the link between self-reported types of impulsivity with speed, accuracy and preference for speed over accuracy in a simple visual comparison task
3. to study the association of the self-reported impulsivity, impulsive performance and impulsive behavioural outcome with two markers of serotonergic system, the short allele of the promoter polymorphism of 5-HTT gene and platelet MAO activity
4. to study whether the behavioural outcome of self-reported trait impulsivity or predisposition to impulsivity due to less effective serotonergic functioning is moderated by cognitive abilities or risk acknowledgement
5. to study whether certain types of self-reported impulsivity are higher in the carriers of 5-HTTLPR S allele, a genotype leading to less efficient serotonin system, and whether this effect depends on family relations.

3. MATERIALS AND METHODS

3.1. Subjects

3.1.1 Car drivers (Papers I, II and III)

Subjects with different types of traffic violations were collected for studying the association of self-reported impulsivity and platelet MAO activity with risky behaviour as behavioural expression of impulsive temperament.

Data of drunk drivers was collected during the year 2001 (**Papers I, II, and III**). Data of drivers exceeding the speed limits and committing other violations (**Paper III**) was collected in 2002–2003 (Paper III). The groups of drunk drivers and drivers exceeding the speed limits were formed of the male subjects from the police database of driving violations. The control groups were formed of male subjects with a driving licence and were derived from the driving licence database of Estonian Motor Vehicle Registration Centre by computerised random choice; their police records were checked. Subjects were contacted by telephone, and the description and aims of the study were provided.

The drunk drivers' group consisted of persons who were caught driving drunk by the police at least once during the previous year (n=203). The control group consisted of 211 persons. In the study on drivers exceeding the speed limits, 610 men (33% of the contacted people) agreed to participate. One subject dropped out of the study at the stage of filling the questionnaires. After controlling the subjects for additional violations in the police database, 13 subjects who had repeatedly exceeded speed limits but, in addition, had been driving drunk were removed from the database. Drivers exceeding the speed limits were divided into two groups: (1) speed limit exceeders, subjects exceeding speed limits at less than 20 km/h at least twice or more than 20 km/h once during the previous year (n=127) and (2) high-risk drivers, subjects exceeding speed limits at more than 20 km/h at least twice during the previous year (n=165). The size of the control group was n=304.

The control groups of the two studies were merged for the comparative analyses of drunk drivers and high-risk drivers. Six persons from the control groups participated in both studies and in the comparative study; we used their data from the years 2002–2003. The size of the final merged control group was n=509.

3.1.2. Schoolchildren (Papers IV and V)

Another sample used in current thesis is a population-based sample of adolescents. The sample was based on the younger cohort of the European Youth Heart Study (EYHS) conducted in Estonia in 1998/99, which was incorporated

into the longitudinal Estonian Children Personality, Behaviour and Health Study (ECPBHS) (Harro et al. 2001). The present study was conducted during the follow-up in 2004 where we managed to recruit 83% (n=483) from the original sample, including 222 boys and 261 girls. Children and their parents signed informed consent letter. Permission for the study was obtained from the Committee of Ethics of the University of Tartu, Estonia. The mean age of the subjects studied in 2004 was 15.3, SD = 0.5.

3.2. Measures

3.2.1. Adaptive and maladaptive impulsivity scale (AMIS, Papers I, II, III, IV and V)[1]

The scale is a short instrument consisting of four subscales based on the Dickman impulsivity inventory (Dickman 1990), measuring functional and dysfunctional impulsivity, and of impulsivity related subscales of NEO-PI (Neuroticism Extraversion Openness Personality Inventory, Costa and McCrae 1989, adapted into Estonian by Pulver et al. 1995), Impulse Control subscale under the domain of Neuroticism and Excitement Seeking subscale under the domain of Extraversion. Two of the four subscales of AMIS, Thoughtlessness and Disinhibition, measure the maladaptive types of impulsivity and the other two, Fast Decision-Making and Excitement Seeking, measure the adaptive types of impulsivity.

For comparison of AMIS with the UPPS scale developed by Whiteside and Lynam (2001) factor analysis of the items from most well-known impulsivity scales, we suggest that Thoughtlessness is theoretically comparable with the Lack of Premeditation, Disinhibition with Urgency, and Excitement Seeking with Sensation Seeking. Fast Decision-Making (based on the items in the functional impulsivity scale by Dickman, 1990) is measured separately from Excitement Seeking in our scale, which differs from the UPPS scale, where these two are united under Sensation Seeking.

3.2.2. Barratt Impulsiveness Scale (Papers IV and V)

Barratt Impulsiveness Scale (BIS-11) (Patton et al. 1995) was adapted into Estonian on 683 subjects with mean age 19±8 years of age ranging from 14–66. Twenty seven out of the original 31 items formed a single scale with average inter-item correlation r=0.13 and inner reliability expressed as Cronbach

[1] In the earlier stages of the studies of impulsivity, Thoughtlessness was referred to as Dysfunctional Impulsivity, Fast Decision-Making as Functional Impulsivity, and Disinhibition as NEO-PI Impulsivity (Papers I, II and III)

Alpha=0.80. The English version of BIS-11 consists of motor, cognitive/ attentional and non-planning components, however the items were originally designed to be used as a homogenous measure of impulsiveness that would be separate from affective constructs like anxiety. The analyses by Miller et al. (2004) and Whiteside and Lynam (2001) have demonstrated that the three subscales of BIS-11 have mutual inter-correlations over 0.5; and in a common factor analysis with other measures of impulsivity, all three scales of BIS have significant loadings into the same factor. Thus, in analyses we used the BIS-11 total score.

3.2.3. General self-esteem

Rosenberg Self-Esteem Scale (Rosenberg 1965, adapted into Estonian by Pullmann & Allik, 2000) was used for measuring Global Self-Esteem.

3.2.4. General cognitive abilities (Paper IV)

Raven's Standard Progressive Matrices (SPM) test (Raven 1981), (standardized on Estonian population by Lynn et al. 2002) subtests C and D were used to measure the intellectual abilities of the adolescent participants. The SPM is commonly regarded as a high-quality measure of pure non-verbal reasoning ability, which is relatively independent of specific learning acquired in a particular cultural or educational context (Jensen 1998). The test was administered without time limits.

3.2.5. Assessment of traffic behaviour (Papers II and III)

The traffic behaviour questionnaire used in **Paper II** included questions about the duration of having the driving licence, having driven while impaired by alcohol during previous year, frequency of car driving, using the seat-belt, breaking the speed limits, paying for parking, stopping before the pedestrians' crossings and overtaking the preceding car, all during previous year.

In **Paper III**, for comparison of the drunk drivers and high-risk drivers, questions about frequency of car driving, the frequencies of using the seat belt, of exceeding the speed limits, of paying for parking, of stopping before zebra crossing and of overtaking the afore-driving car during the past year and the duration of having the driving licence were included. For the comparison of high-risk drivers denying and admitting the risk of "driving too fast" to appropriate controls (Paper III), more specific questions were added. A list of several possible driving hazards (21 items), based on internal driving risks

questionnaire by Hatakka (1998) with “yes” or “no” answers, were also scored, leaving out the hazard of “driving too fast”. The scores were divided on the basis of the median value to low and high.

3.2.6. Risk acknowledgement (Paper III)

A list of several possible driving hazards, based on internal driving risks questionnaire by Hatakka (1998) with “yes” or “no” answers was given to the subjects with the instruction of marking their own qualities or habits, which they evaluate as bringing risk to them in traffic. One of the mentioned internal driving risks was “driving too fast”. Subjects were divided into four subgroups of high-risk drivers admitting the risk of speeding, and high-risk drivers denying the risk of speeding, controls admitting the risk of speeding and controls denying the risk of speeding, according to how they replied to this question.

3.2.7. Assessment of socio-demographic data, alcohol use and smoking (Papers I, II and III)

Socio-demographic data were collected in the studies with drivers by a self-reported questionnaire (**Papers I, II and III**). Age, marital status, education and monthly income were measured. For analyses, we used the following categories: “single” and “living as a couple” for marital status, “lower education” and “higher (university) education” and “lower income” as monthly income below 10,000 EEK (€641) and “higher income” as monthly income above 10,000 EEK (€641).

Smoking status was coded as “non-smokers”, “ex-smokers”, and “subjects smoking 10 or less cigarettes per day”, “11–19 cigarettes per day” or “20 or more cigarettes per day” in **Paper I**; “smokers” (daily smokers) and “non-smokers” (people who had never smoked and ex-smokers) in **Papers II and III**; and “non-smokers” (subjects smoking less than daily) and “smokers” (subjects smoking daily) in **Paper IV**.

3.2.8. Visual comparison test (Paper IV)

The stimuli used in the VCT in this experiment, which was based on Dickman & Mayer (1988), were geometric figures made up of multiple *X*s (**Fig 1, Paper IV**). Each figure was created by removing one or more *X* from an array that was 5 *X*s high and 10 *X*s wide. Each figure created in this way was paired with itself to form a *same* figure pair. For *different* pairs, one of the figures in a same pair

was altered by changing the position of a single *X* in the periphery of the figure. Twenty pairs were created in this fashion; *same* and *different* pairs were randomly intermixed. The random generation and presentation of the figure pairs and recording of the responses was controlled by a computer. The figure pairs were presented in the centre of the computer display screen. On the keyboard, one key was marked with green, for answering "*same figures*", and one with red for "*different figures*". Before the figures appeared on the screen, the punishment points (either -2, -10 or -50) for making an error were presented. The computer recorded each person's answers and time on every comparison.

Subjects were tested in sessions that lasted approximately 15 min. They were instructed to press the green key on the keyboard when the two figures were same and the red key on the keyboard when the two figures were different. They were told to perform as quickly and accurately as possible. They were told that before every trial they are notified how many minus-points they would get for an error. Subjects were allowed to practice on a set consisting of five figure pairs. The subjects were then asked whether they had understood what they were supposed to do and when requested, offered another trial set. The trial session was followed by a test session, where subjects were given 20 pairs of figures for comparison. After every response, subjects received feedback whether they performed correctly.

The accuracy of responding was expressed as percentage of correct answers and the speed of responding was measured in milliseconds. Impulsivity score (I-score) was calculated for estimating speed-accuracy trade-off as a measure of impulsivity (Morgan 1998) according to the formula of Messer & Brodzinsky (1981), subtracting the standard score of the mean latency (Z_t) from the standard score of the total number of errors committed (Z_e).

3.2.9. Measurement of platelet MAO activity (Papers I, II, III and IV)

Venous blood samples were collected into 4.5-ml test tubes containing K_3EDTA as an anticoagulant. Platelet MAO activity was analysed in platelet-rich plasma by a radioenzymatic method with [^{14}C]-β-phenylethylamine (β-PEA) ("Amersham") as the substrate according to the procedure described by Hall-man et al. (1987) after modification by Harro et al. (2001). Blood samples were collected by antecubital venipuncture into 4.5 ml Vacutainer® tubes containing DTA as an anticoagulant. The samples were centrifuged for 10 min with 800 rpm, obtaining platelet-rich plasma. Part of the obtained plasma (200 µl) was used for counting platelets in certified laboratories in the Tartu University Hospital and HTI Laboratory Services in Tallinn. One ml of platelet-rich plasma was stored at -80˚C until the measurement of MAO activity. After melting the platelet-rich plasma on ice, platelets were sonicated with Bandelin Sonopuls

Ultrasonic Homogenizer HD2070 4 x 10 s with intervals of 5 s at 4˚C. Then 40 µl of 0.1 mM [^{14}C]-β-PEA was mixed with 50 µl of sonicated plasma, followed by 4 min incubation in 37˚C water bath. After that, 30 µl of 1.0 M HCl was added to stop the reaction and all the tubes were put onto an ice bath for another 10 minutes. After adding 750 µl solution of toluene and ethylacetate (1:1), all the samples were mixed on a shaker (Vibromax 110, Heidolph) for 30 s at 1700 rpm, and thereafter centrifuged for 5 min at 2000 rpm. From the organic phase 500 µl was pipetted into vials with 8 ml of scintillation liquid (Optiphase "HiSafe"3, Wallac). For standard samples 50 µl of 0.1 mM [^{14}C]-β-PEA was added to 8 ml of scincillation cocktail. All the samples were analysed in duplicate and blindly and corrected using a reference sample. Radioactivity was measured in a β-counter (Wallac Guardian 1414 Liquid Scincillation Counter). MAO activity was calculated using the following formula: [the amount of the substrate (nmol) x β-count of the sample (cpm) x 1.5]/[β-count of the standard (cpm) x incubation time (min) x the count of platelets in 50 µl of platelet-rich plasma (10^{10} of platelets)] and expressed as nmol of substrate oxidized per 10^{10} platelets per min (nmol x min^{-1} x10^{10} $platelets^{-1}$).

3.2.10. Assessment of family relations (Paper V)

Relationships in the family were measured by a child-report scale with four subscales: closeness, support, misprize, and emotional and physical abuse in the family. These four subscales were extracted by principal components factor analysis using the Cattell criterion. Items with factor loadings less than 0.4 were excluded. Items were presented in terms of 4 or 5-point Likert scale. Internal-consistency reliability (Cronbach's α) of the subscales was between 0.83 and 0.94. The subscales of closeness and support were added together under a common name „warmth in family" and the subscales of abuse and misprize were added together under a common name „maltreatment".

3.2.11. Genotyping of the 5-HTT gene (Papers IV and V)

The alleles at the 5-HTTLPR locus were amplified from genomic DNA using PCR. The polymorphic region was amplified using the primers 5-HTTLPR-F: CAA CCT CCC AGC AAC TCC CTG TA, 5-HTTLPR-R: GAG GGA CTG AGC TGG ACA ACC AC, where the forward primer was fluorescently labeled with a 5'-FAM. Reagents and conditions for the PCR reaction were: 1x PCR buffer (Perkin Elmer, AmpliTaq Gold buffer II), 200 µM dNTP with 50% of dGTP replaced with 7-deaza-dGTP, 2 mM $MgCl_2$, 1 µM of each primer, 1 U Taq polymerase (Perkin Elmer, AmpliTaq Gold), and 20 ng genomic DNA, in a total reaction volume of 10 µL. The reaction started with 10 min at 95ºC,

followed by 40 cycles with 30 s at 95ºC, 30 s at 59ºC, 30 s at 72ºC, and ended with 7 min at 72ºC. PCR products were then run on an ABI PRISM 3700 DNA analyzer (Applied Biosystems, U.S.A.), and scored using the software Gene-Marker 1.5 (SoftGenetics, U.S.A.). All genotypes were manually checked on chromatograms to detect inconsistencies, and where needed, amplified and scored a second time.

There were 191 (44%) subjects being homozygous with regard to the long 5-HTTLPR allele, 189 (43%) were heterozygous and 55 (13%) homozygous for the short allele (Papers IV and V). Genotype frequencies were in Hardy-Weinberg equilibrium.

3.3. Data analysis

Self-reported impulsivity measures were standardised into z-scores indicating how far and in what direction the individual deviates from the whole sample's mean expressed in units of its distribution's standard deviation, according to the formula $Z_X=X-M_X/SD_X$, where Z_X accounts for the z-score, X for personality measure's score, M for the sample's mean and SD for standard deviation of the mean (**Papers III and IV**). Analysis of variance (ANOVA) and multivariate analysis of variance (MANOVA) were used for identifying interactive effects between variables (**Papers I, II, III, IV and V**), with Fisher LSD, Scheffé and Bonferroni-corrected *post-hoc* multiple comparison procedures for comparing continuous variables in the groups. Covariation analysis was used for controlling the effect of a third continuous variable. Kruskal–Wallis analysis of variance was used for comparing non-parametrically distributed variables like traffic accidents (**Paper III**). People were divided into subgroups of low, medium and high MAO activity according to lower and higher quartile values (the quartile values calculated for boys and girls separately) (**Papers III and IV**). Median was used for dividing subjects into two groups with low or high level of the given variable (**Papers IV and V**). Polytomous logistic regression was used for analysing traffic behaviour and socio-economic status (**Paper III**).

4. RESULTS AND DISCUSSION

4.1. Self-reported types of impulsivity and their expression in behaviour

4.1.1. Inter-correlations of the self-reported measures (unpublished data)

In this thesis, an attempt was made to validate different the types of impulsivity by describing their expression in risky behaviour, cognitive performance and association with serotonergic function. The scales for measuring impulsivity (Thoughtlessness, Fast Decision-Making, Disinhibition, Excitement Seeking and BIS-11) were selected with an attempt to use the theoretical knowledge obtained in the factor-analytic studies by Miller et al. (2004), Whiteside & Lynam (2001), and Flory et al. (2006) in their composition. The first four scales also differentiate the adaptive and maladaptive side of impulsivity and BIS-11 is specially designed to measure the impulsivity which has a cognitive origin.

Table 5.1 Correlations between the types of impulsivity and with general self-esteem in the sample of adolescents (n = 483, below) and drivers (n = 1004, above)

	(1)	(2)	(3)	(4)	(5)
General Self-Esteem (1)		–0.28***	0.16***	0.25***	–0.24***
Disinhibition (2)	–0.21***		0.29***	0.09**	0.65***
Excitement Seeking (3)	0.21***	0.22***		0.51***	0.20***
Fast Decision-Making (4)	0.33***	0.10*	0.54***		0.07*
Thoughtlessness (5)	–0.22***	0.62***	0.29***	0.11*	
BIS-11 (6) [1]	–0.30***	0.54***	0.22***	0.04	0.61***

* p<0.05, ** p<0.01, *** p<0.0001

[1] BIS-11 was not applied on the sample of drivers

Inter-correlations between these types of impulsivity and their association with general self-esteem in the sample of drivers and adolescents are presented in **Table 5.1**. The inter-correlations between the scales were similar in the two samples — adult male drivers and a representative sample of schoolchildren. The correlation with general self-esteem is given with the purpose of demonstrating the general adaptiveness of those types of impulsivity. There was a strong interrelation between the two impulsivity scales theoretically representing the maladaptive aspect of impulsivity — thoughtlessness and disinhibition. Disinhibition is composed of the items of the impulse control subscale under the neuroticism facet of NEO Personality Inventory, which is generally

considered a trait rising problems, worries, anxiety and negative moods (Costa & McCrae, 1989), while thoughtlessness was based on the dysfunctional impulsivity subscale (Dickman 1990), which has been described as a tendency to ignore hard facts when making decisions, acting without fore-thought, and engage in rapid, error-prone information processing. As expected, fast decision-making, measured by a scale construced based on the functional impulsivity in DII and described as an ability to think and act quickly in appropriate situations (Dickman 1990), was related to excitement seeking, a NEO-PI sub-scale under the facet of extraversion, which is generally considered to be more adaptive, and related to positive moods, energy and activity (Costa & McCrae, 1989). These two features (excitement seeking and fast decision-making) can also be compared with venturesomeness in I_7 (Claes et al. 2000).

Global self-esteem correlated positively with fast decision-making and excitement seeking, and negatively with thoughtlessness and disinhibition. It is appropriate to assume that personality traits considered maladaptive and problem rising would relate to lower self-esteem, while self-enhancing personality traits associated with higher self-esteem could be considered adaptive.

4.1.2. Self-reported and police-reported drunk driving and impulsivity (Paper II)

It is well known that in the case of violating rules, people might want to show themselves in a socially more desirable way, thus the research based only on self-reported questionnaires for behaviour in traffic might not be fully reliable. In addition, the police does not catch all subjects who drink and drive. Thus the police database and the self-reported data were used to identify people who had been driving drunk during the previous year. The controls and police-referred drunk drivers were separated according to whether they reported or denied drunk driving. Hence, the following groups were obtained: Control I (129 subjects) — random choice from driving licence database who denied DAD during the previous year; Control II (81 subjects) — random choice from driving licence database who reported DAD some times or often per year; DWI I (45 subjects) — DWI subjects who denied DAD during the previous year; and DWI II (157 subjects) — DWI subjects who reported DAD some times or often per year.

Table 5.2 The types of impulsivity (mean ± SD) according to the self-reported driving after drinking in convicted drunk drivers and control groups

	Control I n=129	Control II n=81	DWI I n=45	DWI II n=157
Disinhibition	16.3 ± 4.6	17.8 ± 4.0[aa]	17.9 ± 4.9[a]	18.8 ± 4.0 [aaa]
Excitement Seeking	20.0 ± 4.9	20.6 ± 5.5	18.7 ± 5.7	21.4 ± 5.2 [ac]
Thoughtlessness	13.9 ± 4.6	15.4 ± 4.5[a]	15.5 ± 4.6	16.8 ± 4.9 [ab]
Fast Decision-Making	19.6 ± 4.8	19.7 ± 4.7	20.4 ± 3.6	20.3 ± 4.2

[a] — $p<0.05$ [aaa] — $p<0.00001$ vs Control I, [b] — $p<0.05$ [bb] — $p<0.01$ vs Control II, [c] — $p<0.05$ vs DWI I. Significant differences are calculated using Fisher post-hoc test

The means and standard deviations of the impulsivity types in these four groups are presented in **Table 5.2**. Significant differences between the groups appeared in the measures of thoughtlessness ($F_{3,408}=8.55$, $p<0.00001$), disinhibition ($F_{3,408}=8.37$, $p<0.0001$), and excitement seeking ($F_{3,408}=3.69$, $p<0.05$). *Post-hoc* analysis revealed that the scores of thoughtlessness and disinhibition were higher in the DWI II group compared to Control I subjects and the score of excitement seeking compared to both Control I and DWI I groups. DWI I were higher than Control I subjects by their disinhibition and Control II subjects were higher than Control I subjects by their thoughtlessness. The groups of drunk drivers and controls did not differ by fast decision-making, which showed only a tendency to be higher in DWI groups. However, as DWI II subjects were younger compared to controls and DWI I subjects (**Table 1, Paper II**), the covariate effects of age were explored. Age had significant covariate effects on disinhibition ($F_{3,408}=19.3$, $p<0.0001$) and excitement seeking ($F_{3,408}=78.0$, $p<0.0001$). The effect of excitement seeking turned non-significant ($F_{3,408}=1.35$, $p=0.3$) and the effect of disinhibition decreased when accounting for age as a covariate ($F_{3,408}=6.41$, $p<0.0001$). The fact that the effect of excitement seeking disappeared but the effect of thoughtlessness remained after controlling for age suggests that younger subjects violate the rules more probably due to the need for stimulation (excitement seeking), while risk-taking in all ages may rather be associated with thoughtlessness. An earlier study on risk-taking older drivers demonstrated higher Narrow Impulsivity, but not Venturesomeness according to I_7 impulsivity questionnaire (Owsley et al. 2003). Another study on juvenile drivers on the contrary, demonstrated higher Venturesomeness but not Narrow Impulsivity in traffic violators (Renner and Anderle 2000). Similarly, Jonah (1997) in his review article on sensation seeking and risky driving observed that the association between sensation seeking and drunk driving declined with age.

DWI II group was also most deviant by other measures: these subjects had more alcohol-related problems, consumed alcohol more often, used seat belt and

paid for parking less often compared to the Control I subjects (**Table 3, Paper II**). The measures of alcohol related problems and traffic behaviour differentiated drunk drivers and controls even better than the measures of impulsivity and platelet MAO activity. Several studies have similarly shown that when including the alcohol use and socio-economic measures into a common multiple regression model with personality traits predicting drunk driving, or alcohol-related injuries, the alcohol use measures weigh out the effect of personality (Begg et al. 2003, Vingilis et al. 2004, Bazargan-Hejazi et al. 2007). It may be that the alcohol-related problems and other violations of traffic rules are themselves correlated with the impulsivity measures, thus due to multi-collinearity the latter are regressed out from the multiple regression or discriminant models.

4.1.3. Different types of risk-taking in traffic as a behavioural expression of impulsivity (Papers II and III)

The next question was whether drunk driving and other types of driving violations are a behavioural expression of similar types of impulsivity. High-risk drivers who had been caught with repetitive violations of more than 20 km/h over the speed limits had higher scores in both adaptive impulsivity subtypes (fast decision-making and excitement seeking) and thoughtlessness compared to controls (**Fig 5.1a in the thesis** or **Fig 1a, Paper III**). Drunk drivers had higher scores only in the maladaptive impulsivity subtypes (disinhibition and thoughtlessness) (**Fig 5.1a in the thesis** or **Fig 1a, Paper III**). Higher excitement seeking among high-risk drivers can be compared with the higher sensation seeking in high-risk drivers shown in several studies (Jonah 1997). In earlier studies demonstrating the similarity of drunk drivers and high-risk drivers on the personality trait measures, the focus has not been on different aspects of impulsivity (Donovan et al. 1985; Wilson 1992). In our study, thoughtlessness was higher in both, drunk drivers and high-risk drivers compared to controls, but in turn, thoughtlessness of drunk drivers was even higher compared to high-risk drivers (**Fig 5.1a in the thesis** or **Fig 1a, Paper III**) which is partly similar to the results by Wilson (1992). The speeding drivers (with violations less than 20 km/h over the speed limits) had only tendencies to score higher in excitement seeking and fast decision-making compared to controls (**Fig 5.1a in the thesis or Fig 1a, Paper III**).

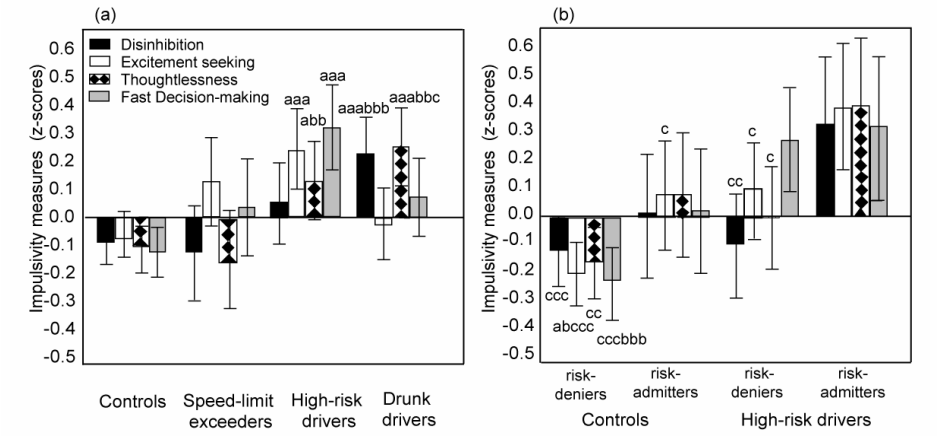

Figure 5.1 (a) The types of impulsivity in speeding drivers, high-risk drivers, drunk drivers and controls. (a) The types of impulsivity in speed-limit exceeders, high-risk drivers and drunk drivers compared to controls. a — $p< 0.05$, aa — $p< 0.01$, aaa — $p<0.001$ difference from controls, bb — $p< 0.01$, bbb — $p< 0.001$ difference from speed-limit exceeders, c — $p< 0.05$ difference from high-risk drivers; **(b)** The types of impulsivity in high-risk drivers and controls denying and admitting the risk of driving too fast. a — $p< 0.05$ — difference from risk-admitting controls; b — $p< 0.05$, bbb — $p< 0.01$ — difference from risk-denying high-risk drivers; c — $p< 0.05$, cc — $p< 0.01$, ccc — $p<0.001$ — difference from risk-admitting high-risk drivers
Whiskers mark 95% confidence intervals. The Scheffe *post-hoc* differences between the groups are given accounting for age as a covariate.

It has been suggested earlier that the variety inside the risky drivers group is high; thus, risk-takers need to be divided into subgroups, for example, according to sex, age or personality profile (Wilson 1992). A variety inside traffic risk-takers also appeared in our study, where drunk drivers, although similar to high-risk drivers in thoughtlessness, were higher from them in fast decision-making and excitement seeking.

These results add ecological validity to the division of impulsivity into maladaptive and adaptive types. The common part of the measured traits is that all of the measured impulsivity types lead to higher risk-taking, and the diverse part differentiating the types of impulsivity from each other is that the associated risky behaviours and socio-economic background are of different kind.

4.1.4. The types of impulsivity in high-risk drivers admitting and denying the risk of "driving too fast" (Paper III)

While lower risk perception may bring along risky behaviours, it is concluded that the awareness of personal risks is not a sufficient reason for avoiding risky behaviour (Hatakka 1998, Gibbons et al. 2006). Safety problems may exist not only because drivers are unaware of the risk but because of many reasons like time pressure, ego gratification, inattention or tension relief (Gabany et al. 1997), acceptance of risk as a cost or risk seeking (Harre 2000). While independent effects of both low risk perception and high impulsivity on risky driving have been demonstrated (Ryb et al. 2006), a less studied issue is how the risk acknowledgement interacts with impulsive traits in the formation of risky behaviour.

High-risk drivers (who had mostly been caught with repetitive speed-limit exceeding) were divided into subgroups by their self-reported admitting and denying the risk of "driving too fast". Two thirds of drivers who had been repeatedly caught by the police violating traffic rules denied the risk accompanying this kind of behaviour (**Paper III**). The only impulsivity type that was higher in risk-denying high-risk drivers after adjustment to age was fast decision-making **(Fig 5.1b)**. This type of impulsivity is defined by a self-perceived higher capability to process information and to decide quickly in situations where this is necessary (Dickman 1993). It is natural that a person who is convinced in his ability to react fast e.g., to unexpected stimuli on the road, perceives fast driving as a smaller risk to himself. It is possible that they indeed manage to reduce the risk despite their violations of traffic laws, because they were similar to controls by their number of traffic accidents. The risk admitting high-risk drivers, on the other hand, had higher number of accidents compared to controls. The risk-denying high-risk drivers had also a different self-reported traffic behaviour profile (**Table 2, Paper III**), but they were similar to risk-admitters and controls by their socio-demographic profile.

One third of the high-risk drivers exceed speed limits despite acknowledging the risk of this behaviour (**Paper III**). The maladaptive impulsivity features and excitement seeking were more deviant in risk-admitting high-risk drivers in comparison with controls, but also in comparison with risk-denying high-risk drivers (**Fig 5.1b).** It has been claimed earlier that risk-taking behaviour is most probable in people combining high sensation seeking and impulsive decision-making style (Donohew et al. 2000). The combination of different types of impulsivity may lead to acknowledged risk-taking cumulatively (Torgersen & Vollrath 2006) — while excitement seeking is responsible for one's need for new and exciting stimuli, impulsive cognitive style does not allow the person to inhibit these needs. Earlier studies have compared two groups of high-anger drivers — those who report their reckless driving as a problem and those who

do not — in the first group, bigger intensity and frequency of anger was found (Deffenbacher et al. 2003). It has been found that drivers with intention to speed are characterised rather by general deviance than a tendency to underestimate the negative consequences (Lawton et al. 1998).

Although both risk-admitting and risk-denying high-risk drivers had higher fast decision-making, these two phenotypes were clearly different by their other qualities. In studies on personality and risk-taking, the highest descriptive power has been found when using the types of personality instead of traits, because one personality feature often leads to risky behaviour only in the presence of another (e.g., impulsive extraverts have the highest risk in traffic, while non-impulsive extraverts have the lowest risk) (Torgersen and Vollrath 2006).

One of the main qualities of impulsivity is lack of premeditation (Whiteside & Lynam 2001, Evenden 1999), and sometimes the actions of impulsive persons have been ascribed to the lack of acknowledgement of risks, low reflection of possible negative consequences, and difficulties in monitoring their own behaviours (Barratt et al. 2005, Eysenck, S.G.B. 1993, Gerrard et al. 2006). However, our results refer to the interpretation that people scoring high simultaneously by several types of impulsivity know the risks well, but have problems inhibiting their reaction in circumstances, in certain state of mind or due to lack of skills needed in this situation, the aspect emphasized in other theories of impulsivity (Shoda et al. 1990, Wright and Mischel 1987, Gibbons et al. 2006). It is also possible that the risk-admitting high-risk drivers search for risks, reflected in the construct of impulsive sensation seeking (Zuckerman & Kuhlman 2000) and venturesomeness (Eysenck, S.G.B. 1993). As a contrast, the subgroup of risk-denying high-risk drivers, who were high in only one impulsivity subtype (fast decision-making) rather seem to be convinced in their ability to cope with the situation of driving at high speeds and not consider this as a risk to themselves. They also reported lower use of seat-belt (**Table 2, Paper III**), which may signal about their lesser perceived accident risk. In fact, their estimation of their own lower risk may be correct, because of their similar number of traffic accidents compared to controls demonstrated in **Paper III**. The risk-denying high-risk drivers were also older and therefore probably more experienced. With growing driving–experience risks are getting smaller — and are also perceived smaller (Heino et al. 1996).

4.1.5. Self-reported impulsivity, cognitive abilities and impulsive performance in adolescents (Paper IV and unpublished data)

The self-reported impulsivity scales were applied to a population-based sample of adolescents who also performed a laboratory test of comparing figures in different payoff conditions measuring speed, accuracy and speed-accuracy trade-off strategy (Visual Comparison Test, VCT). The correlations of the speed,

accuracy and I-score in VCT with the self-reported types of impulsivity and cognitive abilities measured by Raven standard progressive matrices are shown in **Table 5.3**. BIS-11 whole score had a significant negative correlation with the I-score and speed of responding. Higher BIS-11 score was related to higher I-score and faster responding in VCT, while disinhibition was related with faster responding. Thoughtlessness, excitement seeking and fast decision-making did not have significant correlations with speed, accuracy and I-score in VCT, a similar result to earlier studies finding no correlation between self-reported and performance measures of impulsivity (Nietfield & Bosma 2003, Reynolds et al. 2006). Thus only BIS-11 score as a self-reported measure of cognitive impulsivity was used in further analysis. Cognitive abilities were positively correlated with accuracy of responding in VCT.

Table 5.3 Intercorrelations (Pearson r) of impulsivity measures and cognitive abilities with speed, accuracy and impulsive performance in VCT

	Time per item	% correct	Impulsivity score
Disinhibition	–0.13*	0.04	0.06
Excitement Seeking	–0.01	0.06	–0.03
Thoughtlessness	–0.11	0.00	0.06
Fast Decision-Making	–0.07	0.07	0.00
BIS-11	–0.14*	–0.11	0.15**
General cognitive abilities	–0.04	–0.29***	–0.20***

* — $p<0.05$, ** — $p<0.01$, *** — $p<0.0001$

As a next step, subjects were divided into four groups according to the median values of speed and accuracy. The speed-accuracy trade-off was further analysed only in association with BIS-11 score, because other scales of impulsivity failed to show sufficient associations with performance. The groups with different speed-accuracy trade-off strategies were significantly different in the mean score of BIS-11 ($F_{3,333}=4.28$, $p<0.01$), the *post hoc* analysis demonstrating that the main group effect was attributed to the difference of the slow/accurate group from fast/accurate and fast/inaccurate groups (**Fig 5.2a**). There was a significant main group effect on cognitive abilities ($F_{3,352}=5.02$, $p<0.01$), difference in *post-hoc* tests being mainly attributable to fast/accurate and slow/accurate groups, who had a significantly higher score of general cognitive abilities compared to the fast/inaccurate group (**Fig 5.2b**). The covariate effect of cognitive abilities was not significant on the association between self-reported impulsiveness and performance in VCT ($p=0.292$).

Analysing the behaviour of all four groups it is possible to conclude that there exists an impulsive type of individuals who react fast but do not pay with more errors and who report high impulsivity and have high cognitive abilities (**Fig 5.2ab**). Rozencwajg & Corroyer (2005) and Nietfield & Bosma (2003) also

detected higher cognitive ability in the fast/accurate group according to MFFT. Intelligence has been associated with the speed of information processing according to some theories (Vernon 1997). One line of interpretation is that although these subjects are impulsive and react fast, due to higher intelligence they do not pay with errors. Thus, higher cognitive abilities may protect from errors and thus lead to more adaptive expression of impulsivity. It should be noted though that inside the fast/accurate group the impulsive subjects and subjects with higher cognitive ability may not coincide. Fast/inaccurate subjects had high impulsivity and co-occuring low cognitive abilities. Thus the high self-reported impulsivity measured by BIS-11 in fast/accurate subjects and in fast/ inaccurate subjects are probably of a different origin, which the used self-reported questionnaire could not differentiate. It has earlier been shown that lower ability to analyse data often brings along impulsive behaviour (Vigil-Colet & Morales-Vives 2005, Brannigan et al.1980). Inferior performance in neuropsychological tests of disinhibition is rather a characteristic of dysfunctional than functional impulsives (Dickman 1993). Speed of information processing has been related to functional impulsivity in some studies (Brunas-Wagstaff et al. 1996, Reeve 2007), while others failed to demonstrate this (Vigil-Colet & Codorniu-Raga 2004).

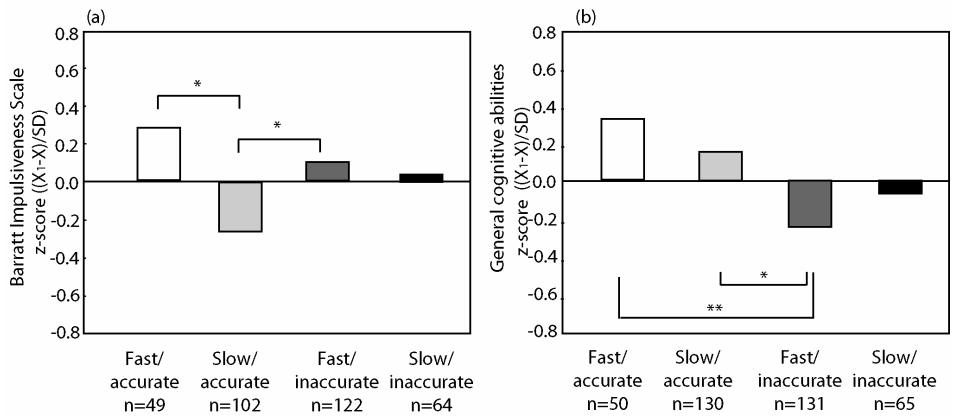

Figure 5.2 The self-reported impulsiveness score (a) and general cognitive abilities (b) in the groups demonstrating fast/accurate, slow/accurate, fast/inaccurate and slow/ inaccurate response style in Visual Comparison Test. * — $p<0.05$, ** — $p<0.01$ the Bonferroni-corrected *post-hoc* differences between the groups

Subjects with high impulsivity and low cognitive abilities had higher error-rate when comparing two different figures and were faster responding in the condition of two *same* figures compared to subjects with low impulsivity and high cognitive

abilities (**Table 5.4**). This was in accordance with the original study by Dickman & Meyer (1988), where impulsive subjects gave more false "*same*" answers. If the subject observes the stimuli systematically, comparing two identical figures should take more time than detecting the difference in a task with two different figures. Also, detecting a difference is naturally more error-prone due to faster responding in this condition. Thus the observed higher error-rate in different-figure task combined with faster responding in *same*-figure task in subjects, who reported to be more impulsive and had lower cognitive abilities probably expresses their more arbitrary and impatient style in this task.

Table 5.4 The means and standard deviations of speed and accuracy of comparing the figures in Visual Comparison Test in the condition of the *same* and *different* figures in subjects according to their impulsiveness and general cognitive abilities

	The condition of comparing *same* or *different* figures			
	Same		*Different*	
	Time per item (s)	% correct	Time per item (s)	% correct
	8.8 (3.9)	94.4 (10.6)	5.7 (2.5)	82.2 (18.1)
BIS-11[1]				
Non-impulsive (n=170)	9.3 (4.2)	95.0 (9.5)	5.8 (2.7)	84.3 (17.2)
Impulsive (n=169)	8.3 (3.6)*	94.2 (10.9)	5.4 (2.0)	79.8 (17.8)*
Cognitive abilities score				
Low (n=160)	8.3 (4.1)	93.3 (11.8)	5.6 (2.7)	77.0 (18.6)
High (n=196)	9.3 (3.7)*	95.4 (9.3)	5.7 (2.2)	86.6 (15.7)***

* — $p<0.05$, ** — $p<0.01$, *** — $p<0.0001$ statistical significance of the t values in pair-wise comparisons of high impulsive group vs non-impulsive group and subjects with high vs subjects with low cognitive abilities.

In conditions of different punishment points (**Table 5.5**), the impulsive subjects by self-reported measure responded faster in the condition of -2 points and were also less accurate in this condition. However, in the condition of -50 punishment points they replied as slow and were as accurate as non-impulsive subjects. This suggests that impulsive individuals have a strategy to prefer fast responding when the number of points to lose is fractional, but respond as fast and as accurately as non-impulsive subjects in case of a considerable number of points to lose. Subjects with lower cognitive abilities gave significantly less correct answers in all payoff conditions, but did not differ by speed in any of the conditions. These patterns of responding in impulsive subjects and subjects with lower abilities confirm that the more impulsive subjects indeed have a style of fast and error-prone responding, which is different from the ability-related error-proneness.

Table 5.5 The means and standard deviations of speed and accuracy of comparing the figures in Visual Comparison Test in three payoff conditions according to the subject's impulsiveness and general cognitive abilities

	Payoff condition (expected cost of error)					
	–2 points		–10 points		–50 points	
	Time per item (s)	% correct	Time per item (s)	% correct	Time per item (s)	% correct
	7.2 (3.3)	87.3 (16.3)	7.3 (3.2)	88.1 (14.6)	7.4 (3.3)	88.8 (15.4)
BIS-11[1]						
Non-impulsive (n=170)	7.6 (3.6)	89.3 (14.4)	7.6 (3.5)	89. 9 (13.2)	7.6 (3.7)	89.6 (14.3)
Impulsive (n=169)	6.7 (2.6)*	85.1(17.8)*	6.9 (3.1)	86.3(15.3)*	7.0 (2.9)	88.2 (15.7)
Cognitive abilities [1]						
Low (n=160)	7.0 (3.5)	83.9 (18,5)	6.9 (3.6)	85.3 (15.9)	7.0 (3.4)	85.1 (17.5)
High (n=196)	7.3 (2.9)	90.2 (13.4)***	7.5 (3.1)	90.7 (12.4)***	7.6 (3.3)	91.8 (12.8)***

* p<0.05, ** p<0.01, *** p<0.0001 statistical significance of the t values in pair-wise comparisons of high impulsive group vs non-impulsive group and subjects with high vs subjects with low cognitive abilities.

4.2. The association of self-reported impulsivity and risky behaviour/impulsive performance with the biomarkers of the function of serotonin system

4.2.1. Platelet MAO activity and alcohol-related risky behaviour (Papers I and II)

Platelet MAO activity was measured in the group of male subjects, who had been caught driving drunk during the previous year. As drunk drivers smoked more (**Table 1, Paper II**), and due to the direct inhibiting effect of cigarette smoke on platelet MAO activity (Fowler et al. 2003), smoking status was controlled for in this analysis. **Fig 1** (**Paper I**) demonstrates the platelet MAO in drunk drivers and controls according to their smoking status. It is apparent that smoking inhibited platelet MAO activity in a dose-related manner, which was similar to the results of Whitfield et al. (2000). However, the platelet MAO activity of non-smokers and ex-smokers inside the group of the drunk drivers was significantly lower compared to non-smokers and ex-smokers in the control

group. This result confirms that despite the distorting effect of smoking, platelet MAO activity can be regarded as a marker of the deviant and impulsive behaviour of driving while impaired. This conclusion is supported by other studies, where smoking could not have any effect, like the study demonstrating low platelet MAO activity in non-human primates, who had had significantly higher alcohol intake (Fahlke et al. 2002). Also, while smoking has a dose-related inhibitory effect on platelet MAO activity, a longitudinal study in our laboratory has shown that subjects with pre-existing low MAO activity have higher likelihood of becoming a regular smoker (Harro et al. 2004). The results presented in **Paper I** suggest that among non-smoking humans, low platelet MAO activity is associated with excessive alcohol use combined with antisocial behavior.

Further comparison of drunk-driving-deniers and -reporters (DWI I and DWI II) in the police-referred drunk driver group in **Paper II** revealed that they did not differ from each other with respect to MAO activity, and both groups had significantly lower platelet MAO compared to both control groups (**Fig 1, Paper II**). This brings to a supposition that the DWI I subjects who denied their drunk driving may have been biased towards socially desirable responding. This is supported by fact that they were similar to more DAD denying control group (Control I) by their other traffic behaviour measures (**Table 2, Paper II**), but resembled the other drunk drivers group (DWI II) by their platelet MAO activity (**Fig 1, Paper II**). Other possibilities to consider are that DWI I subjects were not aware of their drunkenness while driving, because they may have been caught in hangover.

The subjects who reported drunk driving during previous year but had managed to avoid being caught by the police (Control II) exceeded speed limits even more often compared to the DWI II subjects, had higher education (**Table 1, Paper II**), higher platelet MAO activity (**Fig 1, Paper II**), lower thoughtlessness (**Table 5.2**), and lower alcohol related problems (**Table 1, Paper II**), but were similar to them by seat belt use, paying for parking (**Table 2, Paper II**), and general alcohol consumption (**Table 1, Paper II**). Thus, this risk-group has similar MAO, but is still more impulsive compared to controls. Despite higher general alcohol use, they do not report alcohol-related problems, which may mean that the lower MAO is especially a marker of the impulsivity of problem drinkers. Control II group may also represent the better adjusted risk-takers similarly to the subgroup of risky drivers in the study by McMillen (1991), who similarly found the arrested drunk drivers to be deviant on several personality markers, while the non-arrested drunk drivers did not differ from controls. Subjects with lower general abilities (which may be reflected in the lower education in DWI groups) may be more susceptible to alcohol's effect increasing impulsive behaviour as shown in the study by Finn et al. (1999).

In our study, platelet MAO activity was negatively correlated with alcohol-related problems, but not with any measures of alcohol consumption (**Table 1, Paper II**). Studies with alcohol-dependent subjects have found that low MAO

activity in platelets is associated with type 2 alcoholism (von Knorring & Oreland, 1996), which is characterized by several social complications, impulsivity, and an early debut of the abuse (Cloninger et al. 1996). Our results are in accordance with the notion that platelet MAO activity is associated with alcohol-related problems and alcohol-related impulsive behaviour, rather than simple alcohol consumption (Oreland 2004).

4.2.2. Platelet MAO activity and alcohol-related versus non-alcohol related traffic violations (Paper III)

In this study it was found that high-risk drivers with multiple non-alcohol-related driving violations (mainly speed-limit exceeding), despite higher scores in fast decision-making, excitement seeking and thoughtlessness had a similar platelet MAO activity to controls (**Paper III**), while drunk drivers had lower platelet MAO activity (**Papers I, II and III**). Central serotonergic activity is associated with alcohol abuse (LeMarquand et al. 1994) as well as with impulsive behavioural tendencies (Evenden 1999). Knowing the interrelatedness of impulsivity and alcohol abuse (Gibbons et al. 2006, Caspi et al. 1997), we may infer that while low platelet MAO activity is clearly associated with alcohol-related risk-taking or impulsivity leading to alcohol abuse, non-alcohol-related impulsive and risky behaviours do not have a so-clear association with MAO activity. Our fairly large sample was a normal healthy population, as opposed to majority of studies carried out on psychiatric populations or samples high in substance abuse with impulsivity as one symptom in their pathology. High-risk drivers unlike drunk drivers scored high in adaptive types of impulsivity; and majority of studies on MAO activity and impulsiveness have not differentiated between the types of impulsivity by its adaptiveness. Still a study by Schalling et al. (1988) found no correlation between MAO activity and venturesomeness (which is clustered together with the adaptive types of impulsivity), while there was a significant correlation with Narrow Impulsiveness on the scale of I_7. Af Klinteberg et al.(1992), observing higher levels of monotony avoidance and one subscale of impulsivity in pilots, showed that they, at the same time, did not present deviances in neuropsychological tests of disinhibition, in platelet MAO activity and in another subscale of impulsivity. In another study, Longato-Stadler et al. (2002) presented that criminal offenders with accompanying personality disorder and problems with drug abuse had simultaneously lower platelet MAO activity, while other criminal offenders had MAO activity similar to controls. All available evidence together suggests that low platelet MAO activity is associated with impulsive behaviour rather in a sub-population of people with drug problems.

4.2.3. The impulsivity profile and platelet MAO activity in high-risk drivers admitting and denying the risk of "driving too fast" (Paper III).

Dividing high-risk drivers and speed limit exceeders according to their admittance of traffic risks, risk-admitting high-risk drivers had significantly higher platelet MAO activity compared to risk-denying high-risk drivers and risk-admitting controls (**Fig 5.3 in the thesis or Fig 2, Paper III**). One possibility is to interpret high platelet MAO activity in risk-admitting high-risk drivers in the context of previous research suggesting association of high platelet MAO activity with anxiety (Irving et al. 1989), agitated depression (Davidson et al. 1980) or neuroticism (Kirk et al. 2001). Anxiety or depression in certain cases bring along impulsive behaviour (Wallace et al. 1991, Corruble et al. 2003, d'Acremont & van der Linden 2007), possibly because people may engage in risky behaviours to relieve their anxiety. Two types of traffic risk takers based on different personality profiles — one is high in sensation seeking and low in anxiety, and another is high in both — have been identified by Ulleberg (2001). These subtypes were also different in risk evaluations — the latter ones perceived traffic risks higher. As discussed earlier (see 4.1.4.), risk-admitting high-risk drivers were more deviant in both adaptive and maladaptive types of impulsivity types as well as self-reported traffic behavioural indices compared to risk deniers. Thus, our risk-admitting high-risk drivers with higher platelet MAO activity might have been similar to the subgroup of anxious sensation seekers in Ulleberg's (2001) study. It has been demonstrated that impulsive and anxious subgroup was considerably different in their behavioural and psychopathological profiles than impulsive and nonanxious subjects (Askenazy et al. 2003). It has been concluded that the explanatory power of personality traits predicting risky behaviours is higher when the combinations of traits (personality types) are considered (Torgersen & Vollrath 2006).

The finding that risk-taking and law-breaking behaviour can be related to lower as well as higher platelet MAO activity is in accordance with previous studies showing non-linear associations of behaviour or personality traits and monoaminergic functioning. Several items of I_7 were shown to be associated with MAO activity either lower or higher than average (Schalling et al. 1988).

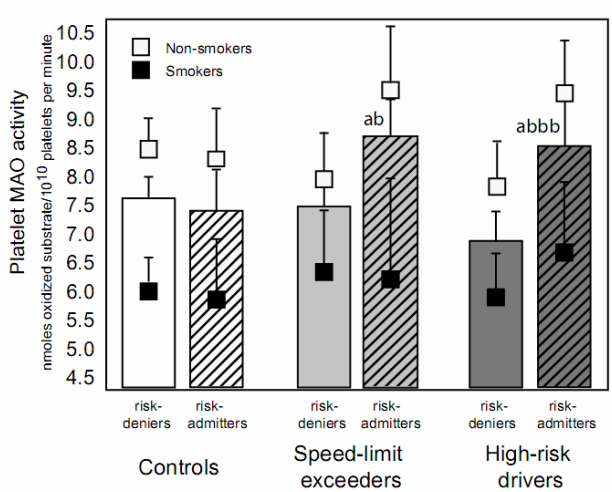

Fig 5.3. Platelet MAO activity in risk-admitting vs risk-denying high-risk drivers, speed-limit exceeders and controls.
a — $p<0.05$ vs risk-admitting controls, b — $p<0.05$, bbb — $p<0.001$ vs risk-denying high-risk drivers; Whiskers mark 95% confidence intervals

Similarly with impulsivity, the association between platelet MAO activity and anxiety shows a tendency for nonlinearity (Schalling et al. 1987) — e.g. subjects with high MAO activity being the most anxious and subjects with low MAO activity being slightly less anxious, however, more anxious compared to subjects with medium MAO activity. In the study by Kirk et al. (2001), the positive association between MAO activity and neuroticism was strengthened when adjusting for the effect of smoking. Harro et al. (2004) have demonstrated in a prospective longitudinal study that the likelihood of starting to smoke is bigger among adolescents with lower as well as higher MAO activity. af Klinteberg et al. (1987) have shown that male subjects with lower as well as higher platelet MAO activity show more disinhibited responses in neuropsychological tests (low-MAO subjects responding faster to new stimuli and high-MAO subjects spending less time inspecting the labyrinth). This is also in accordance with animal studies which show that serotonergic activity is associated with impulsivity in several, sometimes opposite, ways (Evenden 1999). Therefore, actual associations between traits like neuroticism and high platelet MAO activity may have remained hidden in many investigations by the direct effect of smoking.

4.2.4. Function of the serotonin system and self-reported and performance measures of impulsivity (Paper IV)

4.2.4.1. Platelet MAO activity, 5-HTTLPR S allele and speed and accuracy of responding in VCT (Paper IV)

Lower MAO activity was related to higher error-rate in VCT, but was not related to the speed of information processing (**Table 1, Paper IV**). Platelet MAO activity was the highest in the group with slow/accurate style of responding in VCT, and the lowest in the slow/inaccurate subjects (**Fig 5.4**). The impulsivity score in VCT was also related to lower platelet MAO activity (**Table 1, Paper IV**). The higher performance impulsivity in subjects with low platelet MAO activity has been demonstrated earlier (af Klinteberg et al. 1990, Shekim et al. 1986).

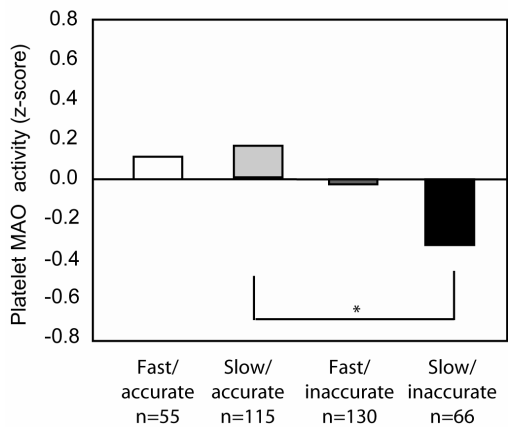

Figure 5.4 The platelet MAO activity in the groups demonstrating fast/accurate, slow/accurate, fast/inaccurate and slow/inaccurate response style in Visual Comparison Test. * — $p<0.05$ the Bonferroni-corrected *post-hoc* difference between the groups

The 5-HTTLPR S allele carriers made significantly more errors and had higher impulsivity score in VCT (**Table 1, Paper IV**), but S allele was not related to speed of information processing. When comparing the groups with different speed-accuracy trade-off strategies by their S allele prevalence, it appeared that the fast/inaccurate subjects had higher odds to have 5-HTTLPR S allele compared to slow/accurate subjects (**Table 5.6**).

Table 5.6 The odds ratios and appropriate 95% confidence intervals for carrying a 5-HTTLPR S allele in the four groups with high or low speed and accuracy in VCT in comparison with the group with slow/accurate responding style

	LL n (%)	SL/SS n (%)	OR (in comparison with slow/accurate)	95% CI
Slow/accurate (n=109)	52 (48%)	57 (52%)		
Fast/accurate (n=50)	23 (46%)	27 (54%)	1.01	0.95–1.06
Fast/inaccurate (n=123)	43 (35%)	80 (65%)	**1.04**	**1.00–1.08**
Slow/inaccurate (n=61)	28 (45%)	33 (55%)	1.01	0.96–1.06

It is not surprising that the S allele, which leads to lower expression of serotonin transporter and therefore less flexible serotonergic neurotransmission, is associated with more impulsive performance in a visual comparison task. There are several studies in which impulsive performance has been altered with serotonergic manipulations. Most reliably an increase in impulsivity with decreasing the serotonergic function has been found (Cherek & Lane 1999, Murphy et al. 2002, Walderhaug et al. 2002). Still, no effect of S allele on impulsive responding in a laboratory task of disinhibition (Clark et al. 2005) and Go/No-go task (Fallgatter et al. 1999) was found.

The S allele carriers have lower grey-matter volume in the amygdala-cingulate feedback system (Pezawas et al. 2005), an important area in affect regulation, which may lead to problems in impulse regulation. At least one study has shown lower serotonergic innervation in the anterior cingulate in impulsively aggressive subjects, by positron emission tomography (PET) (Frankle et al. 2005). Given the knowledge on the significant role of anterior cingulate in the processing and monitoring of errors in the commission of effortful tasks (Brazdil et al. 2005) and tasks with conflicting information which may result in errors (Botvinick et al. 1999), the changes in the activity of cingulate may explain the more error-prone and impulsive performance of S allele carriers, which is at least partly independent of general cognitive abilities.

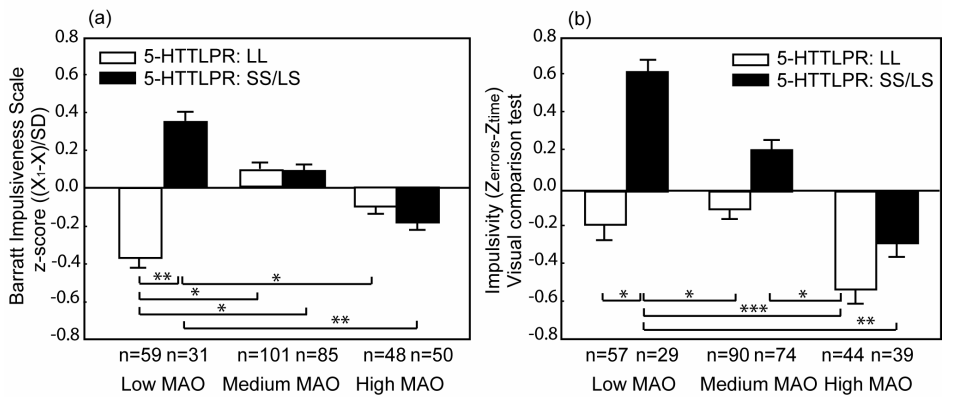

Fig 5.5 The effect of platelet MAO activity and 5-HTTLPR on self-reported impulsiveness (a) and the impulsivity score in Visual Comparison Test (b). * $p<0.05$, ** $p<0.01$, *** $p<.001$ — Fisher LSD post-hoc following significant multivariate analysis of variance including platelet MAO (low, medium, high according to higher and lower quartile values) and 5-HTTLPR (LL vs SL/SS) as grouping variables. Whiskers represent standard error of the mean values.

A significant interactive effect of the two serotonergic markers appeared in the prediction of self-reported impulsivity measured with BIS-11 (**Fig 5.5a in the thesis** or **Fig 1a, Paper IV**). The effect of low platelet MAO activity on impulsivity appeared only in the subgroup of S allele carriers. Similarly, the effect of platelet MAO activity on performance measure of impulsivity was present only in the subgroup of S allele carriers (**Fig 5.5b in the thesis** or **Fig 1b, Paper IV**). As the combined effect of S allele and low MAO were partly similar on performance impulsivity and BIS-11 whole score, and also the BIS-11 whole score was higher in subjects with high I-score (**Table 1, Paper IV**), these two different ways of measurement confirm the association of impulsivity with lower serotonergic function. There is a clear synergistic effect of a gene leading to less effective serotonergic function and a peripheral indicator of less effective serotonergic function on impulsive performance and cognitive type of impulsivity.

4.2.4.2. The role of cognitive abilities in the association between serotonergic function and impulsive performance (Paper IV)

If subjects with lower serotonergic activity respond more impulsively and make more errors in neuropsychological tests measuring disinhibition as well as cognitive abilities, it is not clear, whether the disturbances in serotonergic functioning are only related to disinhibition or also to decreased general cognitive abilities. As described earlier, drunk drivers with low MAO activity had also lower education, while high-risk drivers who had average MAO

activity had similar education-level to controls, and this did was not associated with risk admitting (**Table 1, Paper III**).

Thus the covariate effect of general cognitive abilities on the association between serotonergic markers and impulsive performance was examined in the adolescent sample. Subjects with S allele as well as subjects with low platelet MAO made significantly more errors (**Table 1, Paper IV**) and had significantly higher score of impulsivity in VCT (**Table 1** and **Fig 2b, Paper IV**). While subjects with low cognitive abilities had remarkably higher error-rate in VCT, they did not reply significantly faster (**Table 1, Paper IV**). When general cognitive abilities were controlled for, the effect of S allele carrying on error-rate as well as on impulsivity in VCT diminished, but remained significant. The effect of platelet MAO on the error-rate in VCT remained significant, but the effect of MAO on the impulsivity in VCT turned non-significant, when general cognitive abilities were controlled for.

Thus the effects of cognitive abilities and serotonergic measures on performance in VCT are at least partly independent of each other. Our result of the higher error-proneness independent of cognitive abilities in low MAO subjects is consistent with the small study of Shekim et al. (1984) showing a higher number of errors in a simple task in children with low platelet MAO activity, independent of general cognitive abilities.

When speed-accuracy tradeoff probably reflects impulsive information-processing, the results obtained on the speed and accuracy of information-processing separately may reflect other cognitive constructs. The accuracy separately from the speed of responding had only a tendency to be lower in impulsive adolescents divided by BIS-11 in our study (**Table 1, Paper IV**). Thus, the higher error-rate in subjects with low MAO activity or 5-HTTLPR S allele may reflect some other cognitive processes, for example their higher fatigue, as the experimental design included several measurements and lasted during the whole schoolday. This would be in line with our preliminary data suggesting that low platelet MAO is associated with higher fatigue after mental and physical effort (Paaver et al. 2006). Also a PET study has demonstrated lower serotonin transporter density in the anterior cingulate of the chronic fatigue patients (Yamamoto et al. 2004) which is similar to the 5-HTTLPR S allele carriers. Another study demonstrated the blunted responses to serotonergic combined with dopaminergic challenge were related to higher scores on asthenia- and fatigue-related items in the harm avoidance subscale of Cloninger Tridimensional Personality Questionnaire (Hennig et al. 2000).

Low platelet MAO activity and S allele were not associated with the speed of responding in VCT, and neither with fast/accurate style of responding. However, speed of responding and fast/accurate style of responding were associated with higher BIS-11 impulsivity (**Table 1, Paper IV and Fig 5.2b in the thesis**). Speed of information processing is a component of impulsive responding (Barratt 1993, Dickman 1993), but it is also significantly associated with

general intelligence (Vernon 1997). If fast/accurate style of responding reflects adaptive impulsivity (see 4.1.5.), it suggests that adaptive performance impulsivity has a different psychobiological background from the impulsivity that is related to fast and error-prone style. Low MAO and S allele in earlier studies have shown associations with mostly the maladaptive impulsive behavioural tendencies — impulsive aggression, substance abuse and suicidality (Haberstick et al. 2006, Lesch & Merchdorf 2000, Lesch 2005, Li & He 2007, Eklund et al. 2005, Longato-Stadler et al. 2002, Oreland 1985).

4.2.4.3 Platelet MAO activity, 5-HTTLPR and self-reported measures of impulsivity (Papers III, IV and V)

Despite the association of platelet MAO activity with observed risky behaviours like drunk driving (**Fig 1, Paper I and Fig 1, Paper II**), risk-admitting high-risk driving (**Fig 2, Paper III**), error-rate and I-score in VCT (**Table 1, Paper IV**), no simple correlation of platelet MAO with self-reported types of impulsivity occurred in these studies (**Papers II**, **III, and IV**). Our result does not confirm the earlier results demonstrating the negative correlation between self-reported impulsivity and MAO activity (Schalling et al 1988, Oreland 2004, Longato-Stadler et al. 2002, von Knorring et al. 1984). But the earlier studies used mostly maladaptive measures of impulsivity and many of them were conducted on or special populations like psychiatric patients or prison inmates or adults who are more prone to for smoking. However, the effect of platelet MAO on self-reported impulsivity measured by BIS-11 appeared, when it was analysed together with 5-HTT genotype. The clear association of lower MAO with BIS-11 impulsivity appeared in S allele carriers (**Fig 5.5a in the thesis or Fig 2a, Paper IV**).

The S allele carriers did not have significantly higher scores in self-reported impulsivity scale (BIS-11) (**Papers IV and V, text**), fast decision-making, excitement seeking, and thoughtlessness (**Paper V, text**) compared to subjects with LL genotype. The S allele carriers had higher disinhibition compared to LL homozygotes (**Paper V, text**). This association may be compared with a wide variety of earlier results supporting the association between the 5-HTTLPR S allele and anxiety (Lesch et al. 1996). Disinhibition scale in our studies is a measure of maladaptive impulsivity of affective origin and was originally a subscale of neuroticism in NEO personality inventory. Anxiety and neuroticism are in association with a weak affect regulation and impulsive behaviour, especially in adolescence (Brotman et al. 2006). The scale of disinhibition includes items about affect regulation, and it is well proved that S allele carriers are emotionally more reactive due to their higher amygdala responsiveness to threatening stimuli (Hariri et al. 2002).

The results of **Paper III** and **Paper IV** together lead to an assumption that behavioural and performance measures of impulsivity are more directly associated with the biological predispositions to react than self-reported measures.

Self-reported measures of impulsivity presuppose a certain ability to analyse and monitor one's behaviour, which may be impaired in impulsive subjects (Barratt et al. 2005). Also, as impulsivity is more often considered a maladaptive trait, self-reported impulsivity measures may be more vulnerable to the bias of socially desirable responding, thus their association with biological markers may be less explicit. It has also been found earlier that while some performance measures of impulsivity (e.g. commission errors in a vigilance task and delay errors in a delay task) were associated with higher platelet MAO activity in boys with disruptive behaviour disorders, the self-report scales of impulsivity indicated no associations with MAO activity (Stoff et al. 1989). While laboratory performance tests measure narrow cognitive tendencies to respond quickly and make mistakes, questionnaire measures contain a much wider meaning, including, e.g., social, situational, emotional and motivational dimensions.

4.2.5. Gene x environment interaction: does the effect of S allele in 5-HTTLPR on impulsivity depend on family relations? (Paper V)

A possible interaction of 5-HTTLPR S allele with environmental adversity on the self-reported types of impulsivity was explored in the sample of adolescents. As earlier studies have demonstrated gender-specific effects of environmental factors on S allele carriers (e.g. Sjöberg et al. 2005, Grabe et al. 2005, Barr et al. 2004), the analysis was performed separately in boys and girls. As interaction with caregivers is potentially an important environmental factor in the development of child's impulsivity (Olson et al. 1990, Straus & Mouradian 1998), family relations were analysed in interaction with the S allele in the promoter region of 5-HTT.

Low warmth in the families of the S allele carrying girls of 5-HTTLPR was associated with their higher thoughtlessness (**Fig 5.6 in the thesis** or **Fig 1, Paper V**), disinhibition and whole score of BIS-11 (**Table 1, Paper V**). This is in accordance with several earlier studies demonstrating the interaction of the S allele with environmental adversity on personality traits that are similar to impulsivity by their maladaptiveness and association with affect-regulation such as neuroticism (Sen 2004), and also on the risk for depression (Caspi et al. 2003, Taylor et al. 2006, Kaufman et al. 2006). There are no earlier studies on the influence of 5-HTTLPR S allele and family relations on the trait of impulsivity in a population-based sample of adolescents, but positive association of S allele with aggression (Haberstick et al. 2004), suicidality (Li & He 2007), higher response to alcohol (Hinckers et al. 2006), and higher alcohol consumption in case of „bad" family relations in adolescents (Nilsson et al. 2005) have been demonstrated. Also, impulsivity has been shown to be associated with depression (Corruble et al. 2003), especially in adolescents (d'Acremont & van der Linden 2007).

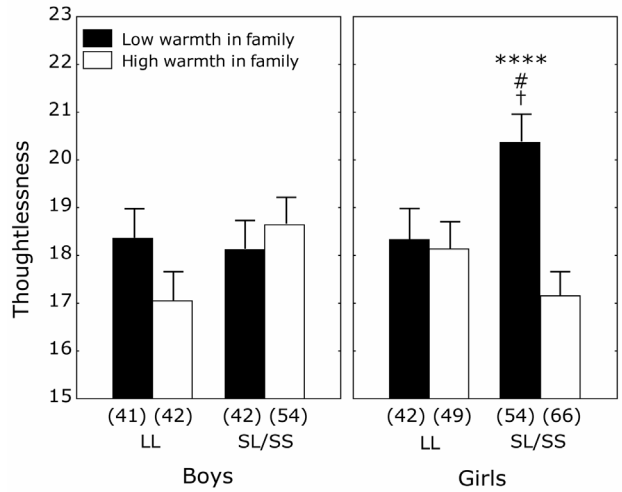

Fig 5.6 The significant interaction effect of 5-HTTLPR X warmth in family X sex on the score of thoughtlessness. Interaction of genotype X sex X warmth in family [$F(1, 382)= 8.2$, $p < 0.01$]. **** $p < 0.0001$ vs S allele+high warmth girls, # $p < 0.05$ vs LL+low warmth girls, † $p < 0.05$ vs LL+high warmth girls

While low warmth and maltreatment in family led to impulsiveness in the girls carrying the S allele, unlike in girls with LL genotype, maltreatment by parents was associated with higher impulsiveness in boys with both LL as well as SL/SS genotypes (**Table 1, Paper V**). Our results are in accordance with earlier studies demonstrating that 5-HTTLPR S allele x adverse environment interaction is stronger in female subjects, expressing in higher vulnerability to depression and lower agreeableness in S allele carrying women (Lesch & Merchdorf 2000, Sjöberg et al. 2005, Grabe et al. 2005, Eley et al. 2004). Also, the S allele in females is associated with higher stress-sensitivity, e.g., peer-reared female rhesus macaques with rh5-HTTLPR S allele have increased adrenocorticotropic hormone and lower cortisol responses to stress, which does not happen among males (Barr et al. 2004). On the contrary, many of the studies which do not consider the impact of stressful life events demonstrate the association between S allele and suicidality (Limosin et al. 2005) or neuroticism (Du et al. 2000) solely among males. One possible reason for the described difference between the sexes is that the effect and significance of serotonin transporter may be different in male and female brain and its development (Xu et al. 2001), possibly due to the effect of gonadal steroids on serotonin transporter (Attali et al. 1997). In the field of genetics of personality, several studies have shown that the path from gene to behaviour may be different in males and females (Kendler and Greenspan 2006).

The influence of 5-HTTLPR S-allele and adverse family relations on impulsivity is rather developmental than direct, as serotonin has an important role in brain development (Lesch & Gutknecht 2005). Familial adversity may have more impact on S-allele carriers, as several studies report higher sensitivity of their amygdala to negative emotional stimuli (Hariri et al. 2002), and lower neuronal density in their affect-regulating regions like cingulate and prefrontal cortex (Graff-Guerrero et al. 2005, Pezawas et al. 2005, Heinz et al. 2005). Prefrontal cortex and cingulate which are potentially important structures in impulse and emotion regulation and are more active in response to stimuli in 5-HTTLPR S allele carriers continue post-natal development through adolescence until adulthood (Nelson 2006).

The S allele of 5-HTTLPR in combination with adverse family environment predicted only maladaptive types of impulsiveness in girls (thoughtlessness and disinhibition), while the adaptive types of impulsivity (excitement seeking, fast decision-making) depended neither on family relations nor on genotype in girls (**Table 1, Paper V**). In boys, though, the adaptive types of impulsiveness like excitement seeking and fast decision-making were associated with positive relations in family. This may mean that girls are more vulnerable to dys-functions in case of adversity in family, while boys can take more advantage of positive parenting in the development of adaptive traits.

5. CONCLUSIVE REMARKS

Subjects who had been caught by the police driving drunk had lower platelet MAO activity and higher maladaptive types of impulsivity compared to controls and to subjects who had been caught with other driving violations. Exceeding speed-limits and other non-alcohol-related driving violations were related rather to adaptive types of impulsivity and to average platelet MAO activity. Furthermore, the subtypes of risky traffic-behaviour with and without associated risk-admitting had a different psychobiological background and profile of impulsivity: risk-admitting high-risk drivers had higher platelet MAO activity and the most deviant scores in all types of impulsivity measured, while risk-denying high-risk drivers had similar platelet MAO activity and higher fast decision-making compared to controls. These results add ecological validity to the division of impulsivity into different types. What is common about the measured impulsive traits is that they all lead to higher risk-taking, while these risky behaviours can be of a different kind, and be associated with different function of serotonin system. The results also suggest that low serotonergic activity characterizes especially these subtypes of impulsivity that lead to alcohol-related risky behaviour.

A genotype leading to weaker serotonergic neurotransmission (5-HTTLPR S allele) and a peripheral marker of low serotonergic activity (platelet MAO) were both associated with higher error-proneness and impulsive performance in a simple task of visual comparison. This association was at least partly independent of general cognitive abilities. Furthermore, these two markers of weaker function of central serotonin system had a synergistic effect on the performance impulsivity and self-reported cognitive impulsivity. This confirms the role of serotonin function in impulsive cognitive style in a population-based sample.

While low warmth and perceived maltreatment in family led to impulsiveness in 5-HTTLPR S allele carrying girls, unlike in girls with LL genotype, perceived maltreatment by parents was associated with higher impulsiveness in boys with both LL and SL/SS genotypes. This confirms that the association between serotonin function and impulsivity may have different routes in males and females, and that females may be especially vulnerable to the combination of lower potential of serotonin system and lack of warmth in the development of maladaptive impulsivity.

Unlike impulsive performance in visual comparison task and impulsive behaviour in traffic, the self-reported types of impulsivity in the studied general populations mostly did not have simple associations with the markers of serotonergic function. However, the association between impulsivity and serotonergic function appeared when impulsivity was measured through speed and accuracy of performance or real-life risky behaviour. In addition, the association between self-reported impulsivity and serotonergic function appeared when subjects' sex or environmental factors like adverse family relations were con-

sidered. This adds support to an assumption that behavioural and performance measures of impulsivity reflect more directly the biological predispositions to react, while self-reported measures of impulsivity have less direct or mediated associations with serotonergic function.

6. ACKNOWLEDGEMENTS

I am indebted to several people, who have more or less directly contributed to the completion of this dissertation. I am most grateful to my supervisor Professor Jaanus Harro for his personal devotion to all the projects I have had chance to work for, for inspiration as well as practical opportunities, and for being strict in the matter of dead-lines, while being flexible in the matter of ideas.

I want to thank all the personnel and fellow-students in the Department of Psychology for making the process of studying an interesting and positive experience and really a combination of fun and work. I sincerely thank my collegues from different institutions, which I have had opportunity to co-operate with, Maarike Harro, Lea Laht, Helle-Mai Loit from the National Institute for Health Development; Diva Eensoo, Liis Merenäkk and Ludmilla Jakobson from the Institute of Public Health; and Jüri Parik from Institute of Molecular and Cell Biology; and also my co-authors Lars Oreland and Niklas Nordquist from the Department of Neuroscience, Pharmacology in the University of Uppsala. I thank Triin Kurrikoff, Helina Voogne, Jarek Mäestu and Katrin Kaasik for their valuable help in the laboratory work and practical matters. I am indebted to my collegues Kenn Konstabel, Kirsti Akkermann, Maali Käbin and Professor Aleksander Pulver for the inspiration, and ideas and sharing my enthusiasm in the field of impulsivity.

I am grateful to the people and institutions who have given their financial and practical contribution into the study of car drivers — Toomas Ernits from the Estonian Road Administration, Boris Põldre from Estonian Motor Vehicle Registration Centre and Vallo Pensa from the Police Board.

I feel gratitude for all of the people, who took their time to participate in our study out of pure enthusiasm and wish to be useful.

And finally, I owe my thanks to my family — my mother and father for encouragement and letting me decide things on my own throughout my life, my grandmother for helping me to value and prioritize my work, and my grandfather for injecting me with passion for science from the very early age. I am happy to have had friends beside me, and I specially thank Taimar for understanding and support — without them writing this dissertation would have been far more difficult.

7. REFERENCES

Ainslie, G. (1975) Specious reward: a behavioural theory of impulsiveness and impulse control. Psychological Bulletin 82, 463–495.

Alm, P.O., Klinteberg, B., Humble, K., Leppert. J., Sörensen, S.M., Thorell, L.H., Lidberg, L., & Oreland, L. (1996) Psychopathy, platelet MAO activity and criminality among former juvenile delinquents. Acta Psychiatrica Scandinavica 94, 105–111.

Amador-Campus J, Kirchner-Nebot T (2001) Childrens embedded figures test and Matching Familiar Figures Test-20: factorial structure for boys and girls from 6 to 11 years old. Perceptual and Motor Skills 93, 709–712.

Anderson, I.M., Richell, R.A., & Bradshaw, C.M. (2003) The effect of acute tryptophan depletion on probabilistic choice. Journal of Psychopharmacology 17, 3–7.

Anthenelli, R.M., Tipp, J., & Li, T.-K. (1998) Platelet monoamine oxidase (MAO) activity in subgroups of alcoholics and controls: results from the COGA study. Alcoholism: Clinical and Experimental Research 22, 598–604.

Askénazy, F.L., Sorci, K., Benoit, M., Lestideau, K., Myquel, M., & Lecrubier, Y. (2003) Anxiety and impulsivity levels identify relevant subtypes in adolescents with at-risk behavior. Journal of Affective Disorders 74, 219–228.

Attali, G., Weizman, A., Gil-Ad, I., & Rehavi, M. (1997) Opposite modulatory effects of ovarian hormones on rat brain dopamine and serotonin transporters, Brain Research 756, 153–159.

Barr, C. S., Newman, T. K., Schwandt, M., Shannon, C., Dvoskin, R.L., Lindell, S. G., Taubman, J., Thompson, B., Champoux, M., Lesch, K.P., Goldman, D., Suomi, S. J., & Higley J. D. (2004) Sexual dichotomy of an interaction between early adversity and the serotonin transporter gene promoter variant in rhesus macaques, Proceedings of National Academy of Sciences USA 33, 12358–12363.

Barratt, E.S., Lijffijt, M., & Moeller, E.G. (2005) When does impulsivity become pathologic? Psychiatric Times 22, 8.

Barratt, E.S. (1993) Impulsivity: integrating cognitive, behavioral, biological and environmental data. In: McCown, W.B., Johnson, J.L., & Shure, M.B. (eds) The impulsive client: theory, research and treatment. Washington D.C., American Psychological Association, pp 39–56.

Barratt, E.S., & Slaughter, M.D. (1998) Defining, measuring and predicting impulsive aggression: a heuristic model. Behavioral Sciences and the Law 16, 285–302.

Bazargan-Hejazi, S., Gaines, T., Duan, N., & Cherpitel, C.J. (2007) Correlates of injury among ed visits: effects of alcohol, risk-perception, impulsivity, and sensation seeking behaviors The American Journal of Drug and Alcohol Abuse 33, 101–108.

Begg, D. J., Langley, J. D., & Stephenson, S. (2003) Identifying factors that predict persistent driving after drinking, and driving after using cannabis among young adults. Accident Analysis and Prevention 35, 669–675.

Bennett, A.J., Lesch, K.P., Heils, A., Long, J.C., Lorenz, J.G., Shoaf, S.E., Champoux, M., Suomi, S.J., Linnoila, M.V., & Higley, J.D. (2002) Early experience and serotonin transporter gene variation interact to influence primate CNS function, Molecular Psychiatry 7, 118–122.

Bernfeld, G.A., & Peters, R.V. (1986) Social reasoning and social behaviour reflective and impulsive children. Journal of Clinical and Child Psychology 15, 221–227.

Botvinick, M., Nystrom, L.E., Fissell, K., Carter, C.S., & Cohen, J.D. (1999) Conflict monitoring versus selection-for-action in anterior cingulate cortex. Nature 402, 179–181.

Brannigan, G.G., Ass, T., & Margolis, H. (1980) Impulsivity-relfectivity and children's intellectual performances. Journal of Personality Assessment 44, 41–43.

Brázdil, M., Roman R., Daniel, P., & Rektor, I. (2005) Intracerebral error-related negativity in a simple Go/No-go task. Journal of Psychophysiology 19, 244–255.

Brotman, M.A., Schmajuk, M., Rich, B.A., Dickstein, D.P., Guyer, A.E., Costello, E.J., Egger, H.L., Angold, A., Pine, D.S., & Leibenluft, E. (2006) Prevalence, clinical correlates, and longitudinal course of severe mood dysregulation in children. Biological Psychiatry 60, 991–997.

Brown, G.I., Ebert, M., Goyer, P.F., Jimerson, D.C., Klwin, W.J., Bunney, W.E., & Goodwin, F.K. (1982) Aggression, suicide, and serotonin: relationships to CSF amine metabolites. American Journal of Psychiatry 139, 741–746.

Brunas-Wagstaff, J., Bergquist, A., Morgan, K., & Wagstaff, G.F. (1996) Impulsivity, interference on perceptual tasks and hypothesis testing. Personality and Individual Differences 20, 471–482.

Brunas-Wagstaff, J., Bergquist, A., & Richardson, P., (1995) The relationships between functional and dysfunctional impulsivity and the Eysenck personality questionnaire. Personality and Individual Differences 18, 681–683.

Brunas-Wagstaff, J., Bergquist, A., & Wagstaff, G.F. (1994) Cognitive correlates of functional and dysfunctional impulsivity. Personality and Individual Differences 17, 289–292.

Buchsbaum, M.S., Coursey, R.D., & Murphy, D.L. (1976) The biochemical high-risk paradigm: behavioural and familial correlates of low platelet monoamine oxidase activity. Science 194, 513–341.

Bütz, M., & Austin, S. (1993) Management of the adult impulsive client: identification, timing and methods of treatment In: McCown WB, Johnson JL, Shure MB (eds) The impulsive client: theory, research and treatment. American Psychological Association, Washington DC, pp 323–345

Carlson, E.A., Jacobvitz, D., & Sroufe, L.A. (1995) A developmental investigation of inattentiveness and hyperactivity. Child Development 66, 37–54.

Caspi, A., Sugden, K., Moffitt, T.E., Taylor, A., Craig, I.W., Harrington, H., McClay, J., Mill, J., Martin, J., Braithwaite, A., & Poulton, R. (2003) Influence of life stress on depression: moderation by a polymorphism in the 5-HTT. Science 301, 386–389.

Caspi, A., Begg, D., Dickson, N., Harrington, H., Langley, J., Moffitt, T.E., & Silva, P.A. (1997) Personality differences predict health-risk behaviors in adulthood: evidence from a longitudinal study. Journal of Personality and Social Psychology 5, 1052–106.

Chamberlain, S.R., & Sahakian, B.J. (2007) The neuropsychiatry of impulsivity. Current Opinion in Psychiatry 20, 255–261.

Chen, K., & Shih, J.C. (1988) Monoamine oxidase A and B: Structure, function and behaviour. Advances in Pharmacology 42, 292–296.

Cherek, D.R., & Lane, S.D. (1999) Effects of d,l-fenfluramine on aggressive and impulsive responding in adult males with a history of conduct disorder. Psychopharmacology 146, 473–481.

Claes, L., Katholieke, U., Vertommen, H. & Braspenning, N. (2000) Psychometric properties of the Dickman Impulsivity Inventory. Personality and Individual Differences, 29, 27–35.
Clark, L., Robbins, T.W., Erche, K.D., & Sahakian, B.J. (2006) Reflection impulsivity in current and former substance users. Biological Psychiatry 60, 512–522.
Clark, L., Roiser, J.P., Cools, R., Rubinsztein, D.C., Sahakian, B.J., & Robbins, T.W. (2005) Stop-signal response inhibition is not modulated by tryptophan depletion or the serotonin transporter polymorphism in healthy volunteers: implications for the 5-HT theory of impulsivity. Psychopharmacology 182, 570–578.
Cloninger, C. R. (1996) Monoamines, personality, and early-onset alcoholism. Biological Psychiatry 39, 560–561.
Coccaro, E.F., Silverman, J.M., Klar, H.M., Horvath, T.B., & Siever, L.J. (1994) Familial correlates of reduced central serotonergic system function in patients with personality disorders. Archives Of General Psychiatry 51, 318–24.
Coccini, T., Randine, G., Gastoldi, A.F., Balloni, L., Baiardi, P., & Manzo, L. (2005) Lymphocyte muscarininc receptros and platelet monoamine oxidase-B as biomarkers of CNS function: effects of age and gender in healthy humans. Environmental Toxicology and Pharmacology 19, 715–720.
Corr, P.J. (2006) Understanding Biological Psychology. Oxford, UK: Blackwell Publishing Ltd., pp 537–538.
Corruble, E., Benyamina, A., Bayle, F., Falissard, B., & Hardy, P. (2003) Understanding impulsivity in severe depression? A psychometrical contribution. Progress in Neuro-Psychopharmacology and Biological Psychiatry 27, 829–833.
Costa, P.T. Jr, & McCrae, R.R. (1989) The NEO-PI/NEO-FFI manual supplement. Psychological Assessment Resources, Odessa, FL
d'Acremont, M., & Van der Linden, M. (2007) How is impulsivity related to depression in adolescence? Evidence from a French validation of the cognitive emotion regulation questionnaire. Journal of Adolescence 30, 271–282.
Da Prada, M., Cesura, A.M., Launay, J.M., Richards, J.G. (1988) Platelets as a model for neurones? Experientia 44, 115–126.
Dahlen, E.R., Martin, R.C., Ragan, K., & Kuhlman, M.M. (2005) Driving anger, sensation seeking, impulsiveness, and boredom proneness in the prediction of unsafe driving. Accident Analysis and Prevention 37, 341–348
Davidson, J.R.T., McLeod, M.N., Turnbull, C.D., White, H.L., & Feuer, E.J. (1980) Platelet monoamine oxidase activity and the classification of depression. Archives of General Psychiatry 37, 771–773.
Deffenbacher, J.L., Lynch, R.S., Filetti, L.B., Dahlen, E.R., & Oetting, E.R. (2003) Anger, aggression, risky behavior, and crash-related outcomes in three groups of drivers. Behavior Research and Therapy 41, 333–349.
Depue R. A. (1995) Neurobiological factors in personality and depression. European Journal of Personality 9, 413–439.
Dickman, S.J. (1993) Impulsivity and information processing. In: McCown, W.B., Johnson, J.L., & Shure, M.B. (eds) The impulsive client: theory, research and treatment. Washington, D.C., American Psychological Association, pp 151–184.
Dickman, S.J., & Meyer, D.E. (1988) Impulsivity and speed-accuracy tradeoffs in information processing. Journal of Personality and Social Psychology 54, 274–290.

Dickman, S.J. (1985) Impulsivity and perception: individual differences in the processing of the local and global dimensions of stimuli. Journal of Personality and Social Psychology 48, 133–149.

Dickman SJ (1990) Functional and dysfunctional impulsivity: personality and cognitive correlates. Journal of Personality and Social Psychology 58, 95–102.

Dom, G., Wilde, B.D., Hulstijn, W., Sabbe, B. (2007) Dimensions of impulsive behaviour in abstinent alcoholics. Personality and Individual Differences 42, 465–476.

Donohew, L., Zimmerman, R. & Cupp, P. S. Novak, S., Colon, S. & Abell, R (2000) Sensation Seeking, impulsive decision-making and risky sex: implications for risk-taking and design of interventions. Personality and Individual Differences 28, 1079–1091.

Donovan, D. M., Queisser, H. R., Salzberg, P. M. & Umlauf, R. L. (1985) Intoxicated and bad drivers: subgroups within the same population of high-risk men drivers. Journal of Studies on Alcohol 46, 375–382.

Du, L., Bakish, D., & Hrdina, P. (2000) Gender differences in association between serotonin transporter gene polymorphism and personality traits. Psychiatric Genetics 10, 159–164.

Ebstein, R.P. (2006) The molecular genetic architecture of human personality: beyond self-report questionnaires. Molecular Psychiatry 11, 427–445.

Eklund, J., Alm, P.O., af Klinteberg, B. (2005) Monoamine oxidase activity and triiodothyronine level in violent offenders with early behavioural problems. Neuropsychobiology 52, 122–129.

Eley, T.C., Sugden, K., Corsico, A., Gregory, A.M., Sham, P., McGuffin, P., Plomin R., & Craig, I.W. (2004) Gene-environment interaction analysis of serotonin system markers with adolescent depression, Molecular Psychiatry 9, 908–915.

Evenden, J.L. (1999) Varieties of impulsivity. Psychopharmacology 146, 348–361.

Eysenck H.J. (1993) The nature of impulsivity In: McCown, W.B., Johnson, J.L., Shure, M.B. (eds) The impulsive client: theory, research and treatment. Washington D.C., American Psychological Association, pp 57–69.

Eysenck, S.G.B. (1993) The I_7: development of a measure of impulsivity and its relationship to the superfactors of personality. In: McCown, W.B., Johnson, J.L., Shure, M.B. (eds) The impulsive client: theory, research and treatment. Washington D.C., American Psychological Association, pp 141–149

Fahlke, C., Garpenstrand, H.,Oreland, L.,Suomi, S.J., & Higley, J.D. (2002) Platelet monoamine oxidase activity in a non-human primate model of type 2 excessive alcohol consumption. American Journal of Psychiatry 159, 2107–2109.

Fairbanks, L.A. Melega, W.P., Jorgensen, M.J., Kaplan, J.R. & McGuire, M.T. (2001) Social impulsivity inversely associated with CSF 5-HIAA and fluoxetine exposure in vervet monkeys. Neuropsychopharmacology 24, 370–378.

Fallgatter, A.J., Jatzke, S., Bartsch, A.J., Hamelbeck, B., & Lesch, K.P. (1999) Serotonin transporter promoter polymorphism influences topography of inhibitory motor control. International Journal of Neuropsychopharmacology 2, 115–120.

Fillmore, M.T. (2003) Drug abuse as a problem of impaired control: current approaches and findings. Behavioral and Cognitive Neuroscience Reviews 2, 179–197.

Fink, A.D. & McGown, W.G. (1993) Impulsivity in children and adolescents: measurement, causes and treatment. In: McCown, W.B., Johnson, J.L., Shure, M.B., (eds) The impulsive client: theory, research and treatment. Washington D.C. American Psychological Association, pp 279–308

Finn, P.R., Justus, A., Mazas, C., Steinmetz, J.E. (1999) Working memory, executive processes and the effects of alcohol on Go/No-go learning: testing a model of behavioral regulation and impulsivity. Psychopharmacology 146, 465–472.

Flory, J.D., Harvey, P.D., Mitropoulou, V., New., A.S., Silverman, J.M., Siever, L.J., & Manuck, S.B. (2006) Dispositional impulsivity in normal and abnormal samples. Journal of Psychiatric Research 40, 438–447.

Fowler, J.S., Logan, J., Wang, G.-J., Volkow, N.D., Telang, F., Zhu, W., Francheschi, D., Pappas, N., Ferrieri, R., Shea, C., Garza, V., Xu, Y., Schlyer, D., Gatley, S. J., Ding, Y.-S., Alexoff, D., Warner, D., Netusil, N., & Carter, P. (2003) Low monoamine oxidase B in peripheral organs in smokers. Proceedings of the National Academy of Sciences of the United States of America 100, 11600–11605.

Frankle, W.G., Lombardo, I., New, A.S., Goodman, M., Talbot, P.S., Huang, Y.H., Hwang, D.R., Slifstein, M., Curry, S., Abi-Dargham, A., Laruelle, M., & Siever, L.J. (2005) Brain serotonin transporter distribution in subjects with impulsive aggressivity: a positron emission study with [^{11}c]mcn 5652. American Journal of Psychiatry 5, 915–923.

Gabany, S.G., Plummer, P., & Grigg, P. (1997) Why drivers speed: the speeding perception inventory. Journal of Safety Research 28, 29–36.

Gabel, S., Stadler, J., Bjorn, J., Shindledecker, R. & Bowden, C. L. (1994) Monoamine oxidase and homovanillic acid in boys with predispositions to substance abuse. Alcoholism: Clinical & Experimental Research 18, 1137–42.

Gerra, G., Garofano, L., Santoro, G., Bosari, S., Pellegrini, C., Zaimovic, A., Moi, G., Bussandri, M., Moi, A., Brambilla, F., & Donnini, C. (2004) Association between low-activity serotonin transporter genotype and heroin dependence: behavioral and personality correlates. American Journal of Medical Genetics 126B, 37–42.

Gerrard, M., Gibbons, F.X., Stock, M.L., Houlihan, A.E., & Dykstra, J.L. (2006) Temperament, self-regulation, and the prototype/willingness model of adolescent health risk behaviour. In: Self-regulation in health behaviour, de Ridder, D., de Wit. J. (eds) West Sussex, England, John Wiley and Sons, Ltd, pp 97–119.

Gibbons, F.X., Gerrard, M., Reimer, R.A., & Pomery, E.A. (2006) Unintentional behaviour: a subrational approach to health risk In: Self-regulation in health behaviour, de Ridder, D., de Wit. J. (eds) West Sussex, England, John Wiley and Sons, Ltd, pp 45–71.

Golias, I., & Karlaftis, M.G. (2002) An international comparative study of self-reported driver behavior. Transportation Research Part F: Traffic Psychology and Behavior 4, 243–256.

Grabe, H.J., Lange, M., Wolff, B., Völzke, H., Lucht, M., Freyberger, H.J., John, U., & Cascorbi, I. (2005) Mental and physical distress is modulated by a polymorphism in the 5-HT transporter gene interacting with social stressors and chronic disease burden. Molecular Psychiatry 10, 220–224.

Graff-Guerrero, A., De la Fuente-Sandoval, C., Camarena, B., Gómez-Martin, D., Apiquián, R., Fresán, A., Aguilar, A., Méndez-Núñez, J.C., Escalona-Huerta, C., Drucker-Colín, R., & Nicolini, H. (2005) Frontal and limbic metabolic differences in subjects selected according to genetic variation of the SLC6A4 gene polymorphism, NeuroImage 25, 1197–1204.

Haberstick, B.C., Smolen, A., & Hewitt, J.K. (2006) Family-based association test of the 5HTTLPR and aggressive behavior in a general population sample of children, Biological Psychiatry 59, 836–843.

Hallikainen, T., Saito, T., Lachman, H.M., Volavka, J., Pojhanen, T., Ryynänen, O.P., Kauhanen, J., Syvalahti, E., Hietala, J., & Tiihonen, J. (1999) Association between low activity serotonin transporter promoter genotype and early onset alcoholism with habitual impulsive violent behavior. Molecular Psychiatry 4, 385–388.

Hallman J.,Oreland, L., Edman, G., & Schalling, D. (1987) Thrombocyte monoamine oxidase activity and personality traits in women with severe premenstrual syndrome. Acta Psychiatrica Scandinavica 76, 225–234.

Hariri, A.R., Mattay, V.S., Tessitore, A., Kolachana, B., Fera, F., Goldman, D., Egan, M.F., & Weinberger, D.R. (2002) Serotonin transporter genetic variation and the response of the human amygdala. Science 297, 400–404.

Harre, N. (2000) Risk evaluation, driving, and adolescents: a typology Developmental Review 20, 206–226.

Harro J., Fischer, K., Vansteelandt, S., & Harro, M. (2004) Both low and high activity of platelet monoamine oxidase increase the probability of becoming a smoker. European Neuropsychopharmacology 14, 65–69.

Harro, M., Eensoo, D., Kiive, E., Merenäkk, L., Alep, J., Oreland, L., & Harro, J. (2001) Platelet monoamine oxidase in healthy 9- and 15-year old children: the effect of gender, smoking and puberty. Progress in Neuro-psychopharmacology and Biological Psychiatry 25, 1497–1511.

Hatakka, M. (1998) Novice drivers' risk- and self-evaluations. Turku, Finland, Department of Psychology, University of Turku, Painosala Oy.

Heino, A., van der Molen, H.H., & Wilde, G. J.S. (1996). Risk perception, risk taking, accident involvement and the need for stimulation. Safety Science 22, 35–48.

Heinz, A., Higley, J.D., Gorey, J.G., Saunders, R., Jones, D.W., Hommer, D., et al. (1998) In vivo association between alcohol intoxication, aggression and serotonin transporter availability in non-human primates. Am J Psychiatry 155, 1023–1028.

Heinz, A., Braus, D.F., Smolka, M.N., Wrase, J., Puls, I., Hermann, D., Klein, S., Grüsser, S.M., Flor, H., Schumann, G., Mann, K., Büchel, C. (2005) Amygdala-prefrontal coupling depends on a genetic variation of the serotonin transporter. Nature Neuroscience 8, 20–21.

Helmers, K.F., Young, S.N., & Pihl, R.O. (1995) Assessment of measures of impulsivity in healthy male volunteers. Personality and Individual Differences 19, 927–935.

Hennig, J., Toll, C., Schonlau, P., Rohrmann, S., & Netter, P. (2000) Endocrine responses after d-fenfluramine and ipsapirone challenge: further support for Cloninger's tridimensional model of personality. Neuropsychobiology 41, 38–47.

Hinckers, A. S., Laucht, M., Schmidt, M.H., Mann, K.F., Schumann, G., Schuckit, M.A., & Heinz, A. (2006) Low level of response to alcohol is associated with serotonin transporter genotype and high alcohol intake in adolescents, Biological Psychiatry 60, 282–287.

Hoyle, R. H. (2000) Personality Processes and Problem Behaviour. Journal of Personality 68, 954–966.

Irving, J.B., Coursey, R.D., Buchsbaum, M.S., & Murphy, D.L. (1989) Platelet monoamine oxidase activity and life stress as predictors of psychopathology and coping in a community sample. Psychological Medicine 19, 79–90.

Johnson, W.L., Malow, R.M., Corrigan, S.A., & West, J.A. (1993) Impulsive behaviour and substance abuse In: McCown, W.B., Johnson, J.L., Shure, M.B. (eds) The impulsive client: theory, research and treatment. Washington D.C., American Psychological Association, pp 225–246.

Jonah, B. A. (1997) Sensation seeking and risky driving: a review and synthesis of the literature. Accident Analysis end Prevention 29, 651–665.

Kagan, J., Rosman, B., Day, D., Albert, J., & Phillips, W. (1964) Information processing in the child: Significance of analytic and reflective attitudes. Psychological Monographs, 78 (1, Whole No. 578)

Kas, M.J.H., Fernandes, C., Schalkwyk, L.C., & Collier, D.A. (2007) Genetics of behavioural domains across the neuropsychiatric spectrum; of mice and men. Molecular Psychiatry 12, 324–330.

Kaufman, J., Yang, B.Z., D-Palumberi, H. Grasso, D. Lipschitz, D. Houshyar, S. Krystal, J.H., Gelernter, J. (2006) Brain-derived neurotrophic factor-5-HTTLPR gene interactions and environmental modifers of depression in children, Biological Psychiatry 59, 673–680.

Kendler, K.S., & Greenspan, R.J. (2006) The nature of genetic influences on behavior: lessons from "simpler" organisms American Journal of Psychiatry 163, 1683–1694.

Kindlon, D., Mezzacappa, E., & Earls, F. (1995) Psychometric properties of impulsivity measures: temporal stability, validity and factor structure. Child Psychology and Psychiatry 6,645–61.

Kirk, K.M., Whitfield, J.B., Pang, D., Heath, A.C., & Martin, N.G. (2001) Genetic covariation of neuroticism with monoamine oxidase activity and smoking. American Journal of Medical Genetics 105, 700–706.

af Klinteberg, B., Levander, S.E., Oreland, L., Asberg, M., Schalling, D. (1987) Neuropsychological correlates of platelet monoamine oxidase (MAO) activity in female and male subjects. Biological Psychology 24,237–252.

af Klinteberg, B., Oreland, L., Hallman, J., Wirsen, A., Levander, S.E., & Schalling, D. (1990) Exploring the connections between platelet monoamine oxidase activity and behaviour: relationships with performance in neuropsychological tasks. Neuropsychobiology 23, 188–196

af Klinteberg, B., Hallman, J., Oreland, L., Wirsen, A., Löevander, S.E., & Schalling, D. (1992) Exploring the connections between platelet monoamine oxidase activity and behavior II: Impulsive personality without neuropsychological signs of disinhibition in air force pilot recruits. Neuropsychobiology, 26, 136–145.

von Knorring, L., & Oreland, L. (1996) Platelet MAO activity in type1/type2 alcoholics. Alcoholism: Clinical and Experimental Research 20, 224–230.

von Knorring, L., Oreland, L., & Winblad, B. (1984) Personality traits related to monoamine oxidase activity in platelets. Psychiatry Research 12, 11–26.

Lawton, R., Parker, D., Stradling, S.G., & Manstead, A.S.R. (1998) Self-reported attitude towards speeding and its possible consequences in five different road contexts. Journal of Community Applied Social Psychology 7, 153–165.

LeMarquand, D., Pihl, R. O., & Benkelfat, C. (1994) Serotonin and alcohol intake, abuse, and dependence: Clinical evidence. Biological Psychiatry 36, 326–337.

Lesch, K.P., Bengel, D., Heils, A., Sabol, S.Z., Greenberg, B.D., Petri, S., Benjamin, J., Müller, C.R., Hamer, D.H., & Murphy, D.L. (1996) Association of anxiety-related

traits with a polymorphism in the serotonin transporter gene regulatory region. Science 274, 1527–1531.
Lesch, K.P., & Gutknecht, L. (2005) Pharmacogenetics of the serotonin transporter. Progress in Neuropsychopharmacology and Biological Psychiatry 29, 1062–1073.
Lesch, K.P. (2005) Alcohol dependence and gene x environment interaction in emotion regulation: is serotonin the link? European Journal of Pharmacology 526, 113–124.
Lesch, K. P. & Merschdorf, U. (2000) Impulsivity, aggression, and serotonin: a molecular psychobiological perspective. Behavioral Sciences and the Law 18, 581–604.
Li, D. & He, L. (2007) Meta-analysis supports association between serotonin Transporter (5-HTT) and suicidal behavior. Molecular Psychiatry 12, 47–54.
Limosin, F., Loze, J.-Y., Boni, C., Hamon, M., Ades, J., Rouillon, F., & Gorwood, P. (2005) Male-specific association between the 5-HTTLPR S allele and suicide attempts in alcohol-dependent subjects. Journal of Psychiatry Research 39, 179–182.
Linnoila M. (1983) Low cerebrospinal fluid 5-hydroxyindoleacetic acid concentration differentiates impulsive from non-impulsive violent behavior. Life Sciences 33, 2609–2614.
Longato-Stadler, E., af Klinteberg, B., Garpenstrand, H., Oreland, L., Hallman, J. (2002) Personality traits and platelet monoamine oxidase activity in a Swedish male criminal population. Neuropsychobiology 46, 202–208.
Lopez-Ibor, J.J., Saiz-Ruiz, J., & Perez de Los Cobos, J.C. (1985) Biological correlates of suicide and aggresivity in major depressions with melancholia: 5-hydroxyindoleacetic acid and corticol in cerebral spinal fluid, dexamethasone suppression test and therapeutic response to 5-hydroxytyryptophan. Neuropsychobiology 14, 67–74.
Lynn, J., Allik, J., Pullmann, H., & Laidra, K. (2002) A study of intelligence in Estonia. Psychological Reports 91, 1022–1026.
Manuck, S.B., Flory, J.D., Ferrell, R.E., & Muldoon, M.F. (2004) Socio-economic status covaries with central nervous system serotonergic responsivity as a function of allelic variation in the serotonin transporter gene-linked polymorphic region. Psychoneuroendocrinology 29, 651–668.
Manuck, S.B. (2005) Brain serotonin and aggressive disposition in humans and non-human primates In: Nelson RJ (ed) Biology of aggression. Cary, NC, USA: Oxford University Press, pp 79–84.
Masoliver**,** E., Menoyo, A., & Pérez, V. (2006) Serotonin transporter linked promoter (polymorphism) in the serotonin transporter gene may be associated with antidepressant-induced mania in bipolar disorder, Psychiatric Genetics, 16 25–29.
McGue, M., & Bouchard, J.B. (1998) Genetic and environmental influences on human behavioural differences. Annual Review of Neuroscience 21, 1–24.
McMillen, D. L., Pang, M. G., Wells-Parker, E. & Anderson, B. J. (1991) Behavior and personality traits among DUI arrestees, nonarrested impaired drivers, and non-impaired drivers. International Journal of the Addictions, 26, 227–235.
McMillen, D. L., Adams, M. S., Wells-Parker, E., Pang, M. G. & Anderson, B. J. (1992) Personality traits and behaviors of alcohol-impaired drivers: a comparison of first and multiple offenders. Addictive Behaviors 17, 407–414.
Milich, R., & Kramer, J. (1984) Reflections on impulsivity: An empirical investigation of impulsivity as a construct. Advances in Learning and Behavioral Disabilities 3, 57–94.

Miller, E., Joseph, S., Tudway, J. (2004) Assessing the component structure of four self-report measures of impulsivity. Personality and Individual Differences 37, 349–358.
Mischel, W., Shoda, Y., & Rodriguez, M. L. (1989) Delay of gratification inchildren. Science 244, 933–938.
Morgan, M.J. (1998) Recreational use of „ecstasy" (MDMA) is associated with elevated impulsivity. Neuropsychopharmacology 19, 252–264.
Moeller, F. G., Barratt, E. S., Doughety, D. M., Schmitz, J. M. & Swann, A. C. (2001) Psychiatric aspects of impulsivity. American Journal of Psychiatry 158, 1783–1793.
Munafo, M.R., Clark, T.G., Moore, L.R., Payne, E., Walton, R. & Flint, J. Genetic polymorphisms and personality in healthy adults: a systematic review and meta-analysis Molecular Psychiatry (2003) 8, 471–484
Murphy, F.C., Smith, K.A., Cowen, P.J., Robbins, T.W., & Sahakian, B.J. (2002) The effects of tryptophan depletion on cognitive and affective processing in healthy volunteers. Psychopharmacology 163, 42–53.
Nelson, C. A. (2006) Neurobehavioral development in the context of biocultural co-constructivism. In: Lifespan development and the brain: the perspective of biocultural co-constructivism, Baltes, P.B., Reuter-Lorenz, P.A., & Rösler, F. (eds) Cambridge University Press, USA, NY, pp 61–81.
Netter, P., Hennig, J. Roed, I. S. (1996) Serotonin and dopamine as mediators of sensation seeking behavior. Neuropsychobiology 34, 155–165.
Nietfeld, J. & Bosma, A. (2003) Examining the self-regulation of impulsive and respective response styles on academic tasks. Journal of Research in Personality 32, 118–140.
Nilsson, K.W., Sjöberg, R.L., & Damberg, M. (2005) Role of the serotonin transporter gene and family function in adolescent alcohol consumption. Alcoholism: Clinical and Experimental Research 29, 564–570.
Norman, T. R., Chamberlain, C. J. & French, M. A. (1987). Platelet monoamine oxidase: low activity in cigarette smokers. Psychiatry Research 20, 199–205.
O´Keefe, E.J. (1975) Porteus Maze Q score as a measure of impulsivity. Perceptual and Motor Skills 41, 675–678.
Olson, S.L. (1989) Assessment of impulsivity in preschoolers: cross-measure convergences, longitudinal stability, and relevance to social competence. Journal of Clinical Child Psychology 18, 176–183
Olson, S.L., Schilling, E.M., Bates, J.E. (1999) Measurement of impulsivity: construct coherence, longitudinal stability, and relationship with externalizing problems in middle childhood and adolescence. Journal of Abnormal Child Psychology 27, 151–165.
Olson, S.L., Bates, J.E., & Bayles, K., (1990) Early antecedents of childhood impulsivity: The role of parent-child interaction, cognitive competence, and temperament, Journal of Abnormal Child Psychology 18, 317–334.
Oreland, L. (2004) Platelet monoamine oxidase, personality and alcoholism: the rise, fall and resurrection. Neurotoxicology 25, 79–89.
Oreland, L., Damberg, M., Hallman, J., Garpenstrand, H. (2002) Smoking only explains part of the associations between platelet monoamine oxidase activity and personality. Journal of Neural Transmission 109, 963–975.
Oreland, L., Wiberg, Å., Åsberg, M., Träskman, L., Sjöstrand, L., Thorén, P., Bertilsson, L., & Tybring, G. (1981) Platelet MAO activity and monoamine metabolites in

cerebrospinal fluid in depressed and suicidal patients and in healthy controls. Psychiatry Research 4, 21–29.
Oxenstierna, G., Edman, G., Iselius, L., Oreland, L., Ross, S., & Sedwall, G. (1986) Concentrations of monoamine metabolites in the CNS of twins and unrelated subjects: a genetic study. Journal of Psychiatric Research 20, 19–29.
Owsley C, McGwin G., & McNeal, S.F. (2003) Impact of impulsiveness, venturesomeness, and empathy on driving by older adults. Journal of Safety Research 34, 353–359.
Paaver, M., Kreegipuu, K., Tamm, M., Harro, M., & Harro, J. (2006) Platelet MAO activity is associated with vulnerability to fatigue and accuracy and speed of information processing in the tasks of visual cognition. International Journal of Neuropsychopharmacology 9, S200.
Patton, J.H., Stanford, M.S., Barratt, E.S. (1995) Factor structure of the Barratt Impulsiveness Scale. Journal of Clinical Psychology 51, 768–774.
Pedersen, N.L., Oreland, L., Reynolds, & C., Mclearn, G.E. (1993) Importance of genetic influence on trombocyte MAO activity in twins reared together. Psychiatry Research 6, 239–251.
Petry, N.M. (2001) Substance abuse, pathological gambling, and impulsiveness. Drug and Alcohol Dependence 63, 29–38.
Petry, N.M., & Casarella, T. (1999) Excessive discounting of delayed rewards in substance abusers with gambling problems. Drug and Alcohol Dependence 56, 25–32.
Pezawas, L., Meyer-Lindenberg, A., Drabant, E.M., Verchinski, B.A., Munoz, K.E., Kolachana, B.S., Egan, M.F., Mattay, V.S., Hariri, A.R., Weinberger, D.R. (2005) 5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: a genetic susceptibility mechanism for depression. Nature Neuroscience 8, 828–834.
Pletcher, A. (1987) The 5-hydroxytryptamine system of blood platelets: physiology and pathophysiology. International Journal of Cardiology 14, 177–188.
Raven, J. (1981) Manual for Raven's Progressive Matrices and Mill Hill vocabulary scales. Oxford: Oxford Psychologists Press.
Reeve, C.L. (2007) Functional impulsivity and speeded ability test performance. International Journal of Selection and Assessment 15, 56–62.
Rachlin, H. (2000) The science of self-control. Cambridge, MA, US, Harvard University Press, p 220
Reynolds, B., Ortengren, A., Richards, J.B., & de Wit, H. (2006) Dimensions of impulsive behavior: personality and behavioral measures. Personality and Individual Differences 40, 305–315.
Renner, W., Anderle, F.G. (2000) Venturesomeness and extraversion as correlates of juvenile drivers' traffic violations. Accident Analysis and Prevention 32, 673–678
Rosenberg, M. (1965) Society and the adolescent self-image. Princeton, NJ: Princeton University Press.
Rozencwajg, P., Corroyer, D. (2005) Cognitive processes in the reflective-impulsive cognitive style. Journal of Genetic Psychology 166, 451–463.
Ryb, G.E., Dischinger, P.C., Kufera, J.A., & Read, K.M. (2006) Risk perception and impulsivity: Association with risky behaviors and substance abuse disorders. Accident Analysis and Prevention 38, 567–573.

Schinka, J.A., Busch, R.M., & Robichaux-Keene, N. (2004) A meta-analysis of the association between the serotonin transporter gene polymorphism (5-HTTLPR) and trait anxiety. Molecular Psychiatry 9, 197–202.
Schmidt, L. G., Dufeu, P., Heinz, A., Kuhn, S., & Rommelspacher, H. (1997) Serotonergic dysfunction in addiction: effects of alcohol, cigarette smoking and heroin on platelet 5-HT content. Psychiatry Research 72, 177–85.
Schnaitman, C., Erwin, V.G., & Greenwalt, J.W. (1967) The submitochondrial localization of monoamine oxidase. An enzymatic marker for the outer membrane of rat liver mitochondria. The Journal of Cell Biology 32, 719–735.
Schalling, D., Edman, G., Asberg, M. & Oreland, L. (1988) Platelet MAO activity associated with impulsivity and aggressivity. Personality & Individual Differences 9, 597–605.
Schalling, D., Åsberg, M., Edman, G. & Oreland, L. (1987). Markers for vulnerability to psychopathology: temperament traits associated with platelet MAO activity. Acta Psychiatrica Scandinavica 76, 172–182.
Schmidt, L.G., Dufeu, P., Heinz, A., Kuhn, S., & Rommelspacher, H. (1997) Serotonergic dysfunction in addiction: effects of alcohol, cigarette smoking and heroin on platelet 5-HT content. Psychiatry Research 72, 177–185.
Shekim, W.O., Hodges, K., Horwitz, E., Glaser, R.D., Davis, L., & Bylund, D.B. (1984) Psychoeducational and impulsivity correlates of platelet MAO in normal children Psychiatry Research 11, 99–106.
Shekim, W.O., Bylund, D.B., Alexson, J.G., Robert D.J., Susan B., Hodges, K., & Perdue, S. (1986) Platelet MAO and measures of attention and impulsivity in boys with attention deficit disorder and hyperactivity. Psychiatry Research 18, 179–188.
Shoda, Y., Mischel, W., & Peake, P.K. (1990) Predicting adolescent cognitive and self-regulatory competencies from preschool delay of gratification: identifying diagnostic conditions. Developmental Psychology 26, 978–986.
Simonsson, P., Träskman, L.T., Alling, C., Oreland, L., Regnell, G., & Öhman, R. (1991) Peripheral serotonergic functioning in patients with suicidal behaviour. European Neuropharmacology 1, 503–510.
Sjöberg, R. L., Nilsson, K. W., Nordquist, N., Öhrvik, J., Leppert, J., Lindström, L., & Oreland, L. (2005) Development of depression: sex and the interaction between environment and a promoter polymorphism of the serotonin transporter gene, International Journal of Neuropsychopharmacology 9, 1–7.
Smeraldi, E., Zanardi, R., Benedetti, F., DiBella, D., Perez, J., & Catalano, M. (1998) Polymorphism within the promoter of the serotonin transporter gene and antidepressant efficacy of fluvoxamine. Molecular Psychiatry 3, 508–511.
Smillie, L.D., & Jackson, C.J. (2006) Functional impulsivity and reinforcement sensitivity theory. Journal of Personality 74, 47–83.
Solanto, M.V., Abikoff, H., Sonuga-Barke, E., Schachar, R., Logan, G.D., Wigal, T., Hechtman, L., Hinshaw, S., & Turkel, E. (2001) The ecological validity of delay aversion and response inhibition as measures of impulsivity in ADHD: a supplement to the NIMH multimodal treatment study of ADHD. Journal of Abnormal Child Psychology 29, 215–28.
Spinella, M. (2004) Neurobehavioral correlates of impulsivity: evidence of prefrontal involvement. International Journal of Neuroscience 114, 95–104.

Solanto, M.V., Abikoff, H., Sonuga-Barke, E., Schachar, R., Logan, G.D., Wigal, T., Hechtman, L., Hinshaw, S., & Turkel E. (2001) The ecological validity of delay aversion and response inhibition as measures of impulsivity in ad/hd: a supplement to the nimh multimodal treatment study of ADHD. Journal of Abormal Child Psychology 29, 215–228.

Soubrie, P. (1986) Reconciling the role of central serotonin neurones in human and animal behaviour. Behavioral and Brain Sciences 9, 319–364.

Steiger, H., Young, S.N., Ng Ying Kin, N.M.K., Koerner, N., Israel, M., Lageix, P., & Paris, J. (2001) Implications of impulsive and affective symptoms for serotonin function in bulimia nervosa. Psychological Medicine 31, 85–95.

Stoff, D.M., Friedman, E., Pollock, L.,Vitiello, B., Kendall, P.C., & Bridger, W. (1989) Elevated platelet MAO is related to impulsivity in disruptive behaviour disorder. Journal of American Academy of Child Psychogy 28, 754–760.

Straus, M.A., & Mouradian, V.E. (1998) Impulsive corporal punishment by mothers and antisocial behavior and impulsiveness of children, Behavioral Sciences and the Law, 16 353–374.

Swann, A.C., Bjork, J.M., Moeller, G., & Dougherty, D.M. (2002) Two models of impulsivity: relationship to personality traits and psychopathology. Biological Psychiatry 51, 988–994.

Taylor, S.E., Way, B.M., Welch, W.T., Hilmert, C.J., Lehman, B.J., & Eisenberger, N. I. (2006) Early family environment, current adversity, the serotonin transporter promoter polymorphism, and depressive symptomatology. Biological Psychiatry 60, 671–676.

Torgersen, S., & Vollrath, E.M. (2006) Personality types, personality traits and risky health behavior. In: Handbook of personality and health, Vollrath, E.M. (ed) John Wiley and Sons, Ltd, West Sussex, England pp 215–235.

Ulleberg, P. (2001) Personality subtypes of young drivers. Relationship to risk-taking preferences, accident involvement, and response to a traffic safety campaign. Transportation Research Part F Traffic Psychology and Behavior 4, 279–297.

Vernon, P. A. (1997) Behavioral genetic and biological approaches to intelligence. In: The scientific study of human nature: tribute to Hans J. Eysenck at eighty. Nyberg, H. (ed) Oxford, UK, Elsevier/Pergamon, pp 241–256.

Vigil-Colet, A., & Morales-Vives, F. (2005) How impulsivity is related to intelligence and academic achievement. Spanish Journal of Psychology 8,199–204.

Vigil-Colet, A., & Codorniu-Raga, M.J. (2004) Aggression and inhibition deficits, the role of functional and dysfunctional impulsivity. Personality and Individual Differences 37, 1431–1440.

Vingilis, E., Stoduto, G., Macartney-Filgate, M. S. & Liban, Carolyn, B. (1994) Psychosocial characteristics of alcohol-involved and nonalcohol-involved seriously injured drivers. Accident Analysis & Prevention 26, 195–206.

Walderhaug, E., Lunde, H., Nordvik, J.E., Landro, N.I., Refsum, H., & Magnusson, A. (2002) Lowering of serotonin by rapid tryptophan depletion increases impulsiveness in normal individuals. Psychopharmacology 164, 385–39.

Wallace, J.F., Newman, J.P., Bachorowski, J. (1991) Failures of response modulation: impulsive behavior in anxious and impulsive individuals. Journal of Research on Personality 25, 23–44.

Ward, P.B., Catts, S.V., Norman, T.R., Burros, G.D., & McGonaghy, N. (1987) Low platelet monoamine oxidase and sensation seeking in males: an established relationship? Acta Psychiatrica Scandinavica 75, 86–90.

Weijers, H.-G., Wiesbeck, G. A., Jakob, F., & Böning J. (2001) Neuroendocrine responses to fenfluramine and its relationship to personality in alcoholism. Journal of Neural Transmission 108, 1093–1105.

Wendland, J.R., Lesch, K.-P., Newman, T.K., Timme, A., Gachot-Neveu, H., Thierry, B., & Suomi, S.J. (2006) Differential functional variability of serotonin transporter and monoamine oxidase a genes in macaque species displaying contrasting levels of aggression-related behavior. Behavior Genetics 36, 163–172.

Whiteside, S. P. & Lynam, D. R. (2001) The Five Factor Model and impulsivity: using a structural model of personality to understand impulsivity. Personality & Individual Differences 30, 669–689.

Whiteside, S.P., Lynam, D.R., Miller, J.D., & Reynolds, S.K. (2005) Validation of the UPPS impulsive behaviour scale: a four-factor model of impulsivity. European Journal of Personality 19, 559–574.

Whitfield, J. B., Pang, D., Bucholz, K. K., Madden, P. A. F., Heath, A. C., Statham, D. J., & Martin, N. G. (2000) Monoamine oxidase: association with alcohol dependence, smoking, and other measures of psychopathology. Psychological Medicine 30, 443–454.

Wilson, R. J. (1991) Subtypes of DWIs and high risk drivers: Implications for differential intervention. Alcohol, Drugs and Driving 7, 1–12.

Wilson, R. J. & Jonah, B. A. (1985) Identifying impaired drivers among the general driving population. Journal of Studies on Alcohol 46, 531–537.

Wilson, R. Jean, & Jonah, Brian A. (1988) The application of Problem Behavior Theory to the understanding of risky driving. Alcohol, Drugs & Driving 4, 173–191.

Winblad, B., Gottfries, C.G., Oreland, L., & Wiberg, A. (1979) Monoamine oxidase in platelets and brains of non-psychiatric and non-neurological geriatric patients. Medical Biology 57, 129–132.

de Wit, H., Enggasser, J.L., & Richards, J.B. (2002) Acute administration of d-amphetamine decreases impulsivity in healthy volunteers. Neuropsychopharmacology, 27, 813–826.

Wright, J.C., & Mischel, W. (1987) A conditional approach to dispositional constructs: the local predictability of social behavior. Journal of Personality and Social Psychology 53, 1159–1177

Xu, Z., Seidler, F.J., Ali, S.F., Slikker, W., & Slotkin, T.A. (2001) Fetal and adolescent nicotine administration: effects on CNS serotonergic systems. Brain Research 914, 166–178.

Yamamoto, S., Ouchi, Y., Onoe, H., Yoshikawa, E., Tsukada, H., Takahashi, H., Iwase M., Yamaguti, K., Kuratsune, H., & Watanabe, Y. (2004) Reduction of serotonin transporters of patients with chronic fatigue syndrome. Neuroreport 15, 2571–2574.

Young, W. F., Cohen, G. J., Waldo, M. C., Feiz, R. & Roth, J. A. (1980) Platelet monoamine oxidase acitivity in children and adolescents with psychiatric disorders. Schizophrenia Bulletin 6, 324–33.

Zuckerman, M., & Kuhlman, D.M. (2000) Personality and risk-taking: common biosocial factors. Journal of Personality 68, 999–1029.

Zuckerman, M. (2005) Psychobiology of personality. 2nd ed. Cambridge University Press NY, USA pp 169–212.

8. SUMMARY IN ESTONIAN

Impulsiivsuse tüübid, väljendumine käitumises ja seos serotoniinisüsteemi talitluse biomarkeritega

Impulsiivsuse mõistet on kasutatud omavahel suhteliselt nõrgalt seotud temperamendiomaduste, käitumisviiside, infotöötlemise stiilide ning psühhiaatriliste häirete ja sümptomite kohta. Impulsiivsust on mõõdetud nii küsimustike kui sooritustestide abil ning see võib erinevate kirjelduste kohaselt hõlmata kalduvust reageerida, otsustada ja käituda vahetult, kiiresti ja mõtlematult, raskusi oma impulsside ja emotsioonide vaoshoidmisel ja üksluiste olukordade talumisel ning kannatamatust oma soovide realiseerimisel. Sageli seostatakse impulsiivset käitumist madala serotoniinisüsteemi aktiivsusega. Viimase aja uurimustes püütakse ühendada erinevate valdkondade impulsiivsuse käsitluste ning leida seost kasutusel olevate impulsiivsuse määratluste vahel. Eneseraporteeritud ja sooritusimpulsiivsus on osutunud omavahel suhteliselt nõrgalt või üldse mitte seotuks, kuid mõlemad ennustavad käitumist reaalsetes olukordades ja mitmete psüühikahäirete väljakujunemist. Samuti on nii eneseraporteeritud kui sooritusimpulsiivsus seotud muutustega serotoniinisüsteemi talitluses. Kuid suurem osa uurimustest, mis on näidanud kehvema serotoniinisüsteemi talitluse seost impulsiivsusega, on läbi viidud suhteliselt hälbiva käitumisega populatsioonide sees nagu psühhiaatriliste häiretega indiviidid, uimastite kuritarvitajad või vägivaldsed kurjategijad.

Arvestades impulsiivsuse mitmetahulisust üritab väitekiri vastata küsimusele, millist tüüpi impulsiivse temperamendi, kognitiivse stiili ja käitumise eest on vastutav madal kesknärvisüsteemi serotonergiline aktiivsus populatsioonis. Et impulsiivse temperamendi kujunemist mõjutab oluliselt ka kasvukeskkond, tegeleb väitekiri ka küsimusega, kuidas mõjub impulsiivsusele serotoniinisüsteemi haavatavus koosmõjus kehvade peresuhetega.

Väitekiri üritab esmalt kokku tuua andmed indiviidi impulsiivsuse kohta eneseraporteeritud skaaladel, sooritustestides ja reaalses riskikäitumises ning järgnevalt uurida nende eri tüüpi impulsiivsust väljendavate näitajate seost kesknärvisüsteemi serotoniinisüsteemi talitluse markeritega. Serotoniinisüsteemi talitluse markeriteks väitekirjas on vereliistakutest mõõdetav ja tõenäoliselt peaaju serotoniinineuronitega ühise geneetilise kontrolli all olev indikaator monoamiinide oksüdaasi (MAO) aktiivsus ning teiseks serotoniinisüsteemi vähemefektiivsele talitlusele viiv lühike (S) alleel serotoniini transporteri (5-HTT) geeni promootoripiirkonnas (5-HTTLPR). Impulsiivsuse tüüpide seost riskikäitumise ja vereliistakute MAO aktiivsusega uuritakse meessoost sõidukijuhtide valimil, kellest pooled on erinevate seaduserikkumistega liikluspolitsei poolt tabatud ning teise poole valimist moodustavad juhid, kellel registreeritud seaduserikkumisi liikluses ei ole. Eneseraporteeritud impulsiivsuse tüüpide ja

sooritusimpulsiivsuse seost vereliistakute MAO aktiivsuse ja 5-HTTLPR genotüübiga ning genotüübi efekti sõltuvust peresuhetest uuritakse populatsioonipõhisel koolilaste valimil.

Kui joobes autot juhtinud meessoost katseisikud said kontrollgrupist kõrgema tulemuse mitteadaptiivseid impulsiivsuse tüüpe mõõtvatel skaaladel, siis korduvalt kiirusepiirangute ületamise ja muude alkoholist sõltumatute seaduserikkumistega liikluspolitsei poolt tabatud isikud said kõrgemad tulemused adaptiivsete impulsiivsuse tüüpide skaaladel (**Artikkel III**). Vereliistakute MAO aktiivsus oli madalam alkoholiga seotud riskikäitumiste (joobes juhtimine) puhul ka peale suitsetamise võimaliku maskeeriva mõju kontrollimist (**Artiklid I ja II**). Joobes juhtimist tunnistavatel ja eitavatel politsei poolt tabatud katseisikutel oli ühtviisi madal MAO aktiivsus (**Artikkel II**). Seejuures oli korduva kiiruseületamise tõttu süüdi mõistetud isikutel keskmine vereliistakute MAO aktiivsus. Küll aga ilmnes korduva kiirusepiirangute ületamise eest karistatute jagamisel rühmadesse nende riskiteadlikkuse alusel, et riski teadvustavaid kiirusepiirangute rikkujaid iseloomustasid kõige hälbivamad skoorid kõigil kasutatud impulsiivsuse alaskaaladel (pidurdamatus, mõtlematus, elamustejanu ja kiire otsustamisstiil) ja kontrollgrupist oluliselt kõrgem vereliistakute MAO aktiivsus (**Artikkel III**).

Uurides eneseraporteeritud impulsiivsuse tüüpide seost infotöötluse kiiruse, täpsuse ja kiiruse eelistamisega täpsusele lihtsas visuaalse võrdluse katses (**Käsikiri IV ja Väitekiri**), ilmnes et peale spetsiaalselt kognitiivset impulsiivsuse komponenti mõõtva eneseraporteeritud skaala (BIS-11) tulemuse ei seostunud ükski eneseraporteeritud impulsiivsuse tüüpidest sooritusimpulsiivsusega ehk kiire ja ebatäpse vastamisstiiliga, mis on kooskõlas mitmete teiste uurimuste tulemustega.

Jagades katseisikud infotöötluse kiiruse ja täpsuse alusel nelja gruppi, ilmnes et nii kiire/ebatäpse vastamistiiliga kui ka kiire/täpse vastamisstiiliga indiviide iseloomustas kõrgem impulsiivsus BIS-11 skaalal. Kiire/täpne stiil seostus samaaegselt kõrge vaimse võimekuse, keskmise vereliistakute MAO aktiivsuse ja tavapärase tõenäosusega olla 5-HTTLPR S alleeli kandja. Kiire/ebatäpse vastamisstiiliga indiviide aga iseloomustas aga madal vaimne võimekus, keskmine MAO aktiivsus, kuid suurem tõenäosus kanda 5-HTTLPR S alleeli. Võime vastata kiiresti, kuid jääda seejuures täpseks, mille puhul oli impulsiivsus küll kõrgem, kuid serotoniinisüsteemi talitlus optimaalne, võib olla näide adaptiivselt väljenduvast impulsiivsusest.

Nii S alleeli kandlus kui madal MAO aktiivsus seostusid suurema vigade arvuga ja impulsiivsuse skooriga visuaalse võrdluse katses. Uurides kahe serotoniinisüsteemi aktiivsuse markeri kombinatsiooni mõju impulsiivsusele ilmnes, et madal vereliistakute MAO aktiivsus seostus nii eneseraporteeritud kognitiivse impulsiivsuse (BIS-11) kui sooritusimpulsiivsusega VCT testis ainult 5-HTTLPR S alleeli kandjate seas. Seega on kahel erineval nõrga serotoniinergilise aktiivsuse näitajal ajus sünergiline roll impulsiivsuse kujundamisel. Kuigi

madala vereliistakute MAO aktiivsuse ja 5-HTTLPR S alleeli kandluse mõju vigade arvule visuaalse võrdluse katses vähenes juhul, kui vaimne võimekus lülitati kaasvarieeruva muutujana analüüsi, oli osa serotoniinisüsteemi talitluse markerite mõjust vastamise täpsusele sõltumatu vaimsetest võimetest. See kinnitab serotoniinisüsteemi rolli võimetest osaliselt sõltumatutes pidurdusprotsessides (**Käsikiri IV**).

Käsikirjas V uuriti, kas enese-raporteeritud impulsiivsuse tüüpidel on seos 5-HTTLPR S alleeli kandlusega ning kas seda seost mõjutavad suhted uuritava päritoluperes. Vähene soojus ja tajutud väärkohtlemine peres seostusid mitteadaptiivsete impulsiivsuse tüüpidega S alleeli kandvatel tüdrukutel, kuid LL genotüübiga tüdrukute impulsiivsust peresuhted ei mõjutanud. Poistel aga seostus tajutud väärkohtlemine peres kõrgema mitteadaptiivse impulsiivsusega sõltumata 5-HTTLPR genotüübist.

Käesolevas doktoritöös esitatud uurimuste tulemused kinnitavad, et impulsiivselt ja riskeerivalt käituvaid inimrühmi saab eristada impulsiivsuse tüüpide alusel, millest osad on adaptiivsemad ja teised üldiselt vähem adaptiivsed. Enamikul eneseraporteeritud impulsiivsuse tüüpidel ei ilmnenud lihtsat seost serotoniinisüsteemi talitluse markeritega uuritud populatsioonidel, kuid nõrgema serotoniinisüsteemi talitluse mõjud ilmnesid juhul kui impulsiivsust mõõdeti riskikäitumise või soorituse kiiruse ja täpsuse kaudu. Samuti ilmnes seos eneseraporteeritud impulsiivsuse ja serotoniinisüsteemi talitlust mõjutava genotüübi vahel siis kui geeni mõju uuriti interaktsioonis keskkonnateguritega nagu halvad peresuhted.

9. PAPERS

I

Eensoo, D., Paaver, M., Pulver, A., Harro, M., & Harro, J. (2004) Low platelet MAO activity, high dysfunctional impulsivity and antisocial behaviour: evidence from drunk drivers. *Psychopharmacology* 172, 356–359.

II

Eensoo, D., Paaver, M., Harro, M., & Harro, J. (2005). Predicting drunk driving: contribution of alcohol use and related problems, traffic behaviour, personality and platelet monoamine oxidase (MAO) activity. *Alcohol and Alcoholism* 40, 140–146.

III

Paaver, M., Eensoo, D., Pulver, A., & Harro, J. (2006) Adaptive and maladaptive impulsivity, platelet monoamine oxidase (MAO) activity and risk-admitting in different types of risky drivers. *Psychopharmacology* 186, 32–40

IV

Paaver, M., Nordquist, N., Parik, J., Harro, M., Oreland, L., & Harro, J. (2007) Platelet MAO activity and the 5-HTT gene promoter polymorphism are associated with impulsivity and cognitive style in visual information processing. (resubmitted to *Psychopharmacology*)

Platelet MAO activity and the 5-HTT gene promoter polymorphism are associated with impulsivity and cognitive style in visual information processing

Marika Paaver[1], Niklas Nordquist[2], Jüri Parik[3], Maarike Harro[4], Lars Oreland[2], Jaanus Harro[1]

[1] Department of Psychology, Estonian Centre of Behavioural and Health Sciences, University of Tartu, Estonia
[2] Department of Neuroscience, Pharmacology, University of Uppsala, Sweden
[3] Institute of Molecular and Cell Biology, University of Tartu, Estonia
[4] National Institute for Health Development, Estonian Centre of Behavioural and Health Sciences, Tallinn, Estonia

Acknowledgements

This study was supported by grants from the Estonian Ministry of Education and Science (No 0182643 and 0942706) and the Estonian Science Foundation (No 6932 and 6788), the Swedish Science Foundation (VR) and the AFA insurance company. The skilful technical assistance by Ms Erika Comasco is gratefully acknowledged. We are grateful to the participants of the ECPBHS, and to the whole ECPBHS Study Team.

ABSTRACT

Rationale: Low capacity of the central serotonergic system has been associated with impulsive behaviour. Both low platelet monoamine oxidase (MAO) activity and the short (S) allele of the serotonin transporter gene promoter region polymorphism (5-HTTLPR) are proposed to be markers of less efficient serotonergic functioning.

Objectives: The effect of the two markers for serotonin system efficiency on performance in a visual comparison task (VCT) and self-reported impulsiveness (Barratt Impulsiveness Scale, BIS-11) were investigated in healthy adolescents participating in the Estonian Children Personality Behaviour and Health Study. Possible confounding effect of general cognitive abilities on the performance in VCT was controlled for.

Results: Low platelet MAO activity and carrying of the S allele of 5-HTTLPR were both associated with higher error-rate and more impulsive performance in VCT. Platelet MAO activity and 5-HTTLPR S allele had a significant interactive effect on self-reported impulsivity (BIS-11). The effect of platelet MAO activity on both self-reported and performance impulsivity was significant only in the S

allele carriers. The effect of 5-HTTLPR S allele on impulsive performance remained significant after controlling for general cognitive abilities.
Conclusions: The two markers of lower serotonergic capacity, 5-HTTLPR S allele and low platelet MAO activity, have a similar and partly synergistic influence on self-reported as well as performance measures of impulsivity.

Keywords: Impulsiveness, cognitive abilities, platelet monoamine oxidase, serotonin, speed and accuracy of information processing, 5-HT transporter gene

INTRODUCTION

The association of impulsive behaviour with a low capacity of the serotonergic system has been demonstrated in both rodents (Evenden 1999) and primates (Fairbanks et al. 2001). Human studies linking impulsiveness to the serotonergic system have found lower levels of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) in the cerebrospinal fluid of violent criminals (Nelson 2005) and impulsive suicide committers (Brown et al. 1982). Furthermore, effects of serotonergic drugs on the performance in impulsivity tests have been shown (Talpos et al. 2006). Studies on the role of serotonin in information processing have mainly been concentrated on inhibition processes, learning and memory. Depletion of the serotonin precursor tryptophan has been shown to result in a slower response in a visual discrimination task (Murphy et al. 2002). Lowering serotonin by tryptophan depletion has resulted in a decreased ability to discriminate between stimuli and in increased impulsivity in healthy individuals (Walderhaug et al. 2002), while acute increase in serotonin levels results in decreased impulsivity in a reward-delay task (Cherek and Lane 1999). However, brain monoamines have no direct association with simple visual information processing speed (Harrison et al. 2002), and thus it may be presumed that the tryptophan depletion effect most probably depends on more complex cognitive processes like behavioural inhibition or attention.

The expression of the 5-HT transporter (5-HTT) gene (SLC6A4) is critical to the development and plasticity of distinct neurocircuits (Lesch and Gutknecht 2005). Carriers of the 5-HTTLPR short (S) allele have been shown to have more affective dysfunctions, anxiety-related characteristics (Lesch et al. 1996, Ebstein 2006) and lower response to antidepressant treatment with serotonin reuptake inhibitors (Smeraldi et al. 1999). The S allele has been shown to have lower transcriptional activity than the long (L) allele. In functional studies of this variable locus, the SS and SL genotypes were functionally similar with regard to transcriptional activity, whereas the LL genotype displayed higher activity (Lesch et al.1996). Thus, SS homozygotes and SL heterozygotes are functionally equivalent and therefore usually analysed together in comparison with the LL homozygotes.

Monoamine oxidase (MAO) is an enzyme which metabolizes monoamines serotonin, dopamine and noradrenaline, with the B-isoenzyme, present in platelets, showing in vitro substrate preference for dopamine and trace amines. Functionally the activity of platelet MAO, however, appears as a peripheral marker of the capacity of central serotonergic system (see Oreland 2004 for a review). Low platelet MAO activity is associated with a blunted neuroendocrine response to fenfluramine in impulsive psychiatric patients (Soloff et al. 2003). There is a wide variety of studies on the association of low platelet MAO activity with impulsive behavioural tendencies (substance abuse, criminal and violent behaviour, suicide, gambling, drunk driving) (Paaver et al. 2006a, Oreland 2004) and self-reported impulsiveness or novelty seeking (Oreland 2004, Ruchkin et al. 2005, Schalling et al. 1988). Less attention has been paid to impulsive responding in neuropsychological tests which measure impulsive cognitive style. Af Klinteberg et al. (1990) found that low MAO activity was associated with the number of failed inhibitions in a laboratory task of impulsivity. It should also be noticed that some studies have demonstrated a U-shaped relationship between platelet MAO activity and behaviour, e.g, subjects with both low and high MAO activity responded more impulsively in neuropsychological tests (af Klinteberg et al. 1987), had higher probability of becoming a regular smoker (Harro et al. 2004), and had tendency for higher impulsivity (Schalling et al. 1988) and anxiety (Schalling et al. 1987). Only a few studies have controlled for the effect of cognitive abilities on the association of platelet MAO activity and impulsivity. It has been shown that normal children with low and high platelet MAO activity made more errors and had shorter latency periods in neuropsychological tests, while there was no relationship between platelet MAO levels and intellectual abilities or scholastic achievement (Shekim et al. 1984). It has also been shown that in young adults with low MAO, higher intelligence is a protective factor against risk behaviours and substance abuse (von Knorring et al.1984).

Impulsivity is a quality which is closely tied up with information processing (Barratt 1993, Dickman 1993). It is difficult to measure the cognitive component of impulsivity via self-reported scales (Barratt 1993), while performance tests of impulsivity lack the affective and social component more represented in self-reported measures, which lead to the need of using both methods while studying impulsiveness. Commonly the performance tests of impulsivity are divided into rapid-response models (preference for speed over accuracy in situations with high uncertainty), and reward-delay models measuring preference for small immediate reward over bigger delayed reward. It has been shown that impulsivity in rapid-response tests is more significantly associated with Barratt Impulsiveness Scale (BIS-11) (Patton et al.1995) scores compared to impulsivity in reward-delay tests (Swann et al. 2002). One of the most well-known tests of speed-accuracy tradeoff is Matching Familiar Figures Test (MFFT, Kagan 1964) which divides children reliably into the groups with fast/inaccurate (impulsive) and slow/accurate (reflective) style in a visual comparison task. In this test, a

subject has to estimate whether presented figures are similar or different, and both speed and accuracy are used as measures of performance. Reflection-impulsivity measured by MFFT is associated with social aggressiveness and lower motivation (Bernfeld and Peters 1986), but also with lower intelligence (Milich and Kramer 1984, Brannigan et al. 1980), especially in attention- concentration and visual organization domains of intelligence inventories (Brannigan et al. 1980). In general, performance in the tests of cognitive style in children appears to be influenced by two factors — impulsivity and general cognitive abilities (Amador-Campus and Kircher-Nebot 2001) which have been found to be negatively correlated (Vigil-Colet and Morales-Vives 2005). Thus general cognitive abilities need to be considered as an important moderating variable in impulsiveness studies.

We have studied the association of two measures of serotonin system capacity — platelet MAO activity and the polymorphism in the promoter region of the serotonin transporter gene — with impulsive information processing style in a task of visual comparison and self-reported impulsiveness, controlling for the effect of cognitive abilities.

MATERIALS AND METHODS

Sample

The sample was based on the younger cohort of the European Youth Heart Study (EYHS) conducted in Estonia in 1998/99, which was incorporated into the longitudinal Estonian Children Personality, Behaviour and Health Study (ECPBHS) (Harro et al. 2001). The present study was conducted during the follow-up in 2004 where we managed to recruit 83% (n=483) from the original sample, including 222 boys and 261 girls. Children and their parents gave their informed consent. Permission for the study was obtained from the Committee of Ethics of the University of Tartu, Estonia. The mean age of the subjects studied in 2004 was 15.3, SD = 0.5. Platelet MAO activity was measured in 467 subjects, 213 boys and 254 girls. General cognitive abilities were measured in 436 subjects. Barratt Impulsiveness Scale (BIS-11) was filled by 429 children. Data about smoking was available for all children. Visual Comparison Test (VCT) was performed by 378 randomly selected children. 5-HTTLPR genotype was assessed in 435 children.

Measures

Visual comparison test

The stimuli used in the VCT in this experiment, which was based on Dickman and Mayer (1988), were geometric figures made up of multiple *X*s (Figure 1).

Each figure was created by removing one or more *X* from an array that was 5 *X*s high and 10 *X*s wide. Each figure created in this way was paired with itself to form a *same* figure pair. For *different* pairs, one of the figures in a same pair was altered by changing the position of a single *X* in the periphery of the figure. Twenty pairs were created in this fashion; *same* and *different* pairs were randomly intermixed. The random generation and presentation of the figure pairs and recording of the responses was controlled by computer. The figure pairs were presented in the centre of the computer display screen. On the keyboard, one key was marked with green, for answering "*same figures*", and one with red for "*different figures*". The computer recorded each person's answers and time on every comparison.

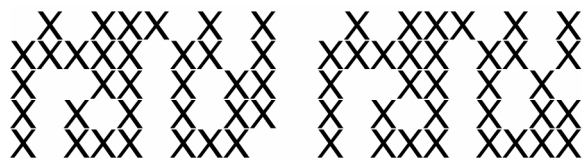

Figure 1. Example of the figures used in the Visual Comparison Test (Dickman and Meyer 1988)

Subjects were tested in sessions that lasted approximately 15 min. They were instructed to press the green key on the keyboard when the two figures were same and the red key on the keyboard when the two figures were different. They were told to perform as quickly and accurately as possible. Subjects were allowed to practice on a set consisting of five figure pairs. The subjects were then asked whether they had understood what they were supposed to do and when requested, offered another trial set. The trial session was followed by a test session, where subjects were given 20 pairs of figures for comparison. After every response, subjects received feedback whether they performed correctly.

The accuracy of responding was expressed as percentage of correct answers and the speed of responding was measured in milliseconds. Impulsivity score (I-score) was calculated for estimating speed-accuracy tradeoff as a measure of impulsivity (Morgan 1998) according to the formula of Messer and Brodzinsky (1981), subtracting the standard score of the mean latency (Z_t) from the standard score of the total number of errors committed (Z_e).

Measurement of platelet MAO activity

Platelet MAO activity was analysed in platelet-rich plasma by a radioenzymatic method with ß-phenylethylamine as the substrate as previously described (Harro et al. 2001, Hallman et al. 1987). All samples were analysed in duplicate and blindly, then corrected using a reference sample.

Genotyping of the 5-HTTLPR polymorphism

The alleles at the 5-HTTLPR locus were amplified from genomic DNA using PCR. The polymorphic region was amplified using the primers 5-HTTLPR-F: CAA CCT CCC AGC AAC TCC CTG TA, 5-HTTLPR-R: GAG GGA CTG AGC TGG ACA ACC AC, where the forward primer was fluorescently labeled with a 5'-FAM. Reagents and conditions for the PCR reaction were: 1x PCR buffer (Perkin Elmer, AmpliTaq Gold buffer II), 200 µM dNTP with 50% of dGTP replaced with 7-deaza-dGTP, 2 mM $MgCl_2$, 1 µM of each primer, 1 U Taq polymerase (Perkin Elmer, AmpliTaq Gold), and 20 ng genomic DNA, in a total reaction volume of 10 µL. The reaction started with 10 min at 95ºC, followed by 40 cycles with 30 s at 95ºC, 30 s at 59ºC, 30 s at 72ºC, and ended with 7 min at 72ºC. PCR products were then run on an ABI PRISM 3700 DNA analyzer (Applied Biosystems, U.S.A.), and scored using the software GeneMarker 1.5 (SoftGenetics, U.S.A.). All genotypes were manually checked on chromatograms to detect inconsistencies, and where needed, amplified and scored a second time. Genotype frequencies were in Hardy-Weinberg equilibrium.

Personality scales

Barratt Impulsiveness Scale (BIS-11) (Patton et al. 1995) was used for measuring impulsiveness. The Estonian version of the scale was adapted on 683 subjects with mean age 19±8 years of age ranging from 14–66. Twenty seven out of the original 31 items formed a single scale with average inter-item correlation r=0.13 and inner reliability expressed as Cronbach Alpha 0.80. In further analyses we used the BIS-11 total score.

General cognitive abilities

Raven's Standard Progressive Matrices (SPM) test (Raven 1981), (standardized on Estonian population by Lynn et al. 2002) subtests C & D were used to measure the intellectual abilities of the adolescent participants. The SPM is commonly regarded as a high-quality measure of pure non-verbal reasoning ability, which is relatively independent of specific learning acquired in a particular cultural or educational context (Jensen 1998). The test was administered without time limits.

Statistical analysis

Z-scores expressing deviance from the mean of each group expressed in standard deviation of the whole sample ($Z_X=X-M_X/SD_X$) were calculated to normalize the data. The analysis was performed using General Linear Models (Statistica 6.0). For some variables (VCT percent correct) that did not follow normal distribution the main effects were retested with non-parametrical methods (median test, Chi-Square statistic), and all main effects presented in this paper remained significant. Multivariate and covariate analysis of variance (MANOVA, ANCOVA) were used for detecting interaction and covariate effects. The Fisher LSD *post-hoc* tests were used for differences between the groups. Multiple regression

analysis was performed for detecting the independent effects of the variables predicting impulsiveness.

RESULTS

Performance in the VCT, self-reported impulsiveness and general cognitive abilities (SPM)

The mean time per item (TI) was 7.3 s (*SD*=3.0) and the mean percentage of correct answers was 88.3 (*SD*=12.1). There were no sex differences in the accuracy and speed of information processing or I-score in the VCT.

More impulsive subjects according to BIS-11 responded faster and had higher I-score, but did not respond significantly less accurately in the VCT (Table 1).

The mean percentage of correct responses on Raven SPM was 71% (*SD*=17.3%) and the median value was 75%. The BIS-11 impulsiveness score was not correlated with general cognitive abilities. Subjects with higher cognitive abilities were more accurate and had lower I-score in VCT, but cognitive abilities were not associated with the speed of responding (Table 1).

Platelet MAO activity

The mean platelet MAO activity was 10.29±3.73 nanomoles oxidized substrate/10^{10} platelets per min, median value 9.6. The mean MAO activity among boys was 9.60±

3.27 and among girls 10.87±4.00, the difference being significant ($F_{1,465}$=13.8, P<0.001). The subjects were divided by the lower and higher quartile values of platelet MAO activity into low-, medium-, and high-MAO activity group. The quartile values were calculated separately for boys and for girls. Platelet MAO activity and general cognitive abilities were weakly positively correlated (r=0.11, P<0.05). MAO activity was not correlated with the BIS-11 score.

5-HTTLPR genotype

There were 191 (44%) subjects being homozygous with regard to the long 5-HTTLPR allele, 189 (43%) were heterozygous and 55 (13%) homozygous for the short allele. The S allele carriers (SL/SS) were not significantly different from subjects with LL genotype in their general cognitive abilities and on the scale of impulsiveness (BIS-11). It appeared that the S allele carriers had lower platelet MAO activity (mean MAO 9.9±3.2) compared to LL genotype (mean MAO 10.8±4.3) ($F_{1,421}$ =4.9, P<0.05). However, when controlling for smoking and sex, this difference became non-significant.

The combined effect of platelet MAO activity and 5-HTTLPR genotype on self-reported impulsiveness

While neither MAO activity nor 5-HTTLPR polymorphism were significantly associated with the BIS-11 total score, a significant interaction effect ($F_{2,368}$=4.5, P<0.05) appeared, showing that subjects with low MAO activity and carrying the S allele had higher scores than subjects with low MAO activity and LL genotype in self-reported impulsiveness (Figure 2a). There was also a significant negative correlation between MAO activity and impulsiveness among the S allele carriers of 5-HTTLPR (r=-0.14, P<0.05), which did not appear in subjects with LL genotype.

Multiple regression analysis of variables predicting I-score in VCT

We included all analysed variables demonstrating significant main effects into a single multiple regression model predicting the I-score for detecting the effect size and independent contribution of the variables. In addition, subjects' sex was included into the initial model as a possible confounding variable. As the results concerning MAO activity may be confounded by smoking and there were 60 subjects in our sample who reported smoking daily or almost every day, we added smoking status into the multiple regression analysis. The effect of sex was not significant in the step-wise regression analyses and was eliminated from the model. The final standardized regression coefficients and partial correlations are presented in Table 2. The effects of cognitive abilities, 5-HTTLPR, and smoking appeared to have statistically significant independent effects when predicting the I-score in VCT. Platelet MAO activity and self-reported impulsiveness (BIS-11) had marginal independent effects, however, they improved the overall goodness of the model and were included. It should be noted that platelet MAO activity has a complex, non-linear relationship with smoking (see Harro et al. 2004).

The effect of platelet MAO activity and 5-HTTLPR genotype on performance in VCT

A significant difference in the percentages of correct answers in VCT between the three MAO groups appeared ($F_{2,363}$=8.0, P<0.0001), *post-hoc* analysis revealing significantly higher error-rate in subjects with low MAO in comparison with subjects with high and medium platelet MAO activity (Table 1). When controlling for the effect of cognitive abilities (ß=0.26, P<0.0001), the significance of the effect of platelet MAO on errors in VCT decreased ($F_{2,341}$=3.4, P<0.05). Platelet MAO activity was not linearly associated with the speed of information processing. Subjects with high platelet MAO activity had higher I-score in comparison with the subjects with low MAO activity (Table 1), however, after controlling for the effect of cognitive abilities (ß=0.17, P<0.001), the effect of MAO activity became non-significant (P=0.11).

Subjects carrying the S allele of 5-HTTLPR made significantly more errors in VCT ($F_{1,341}$ =4.9, P<0.05, Table 1). Cognitive abilities had a significant covariate

effect (ß=0.17, P<0.0001) on this association, and after including cognitive abilities into the analysis, the significance of the effect of 5-HTTLPR decreased ($F_{1,318}$ =4.3, P<0.05). Presence of the S allele was not associated with the speed of responding. S allele carriers had significantly higher I-score compared to subjects with LL genotype ($F_{1, 341}$=5.6, P<0.05), and also after controlling for cognitive abilities ($F_{1,318}$=4.9, P<0.05).

Exploring the combined effect of platelet MAO and 5-HTTLPR polymorphism on I-score in VCT, both the main effect of platelet MAO activity as well as the main effect of 5-HTTLPR S allele were significant ($F_{2,327}$=3.3, P<0.05 and $F_{1,327}$=5.1, P<0.05 respectively). In the comparison of the groups, it appeared that the impact of low platelet MAO on I-score was significant only among the S allele carriers (P<0.01) (Figure 2b).

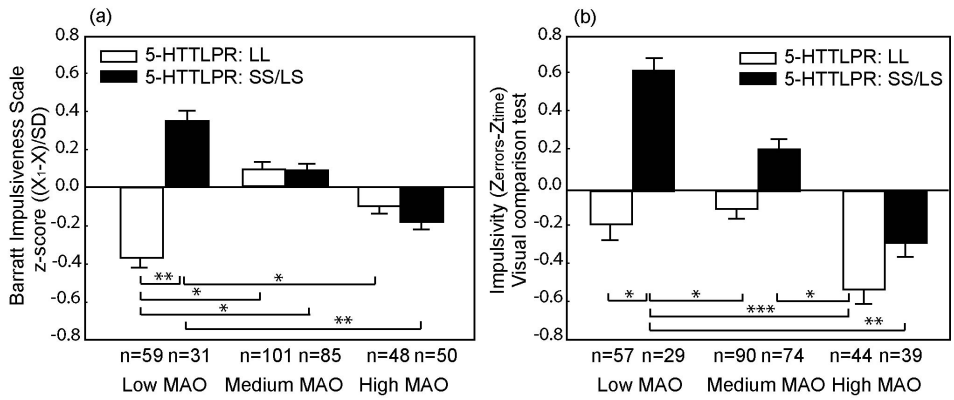

Figure 2. The effect of platelet MAO activity and 5-HTTLPR on self-reported impulsiveness (a) and impulsivity score in Visual Comparison Test (b).

DISCUSSION

Our main aim was to explore the associations of self-reported impulsivity and performance impulsivity with the markers of the function of serotonergic system.

One of the main conclusions derived from the results is that the effect of platelet MAO activity on impulsivity depends on the 5-HTTLPR genotype and vice versa. Subjects with low platelet MAO activity who carried the S allele of 5-HTTLPR had the highest mean score of self-reported impulsiveness compared to all other groups, while subjects with low platelet MAO activity, but concurrent 5-HTTLPR LL genotype had the lowest score on the scale of impulsiveness. Neither MAO activity nor 5-HTTLPR alone had any significant effect on self-reported impulsiveness. A similar result was found regarding the performance impulsivity measure. Again the effect of low MAO activity on impulsive

performance depended on whether the subject carried 5-HTTLPR S allele or not, and vice versa. This interaction may explain why some earlier studies reported significant associations between low platelet MAO activity and impulsivity, while others did not (Oreland 2004, Ruchkin et al. 2005, Paaver et al. 2006a, Kiive et al. 2005). The absence of independent effect of 5-HTTLPR on self-reported impulsivity is in accordance with earlier studies reporting no association between carrying the 5-HTTLPR S allele and impulsivity measured with the Barratt Scale of Impulsivity (Preuss et al. 2000).

It is not surprising that the S allele, which leads to lower expression of serotonin transporter and therefore less flexible serotonergic neurotransmission, is associated with more impulsive performance in a visual comparison task. There are several studies in which impulsive performance has been altered with serotonergic manipulations. Most reliably an increase in impulsivity with decreasing the serotonergic function has been found (Cherek and Lane 1999, Murphy et al. 2002, Walderhaug et al. 2002). Still, no effect of S allele on impulsive responding in a laboratory task of disinhibition (Clark et al. 2005) and Go/No-go task (Fallgatter et al. 1999) was found. It should be noted though that impulsivity is a multifactorial construct and the performance as well as the self-report measures of impulsivity are diverse. Our study included only the speed-accuracy tradeoff measure of impulsivity and one self-reported impulsivity scale, which implies a certain limitation to the conclusions. The higher performance impulsivity in subjects with low platelet MAO activity is, however, in accordance with the earlier results (af Klinteberg et al. 1990).

A wide variety of data supports the association between the 5-HTTLPR S allele and anxiety (Lesch et al. 1996). Anxiety and neuroticism are in association with a weak affect regulation and impulsive behaviour, especially in adolescence (Brotman et al 2006), and impulse control is the subfactor of neuroticism in some personality inventories (NEO-PI, Costa and McCrae 1989). This may be reflected in the impulsiveness of S allele carriers in our study. We did not control for the effect of possible depressive or anxiety disorder, but in a community-based sample of adolescents, the prevalence of these psychiatric disorders is probably not high enough to have a major impact.

The S allele carriers have lower grey-matter volume in the amygdala-cingulate feedback system (Pezawas et al. 2005), an important area in affect regulation, which may lead to problems in impulse regulation. At least one study has shown lower serotonergic innervation in the anterior cingulate in impulsively aggressive subjects, by positron emission tomography (PET) (Frankle et al. 2005). Given the knowledge on the significant role of anterior cingulate in the processing and monitoring of errors in the commission of effortful tasks (Brazdil et al 2005) and tasks with conflicting information which may result in errors (Botvinick et al 1999), the changes in the activity of cingulate may explain the more error-prone performance of S allele carriers.

It was demonstrated that although cognitive abilities had an effect on the error-rate as well as impulsivity score in VCT, the higher error-proneness and impulsive responding in 5-HTTLPR S allele carriers and subjects with low platelet MAO activity were not fully explained by cognitive abilities. The effect of 5-HTTLPR genotype on the error-rate and performance impulsivity remained significant when cognitive abilities were controlled for. The effect of low platelet MAO on error-rate remained significant, however the effect on performance impulsivity was marginalized when cognitive abilities were controlled for. This suggests that the influence of serotonergic system on behaviour depends on both impulsive cognitive style and cognitive abilities. Our result of the higher error-proneness independent of cognitive abilities in low MAO subjects is consistent with the small study of Shekim et al. (1984) showing a higher number of errors in a simple task in children with low platelet MAO activity, independent of general cognitive abilities. The higher error-rate in low-MAO subjects in the task of visual comparison may have been caused by their higher impatience (von Knorring et al. 1984), because the task was a monotonous activity with no mental challenge. The higher error-rate in subjects with low MAO activity or 5-HTTLPR S allele may also reflect their higher fatigue, as the experimental design included several measurements and lasted during the whole schoolday. This would be in line with our preliminary data suggesting that low platelet MAO is associated with higher fatigue after mental and physical effort (Paaver et al. 2006b) and an earlier PET study, which has demonstrated lower serotonin transporter density in the anterior cingulate of the chronic fatigue patients (Yamamoto et al. 2004).

Earlier studies linking 5-HTTLPR with impulsiveness have focused on special target groups, e.g. a higher prevalence of the S allele was found in impulsive suicide attempters (Baca-Garcia et al. 2005) and in violent type 2 alcoholics (Hallikainen et al. 1999). Our study was carried out on a population-based sample of adolescents. As the adolescent brain is more vulnerable to risk-taking and impulsive behaviour due to higher reward sensitivity compared to adults (Galvan et al. 2006), information on this age-group may provide specific insights. Detecting the effect of serotonergic functioning on impulsive cognitive style in adolescence leads to the question, how does their impulsive tendency track into adulthood, and whether and in which circumstances this predisposes the subject to substance abuse disorders or aggressive behaviour as demonstrated in adults carrying the S allele (Hallikainen et al. 1999, Gerra et al. 2004, Baca-Garcia et al. 2005). Whether and how does this cognitive tendency brought about by deviant function of serotonergic system express itself in the subject's further everyday life? This probably depends on the accompanying traits of the individual, and environmental factors. The further development of the observed impulsive tendencies in S allele carriers is especially interesting in the light of the knowledge about the interaction of carrying the 5-HTTLPR S allele with environmental stress, as first demonstrated by Caspi et al. (2003). Detecting the

decisive environmental effects in childhood is of great interest as this may help to prevent the development of problem behaviours. Smoking was one predictor of impulsiveness in the presented multiple regression model. As the permanent neurotoxic effects of nicotine on serotonergic neurons has been described (Xu et al. 2001), smoking may be one environmental factor that may enhance the impulsiveness in adolescents. On the other hand, impulsive cognitive style does not necessarily have to be a problematic trait leading to behavioural problems, but just a fast and error-prone cognitive style, which may in certain cases be adaptive (Dickman 1990). A gene mutation that has survived and spread in the natural selection most probably has an adaptive value in certain environments (Lesch 2005). Indeed, at least one study has demonstrated that the S allele carriers, who had grown up in a supporting environment, had less depression compared to subjects with the LL genotype (Taylor et al. 2006). It is possible that environmental factors direct the development of impulsive cognitive tendencies into adaptive or maladaptive patterns in adulthood.

One important limitation to the interpretation of these results is the fact that we did not use other behavioural impulsivity tests. Still, an advantage for their interpretation is that the self-reported and the performance measure of impulsivity were similarly related to low MAO activity and carrying of the S allele. Similar results on self-reported and behavioural measures of impulsivity are not self-evident, because many impulsivity studies fail to find even a correlation between these measures (Reynolds et al. 2006). In our study, though, the consistency between self-report and performance measures could have been expected, because impulsivity as measured by BIS-11 can be characterized by lability of attention and concentration, motor restlessness, boredom susceptibility, fidgetiness and non-planning, which can be considered as cognitive rather than affective or social dimensions of impulsivity, and therefore be better related to performance. Another issue arises from the fact that a functional G/A single nucleotide polymorphism was recently discovered in the L allele making them, functionally, more similar to S allele carriers by their serotonergic turnover (Hu et al. 2006) and we did not measure this. However, the prevalence of this mutation is very low (Wengland et al. 2006) and therefore most probably it did not have a significant influence on our results.

Conclusively, our study has provided a novel result that two different indicators of the serotonergic system capacity — low platelet MAO activity and presence of the short 5-HTTLPR allele — are associated with higher error-rate and more impulsive responding in a simple cognitive task of visual comparison. It was also demonstrated that these two markers have an interactive effect on self-reported impulsiveness.

REFERENCES

Amador-Campus J, Kirchner-Nebot T (2001) Childrens embedded figures test and Matching Familiar Figures Test-20: factorial structure for boys and girls from 6 to 11 years old. Percept Mot Skills 93:709–712

Baca-Garcia E, Salgadoa BR, Segala HD Lorenzo CV, Acosta MN, Romeroa MA, Hernandez MD, Ruiza JS, Piqueras JF, de Leonc J (2005) A pilot genetic study of the continuum between compulsivity and impulsivity in females: The serotonin transporter promoter polymorphism. Prog Neuropsychopharmacol Biol Psychiatry 29:713–717

Barratt ES (1993) Impulsivity: integrating cognitive, behavioral, biological and environmental data. In: McCown WB, Johnson JL, Shure MB (eds) The impulsive client: theory, research and treatment. American Psychological Association, Washington, DC, pp 39–56

Bernfeld GA and Peters RV (1986) Social reasoning and social behaviour reflective and impulsive children. J Clin Child Psychol 15:221–227

Botvinick M, Nystrom LE, Fissell K, Carter CS, Cohen JD (1999) Conflict monitoring versus selection-for-action in anterior cingulate cortex. Nature 402:179–181

Brannigan GG, Ass T, Margolis H (1980) Impulsivity-relfectivity and children's intellectual performances. J Pers Assess 44:41–43

Brázdil M, Roman R, Daniel P, Rektor I (2005) Intracerebral error-related negativity in a simple Go/No-go task. J Psychophysiol 19:244–255

Brotman MA, Schmajuk M, Rich BA, Dickstein DP, Guyer AE, Costello EJ, Egger HL, Angold A, Pine DS, Leibenluft E (2006) Prevalence, clinical correlates, and longitudinal course of severe mood dysregulation in children. Biol Psychiatry 60: 991–997

Brown GI, Ebert M, Goyer PF Jimerson DC, Klwin WJ, Bunney WE Goodwin FK (1982) Aggression, suicide, and serotonin: relationships to CSF amine metabolites. Am J Psychiatry 139:741–746

Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, McClay J, Mill J, Martin J, Braithwaite A, Poulton R (2003) Influence of life stress on depression: moderation by a polymorphism in the 5-HTT. *Science* 301:386–389

Cherek DR, Lane SD (1999) Effects of d,l-fenfluramine on aggressive and impulsive responding in adult males with a history of conduct disorder. Psychopharmacology 146:473–481

Clark L, Roiser JP, Cools R, Rubinsztein DC, Sahakian BJ, Robbins, TW (2005) Stop signal response inhibition is not modulated by tryptophan depletion or the serotonin transporter polymorphism in healthy volunteers: implications for the 5-HT theory of impulsivity. Psychopharmacology 182:570–578

Costa PT, McCrae RR (1989) The NEO-PI/NEO-FFI manual supplement. Psychological Assessment Resources, Odessa, FL.

Dickman J (1993) Impulsivity and information processing. In: McCown WB, Johnson JL, Shure MB (eds) The impulsive client: theory, research and treatment. American Psychological Association, Washington, DC, pp 39–56

Dickman S, Meyer DE (1988) Impulsivity and speed-accuracy tradeoffs in information processing. J Pers Soc Psychol 54:274–290

Dickman SJ (1990) Functional and dysfunctional impulsivity: personality and cognitive correlates. J Pers Soc Psychol 58:95–102
Ebstein RP (2006) The molecular genetic architecture of human personality: beyond self-report questionnaires. Mol Psychiatry 11:427–445
Evenden JL (1999) Varieties of impulsivity. Psychopharmacology 146:348–361
Fairbanks LA, Melega WP, Jorgensen MJ, Kaplan KR, McGuire MT (2001) Social impulsivity inversely associated with CSF 5-HIAA and fluoxetine exposure in vervet monkeys. Neuropsychopharmacology 24:370–378
Fallgatter AJ, Jatzke S, Bartsch AJ, Hamelbeck B, Lesch KP (1999) Serotonin transporter promoter polymorphism influences topography of inhibitory motor control. Int J Neuropsychopharmacology 2:115–120
Frankle WG, Lombardo I, New AS, Goodman M, Talbot PS, Huang YH, Hwang DR, Slifstein M, Curry S, Abi-Dargham A, Laruelle M, Siever LJ (2005) Brain serotonin transporter distribution in subjects with impulsive aggressivity: a positron emission study with [^{11}c]mcn 5652. Am J Psychiatry 5:915–923
Galvan A, Hare TA, Parra CE, Penn J, Voss H, Glover G, Casey BJ (2006) Earlier development of the accumbens relative to orbitofrontal cortex might underlie risk-taking behavior in adolescents. J Neurosci 26:6885–6892
Gerra G, Garofano L, Santoro G, Bosari S, Pellegrini C, Zaimovic A, Moi G, Bussandri M, Moi A, Brambilla F, Donnini C (2004) Association between low-activity serotonin transporter genotype and heroin dependence: behavioral and personality correlates. Am J Med Genet 126B:37–42
Hallikainen T, Saito T, Lachman HM, Volavka J, Pojhanen T, Ryynänen OP, Kauhanen J, Syvälahti E, Hietala J, Tiihonen J (1999) Association between low activity serotonin transporter promoter genotype and early onset alcoholism with habitual impulsive violent behavior. Mol Psychiatry 4:385–388
Hallman J, Oreland L, Edman G, Schalling D (1987) Thrombocyte monoamine oxidase activity and personality traits in women with severe premenstrual syndrome. Acta Psychiatr Scand 76:225–234
Harrison BJ, Olver JS, Norman TR, Nathan PJ (2002) Brain monoamines and early visual information-processing speed. Int J Neuropsychopharmacol 5:295–300
Harro M, Eensoo D, Kiive E, Merenäkk L, Alep J, Oreland L, Harro J (2001) Platelet monoamine oxidase in healthy 9- and 15-years old children: the effect of gender, smoking and puberty. Prog Neuro-Psychopharmacol Biol Psychiatry 25:1497–1511
Harro J, Fischer K, Vansteelandt S, Harro M (2004) Both low and high activity of platelet monoamine oxidase increase the probability of becoming a smoker. Eur Neuro-psychopharmacol 14:65–69
Hu XZ, Lipsky RH, Zhu G, Akhtar LA, Taubman J, Greenberg BD, Xu K, Arnold PD, Richter MA, Kennedy JL, Murphy DL, Goldman D (2006) Serotonin transporter promoter gain-of-function genotypes are linked to obsessive-compulsive disorder. Am J Hum Gen 78:815–826
Jensen AR (1998) The g factor. Westport, CT: Praeger Kagan J, Rosman B, Day D, Albert J, Phillips W (1964) Information processing in the child: Significance of analytic and reflective attitudes. Psychological Monographs, 78 (1, Whole No. 578)
Kiive E, Merenäkk L, Harro M, Harro J (2005) Changes in platelet monoamine oxidase activity, cholesterol levels and hyperactive behaviour in adolescents over a period of three years. Neurosci Lett 384:310–315

af Klinteberg B, Levander SE, Oreland L, Asberg M, Schalling D (1987) Neuropsychological correlates of platelet monoamine oxidase (MAO) activity in female and male subjects. Biol Psychol 24:237–252

af Klinteberg B, Oreland L, Hallman J, Wirsen A, Levander SE, Schalling D (1990) Exploring the connections between platelet monoamine oxidase activity and behaviour: relationships with performance in neuropsychological tasks. Neuropsychobiology 23:188–196

Lesch KP (2005) Alcohol dependence and gene x environment interaction in emotion regulation: Is serotonin the link? Eur J Pharmacol 526: 113–124

Lesch KP, Gutknecht L (2005) Pharmacogenetics of the serotonin transporter. Prog Neuropsychopharmacol Biol Psychiatry 29:1062 — 1073

Lesch KP, Bengel D, Heils A, Sabol SZ, Greenberg BD, Petri S, Benjamin J, Müller CR, Hamer DH, Murphy DL (1996) Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. Science 274:1527–1531

Lynn J, Allik J, Pullmann H, Laidra K (2002) A study of intelligence in Estonia. Psychol Rep 91:1022–1026

Messer SB, Brodzinsky DM (1981) Three-year stability of reflection-impulsivity in young adolescents. Dev Psychol 17:848–850

Milich R, Kramer J (1984) Reflections on impulsivity: An empirical investigation of impulsivity as a construct. Adv Learn Beh Disab 3:57–94

Morgan MJ (1998) Recreational use of ecstasy (MDMA) is associated with elevated impulsivity. Neuropsychopharmacology 19:252–264

Murphy FC, Smith KA, Cowen PJ, Robbins TW, Sahakian BJ (2002) The effects of tryptophan depletion on cognitive and affective processing in healthy volunteers. Psychopharmacology 163:42–53

Nelson RJ (2005) Biology of aggression. Cary, NC, USA: Oxford University Press, pp 79–84

Oreland L (2004) Platelet monoamine oxidase, personality and alcoholism: the rise, fall and resurrection. Neurotoxicology 25:79–89

Paaver M, Eensoo D, Pulver A, Harro J (2006a) Adaptive and maladaptive impulsivity, platelet monoamine oxidase (MAO) activity and risk-admitting in different types of risky drivers. Psychopharmacology 186:32–40

Paaver M, Kreegipuu K, Tamm M, Harro M, Harro J (2006b) Platelet MAO activity is associated with vulnerability to fatigue and accuracy and speed of information processing in the tasks of visual cognition. Int J Neuropsychopharmacol 9:S200

Patton JH, Stanford, MS, Barratt, ES (1995) Factor structure of the Barratt Impulsiveness Scale. J Clin Psychol 51:768–774

Pezawas L, Meyer-Lindenberg A, Drabant EM, Verchinski BA, Munoz KE, Kolachana BS, Egan MF, Mattay VS, Hariri, AR, Weinberger DR (2005) 5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: a genetic susceptibility mechanism for depression. Nat Neurosci 8:828–834

Preuss UW, Soyka M, Bahlmann M, Wenzel K, Behrens S, Jonge S, Kruger M, Bondy B (2000) Serotonin transporter gene regulatory region polymorphism (5-HTTLPR), [^{3}H] paroxetine binding in healthy control subjects and alcohol-dependent patients and their relationships to impulsivity. Psychiatry Res 96:51–61

Raven J (1981) Manual for Raven's Progressive Matrices and Mill Hill vocabulary scales. Oxford: Oxford Psychologists Press

Reynolds B, Ortengren A, Richards JB, de Wit H (2006) Dimensions of impulsive behavior in personality and behavioral measures. Person Individ Diff 40:305–315

Ruchkin VV, Koposov RA, af Klinteberg B, Oreland L, Grigorenko EL (2005) Platelet MAO-B, personality, and psychopathology. J Abnorm Psychol 114:477–482

Schalling D, Asberg M, Edman G, Oreland L (1987) Markers for vulnerability to psychopathology: temperament traits associated with platelet MAO activity. Acta Psychiatr Scand 176:172–182

Schalling D, Edman G, Asberg M, Oreland L (1988) Platelet MAO activity associated with impulsivity and aggressivity. Pers Individ Diff 9:597–605

Shekim WO, Hodges K, Horwitz E, Glaser RD, Davis L, Bylund DB (1984) Psycho-educational and impulsivity correlates of platelet MAO in normal children Psychiatry Res 11:99–106

Soloff PH, Kelly TM, Strotmeyer SJ, Malone KM, Mann JJ (2003) Impulsivity, gender, and response to fenfluramine challenge in borderline personality disorder. Psychiatry Res 119:11–24

Smeraldi E, Zanardi R, Benedetti F, DiBella D, Perez J, Catalano M (1998) Poly-morphism within the promoter of the serotonin transporter gene and antidepressant efficacy of fluvoxamine. Mol Psychiatry 3:508–511

Swann AC, Bjork JM Moeller FG, Dougherty DM (2002) Two models of impulsivity: relationship to personality traits and psychopathology. Biol Psychiatry 51: 988–994

Talpos JC, Wilkinson LS, Robbins TW (2006) A comparison of multiple 5-HT receptors in two tasks measuring impulsivity. J Psychopharmacol 20:47–58

Taylor SE, Way BM, Welch WT, Hilmert CJ, Lehman BJ, Eisenberger NI (2006) Early family environment, current adversity, the serotonin transporter promoter poly-morphism, and depressive symptomatology. Biol Psychiatry 60:671–676

Vigil-Colet A, Morales-Vives F (2005) How impulsivity is related to intelligence and academic achievement. Spanish J Psychol 8:199–204

von Knorring L, Oreland, L, Winblad, B (1984) Personality traits related to monoamine oxidase activity in platelets. Psychiatry Res 12:11–26

Walderhaug E, Lunde H, Nordvik JE, Landro NI, Refsum H, Magnusson A (2002) Lowering of serotonin by rapid tryptophan depletion increases impulsiveness in normal individuals. Psychopharmacology 164:385–391

Wengland JR, Martin BJ, Kruse MR, Lesch KP, Murphy DL (2006) Simultaneous genotyping of four functional loci of human SLC6A4, with a reappraisal of 5-HTTLPR and rs25531. Mol Psychiatry 11:224–226

Yamamoto S, Ouchi Y, Onoe H, Yoshikawa E, Tsukada H, Takahashi H, Iwase M, Yamaguti K, Kuratsune H, Watanabe Y (2004) Reduction of serotonin transporters of patients with chronic fatigue syndrome. Neuroreport 15:2571–2574

Xu Z, Seidler FJ, Ali SF, Slikker W, Slotkin TA (2001) Fetal and adolescent nicotine administration: effects on CNS serotonergic systems. Brain Res 914:166–178.

Table 1. The speed, accuracy and impulsivity score in theVisual Comparison Test in subjects according to their impulsiveness, general cognitive abilities, platelet MAO activity levels, and the 5-HTTLPR polymorphism

	Mean time (s) per item (SD in brackets)	% correct	I-score
BIS-11[1]			
Non-impulsive (*n*=170)	7.6 (3.4)	89.6 (11.5)	–.20 (.12)
Impulsive (*n*=169)	6.9 (2.6)*	87.3 (11.7)[a]	.22 (.12)*
Cognitive abilities score			
Low (*n*=160)	6.9 (3.3)	81.3 (12.7)	.36 (.13)
High (*n*=196)	7.5 (2.9)	91.0 (10.4) ***	–.29 (.12)***
Platelet MAO[2]			
Low (*n*=98)	7.3 (3.1)	84.7 (14.4)	.29 (.17)
Medium (*n*=180)	7.0 (2.9)	88.8 (11.9)##	.04 (.12)
High (*n*=91)	7.7 (3.1)	91.6 (8.7)###	–.43 (.17)##†
5-HTTLPR:			
LL (*n*=146)	7.6 (2.9)	89.9 (10.9)	–.23 (.14)
SL/SS (*n*=197)	7.0 (3.2)	87.0 (13.4)*	.21 (.12)*

% correct — percentage of correct responses, BIS-11 = Barratt Impulsiveness Scale whole score, I-score = impulsivity score in Visual Comparison Test

[1] Subjects with low and high score of BIS-11 impulsiveness and cognitive abilities are differentiated by median value

[2] Subjects with low, medium and high MAO activity are differentiated by higher and lower quartile values of the sample.

The significance of t-values in comparison of the two groups: * $P<0.05$ *** $P<0.01$

[a] $P=0.07$ *versus* the other group

Fisher LSD *post-hoc* ## $P<0.01$ ### $P<0.00001$ *versus* the low MAO group, † $P<0.05$ versus the medium MAO group

Table 2. Multiple regression analysis predicting VCT impulsivity score as a dependent variable.

	β	Partial correlations	*P*
Cognitive abilities (SPM, z-score)	–.15	.16	.009
Smoking („Yes”=1 „No”=0)	.12	.12	.037
5-HTTLPR (SL/SS=1, LL=0)	.13	.13	.027
Platelet MAO activity (high=1, low+medium=0)	–.11	.12	.063
Self-reported impulsivity (BIS-11, z-score)	.09	.09	.110

The significance of the multiple regression model: $F_{(5.280)}=6.3$, $P<.00001$, $R^2= .10$.

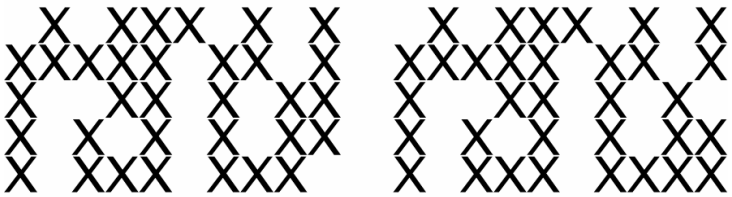

Figure 1. Example of the figures used in the Visual Comparison Test (Dickman and Meyer 1988)

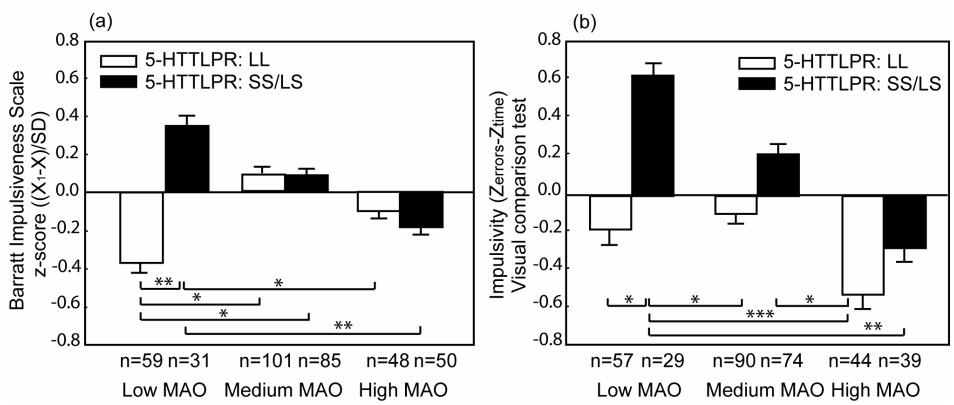

Figure 2. The effect of platelet MAO activity and 5-HTTLPR on self-reported impulsiveness (a) and the impulsivity score in Visual Comparison Test (b).
Fisher LSD *post-hoc*: * $P<0.05$, ** $P<0.01$, *** $P<.001$ following significant multivariate analysis of variance including platelet MAO (low, medium, high according to higher and lower quartile values) and 5-HTTLPR (LL *vs* SL/SS) as grouping variables. Whiskers represent standard error of the mean values.

V

Paaver, M., Kurrikoff, T., Nordquist, N., Oreland, L., & Harro, J. The effect of 5-HTT gene promoter polymorphism on impulsivity depends on family relations in girls. (submitted to *Neuroscience Letters*)

The effect of 5-HTT gene promoter polymorphism on impulsivity depends on family relations in girls

Marika Paaver[1], Triin Kurrikoff[1], Niklas Nordquist[2], Lars Oreland[2], Jaanus Harro[1]

[1] Department of Psychology, Estonian Centre of Behavioural and Health Sciences, University of Tartu, Estonia
[2] Department of Neuroscience, Pharmacology, University of Uppsala, Sweden

ABSTRACT

The short (S) allele of the 5-HTT gene promoter region polymorphism (5-HTTLPR), in combination with adverse environmental influence, leads to higher likelihood of depression. Impulsivity has been related to low serotonin turnover, poor regulation of affect, and problems in family, including child maltreatment. The current study explored the effect of the 5-HTTLPR polymorphism in the serotonin transporter gene and adverse family environment on impulsivity in adolescents. Healthy adolescents participating in the Estonian Children Personality Behaviour and Health Study (n=483) filled the Adaptive and Maladaptive Impulsivity Scale (AMIS), Barratt Impulsiveness Scale (BIS-11), a scale measuring family relations, and were genotyped. While genotype alone was not associated with thoughtlessness, BIS-11 impulsiveness, fast decision making or excitement seeking, 5-HTTLPR S allele carriers, however, had higher scores of disinhibition. In girls, the combination of carrying the S allele with low scores for warmth in family and high scores for maltreatment had significantly higher thoughtlessness and disihibition scores compared to girls with good family relations, and at least one S allele. Adverse family relations did not have any impact on girls with LL genotype. In boys, the effects of family relations on maladaptive impulsivity did not depend on genotype. However, the S allele and high maltreatment in family both independently increased disinhibition and BIS-11 score in boys. Family environment and 5-HTTLPR genotype had no interactive effect on excitement seeking or fast decision making. In summary, carrying the S allele may lead to high maladaptive impulsivity due to higher sensitivity to environmental adversity, which is more significantly expressed in girls.

The 5-HT transporter gene (SLC6A4, 5-HTT) has a polymorphism in the promoter region, which consists of a 20–23 base pair sequence that is repeated either 14 (short) or 16 (long) times. The short (S) allele is associated with a lower expression of the 5-HT transporter [22], lower neuronal density in regions

necessary for regulating negative affect [34], and higher amygdala reactivity to negative stimuli [13,34,18]. Clinical studies have demonstrated that carrying the S allele is associated with anxiety-related characteristics [36], depressive symptoms [20] and other types of affective dysfunctions.

The impact of 5-HTTLPR genotype on depressive symptoms has been shown to depend on environmental stressors. Depressive symptoms only appeared among those S allele carriers who suffered from stressful life events in the early age [5], or had experienced a hostile family environment [21,39]. Furthermore, development of a less efficient serotonergic system was demonstrated among those 5-HTTLPR S allele carriers who had experienced adverse events during childhood [22] or who had been raised in families from low socio-economic background [27].

Poor impulse control in suicide attempters and impulsively aggressive subjects is associated with reduced serotonin transporter binding and lower levels of the serotonin metabolite 5-HIAA in cerebrospinal fluid [23,40,3,35]. Considering the impact of 5-HTTLPR genotype on the development of corticolimbic structures [16], which are involved in the regulation of affect [26], 5-HTTLPR S allele may have a role in inhibiting impulsive behaviour which subserves its effect on affect [23]. Behavioural problems or impulsivity may be one indicator of mood disorder in adolescents [4], since also parents to depressed children rate them to be impulsive and restless [6].

However, not many studies have been carried out on the association between 5-HTTLPR and impulsiveness. Higher prevalence of the S allele in impulsive suicide attempters has been demonstrated [24]. Also, some studies indicate a higher prevalence of the S allele in substance abusers — e.g., violent type 2 alcoholics [15] and aggressive heroin-addicts [11]. An influence of S allele carrying on aggressiveness in children has also been demonstrated [14]. Among individuals with antidepressant-induced mania, a state associated with impulsiveness, an overrepresentation of S allele carriers has been found [28]. Though many studies indicate that the 5-HTTLPR S allele is involved in susceptibility to depression, substance abuse and aggressive behaviour, less is known about its association to the impulsive personality dimension in the normal population.

As to the environmental effects which would potentially bring out the vulnerability in 5-HTTLPR S allele carriers, the development of impulsivity has been shown to depend on parenting styles. For example, Olson et al. [31] found in a longitudinal study that responsive, cognitively stimulating parent-toddler interactions in the 2nd year predicted later measures of cognitive nonimpulsivity and ability to delay gratification. Straus and Mouradian [38] found that corporal punishment was associated with impulsiveness in the child.

The aim of the current study was to explore the effect of 5-HTTLPR and adverse family environment on impulsivity in adolescents. It was hypothesized that the S allele induces higher impulsiveness in the presence of non-supportive family relations.

The sample was based on the younger cohort of the European Youth Heart Study (EYHS) conducted in Estonia in 1998/99, which was incorporated into the longitudinal Estonian Children Personality, Behaviour and Health Study (ECPBHS) [17]. The present study was conducted during the follow-up in 2004 where we could recruit 83% (n = 483) of the original sample, including 222 boys and 261 girls. Children and their parents gave their informed consent. Permission for the study was obtained from the Committee of Ethics of the University of Tartu, Estonia. The mean age of the subjects studied in 2004 was 15.3, S.D. = 0.5.

The alleles at the 5-HTTLPR locus were amplified from genomic DNA using PCR. The polymorphic region was amplified using the primers 5-HTTLPR-F: CAA CCT CCC AGC AAC TCC CTG TA, 5-HTTLPR-R: GAG GGA CTG AGC TGG ACA ACC AC, where the forward primer was fluorescently labeled with a 5'-FAM. Reagents and conditions for the PCR reaction were: 1x PCR buffer (Perkin Elmer, AmpliTaq Gold buffer II), 200 µM dNTP with 50% of dGTP replaced with 7-deaza-dGTP, 2 mM $MgCl_2$, 1 µM of each primer, 1 U Taq polymerase (Perkin Elmer, AmpliTaq Gold), and 20 ng genomic DNA, in a total reaction volume of 10 µL. The reaction started with 10 min at 95ºC, followed by 40 cycles with 30 S at 95ºC, 30 S at 59ºC, 30 S at 72ºC, and ended with 7 min at 72ºC. PCR products were then run on an ABI PRISM 3700 DNA analyzer (Applied Biosystems, U.S.A.), and scored using the software GeneMarker 1.5 (SoftGenetics, U.S.A.). All genotypes were manually checked on chromatograms to detect inconsistencies, and where needed, amplified and scored a second time. 5-HTTLPR genotype was assessed in 435 children and 191 (44%) of subjects were homozygous for L allele, 189 (43%) were heterozygous and 55 (13%) were homozygous for the S allele. Genotype frequencies were in Hardy-Weinberg equilibrium.

Barratt Impulsiveness Scale (BIS-11) [33] and Adaptive and Maladaptive Impulsivity Scale (AMIS) were used to measure different facets of impulsivity (fast decision making, excitement seeking, disinhibition, thoughtlessness) as previously described [9,32]. Self-reported impulsiveness questionnaire AMIS was was filled by 481 and BIS-11 by 429 children.

Relationships in the family were measured by a child-report scale. Four subscales were extracted by principal components factor analysis using Cattell criterion and were named as closeness, support, misprize, and emotional and physical abuse in the family. Items with factor loadings less than 0.4 were excluded. Items were presented in terms of 4 or 5-point Likert scale. Internal-consistency reliability (Cronbach's α) of the subscales was between 0.83 and 0.94. Based on the similarity in results, the subscales of closeness and support were added together under a common name „warmth in family" and the subscales of abuse and misprize were added together under a common name „maltreatment" in the presentation of data.

For detecting gene — environment interaction effects, subjects were divided into two groups according to the median score on family relations subscales. First, main effects of sex and genotype on family relations and impulsivity were calculated. Multiple analysis of variance (MANOVA) was carried out to detect possible three-way interactions between sex-genotype-family relations on impulsivity. As several effects had a significant interaction with sex, further main effects of genotype and family relations and two-way interactions between these were calculated in boys and girls separately. For comparison of the groups, in case of significant interaction effect, Fisher *post-hocs* are given.

Boys scored higher on the scale of fast decision making compared to girls (t(d.f.= 478) = 3.4, $p < 0.001$, while girls scored higher on the scale of disinhibition (t(d.f.= 479) = 2.5, $p < 0.01$); there were no sex differences in other scores of impulsivity. The S allele carriers of 5-HTTLPR had higher disinhibition compared to LL homozygotes (t(d.f.= 433) = 2.8, $p < 0.01$). Genotype alone was associated with neither thoughtlessness, excitement seeking, fast decision making nor BIS-11 impulsiveness. There were no sex differences of scores on the scales of family relations and 5-HTTLPR genotype did not predict childrens' reports on the scale of family relations.

A significant three-way interaction effect of sex-genotype-warmth in family on thoughtlessness is presented on Figure 1. Among girls carrying the S allele, those scoring low on warmth in family were more thoughtless compared to girls reporting high warmth in family, or girls with LL genotype. This interaction could not be detected among boys. As sex had an important effect on the gene-environment interaction, similar to other studies [12, 37], further analysis was carried out in boys and girls separately. Mean scores of impulsivity subtypes according to 5-HTTLPR genotype and family relations among boys and girls are presented in Table 1.

Girls reporting low warmth in family had significantly higher scores on the scales of disinhibition (t(d.f.=239) = 3.4, $p < 0.001$), thoughtlessness (t(d.f.= 238) = 2.7, $p < 0.01$), and BIS-11 (t(d.f.= 215) = 4.7, $p < 0.00001$). Girls with high maltreatment in family had significantly higher scores on the scales of disinhibition (t(d.f.= 255) = 1.9, $p = 0.05$), thoughtlessness (t(d.f.= 254)= 3.0, $p < 0.01$), and BIS-11 (t(d.f.= 232) = 4.7, $p < 0.000001$). Family relations had no effects on excitement seeking or fast decision making in girls. Further two-way analysis of variance in girls revealed interactive effects of low warmth in family and S allele on disinhibition (F(1,209)=5.8, $p < 0.05$), thoughtlessness (F(1,208)=6.4, $p < 0.05$, Figure 1), and BIS-11 (F(1,186)=4.5, $p < 0.05$). *Post-hoc* analysis revealed that the effects of low warmth in family on disinhibition, thoughtlessness and BIS-11 score appeared only among S allele carrying girls and were not significant in girls with LL genotype (Table 1).

Boys reporting high maltreatment in family had significantly higher scores in disinhibition (t(d.f.= 195) = 3.5, $p < 0.001$) and BIS-11 (t(d.f.= 173) = 3.3, $p < 0.001$), and lower score in excitement seeking (t(d.f.= 195) = 2.0, $p < 0.05$).

Boys with high warmth in family had higher score in fast decision making (t(d.f.= 193) = 2.1, $p < 0.05$), and excitement seeking (t(d.f.=193) =2.2, $p < 0.05$). The S allele of 5-HTTLPR was associated with higher disinhibition (t(d.f.=202) = 2.3, $p < 0.05$), and BIS-11 (t(d.f.= 177) = 2.2, $p < 0.05$) scores in boys. In boys, unlike in girls, there were no statistically significant interaction effects between genotype and family relations.

Low warmth in the families of the S allele carrying girls was associated with higher thoughtlessness, disinhibition and impulsivity according to BIS-11. This is in accordance with several earlier studies demonstrating an interaction of the S allele with environmental adversity on personality traits that are similar to impulsiveness by their maladaptiveness and association with affect-regulation such as neuroticism [36], and also on the risk for depression [5,39,21]. There are no earlier studies which have focused on the influence of 5-HTTLPR S allele and family relations on the trait of impulsivity in adolescents, but positive association of S allele carrying with aggression [14], suicidality [24], higher response to alcohol [19], and higher alcohol consumption in case of „bad" family relations in adolescents [30] have been demonstrated.

While low warmth and maltreatment in family led to impulsivity in S allele carrying girls, unlike in girls with LL genotype, maltreatment by parents was associated with higher impulsiveness in boys regardless of 5-HTTLPR genotype. Thus, our results are in accordance with earlier studies demonstrating that 5-HTTLPR S allele and adverse environment interaction is stronger in female subjects, expressing in higher vulnerability to depression and lower agreeableness in S allele carrying women [23,10,12,37]. Also, S allele in females has been reported to be associated with higher stress-sensitivity, e.g, peer-reared female rhesus macaques with the rh5-HTTLPR S allele have increased adrenocorticotropic hormone and lower cortisol responses to stress, which does not happen among males [2]. In contrast, many of the studies in which the impact of stressful life events has not been considered, have demonstrated an association between presence of the S allele and suicidality [25] or neuroticism [8] solely among males. One possible reason for the difference between the sexes might be that the effect of the serotonin transporter on brain development differs between males and females brain [41], possibly due to an effect of gonadal steroids on the serotonin transporter [1].

The impact of 5-HTTLPR S-allele and adverse family relations on impulsivity is suggested to be developmental rather than direct, as serotonin plays an important role in brain development [22]. It can be further speculated that familial adversity may have a greater impact on S-allele carriers, as several studies report higher sensitivity of their amygdala to negative emotional stimuli, and lower neuronal density in their affect-regulating regions like cingulate and prefrontal cortex [13,34,18]. Post-natal development of prefrontal cortex and cingulate, which are potentially important structures in impulse and emotion regulation and are more active in response to stimuli in 5-HTTLPR S allele

carriers, continues through adolescence until adulthood [29]. Impulsiveness, direct maltreatment (as misprize or abuse) or lack of warmth and support in relationships often go hand in hand. Our study however suggests that lack of warmth has a stronger impact on S allele carrying girls, while boys are most influenced by maltreatment by parents, regardless of genotype. This is partly in concordance with the study by Sjöberg and collegues [37], where S allele carrying girls were more sensitive to poor family relations, while boys were vulnerable to low social status, however in that study this only applied for boys with LL genotype. In a recent study by Kaufman and collegues [21] concentrating on the effects of maltreatment and possible protective factors in S allele carriers, it was stated that high social support did not undo the effect of maltreatment, but low social support highly contributes to the depression score of S allele carriers. Lack of warmth or support from caregivers can have as strong impact as maltreatment on childrens's behavioural development [31]. According to the neurodevelopmental view on impulsivity the brain is actually prepared to be impulsive at birth, and the self-regulation skills are the product of learning and positive parenting. Thus harsh treatment, as well as neglect by parents, may both result in the inability to regulate emotions and impulses in child [7].

The S allele of 5-HTTLPR in combination with adverse family environment predicted only maladaptive types of impulsivity in girls, while the adaptive types of impulsivity depended neither on family relations nor on genotype in girls. In boys, however, the adaptive types of impulsiveness like excitement seeking and fast decision making were associated with positive relations in family. This may be interpreted that girls are more vulnerable to dysfunctions in case of adversity in family, while boys can take more advantage of positive parenting in the development of adaptive traits.

Acknowledgements
This study was supported by grants from the Estonian Ministry of Education and Science (No 0182643 and 0942706) and the Estonian Science Foundation (No 6932 and 6788), the Swedish Science Foundation (VR) and the AFA insurance company. The skilful technical assistance by Ms Erika Comasco is gratefully acknowledged. The study was conducted in accordance with the Declaration of Helsinki.

REFERENCES

[1] G. Attali, A. Weizman, I. Gil-Ad, M. Rehavi, Opposite modulatory effects of ovarian hormones on rat brain dopamine and serotonin transporters, Brain Res 756 (1997) 153–159.

[2] C. S. Barr, T. K. Newman, M. Schwandt, C.Shannon, R.L. Dvoskin, S. G. Lindell, J. Taubman, B.Thompson, M. Champoux, K.P. Lesch, D. Goldman, S. J. Suomi, J. D. Higley, Sexual dichotomy of an interaction between early adversity and the serotonin transporter gene promoter variant in rhesus macaques, Proc Natl Acad Sci USA 33 (2004) 12358–12363.

[3] M. Bourgeois, Serotonin, impulsivity and suicide, Hum Psychopharmacol 6 (1991) S31–36.

[4] M. A. Brotman, M. Schmajuk, B. A. Rich, D. P. Dickstein, A. E. Guyer, E. J. Costello, H. L. Egger, A. Angold, D. S. Pine, E. Leibenluft, Prevalence, clinical correlates, and longitudinal course of severe mood dysregulation in children, Biol Psychiatry 60 (2006) 991–997.

[5] A. Caspi, K. Sugden, T.E. Moffitt, A. Taylor, I.W. Craig, H. Harrington, J. McClay, J. Mill, J. Martin, A. Braithwaite, R. Poulton, Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene, Science 301 (2003) 386–389.

[6] M. G. Cataldo, M. Nobile, M. L. Lorusso, M. Battaglia, M. Molteni, Impulsivity in depressed children and adolescents: A comparison between behavioral and neuropsychological data, Psychiat Res 136 (2005) 123– 133.

[7] J. H. Daruna, P. A. Barnes, A neurodevelopmental view on impulsivity. In: W.B. McCown, J.L. Johnson, M.B. Shure (eds) The impulsive client: theory, research and treatment. American Psychological Association, Washington, DC, 1993, pp 39–56.

[8] L. Du, D. Bakish, P. Hrdina, Gender differences in association between serotonin transporter gene polymorphism and personality traits, Psychiat Gen 10 (2000) 159–164.

[9] D. Eensoo, Risk taking in traffic and markers of risk-taking behaviour in schoolchildren and car drivers, Dissertationes Medicinae Universitatis Tartuensis, Tartu University Press, Tartu, 2007, p 58.

[10] T.C. Eley, K. Sugden, A. Corsico, A.M. Gregory, P. Sham, P. McGuffin, R. Plomin I.W Craig, Gene-environment interaction analysis of serotonin system markers with adolescent depression, Mol Psychiatry 9 (2004) 908–915.

[11] G. Gerra, L. Garofano, L. Castaldini, F. Rovetto, A. Zaimovic, G. Moi, M. Bussandri, B. Branchi, F. Brambilla, G. Friso, C. Donnini, Serotonin transporter promoter polymorphism genotype is associated with temperament, personality traits and illegal drugs use among adolescents, J Neural Transm 112 (2005) 1397–1410.

[12] H.J. Grabe, M. Lange, B. Wolff, H. Völzke, M. Lucht, H.J. Freyberger, U. John, I. Cascorbi, Mental and physical distress is modulated by a polymorphism in the 5-HT transporter gene interacting with social stressors and chronic disease burden, Mol Psychiatry 10 (2005) 220–224.

[13] A. Graff-Guerrero, C. De la Fuente-Sandoval, B. Camarena, D.Gómez-Martin, R. Apiquián, A. Fresán, A. Aguilar, J.C. Méndez-Núñez, C. Escalona-Huerta, R. Drucker-Colín, H. Nicolini, Frontal and limbic metabolic differences in subjects

selected according to genetic variation of the SLC6A4 gene polymorphism, NeuroImage 25 (2005) 1197–1204.
[14] B.C. Haberstick, A. Smolen, J.K.Hewitt, Family-based association test of the 5HTTLPR and aggressive behavior in a general population sample of children, Biol Psychiatry 59 (2006) 836–843.
[15] T. Hallikainen, T. Saito, H.M. Lachman, J. Volavka, T. Pojhanen, O.P. Ryynänen, J. Kauhanen, E. Syvalahti, J. Hietala, J. Tiihonen, Association between low activity serotonin transporter promoter genotype and early onset alcoholism with habitual impulsive violent behavior, Mol Psychiatry 4 (1999) 385–388.
[16] A.R. Hariri, V.S. Mattay, A. Tessitore F. Fera, D.R. Weinberger, Neocortical modulation of the amygdala response to fearful stimuli, Biol Psychiatry 53 (2003) 494–501.
[17] M. Harro, D. Eensoo, E. Kiive, L. Merenäkk, J. Alep, L. Oreland, J. Harro, Platelet monoamine oxidase in healthy 9- and 15-years old children: the effect of gender, smoking and puberty, Prog Neuro-Psychopharmacol Biol Psychiatry 25 (2001) 1497–1511.
[18] A. Heinz, D.F. Braus, M.N. Smolka, J. Wrase, I. Puls, D. Hermann, S. Klein, S.M. Grüsser, H. Flor, G. Schumann, K. Mann, C. Büchel, Amygdala-prefrontal coupling depends on a genetic variation of the serotonin transporter, Nat Neurosci 8 (2005) 20–21.
[19] A. S. Hinckers, M.Laucht, M.H.Schmidt, K.F.Mann, G. Schumann, M.A.Schuckit, A. Heinz, Low level of response to alcohol is associated with serotonin transporter genotype and high alcohol intake in adolescents, Biol Psychiatry 60 (2006) 282–287.
[20] B. Hoefgen, T.G. Schulze, S. Ohlraun, O. von Widdern, S. Höfels, M. Gross, V. Heidmann, S. Kovalenko, A. Eckermann, H. Kölsch, M. Metten, A. Zobel, T. Becker, M.M. Nöthen, P. Propping, R. Heun, W. Maier, M. Rietschel, The power of sample size and homogenous sampling: Association between the 5-HTTLPR serotonin transporter polymorphism and major depressive disorder, Biol Psychiatry 57 (2005) 247–251.
[21] J. Kaufman, B.Z.Yang, H.D-Palumberi, D. Grasso, D. Lipschitz, Shadi. Houshyar, J.H. Krystal, J. Gelernter, Brain-derived neurotrophic factor-5-HTTLPR gene interactions and environmental modifers of depression in children, Biol Psychiatry 59 (2006) 673–680.
[22] K.P. Lesch, L. Gutknecht, Pharmacogenetics of the serotonin transporter, Prog Neuropsychopharmacol Biol Psychiatry 29 (2005) 1062–1073.
[23] K. P. Lesch, U. Merschdorf, Impulsivity, aggression, and serotonin: a molecular psychobiological perspective, Behav Sci Law 18 (2000) 581–604.
[24] D. Li, L. He, Meta-analysis supports association between serotonin Transporter (5-HTT) and suicidal behavior, Mol Psychiatry 12 (2007) 47–54.
[25] F. Limosin, J.-Y. Loze, C. Boni, M. Hamon, J. Ades, F. Rouillon, P. Gorwood, Male-specific association between the 5-HTTLPR S allele and suicide attempts in alcohol-dependent subjects, J Psychiat Res 39 (2005) 179–182.
[26] M. Liotti, J. Panksepp, Imaging human emotions and affective feelings: implications for biological psychiatry, In: J. Panksepp (Ed.), Textbook of Biological Psychiatry 2004, Wiley-Liss, Inc., Hoboken, New Jersey pp 33–66

[27] S.B. Manuck, J.D. Flory, R.E. Ferrell, M.F. Muldoon, Socio-economic status covaries with central nervous system serotonergic responsivity as a function of allelic variation in the serotonin transporter gene-linked polymorphic region, Psychoneuroendocrinology 29 (2004) 651–668.
[28] E. Masoliver**,** A. Menoyo, V. Pérez, Serotonin transporter linked promoter (polymorphism) in the serotonin transporter gene may be associated with antidepressant-induced mania in bipolar disorder, Psychiatr Genet, 16 (2006) 25–29.
[29] C. A. Nelson, Neurobehavioral development in the context of biocultural co-constructivism. In: Lifespan development and the brain: the perspective of biocultural co-constructivism, P.B. Baltes, P.A. Reuter-Lorenz, F. Rösler (eds) Cambridge University Press, USA, NY, (2006) pp 61–81.
[30] K.W.Nilsson, R.L.Sjöberg, M. Damberg, P. O. Alm, J. Öhrvik, J. Leppert, L. Lindström, L. Oreland, Role of the serotonin transporter gene and family function in adolescent alcohol consumption, Alcohol Clin Exp Res, 29 (2005) 564–570.
[31] S.L. Olson, J.E. Bates, K. Bayles, Early antecedents of childhood impulsivity: The role of parent-child interaction, cognitive competence, and temperament, J Abnorm Child Psych, 18 (1990) 317–334.
[32] M. Paaver, D. Eensoo, A. Pulver, J. Harro, Adaptive and maladaptive impulsivity, platelet monoamine oxidase (MAO) activity and risk-admitting in different types of risky drivers, Psychopharmacology 186 (2006) 32–40.
[33] J.H. Patton, M.S. Stanford, E.S. Barratt, Factor structure of the Barratt Impulsiveness Scale, J Clin Psychol 51 (1995) 768–774.
[34] L. Pezawas, A. Meyer-Lindenberg, E.M. Drabant, B.A. Verchinski, K.E. Munoz, B.S. Kolachana, M.F. Egan, V.S. Mattay, A.R. Hariri, D.R. Weinberger, 5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: a genetic susceptibility mechanism for depression, Nat Neurosci 8 (2005) 828–834.
[35] D.C. Purselle, C.B. Nemeroff, Serotonin transporter: a potential substrate in the biology of suicide, Neuropsychopharmacol 28 (2003) 613–619.
[36] S. Sen, M. Burmeister, D. Ghosh, Meta-analysis of the association between a serotonin transporter promoter polymorphism (5-HTTLPR) and anxiety-related personality traits, Am J Med Genet B Neuropsychiatr Genet, 127 (2004) 85–89.
[37] R. L. Sjöberg, K. W. Nilsson, N. Nordquist, J. Öhrvik, J. Leppert, L. Lindström, L. Oreland, Development of depression: sex and the interaction between environment and a promoter polymorphism of the serotonin transporter gene, Int J Neuropsychop 9 (2005) 1–7.
[38] M.A. Straus, V.E. Mouradian, Impulsive corporal punishment by mothers and antisocial behavior and impulsiveness of children, Behav Sci Law, 16 (1998) 353–374.
[39] S.E. Taylor, B.M. Way, W.T. Welch, C.J. Hilmert, B.J. Lehman, N. I. Eisenberger, Early family environment, current adversity, the serotonin transporter promoter polymorphism, and depressive symptomatology, Biol Psychiatry 60 (2006) 671–676.
[40] S. Tuinier, W. M. A. Verhoeven, H. M.van Praag, Serotonin and disruptive behaviour: a critical review. Hum Psychopharmacol 11 (1996) 469–482.
[41] Z. Xu, F.J.Seidler, S.F.Ali, W.Slikker Jr., T.A.Slotkin, Fetal and adolescent nicotine administration: effects on CNS serotonergic systems, Brain Res 914 (2001) 166–178.

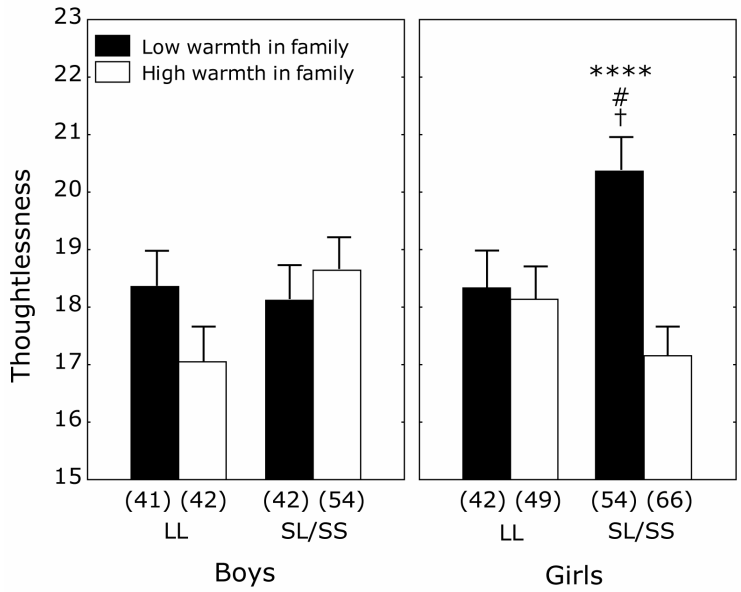

Figure 1. Interaction effect of 5-HTTLPR X warmth in family X sex on the score of thoughtlessness [$F(1, 382)= 8.2$, $p < 0.01$] **** $p < 0.0001$ vs S allele+high warmth in family+girls, # $p < 0.05$ vs LL+low warmth in family+girls, † $p < 0.05$ vs LL+high warmth in family+girls

CURRICULUM VITAE

Marika Paaver

Citizenship: Estonian
Date of birth: February 21th, 1978
Address: Department of Psychology, University of Tartu, Tiigi 78, Tartu 50410
Telephone: +372 520 3301
E-mail: marika.paaver@ut.ee

Education

2003–2007	Doctoral studies, University of Tartu, doctoral student
2001–2003	Master's studies University of Tartu, Department of Psychology MSc in psychology (*cum laude*)
1998	guest student in Tallinn University of Educational Sciences
1996–2001	Bachelor's studies, University of Tartu

Professional employment

Since 2005	Psychologist (0.5) Tartu University Hospital, Psychiatry Clinic
2003–2006	Research fellow and lecturer, The Department of Psychology, University of Tartu
2002–2003	Project manager, University of Tartu, Department of Psychology
2001–2003	Lecturer of psychology in the Higher Art School of Tartu
2000	Personnel consultant in Estonian Landboard

Scientific activity

Main research area is the construct of impulsivity, its adaptiveness, expression in behaviour and association with the function of monoaminergic systems

Membership of professional organisations

Union of Estonian Psychologists
The Estonian Centre of Behavioural and Health Sciences

CURRICULUM VITAE

Marika Paaver

Kodakondsus: Eesti
Sünniaeg ja koht: 21.02.1978, Tartu
Aadress: Tiigi 78, TÜ Psühholoogia osakond, 50410, Tartu
Telefon: +372 520 3301
E-post: marikaps@ut.ee

Haridus

2003–2007	Doktoriõpe, Tartu Ülikool, Psühholoogia
2002–2003	Magistriõpe, Tartu Ülikool, MSc psühholoogia erialal (*cum laude)*
1996–2001	Bakalaureuseõpe, psühholoogia, Tartu Ülikool, BSc
1998	Tallinna Pedagoogikaülikool (külalisüliõpilane)

Teenistuskäik:

2003–2006	Erakorraline teadur, TÜ psühholoogia osakond
Alates 2005	Psühholoog, TÜ Psühhiaatriakliinik, 0,5 koormusega
Alates 2003	Õppeülesande täitja ettevõtulepinguga, Tartu Ülikool
2002–2003	Projektijuht ettevõtulepinguga Maanteeameti tellimuslepingu täitmiseks, Tartu Ülikool
2001	Suhtlemispsühholoogia õppejõud, Tartu Kõrgem Kunstikool
2000	Personalikonsultant, EV Maa-amet

Peamised uurimisvaldkonnad
Impulsiivsuse konstrukt, adaptiivsus, väljendumine käitumises ning seosed närvisüsteemi monoamiinergiliste virgatsainete talitlusega

Kuulumine erialastesse organisatsioonidesse
Eesti Psühholoogide Liit
Eesti Käitumis- ja Terviseteaduste Keskus

DISSERTATIONES PSYCHOLOGICAE UNIVERSITATIS TARTUENSIS

1. **Jüri Kruusvall.** Environmental and social influence on human activity. Tartu, 1994, 135 p.
2. **Dagmar Kutsar.** Transformation in Estonia as reflected in families: Insight into social stress and poverty. Tartu, 1995, 171 p.
3. **Aleksander Pulver.** Measurement of elementary movement vectors in human visual system. Tartu, 1995, 123 p.
4. **Ritva Fagerström.** The correlations between psychological factors and vision in aged cataract operation patients. Tartu, 1996, 145 p.
5. **Eve Kikas.** Conceptual development in school-aged children: The impact of teaching. Tartu, 1997, 112 p.
6. **Anu Realo.** Individualism and collectivism: An exploration of individual and cultural differences. Tartu, 1999, 164 p.
7. **Aaro Toomela.** Cultural-historical psychology: three levels of analysis. Tartu, 2000, 171 p.
8. **Anneli Kolk.** Cognitive development of children with non-progressive unilateral brain lesion. Tartu 2001, 95 p.
9. **Aune Valk.** Two facets of ethnic identity: pride and differentiation. Tartu, 2001, 153 p.
10. **Anu Aluoja.** Depression in the population: assessment, prevalence and relationships with socio-demographic factors and cognitive aspect of social adjustment. Tartu 2002, 73 p.
11. **Talvi Kallasmaa.** Personality traits and ways of coping: their characteristics and interrelations. Tartu 2002, 119 p.
12. **Luule Mizera.** Socialization in Estonian families: attitudes and behavior in comparative perspective. Tartu 2003, 117 p.
13. **Kairi Kreegipuu.** Availability and accessibility of information in perception of moving stimuli. Tartu 2004, 97 p.
14. **Riina Häidkind.** Monoaminergic mechanisms in mood-associated behaviours and neurochemistry in rats. Tartu 2004, 123 p.
15. **Evelin Kiive.** Studies on peripheral markers of central serotonergic activity and behaviour. Tartu, 2005, 113 p.
16. **Helle Pullmann.** The development of intelligence and personality traits among Estonian schoolchildren. Tartu, 2005, 112 p.
17. **Kenn Konstabel.** The structure and validity of self- and peer-reported personality traits. Tartu, 2006, 103 p.
18. **Toivo Aavik.** Lexical analysis of Estonian personal values vocabulary and relation to socially desirable responding and parenting practices. Tartu, 2006, 113 p.

19. **Margus Tõnissaar.** Stress and sociability: individual differences and their neurochemical substrate. Tartu, 2006, 161 p.
20. **Kaia Laidra.** Adolescent personality: Development, interrater agreement, and relation to academic achievement. Tartu, 2007, 117 p.
21. **Iiris Luiga.** Interaction of object perception and visual attentional selection processes. Tartu, 2007, 116 p.