Neurocognitive models of schizophrenia and mood disorders: the role of decision-making and visual information processing

Ph.D. Thesis

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I. ABBREVIATIONS

5-HTT	serotonin transporter
5-HTTLPR	serotonin transporter promoter polymorphism
ACC	anterior cingulate cortex
ANOVA	analysis of variances
BPRS	Brief Psychiatric Rating Scale
CPT	Continuous Performance Test
DLPFC	dorsolateral prefrontal cortex
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders IV
EEG	electroencephalography
fMRI	functional magnetic resonance imaging
GAP-43	growth associated protein
HAM-A	Hamilton Anxiety Rating Scale
HAM-D	Hamilton Depression Rating Scale
IGT	Iowa Gambling Test
IQ	intelligence quotient
K	koniocellular
LOC	lateral occipital complex
LGN	lateral geniculate nucleus
M	magnocellular
MANOVA	multivariate analysis of variances
MDD	major depressive disorder
MINI	Mini International Neuropsychiatric Interview
mRNA	messenger ribonucleic acid
NMDA	*N*-methyl-D-aspartate
OFC	orbitofrontal cortex
P	parvocellular
PET	positron emission tomography
PFC	prefrontal cortex
SANS	Scale for the Assessment of Negative Symptoms
SAPS	Scale for the Assessment of Positive Symptoms
SD	standard deviation
SSRI	selective serotonin reuptake inhibitor
TCI	Temperament and Character Inventory
V1	primary visual cortex
V2	visual area 2
V4	visual area 4
V5	visual area 5
VMPFC	ventromedial prefrontal cortex
VLPFC	ventrolateral prefrontal cortex
WCST	Wisconsin Card Sorting Test

II. AIMS AND SCOPES OF THIS WORK

The prefrontal cortex (PFC) may play an important role in the development of the symptoms of major psychiatric disorders. The aim of our study was to investigate functions related to regions of the PFC using neuropsychological tests. The main hypothesis was that these functions reflect genetic vulnerability and are associated with personality traits and with the state of the illness. Alterations of cognitive functions, including executive functions, attention, verbal memory, and psychomotor speed were described in schizophrenia by several previous studies. However, dysfunctions of low level visual processing are less known. Our purpose was to analyze functional alterations of primary visual information processing pathways and areas as measured by contrast categorization deficit and lateral connectivity impairments in early visual cortex of schizophrenia patients. Some of these deficits might also be called endophenotypes, as being present in healthy relatives of schizophrenia patients as well. However, heredity might have a major contribution in the development of motion-sensitive areas in the dorsal occipito-parietal visual system. Specific genetic and environmental factors, by affecting brain maturation and development, might have a role in higher vulnerability to the illness. Evidence suggests that gene x environment interactions play a crucial role in the pathophisiology of affective disorders, mentioning major depressive disorder in first line. Related to that, we also focused on the role of personality traits associated to genetic factors and cognitive function.

The work presented might be considered somehow heterogeneous, but hopefully lines up with the exciting, enigmatic and colorful research work done in the field of neurocognition in major psychiatric disorders.

Of course the work presented here is not done by one person, but is a real team-work. In order to provide a better understanding and a conceptual frame to the neurocognitive research methods embedded in the clinical work, I include the essential work of my colleagues with their permission.

The aims and scopes of my work included in the present thesis are as follows:

1. Contrast categorization deficit in schizophrenia and healthy relatives

The relationship between the precortical magno (M) and parvocellular (P) pathways was investigated with a new contrast categorization task assessing low level perception, memory, and abstraction. Three task variants including three different contrast ranges were presented to schizophrenic patients, siblings with no history of psychiatric symptoms and healthy control subjects. Patients with schizophrenia showed a generalized dysfunction, which suggests contrast-independent memory and abstraction problems. In contrast, siblings were selectively impaired on the task variant that included the 10-15% contrast range, the transition zone between M and P pathway contrast sensitivity. This might be considered as support for genetic vulnerability associated to schizophrenia.

2. Collinear facilitation in schizophrenia

Contrast thresholds were measured for centrally presented Gabor patches which were surrounded by two collinear or orthogonal flankers presented on a computer screen. The healthy subjects showed lower contrast thresholds for central Gabor patches when collinear flankers were presented. This effect was significantly reduced in unmedicated highly functioning schizophrenia patients who performed normally on the continuous performance test (Nuechterlein et al., 1986). The facilitation effect of collinear flankers is believed to reflect lateral interactions between feature-specific units in early visual cortex (V1) (Polat and Sagi, 1993, Kapadia et al., 1995). Our results therefore suggest abnormal lateral interactions in early visual cortex of schizophrenia patients.

3. Development of motion and form processing in children with increased risk of psychosis

Research focusing on schizophrenia vulnerability claims that motion-sensitive areas in the dorsal occipito-parietal visual system are vulnerable to genetic and environmental factors, which affect brain maturation and development (Braddick et al., 2003). According to this idea, in our follow-up study, we aimed to investigate the possibility that developmental anomalies of directional motion perception can be detected in children of mothers with schizophrenia and bipolar disorder by measuring motion and form coherence thresholds. Results revealed that the rate of development in the motion task was less pronounced in children of mothers with schizophrenia than that in children of mothers with bipolar disorder

and in age-matched controls. The development of form perception was spared. Children of mothers with bipolar disorder showed an intact development in both motion and form perception tasks. These results suggest that the progressive developmental abnormality of motion-sensitive visual areas may be a characteristic feature of schizophrenia-vulnerability. However, the exact nature of motion perception dysfunctions is an important question and might be closely related to early visual processing abnormalities. It is possible that motion perception dysfunctions are related to magnocellular pathology, whereas intact form perception can be explained by relatively preserved parvocellular functions.

5. Decision-making in major depressive disorder

Patients with major depressive disorder show a diversity of neuropsychological impairments, including deficiency of executive functions (working memory, problem solving, planning) (Crews and Harrison, 1995), altered approach-related behavior and decision-making impairments, detected by measuring sensitivity to reward and punishment (Henriques et al., 1994). Executive functions (Wisconsin Card Sorting Test, WCST) (Heaton et al. 1993) and contingency learning based on the cumulative effect of reward and punishment (Iowa Gambling Test, IGT) (Bechara et al., 2000) were assessed in patients with unipolar MDD and healthy control volunteers. Medicated patients with MDD show altered sensitivity to reward and punishment: immediate large reward enhanced related response patterns even when the strategy was disadvantageous and immediate large punishment did not prohibit related response patterns. Impairments in emotional decision-making were not a pure consequence of executive dysfunctions. Our results suggest a global impairment of the PFC in depression, which includes the dorsolateral and ventromedial regions.

6. Personality traits and genetic influences on decision-making

Personality traits and genetic variations might have remarkable influence on decision-making strategies (Brown and Hariri, 2006). Contingency learning based on the cumulative effect of reward and punishment was assessed in patients with unipolar MDD using the ABCD (reward sensitivity) and EFGH (punishment sensitivity) versions of the Iowa Gambling Test. All patients were genotyped for serotonin transporter promoter polymorphism (5-HTTLPR) and received the Temperament and Character Inventory (TCI). Patients with the ‘ll’ genotype achieved higher persistence scores on the TCI and used more optimal decision-making strategy on the task more sensitive to reward compared to the ‘ss’ homozygotes. Higher persistence was associated with better performance on the ABCD task, and higher harm-

avoidance was associated with worse performance on the task more sensitive to punishment. Depressed patients performed poorly on the ABCD test and showed normal performance on the EFGH test. According to our findings, genotype of 5-HTTLPR more prominently predicts decision making functions than depressive symptoms. Personality traits and 5-HTTLPR polymorphism may explain the paradoxical decision-making strategy (selecting high immediate reward) in depressed patients.

III. OVERVIEW

III.1. VISUAL PROCESSING DEFICITS IN SCHIZOPHRENIA

Vision plays a fundamental role in directing human behavior. When opening our eyes, we automatically perceive an integrated image of the world and, seeing other people's faces and their expressions drive motor and cognitive responses as well. Thus, understanding the mechanism of visual processing is an intriguing issue. Recent evidence implicates abnormal visual information processing and visually driven attention in a number of neurodevelopmental and psychiatric disorders, including schizophrenia. Alterations of cognitive functions, including executive functions, attention, verbal memory, and psychomotor speed in schizophrenia were described by several previous studies (Donohoe and Robertson, 2003). However, dysfunctions of low level visual processing are less known. On the other hand, there is evidence suggesting impairment in the complexity of the neural network system of the primary visual cortex in schizophrenia (Freeman et al., 2001). A comprehensive understanding of the human visual system may contribute to an understanding of behavioral impairments connected to schizophrenia or other psychiatric disorders. Our purpose was to study visual information processing pathways and to analyze lateral connectivity in early visual cortex of schizophrenia patients. Human visual information processing involves a complex mechanism. Signals must travel from the photoreceptors of the retina to the retinal ganglion cells and then along the optic nerve and optic tract to the thalamus and midbrain, and through to primary visual cortex, and on into different extra-striate parietal, temporal and frontal regions, where different visual stimulus characteristics are processed quite independently. These different aspects must then be integrated into a global image (Livingstone and Hubel, 1987, Livingstone and Hubel, 1988). Recent research in the field of the human visual system in connection with neurodevelopmental and psychiatric disorders found impairments in perceptual processing and visual integration and attention in schizophrenia (Lubow et al., 2000). A further important feature is delivered by reports demonstrating a correlation between higher-level cognitive and affective impairment, such as working memory, emotion and social perception and early visual processing in schizophrenia (Kee et al., 1998, Brenner et al., 2002, Sergi et al., 2006). These results suggest early visual information processing deficits to be related to a reduction in processing of significance and meaning of visual stimuli, especially when looking at the recent research

evidence showing specific magnocellular impairment in schizophrenia (Butler et al., 2005). These findings further support the early-stage visual processing dysfunction in schizophrenia but also underline the connection to higher cognitive deficits and thus, prediction of community functioning. The magnocellular system operates normally in a nonlinear amplification mode mediated by glutamatergic (*N*-methyl-D-aspartate) receptors. Thus, late evidence also suggests that early stage visual impairment in schizophrenia might be related to decreased nonlinear signal amplification, consistent with glutamatergic theories.

However, in most of the complex neurodevelopmental (e.g. autism) and psychiatric disorders such as schizophrenia, it is not yet clarified if an aetiological role can be attributed to visual processing problems. Our purpose therefore was to analyze deficits in the visual system of schizophrenia patients. Understanding the specific role of neural networks involved in visual perception may also allow progress in understanding the role of attentional symptomatology in schizophrenia and probably other psychiatric disorders. Before this may be achieved we need to take a closer look at the human visual system and how this complex and fascinating network operates. More recent models of visual processing involve mechanisms like fast feedforward, feedback and lateral signals. Explaining this keywords may bring us closer to the background of the visual dysfunctions reported in schizophrenia (Laycock et al., 2007).

In a 1973 study, Kulikowski and Tolhurst were the first to describe a ‘transient’ channel found to be more sensitive to high temporal and low spatial frequencies and another, ‘sustained’ channel which, conversely, was more sensitive to low temporal and high spatial stimulus frequencies. This was the first evidence proving two, psychophysically defined, separate information channels in the human visual system from retina to the cortex (Kulikowski and Tolhurst, 1973). Further support came from anatomical and physiological studies of the primate visual system. Livingstone and Hubel demonstrated that differences found between cell properties at lower levels of the primate visual system correspond to the two visual streams defined, the transient and the sustained channel, respectively (Livingstone and Hubel, 1988). The so called M-pathway which is more sensitive to motion is derived from the magnocellular geniculate subdivisions of the Lateral Geniculate Nucleus (LGN) of the thalamus and originates in the M-type retinal ganglion cells (10%). The smaller, but more populous (80%) P-type retinal ganglion cells serve as the afferent projection of the parvocellular subdivisions of the LGN proceeding in the P-pathway which was described to be sensitive to form and color of visual stimuli (Callaway, 2005). Much less is known about the third, the koniocellular (K) pathway, which is derived from interlaminar cells in the LGN

that seem to have larger receptive fields and more diverse response properties than do the other two cell types (Casagrande, 1999, Hendry and Reid, 2000, Callaway, 2005). Further evidence especially from lesion studies in primates shows that the M-pathway, like the human transient channel, is more sensitive to low contrast stimuli, thus performs best for motion detection and localization of objects in space. Contrary to that, the P-pathway, like the sustained channel, has been proven to preferentially respond to medium to high contrast stimuli and thus, seem to be optimal for recognizing objects and identifying patterns, colors and fine details (Kaplan and Shapley, 1982). However, one should take into account the role of the koniocellular system as well, if considering lesion studies of the laminar layers.

In their study, Livingstone and Hubel also mapped out the visual processing streams including the retino-geniculo-striate projection in an anatomical manner. They proposed that the magnocellular layers project through the dorsal stream to the parietal cortex, while the parvocellular layers project through the ventral stream to the temporal cortex, both of them being completely separated (Livingstone and Hubel, 1988). More recent evidence indicates that the two pathways are not fully segregated and that they carry complementary contributions to the cortical areas involved in the higher-level visual processing (Maunsell et al., 1990, Merigan and Maunsell, 1993). Recent, converging evidence also suggests that not only are there complementarities in the projection of the different layers but the idea that motion processing relies on the dorsal stream only and form processing relies on the ventral stream alone might also be too simplistic. According to this, there is evidence for magnocellular layers projection through the ventral stream (Mace et al., 2005), and, on the other hand, parvocellular contributions through the dorsal stream, although, to a lesser extent (Maunsell et al., 1990).

The challenging demand for explaining how visual information is so rapidly integrated into perception led to a large number of studies examining the hierarchical maps and connections of the human visual system. It was initially proposed that projections proceed mainly in a feedforward manner, from low-order areas such as the primary visual cortex (V1) and visual area 2 (V2) to higher order areas such as V5 in the occipito-parietal areas of the dorsal stream and V4 and the Lateral Occipital Complex (LOC) concerning the inferotemporal areas of the ventral stream (Malach et al., 1995). By taking this ‘road’ increasingly complex characteristics may be processed. However, these findings already raised the question of the role of the interconnections between different regions and the possibility of feedback and lateral projections and interactions. This feedback or top-down conditioning has been recently

proved to be fast enough to decisively affect lower cortical areas and their role in achieving visual awareness. In 2002 Foxe and Simpson published exact data about the information processing time through the visual streams on into the prefrontal cortex in humans found to be within 30 ms after passing V1. Thus, since the visual cortex remains active for about 400m ms, there is sufficient time for multiple, complex interactions at all participating levels of the visual system (Foxe and Simpson, 2002). Besides that, conductions speed differences found between the larger magnocellular and the smaller parvocellular layers might also serve as an explanation for the existence of feedback projections and their role in achieving a rapid, integrated and detailed visual analysis of the real world surrounding us. The magnocellular layers are considered to have an 'advantage' of 25-30 ms in the processing speed and the signal arrival in V1 (Paulus et al., 1999). Thus, according to Bullier and co-workers (Bullier et al., 2001), higher-ordered V5 areas are rapidly activated and feedback projections from the dorsal stream into the primary visual areas are sufficiently rapid to carry global information from cortical areas and thus, to be able to influence visual processing prior to arrival of the P-pathway projection. This seems to be necessary for reaching visual awareness and further discrimination.

III.2. CONTRAST CATEGORIZATION DEFICIT IN SCHIZOPHRENIA

Recent research advances in the field of psychiatric disorders with special regards to schizophrenia discovered discrete alterations sometimes detectable even in the behavior of these patients prior to the full development of the illness. In some cases, these can also be found in healthy relatives and thus, can be named endophenotypes or trait-markers of the illness, if fulfilling definition criteria (Gottesman and Gould, 2003, Keri and Janka, 2004a). These markers might be of great significance in detecting possible genetic vulnerability associated to the disorder, thus hopefully improving early diagnosis and therapy (Keri and Janka, 2004b). A large number of findings suggest impairments in higher-ordered cognitive functions in schizophrenia, however alterations in low perceptual level functions have been described as well. As part of these, we emphasized on low level visual processing deficits, which also have been described in healthy relatives using different and less specific measuring methods (Kremen et al., 1994, Chen and Faraone, 2000, Keri et al., 2004). Thus, we speculated that a task measuring cognitive functions and perception in an integrated manner could provide a conceptual frame to the heterogeneous symptomatology of the illness. The relationship between the magno and parvocellular pathways was investigated with a contrast categorization task studying low level perception, memory and abstraction. The

contrast-categorization paradigm consists of the detection and visual processing of the stimulus involving two pathways which were described earlier in the thesis. The P-pathway processes high contrast stimuli, while the M-pathway low contrast stimuli in the phase of early visual processing.

Our aim was to investigate if deficits in memory, attention and perceptional function can also be detected in healthy first-degree biological relatives, in this case siblings of schizophrenia patients and thus, if one of these measures might be a genetic marker of the illness.

III.3. COLLINEAR FACILITATION IN SCHIZOPHRENIA

Disturbances in visual perception might also be related to impaired neuronal connections. Evidence suggests that impaired neuronal connectivity due to various genetic, developmental, and environmental factors is a hallmark of schizophrenia (Friston, 1998). In this respect, the dorsolateral prefrontal cortex (DLPFC) is one of the most intensively investigated brain regions. Increased neuronal density and reduced interneuronal neuropil have been demonstrated in the DLPFC (Brodmann area 9 and 46) of schizophrenia patients (Selemon, 2001). This neuropathological finding was confined to the dorsolateral parts; in the more ventrally localized Broca's area (Brodmann area 44), cell packing was normal (Selemon et al., 2003). Unexpectedly, increased neuronal density was also found in the primary visual area (V1) of the occipital cortex (Brodmann area 17) (Selemon, 2001). In accordance with this finding, reduced levels of synaptic protein (synaptophysin and GAP-43) mRNAs and altered complex gene expression profiles have been revealed in the occipital cortex of schizophrenia patients (Selemon, 2001). Taylor and his co-workers (Taylor et al., 1997) demonstrated excessive stimulus-evoked regional cerebral blood flow changes in the occipital cortex of schizophrenia patients. Abnormal EEG alpha activity and glucose metabolic rate in the same cortical area have also been described (Danos et al., 2001). Despite these intriguing findings, the functional consequences of occipital abnormalities are not exactly known in sharp contrast to the mounting behavioral evidence on DLPFC dysfunction resulting in impaired executive functions, working memory, and attention in patients with schizophrenia (Donohoe and Robertson, 2003, Ragland et al., 2007). These deficits are associated with molecular and morphological alterations in the DLPFC, each of which could reflect the neuroplasticity of the brain in response to the underlying disease process. Disturbances in excitatory, inhibitory, and modulatory connections of DLPFC circuitry might be related to the heterogenous symptomatolgy and serve as possible novel therapeutic targets (Lewis and Gonzalez-Burgos,

2008). However, impairments in the occipital cortical areas of schizophrenic patients might be related to visual processing and contrast categorization deficits, which we emphasized on in this study. Although visual perception has been studied in schizophrenia, targeted and specific testing of early visual areas is difficult. We used a well-controlled psychophysical method, which is devoted to the testing of lateral connectivity of cells in early visual areas (V1) (Polat and Sagi, 1993, Freeman et al., 2001). Contrast thresholds were measured for centrally presented Gabor patches, named after their inventor, which were surrounded by two collinear or orthogonal flankers.

Based on this data, we investigated lateral connectivity in early visual cortex of schizophrenia patients by measuring contrast thresholds for Gabor patches. The facilitation effect of collinear flankers present in healthy controls is believed to reflect lateral interactions between feature-specific units in early visual cortex (V1). This facilitation effect is attenuated in schizophrenia, suggesting abnormal lateral interactions in early visual cortex of schizophrenia patients.

III.4. DEVELOPMENT OF MOTION AND FORM PROCESSING IN CHILDREN WITH INCREASED RISK OF PSYCHOSIS

Impaired structure and functioning of the occipital cortex in schizophrenia is supported by converging evidence. Research focusing on schizophrenia vulnerability claims that motion-sensitive areas in the dorsal occipito-parietal visual system are vulnerable to genetic and environmental factors, which affect brain maturation and development. These theories suggest that abnormalities of brain development and maturation begin prenatally and continue throughout childhood (Woods, 1998). Results from high-risk studies indicate childhood developmental impairments preceding schizophrenia in cognition, language, motor performance, social adaptation, and emotional functions as well (Niemi et al., 2003). Less severe developmental abnormalities have also been described in children who later develop bipolar disorder, but these seem to be confined to social and emotional functions (Murray et al., 2004). A series of studies have demonstrated a deficit of directional motion processing as compared to global form processing in several developmental disorders, including Williams syndrome (Atkinson et al., 1997), autism (Spencer et al., 2000), childhood hemiplegia (Gunn et al., 2002), fragile X syndrome (Kogan et al., 2004), but not only. Recent studies have consistently demonstrated impaired motion perception in schizophrenia as well (Stuve et al.,

1997, Chen et al., 1999a, Chen et al., 1999b), (Chen et al., 2003, Chen et al., 2004) (Schwartz et al., 1999, Li, 2002, Brenner et al., 2003, Kelemen et al., 2005), but not in bipolar disorder (Chen et al., 2005). Thus, the investigation of motion perception may provide a unique opportunity to gain more insight into developmental abnormalities present in severe mental disorders.

The nature of motion perception dysfunction in psychiatric disorders is an important question. Recent evidence suggests that the magnocellular pathway is especially affected in schizophrenia and that its impairment correlates with higher level cognitive, social, and community functions (Butler and Javitt, 2005). It is possible that motion perception dysfunctions are related to magnocellular pathology, whereas intact form perception can be explained by relatively preserved parvocellular functions. Slaghuis and his colleagues demonstrated that in comparison with normal controls, the threshold for the perception of coherent motion in the group with schizophrenia was significantly higher at the lowest target velocity examined, which was of 6.0 °/s but not at target velocities of 12.0 and 24.0 °/s. Stimulus density was found to have a significant effect on the perception of coherent motion, but it had no differential effect on performance in the groups. The authors concluded that the significant reduction in sensitivity for the perception of coherent motion at the lowest target velocity of 6.0 °/s in the group with schizophrenia is consistent with an impairment in the detection of visual motion at a local level and in parallel for all parts of the image starting from low level visual processing pathways (Slaghuis et al., 2007).

Our purpose was to analyze the possibility that developmental anomalies of directional motion perception can be detected in children of mothers with schizophrenia and bipolar disorder. In a prospective follow-up study we directly measured motion and form perception in children of mothers with schizophrenia and bipolar disorder and compared that with the performance of children with negative family history. Our hypothesis was that the development of motion perception is specifically impaired in children of mothers with schizophrenia.

III.5. DECISION- MAKING IN MAJOR DEPRESSIVE DISORDER

The second part of the thesis focuses on neuropsychological assessment of cognitive abilities in unipolar major depressive disorder. Patients with major depressive disorder show a diversity of neuropsychological impairments, including deficiency of executive functions

(working memory, problem solving, planning), altered approach-related behavior and decision-making impairments, detected by measuring sensitivity to reward and punishment.

Converging evidence from animal models, postmortem and neuroimaging studies suggests that several brain areas are involved in the patophysiology of major depressive disorder, with special regard to the prefrontal cortex, the striatum and limbic structures (the hippocampus, the amygdala, the thalamus) (Drevets, 2001). These structures are interconnected via an extremely busy network. In vivo structural, cerebral blood flow and metabolic differences have been described between patients with MDD and controls in the PFC, amygdala, hippocampus, striatum, and thalamus. These data indicate that the emotional/stress-response system that includes the amygdala is over-activated and it is associated with dysfunctional PFC and monoamine systems that modulate amygdala responses (Drevets, 2001, Hasler et al., 2004). The neuropsychological profile of MDD is consistent with these observations, including the impairments of executive functions (working memory, problem solving, planning, and attentional set-shifting), sustained attention, declarative memory, and motor performance (Crews and Harrison, 1995, Liotti and Mayberg, 2001, Quraishi and Frangou, 2002, Rogers et al., 2004). Evidence also suggests that depression is associated with decreased approach-related behavior. Henriques and co-workers (Henriques et al., 1994) showed that monetary reward failed to alter response patterns in depressed volunteers. The increased sensitivity to negative feedback and punishment was found together with specific deficits in executive and memory tasks characteristic of frontostriatal and temporal lobe dysfunctions (Tavares et al., 2003).

We aimed to investigate decision-making function in MDD. We focused on the relationship between executive functions (attentional set-shifting) and decision-making guided by the cumulative effect of reward and punishment. For the measurement of executive functions, the Wisconsin Card Sorting Test (WCST) was used (R.K. Heaton, 1993), whereas reward and punishment sensitivity was assessed using two versions of the Iowa Gambling Test (IGT) (Bechara et al., 2000). Taking into consideration that patients with MDD are characterized by hypersensitivity to punishment and hyposensitivity to reward, we expected impairments in the version sensitive to punishment of the task assuming that high reward will not outweigh immediate punishment.

III.6. PERSONALITY TRAITS AND GENETIC INFLUENCES ON DECISION-MAKING

In accordance with previous studies, our results revealed that patients with major depressive disorder show suboptimal decision-making strategies in experimental game situations. However, personality traits and genetic variations might have remarkable influence on decision-making strategies. Heredity has major contribution to the development of many human behavioral traits including personality. The influence of personality traits and genetic variations on decision-making strategies is not clear, but clearly of interest. The Iowa Gambling Task administered in our previous study and described in detail earlier in the thesis is sensitive for the lesion of brain areas related to emotional regulation (ventromedial prefrontal cortex and amygdala) (Bechara et al., 1999), which are influenced by the polymorphisms of genes regulating serotonin neurotransmission (Brown and Hariri, 2006). Patients with MDD showed altered sensitivity to reward and punishment: paradoxically, we found immediate large reward to enhance related response patterns even when the strategy was disadvantageous, but immediate large punishment did not prohibit related response patterns (Must et al., 2006). It was unclear how personality traits and genetic factors may influence decision-making performance. We investigated this question by assessing personality traits (Temperament and Character Inventory [TCI], (Cloninger et al., 1993) and serotonin transporter promoter polymorphism (5-HTTLPR) (Heils et al., 1996) in patients with MDD. Here I would like to emphasize on the two main approaches which appear in the genetic research related to psychiatric disorders. Genes possibly involved can be detected in studies of the whole human genome searching for connections or the research can be hypothesis-driven, hunting candidate genes. This hypothesis-driven approach revealed the role of serotonergic pathways and genes, since they are closely related to affective symptomatology and represent target of effective antidepressant treatment. The serotonin transporter (5-HTT) plays a crucial role in serotonergic mechanisms being responsible for the reuptake of serotonin in the synaptic cleft. The polymorphism of the promoter region of the gene encoding the serotonin transporter (5-HTTLPR) has an important role in the regulation of this function. Carrying an ‘s’ or ‘l’ allele in the promoter region affects the amount of the serotonin transporter available in the synaptic junction and its activity pattern as well (Greenberg et al., 1999). Animal studies are consistent with these findings showing the crucial role of serotonergic mechanisms in social function, stress-response and coping strategies. The transient blocking of the 5-HTT with selective serotonin reuptake inhibitors (SSRI) in the early stage of development in mice resulted in measurable affective social behavior alterations

in the adult animal (Ansorge et al., 2004), this being only one example. However, converging evidence from human neuroimaging studies suggests the role of the 5-HTTLPR polymorphism in emotion processing and emotional related behavior. A very elegant study comes from Hariri and his group, who found a significantly increased amygdala response as measured by fMRI to fearful stimuli in the group of healthy people carrying the ‘s’ allele - which is represented in up to 70% of the population - as compared to the ‘ll’ homozygotes (Hariri et al., 2002). These findings were reproduced in a larger sample including 90 healthy volunteers (Hariri et al., 2005). This study beautifully suggests the mutifactorial etiology of the risk for developing major depressive disorder, since genetic susceptibility has to be put into the context of other, especially enviromental factors. However, an environmental risk factor can develop its effect dependent from the person’s genetic capabilities as well as ameliorate the effect of the genetic susceptibility.

Late evidence from functional imaging studies suggests the role of serotonergic neurotransmission in brain structures involved in emotional decision making, with special regard to the amygdala and the subgenual prefrontal cortex (Brown and Hariri, 2006). According to the meta-analysis of Munafo et al. the 5-HTTLPR polymorphism accounts for up to 10% variability in emotion related reactions taking into account differences in amygdala activity (Munafo et al., 2007). However, the authors emphasize on the probably notable effect of the individual personality traits as well. When taking into account the involvement of genetic factors and environmental effects, the famous Dunedin study has to be mentioned. Caspi and his colleagues found correlation between the 5-HTTLPR ‘s’ polymorphism together with three or more stressfull life events in adolescence and early adulthood and the development of anxiety and depressive symptoms in a large sample size cohort study (Caspi et al., 2003). However, the effect of personality traits has been taken into consideration in this approach as well, describing the so called ‘neuroticism’ as a very important modulating factor in connection to the development of more severe depressive symptoms (Jacobs et al., 2006). Previous studies indicated that participants with the short (s) allele of the 5-HTTLPR show higher anxiety-related traits and subclinical depressive symptoms (Schinka et al., 2004, Sen et al., 2004, Munafo et al., 2005)

Suhr and his colleagues examined the effect of mood and personality on the IGT performance in a normal population. According to their findings, negative affect and certain personality traits (e.g. reward seeking) are related to the preference of risky decisions in an independent but separately significant manner (Suhr and Tsanadis, 2007). However, the actual mood and

other individual factors should also be of interest and this is what we did in our study, by using the Cloninger Temperament and Character Inventory. Cloninger et al. have developed a self-report inventory, the TCI, to assess four dimensions of temperament: novelty seeking, harm avoidance, reward dependence and persistence, as well as three dimensions of character: self directedness, cooperativeness and self transcendence. Patients with major depressive disorder have been characterized by high harm avoidance and low self directedness.

We focused on the role of personality traits and genetic influence on emotionally biased decision-making strategies. Our hypothesis was that patients with the s allele will show higher harm-avoidance on the TCI and increased sensitivity for immediate punishment on the Iowa Gambling Test.

IV. MATERIALS AND METHODS

Patients participating in our studies were recruited from the in- and outpatients units of the Department of Psychiatry, University of Szeged and in one study from the outpatient units of the Bács-Kiskun County Hospital, Psychiatry Center, Kecskemét, Hungary. Diagnoses were based on the DSM-IV criteria. Control participants were university and hospital employees and their relatives and friends. All studies presented here were done in accordance with the Declaration of Helsinki and were approved by the local ethics board. After a complete description of the studies, all participants gave their written informed consent. Here we would like to thank all participants involved for their kind help and time accorded.

IV.1. Contrast categorization in schizophrenia and healthy relatives

IV.1.1. Participants

Participants were 25 patients who met the DSM-IV criteria for schizophrenia, 25 healthy siblings of schizophrenia patients and 25 healthy control subjects with no history of any psychiatric disorder. The groups were matched considering age and gender, but the general intellectual functions assessed by the Wechsler Adult Intelligence Scale was proven to be significantly lower compared to the other groups participating. All participants were assessed using the Brief Psychiatric Rating Scale (BPRS), which revealed the severity of symptoms of the patients suffering from schizophrenia. (Table 1).

Table 1. Participants of the study

	Schizophrenia patients (n=25)	**Siblings (n=25)**	**Controls (n=25)**
Age (years)	38.6 (9.3)	40.5 (7.2)	39.2 (10.5)
Gender (m/f)	17/8	12/13	17/8
IQ	95.6 (23.1)	108.0 (11.6)	110.5 (12.0)
Chlorpromazine-equivalent dose (mg/day)	450.6 (165.2)	-	-
BPRS	25.5 (8.6)	<5	<5

Data show mean values with standard deviations (SD)

IV.1.2. Contrast categorization task

During the initial part of the task, participants are asked to memorize standard stimuli for the two, either low or high contrast categories assessed to which they then can compare the new pictures. The decision making and classification of these new stimuli is then possible through abstraction mechanisms (Keri et al., 1999, Keri, 2003). The stimuli presented in the task were sinusoidal markings with luminance minimums and maximums. We used a spatial frequency of 2.3 cycle/angle of sight and a temporal frequency of 3 Hz. We measured in three different contrast ranges, from 2% to 11%, 5% to 23% and 20% to 65%. In the practicing part of the experiment the participants were presented two standard stimuli, exemplifying the minimal and the maximal contrast in the range measured which they then had to memorize. The subjects participating were then asked to categorize the further presented stimuli into one of the two possible contrast groups, the low or the high group, respectively (*Figure 1*).

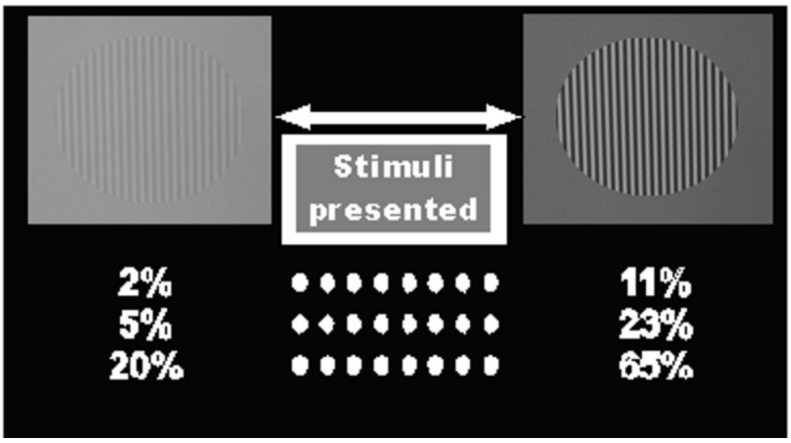


Figure 1. Standard stimuli for the contrast categories and the three contrast ranges

IV.1.3. Data analysis

In every contrast range measured the percentage of stimuli categorized into the high contrast group were compared using ANOVA.

IV.2. Collinear facilitation in schizophrenia

IV.2.1. Participants

Twenty outpatients fulfilling the DSM-IV criteria (DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 1994) for schizophrenia (12 male, 8 female) and 15 healthy control subjects (11 male, 4 female) participated in the study. The patients were selected from a larger sample according to the following criteria: (i) stabilized clinical state; (ii) no antipsychotic medication for at least 3 weeks before testing; (iii) normal intelligence, as measured by the Wechsler Adult Intelligence Scale(Wechsler, 1981); and (iv) spared continuous performance test (CPT) (cut-off, 1.5 SD below the control mean) (Table 2.). In the widely used degraded CPT method of Nuechterlein et al.(Nuechterlein et al., 1986), numbers from '0' to '9' were sequentially presented (1/s, 50 ms exposure time). Stimuli were degraded by reversing 40% of the pixels. Subjects were asked to press a key if a '0' (target) appeared. *d′* was calculated as a measure of perceptual sensitivity to discriminate target from distracters. CPT provides information about basic stimulus encoding abilities and sustained attention. All participants received the MINI-International Neuropsychiatric Interview Plus (Sheehan et al., 1998). Clinical symptoms were determined by the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984) and Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1984) instruments (*Table 2*). History of neurological disorders, head injury, substance abuse, and electroconvulsive therapy were the general exclusion criteria. All participants had normal or corrected-to-normal visual acuity. After a complete description of the study, informed consent was obtained.

Table 2. Age, IQ, attention performance and clinical symptoms of the participants

	Schizophrenia subjects (n=20)	**Control subjects (n=15)**
age (years)	35.8 (12.6)	31.8 (9.9)
IQ	105.6 (10.3)	111.4 (12.5)
CPT d'	2.81 (0.95)	2.76 (0.88)
SAPS	9.3 (4.4)	-
SANS	6.5 (3.0)	-

Data are means (SD). No significant between-group differences were found (t-tests, $p>0.1$). CPT, continuous performance test; SAPS, Scale for the Assessment of Positive Symptoms; SANS, Scale for the Assessment of Negative Symptoms

IV.2.2. Gabor patch and contrast threshold assessment

Stimuli were Gabor patches which are small oriented features defined by luminance contrast (*Figure 2*). The luminance contrast profile of a Gabor patch is formed by the multiplication of a sinusoidal waveform with a Gaussian envelope. Gabor patches are ideal stimuli if we consider the receptive field properties of V1 neurons (Ringach, 2002). Stimuli were presented on a gamma-corrected ViewSonic PF815 monitor (resolution, 800×600 pixels; refresh rate, 100 Hz; VSG graphic card, version 5.02, Cambridge Research System Ltd, Rochester, UK). The monitor was controlled by an IBM-compatible PC. The viewing distance was 100 cm. The mean luminance of the display was 50 cd/m^2 (Spectra Pritchard 1980A-CD photometer).

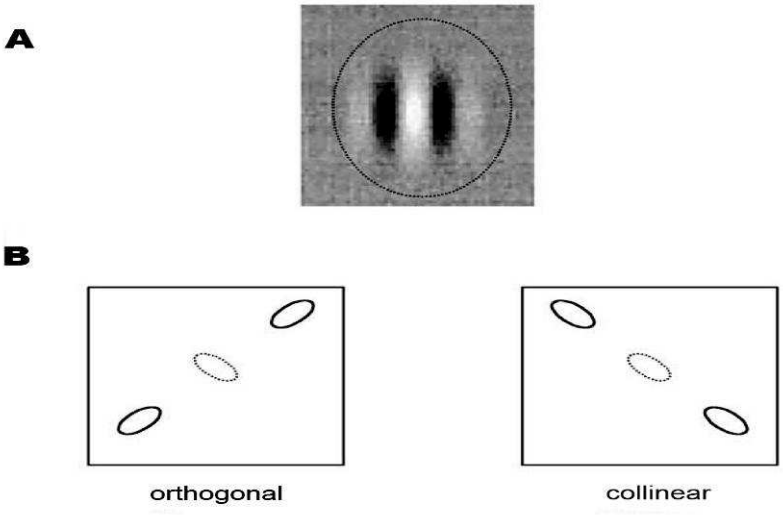


Figure 2. (**A**) Gabor patch. The dotted line (not present during the experiment) indicates stimulus orientation. (**B**) Orthogonal and collinear flankers. Stimulus orientation is indicated as seen above (**A**).

First, subjects were asked to press the space key on the computer keyboard. After this, a fixation display of 300 ms appeared, which contained a central cross and two peripheral bars (length, 0.3° of visual angle; eccentricity, 1.4° of visual angle). The central cross indicated the location of a subsequent target Gabor patch for which contrast threshold (the minimal contrast necessary for detection) was measured. Contrast was defined according to the Michelson formula (the absolute difference between the maximal and minimal luminance divided by their sum). The orientation of the target was either 45° or 135°. The bars indicated the location of two subsequent peripheral Gabor patches (flankers with a contrast of 40%), which have a modulator effect on the contrast threshold of the target. The orientation of the flankers was either collinear or orthogonal to that of the target (*Figure 3*.). The Gabor patches had a

wavelength (λ) and Gaussian distribution equal to 0.15° of visual angle. The spatial frequency was 6.7 cycles/degree. The center-to-center distance between target and flankers was 4λ (Polat and Sagi, 1993, Freeman et al., 2001). Subjects were asked to fixate and focus their attention on the central cross. The experimenter observed the subjects throughout the whole experiment to ensure fixation. After the fixation display, a brief interval of 80 ms appeared during which the Gabor stimuli were presented. Subjects were asked to indicate if they detected the target by pressing separate keys on the computer keyboard (‘1’, yes; ‘9’, no). The next trial was not initiated without a response. Responses with reaction times exceeding 2000 ms were eliminated.

IV.2.3. Data analysis

Contrast threshold was measured by Levitt's staircase method (Levitt, 1971). In the case of three consecutive correct responses (hits), contrast was decreased by 25% (0.1 log unit), whereas in the case of one incorrect response (miss), contrast was increased by 25%. Decrease or increase of contrast was considered as a reversal. One block of trials terminated after eight reversals. Contrast threshold was the average of the last six reversals. Measurements with collinear and orthogonal flankers were performed in separate blocks which were counterbalanced across subjects.

IV.3. Development of motion and form processing in children with increased risk of psychosis

IV.3.1. Participants

Thirty-six children of mothers with schizophrenia (21 boys, 15 girls), 28 children of mothers with type I bipolar disorder with episodes of psychosis (17 boys, 11 girls), and 30 children with negative family history (16 boys, 14 girls) participated in the study. Twenty-seven children of mothers with schizophrenia and 20 children of mothers with bipolar disorder lived with the affected parent. Seven children of mothers with schizophrenia lived with the unaffected parent and 2 lived with adopting parents (mean age at separation from the affected mother: 3.5 years (SD = 2.0)). All 8 children of mothers with bipolar disorder lived with the non-affected parent (mean age at separation from the affected mother: 4.2 years (SD = 2.3)). Schizophrenia and bipolar mothers were recruited from the outpatient units of the Department of Psychiatry, University of Szeged and the Bács-Kiskun County Hospital, Psychiatry Center,

Kecskemét, Hungary. Parents of control participants were university and hospital employees and their relatives and friends. Diagnoses were based on the DSM-IV criteria. All mothers received the MINI-International Neuropsychiatric Interview Plus (Sheehan et al., 1998) and their full medical records were available. Health cards of the children were obtained from their home districts and a detailed history was obtained from the families, including the non-affected parent. The following items were taken into consideration for the general description of the sample: obstetric complications, severe childhood illness, emotional symptoms, conduct problems, and academic impairment in the school. These items were defined according to the medical records of the children, following the methodology of the Helsinki High-Risk Study (Niemi et al., 2005). Children with history of psychosis or pervasive developmental disorders were not included in the study. The children did not receive psychotropic medications. Visual perceptual functions were assessed at 7, 8–9, and 10–11 years of age. Families were followed-up during this period, together with a regular monthly visit for the affected parent at the treating clinician. After a complete description of the study, all parents (including the non-affected parents) gave their written informed consent.

IV.3.2. Motion and form perception task

The tasks administered require the detection of direction of coherently moving dots embedded among randomly oscillating dots (motion task) and the detection of tangentially oriented line-segments embedded among randomly oriented segments (form task). Stimuli were presented on a ViewSonic PF815 monitor controlled by an IBM-compatible PC. In the motion coherence task, stimuli consisted of an array of dots (density = 4 dots/degree^2, stimulus area luminance = 85 cd/m^2). Signal dots moved horizontally at 6°/s and reversed direction every 0.4 s. Noise dots were repositioned randomly on each frame. The task was to locate a 12° × 7° strip that appeared either on the left or the right side of the screen. In the target strip, the coherently moving signal dots oscillated in the phase opposite to that in the surrounding regions (*Figure 5*.). Participants made decisions by pressing different keys on the computer keyboard (1 for left and 9 for right). Coherence was the ratio of signal dots to noise dots. At the beginning of the test, each dot (100%) oscillated coherently. This proportion was reduced until the first error, when a 2-up/1-down staircase was introduced. The threshold was defined as the average of six reversals.

In the form coherence task, stimuli consisted of 0.4°-long line segments (density = 19 segments/degree^2). In a circular area with a radius of 7°, which was localized either to the left

or to the right of the center of the screen, some of the line segments were tangentially oriented to form a circle. The surrounding noise line segments were randomly positioned. The proportion of tangentially oriented segments defined the level of coherence (*Figure 5*.). Similarly to the motion coherence task, participants were asked to decide whether the circle appeared on the left or the right side of the screen.

In both tasks, the level of coherence at the detection threshold characterizes the sensitivity of the visual system. If a higher level of coherence is necessary for the detection of a stimulus (a higher proportion of dots oscillates coherently or a higher proportion of line segments is oriented tangentially), the threshold is higher and the sensitivity of the visual system is lower.

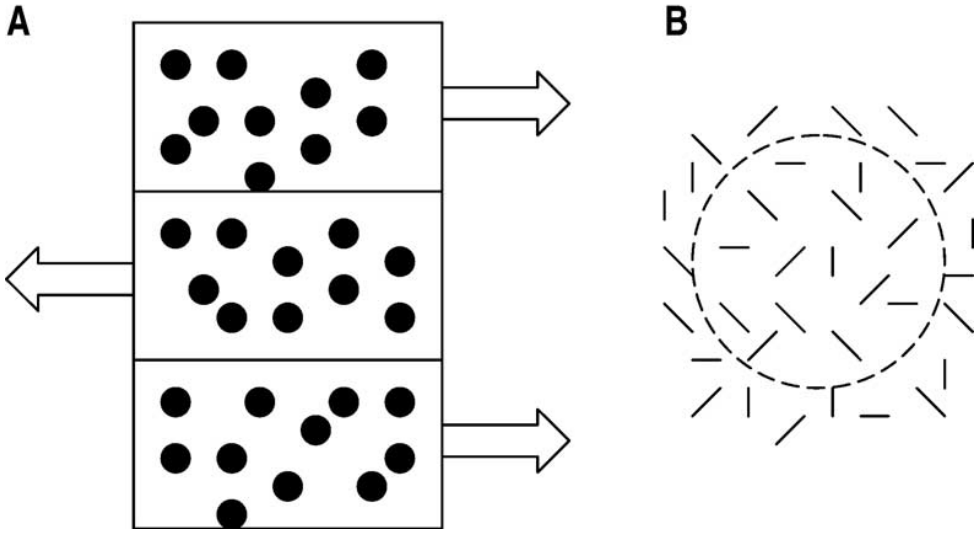


Figure 3. Illustration of the principles involved in the motion and form coherence threshold measurements.
A: Motion coherence threshold. A proportion of the dots in the middle target strip oscillate in the direction opposite to the direction in which the dots in the upper and lower strips are oscillating. If a larger percentage of dots must oscillate coherently to be detected, the motion coherence threshold is higher.

B: Form coherence threshold. Line segments are tangentially organized to compose a circle. Tangentially oriented segments are embedded among randomly oriented segments. The form coherence threshold is defined as the percentage of tangentially oriented segments that is indispensable for the detection of the circle. If a larger percentage of segments must be oriented tangentially, the form coherence threshold is higher. During both tasks, participants were asked to decide whether the moving strip or the circle was on the left or right side of the screen.

IV.3.3. Data analysis

Kolmogorov–Smirnov tests were used to check the normality of data distribution when starting data analysis. Repeated measures analysis of variance (ANOVA) was used (between subject factor: participant group, within subject factor: motion and form coherence task and

age) which was followed by F tests for planned comparisons. Two-tailed Student's t tests were used for post hoc comparisons when the F tests indicated significant differences. The level of significance was alpha < 0.05.

IV.4. Decision- making in major depressive disorder

IV.4.1. Participants

Table 3. Demographical and clinical data of the outpatients participating

	Patients with DSM-IV MDD (n=30)	Controls (n=20)
Gender (f/m)	18/12	11/9
Age	43.8 (9.6)	42.5 (10.7)
Education (years)	15.3 (8.1)	15.1 (9.4)
Duration of illness (years)	14.2 (6.2)	-
Previous depressive episodes	7.3 (4.2)	-
Hamilton Depression Rating Scale (HAM-D) score	15.0 (5.4)	-
Hamilton Anxiety Rating Scale (HAM-A) score	8.2 (4.2)	-
Medication administered (number of patients, average dose)	citalopram (n=8, 20-40 mg/day) mirtazapine (n=6, 30-60 mg/day) paroxetine (n=3, 20-40 mg/day) reboxetine (n=2, 8mg/day) sertraline (n=6, 50-200 mg/day) venlafaxine (n=5, 75-350 mg/day) alprazolam (n=11, 1-6mg/day) clonazepam (n=8, 0.5-4mg /day) valproate (n=1, 800mg /day) lithium (n=3, 800-1200mg /day)	-

Data are mean with standard deviations (SD)

IV.4.2. The Wisconsin Card Sorting Test (WCST)

The Wisconsin Card Sorting Test (WCST) was administered manually according to the standard description by (R.K. Heaton, 1993). Participants were asked to sort test cards to one of four key cards. The number of test cards was 120. The geometric forms on the cards had different shape, color, and number. From these features, only one could be used for sorting (e.g. test cards should have been matched to the key card with the same color). Participants

received oral feedback to ascertain the categorization rule which shifted after ten successful decisions. There were five shifts (color–shape–number–color–shape–number). The number of categories completed and the number of perseverative errors were the dependent measures.

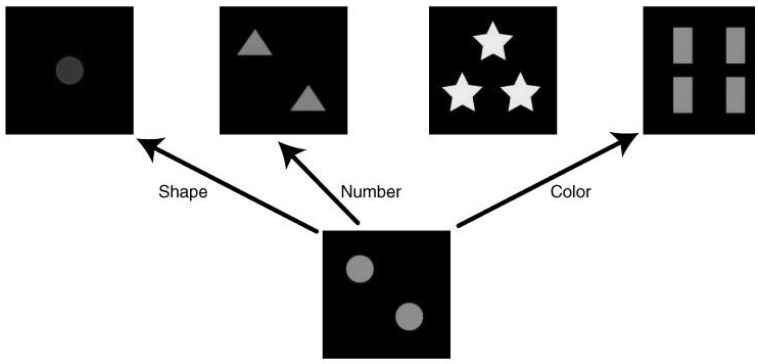


Figure 4. Illustration of the Wisconsin Card Sorting Test (WCST)

IV.4.3. The Iowa Gambling Test (IGT)

The Iowa Gambling Task (IGT) was administered as described by (Bechara et al., 2000) using a personal computer. Participants received standard instructions and were told that the aim of game is to win as much money as possible. In the ABCD version, four decks of cards labeled as A, B, C, and D were presented on the computer screen. Each deck contained 40 cards. The task was to click on a card from any of the decks using the mouse. After picking a card, the amount of money the participant won or lost was depicted on the computer screen, together with a smiley or a sad cartoon face and different sounds. There was a green bar on the top of the screen. Winning and losing money were indicated by an increase and a decrease of the length of the bar, respectively. When the money was added or subtracted, the cartoon face disappeared and the participant could select the next card. The inter-trial interval was 6 s. The game consisted of 100 trials. Participants always won 100$ if they selected a card from deck A or B and always won 50$ if they selected a card from deck C or D. The amount of lost money was 150, 200, 250, 300 or 350$ for deck A (50% of the cards); 1250$ for deck B (10% of the cards); 25, 50 or 75$ for deck C (50% of the cards); and 250$ for deck D (10% of the cards). If there was no loss (50% of cards for decks A and C and 90% for decks B and D), a sentence appeared on the computer screen stating that “You won 100$ (or 50$)”. If there was

a loss, a sentence appeared on the computer screen stating that "You won 100$ (or 50$), but you lost X$". The order of winning and losing cards was randomized and unpredictable. Altogether, decks A and B were associated with high immediate reward but even higher future punishment (*Figure 5*).

The layout and design of the EFGH version were similar. The four decks were labeled as E, F, G, and H. Participants always lost 100$ if they selected a card from deck E or G and always lost 50$ if they selected a card from deck F or H. The amount of received money was 1250$ for deck E (10% of the cards); 25, 50 or 75$ for deck F (50% of the cards); 150, 200, 250, 300 or 350$ for deck G (50% of the cards); and 250$ for deck H (10% of the cards). If there was no winning (50% of cards for decks F and G and 90% of cards for decks E and H), a sentence appeared on the computer screen stating that "You lost 100$ (or 50$)". If participants won some money, a sentence appeared on the computer screen stating that "You lost 100$ (or 50$), but you won X$". Altogether, decks E and G were associated with high immediate punishment but even higher future reward (*Figure 5*).

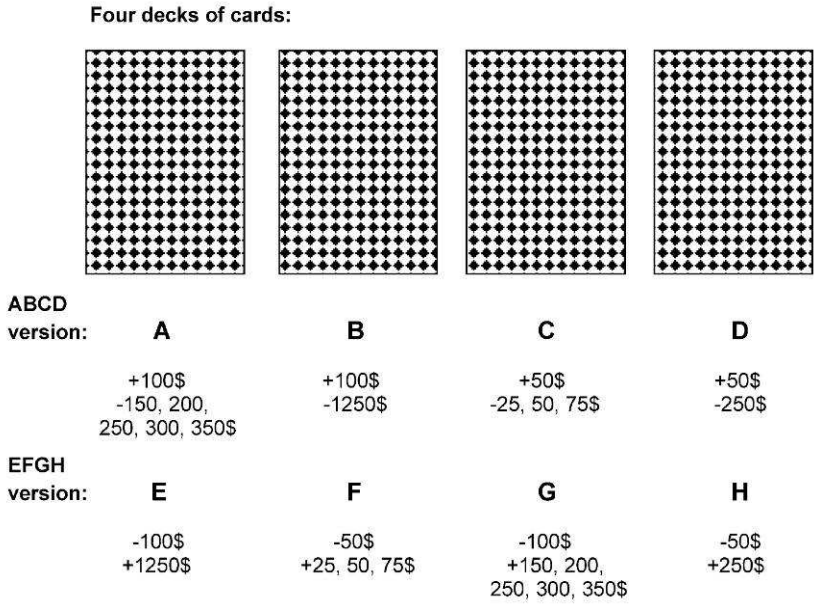


Figure 5. The ABCD version, the disadvantageous decks (A and B) yielded high immediate reward but even higher future punishment (+$ and −$ symbolize winning and losing, respectively). Decks B and D are characterized by less frequent but relatively high amount of loss (10% of the cards), whereas decks A and C are characterized by frequent but relatively small amount of loss (50% of the cards). In the EFGH version, the disadvantageous decks (F and H) yielded low immediate punishment but even lower future reward. Decks E and H are characterized by less frequent but relatively high amount of gain (10% of the cards), whereas decks F and G are characterized by frequent but relatively small amount of gain (50% of the cards).

IV.4.4. Data analysis

For data analysis, the 100 trials were divided into five equal blocks. The dependent measure was the number of cards selected from advantageous decks minus disadvantageous decks as calculated for each block ([C + D] − [A + B] in the ABCD version and [E + G] − [F + H] in the EFGH version). The order of administration of the ABCD and EFGH versions was counter-balanced across participants. The STATISTICA 6.0 package (StatSoft, Inc., Tulsa, Oklahoma) was used for data analysis. Kolmogorov–Smirnov tests were used to check data distribution. WCST results were compared with Mann–Whitney *U* tests because these data showed non-Gaussian distribution. IGT results were analyzed with a group (MDD vs. controls) by IGT type (ABCD vs. EFGH) by trials analysis of variance (ANOVA). Two-tailed t-tests were used for post hoc analysis with Bonferroni corrections for multiple comparisons. Forward stepwise linear regression analysis was used to determine factors that predicted IGT performance. In this analysis, the dependent variable was IGT performance after 100 trials and the independent variables were HAM-D scores, HAM-A scores, and WCST perseverative errors. Pearson's (r) and Spearman's (R) correlation coefficients were calculated for parametric (IGT) and non-parametric analysis (WCST), respectively. The level of significance was alpha < 0.05.

IV.5. Personality traits and genetic influences on decision-making

IV.5.1. Participants

Participants were 124 patients with DSM-IV unipolar MDD (DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 1994) (83 females, 41 males). Patients with history of neurological illness, obsessive–compulsive symptoms, recent suicide attempts (within 2 years), manic/hypomanic episode or mixed states, psychoactive substance-related disorders, impulse control disorders, and cluster A or B personality disorders were excluded. All participants received the MINI-International Neuropsychiatric Interview (Sheehan et al., 1998) and the Hungarian version of the TCI (S. Rózsa, 2005). Mean Hamilton Depression Rating Scale (HAM-D) score and mean Hamilton Anxiety Rating Scale (HAM-A) scores were given for each patient (Mountjoy and Roth, 1982, Maier et al., 1988) . The following medications were used: bupropion, citalopram, duloxetine, escitalopram, mirtazapine, paroxetine, sertraline, venlafaxine, alprazolam, clonazepam, and lithium. Testing was performed during maintenance therapy.

IV.5.2. The Iowa Gambling Task (IGT)

We administered the computherized versions of the Iowa Gambling Task as described in details earlier in the thesis. In the ABCD version decks A and B were associated with high immediate reward but even higher future punishment, this version being prone to measure hypesensitivity to reward. In the EFGH task, decks labeled E and G were associated with high immediate punishment but even higher future reward, this version measuring hypersensitivity to punishment. In both versions, the 100 trials were divided into five equal blocks. The dependent measure was the number of cards selected from advantageous decks minus disadvantageous decks as calculated for the last block.

IV.5.3. 5-HTTLPR plomorphism

All participants were genotyped for the 5-HTTLPR polymorphism using the method of (Heils et al., 1996) and grouped according to their genotype in group ’ss’, ’sl’ or ’ll’.

IV.5.4. Temperament and Character Inventory

The self-report inventory containes 240 items and has been validated to assess four dimensions of temperament: novelty seeking, harm avoidance, reward dependence and persistence, as well as three dimensions of character: self directedness, cooperativeness and self transcendence.

IV.5.5. Data analysis

Data were analyzed using analysis of variance (ANOVA) and two-tailed t-tests. Pearson's correlation coefficients were calculated between TCI and Iowa Gambling Test measures. Linear regression analysis was used to determine the relationship between genetics and task performance. The level of significance was set at alpha < 0.05.

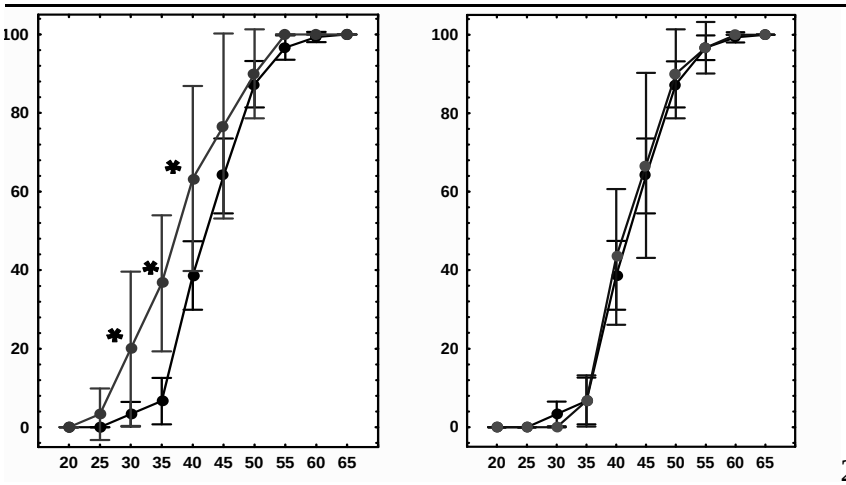
V. RESULTS

V.1. USE OF THE CONTRAST CATEGORIZATION PARADIGM IN ORDER TO INVESTIGATE DEFICITS IN MEMORY, ATTENTION AND PERCEPTIONAL FUNCTION IN SCHIZOPHRENIA PATIENTS AND IN HEALTHY RELATIVES, AS A POSSIBLE GENETIC MARKER OF THE ILLNESS

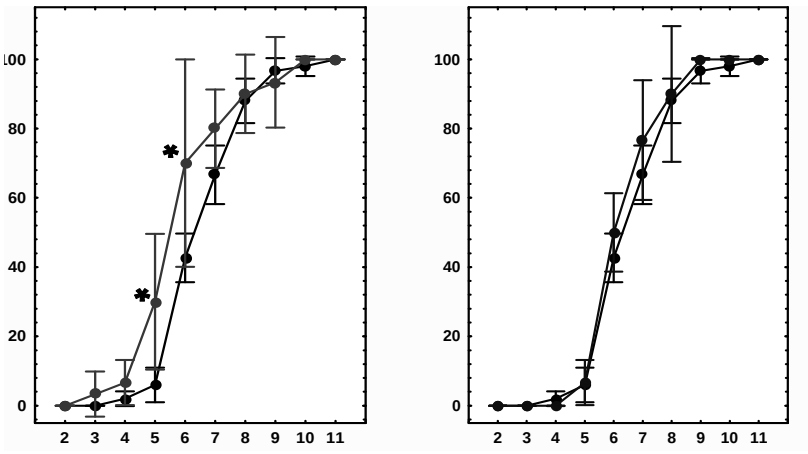
Schizophrenia patients showed significant categorization deficits in every contrast range measured, compared to the healthy control subjects. We found the relatives to be impaired as well, although this was the case in the 10 to 15% contrast range only.

In every contrast range measured the percentage of stimuli categorized into the high contrast group were compared. In the range from 20 to 65% contrast schizophrenia patients were significantly impaired at the 30, 35 and 40% contrast values (ANOVA main effect of group $F=12.62$, $p<0.001$). Healthy siblings made overall similar decisions compared to the control group. In the 2 to 11% contrast range schizophrenia patients were again impaired compared to healthy controls, the stimuli between 5 and 6% contrast values were significantly harder to identify for the patients ($F=5.62$, $p<0.01$). Healthy siblings showed no alteration in contrast categorization capacity. The contrast range between 5 and 23% turned out to be the most interesting one. Schizophrenia patients were again impaired, in this range 9, 11 and 13% contrast stimuli were the most difficult to categorize into the high or low contrast group for the patients ($F=11.87$, $p<0.001$). However, our results revealed that, in this particular range, healthy siblings were also significantly impaired compared to control subjects, at the 9 and 11% contrast, respectively ($F=7.80$, $p<0.01$) (*Figure 6*). Covariance analysis performed for IQ and BPRS measures identified no confounding effect of these two factors on the significantly impaired contrast categorization capacity of schizophrenia patients ($p>0.1$).

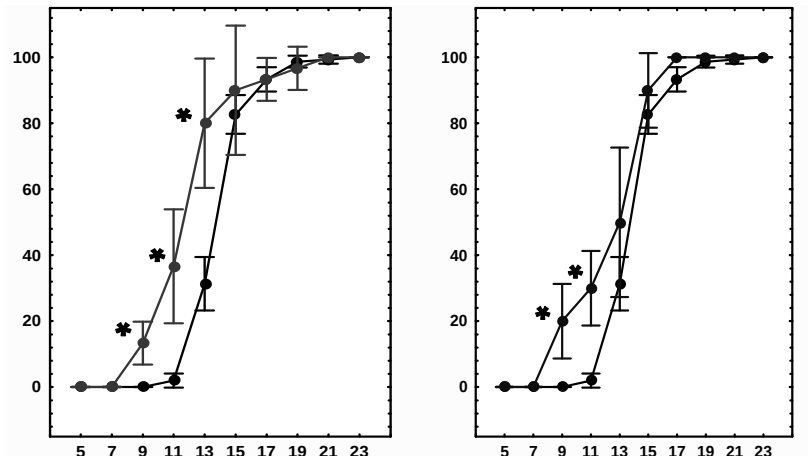
Schizophrenia patients showed significant categorization deficits in every contrast range measured, compared to the healthy control subjects. However, we found the relatives to be impaired as well, although this was the case in the 10 to 15% contrast range only. At this specific contrast level the patients and their relatives grouped the stimuli more often into the high contrast category (*Figure 6*).



20-65% contrast range



2-11% contrast range



5-23% contrast range

schizophrenia siblings

Figure 6. Stimuli grouped as high contrast pictures, left figure always depicting schizophrenia patients compared to controls, right figure showing healthy siblings compared to controls in every contrast range measured. * Significant differences

V.2. GABOR PATCH USED FOR TESTING LATERAL CONNECTIVITY IN EARLY VISUAL AREAS (V1) OF SCHIZOPHRENIA PATIENTS

Significantly reduced effect of collinear flankers on contrast threshold in unmedicated highly functioning schizophrenia patients suggests abnormal lateral interactions in early visual cortex of these patients

Control subjects showed the classic facilitation effect when collinear flankers were presented compared with the orthogonal flanker condition; in the former case, contrast threshold for the target was significantly lower ($t(14)=7.04$, $p<0.0001$). This phenomenon is a fundamental feature of low-level visual processing and lateral interactions in early visual cortex (Polat and Sagi, 1993, Kapadia et al., 1995, Freeman et al., 2001). The main finding of this study was that collinear flankers had a smaller facilitation effect on contrast detection in patients with schizophrenia compared with the controls, while in the case of orthogonal flankers, the patients did not show severe contrast detection deficits (Figure 7). The performance of the patients did not correlate with the clinical symptoms (Spearman's $r<0.2$). These results indicate that lateral interactions between feature-specific processing units in early visual cortex are impaired in patients with schizophrenia.

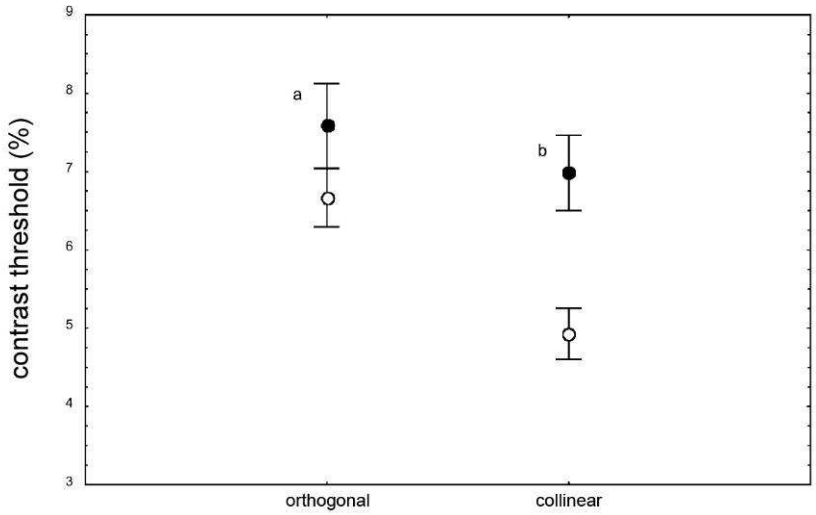


Figure 7. Mean contrast thresholds in the schizophrenia patients (n=20) (filled circles) and in the controls (n=15) (open circles) as a function of flanker orientation (orthogonal vs. collinear). Error bars indicate standard error of mean. Analysis of variance (ANOVA) main effect of group, $F(1,33)=4.15$, $p<0.05$; main effect of flanker orientation, $F(1,33)=39.46$, $p<0.0001$; interaction, $F(1,33)=13.95$, $p<0.001$. (a) No significant between-group difference ($p=0.38$); (b) significant between-group difference ($t(33)=-2.99$, $p<0.01$)

V.3. INVESTIGATING DEVELOPMENTAL ANOMALIES OF DIRECTIONAL MOTION PERCEPTION IN CHILDREN OF MOTHERS WITH SCHIZOPHRENIA OR BIPOLAR DISORDER

Motion coherence thresholds were higher in children of mothers with schizophrenia reflecting motion perception dysfunctions which might be related to magnocellular pathology

At 8–9 years of age, 31 children of mothers with schizophrenia and 25 children of mothers with bipolar disorder were assessed from the original sample. At 10–11 years of age, 28 children of mothers with schizophrenia and 23 children of mothers with bipolar disorder were assessed from the original sample (*Table 4*).

Table 4. Major characteristics of the sample showing the number affected cases/whole sample.

	Children of mothers with schizophrenia	Children of mothers with bipolar disorder	Control children
Obstetric complications	1 / 36	2 / 28	2 / 30
Severe childhood illness	2 / 36	3 / 28	2 / 30
Emotional symptoms	8 / 36	6 / 28	1 / 30
Conduct problems	5 / 36	7 / 28	2 / 30
Academic impairment	6 / 36	5 / 28	2 / 30

Mean coherence thresholds from the motion and form task in children of mothers with schizophrenia and children of mothers with bipolar disorder compared to controls are depicted on Figure 8.

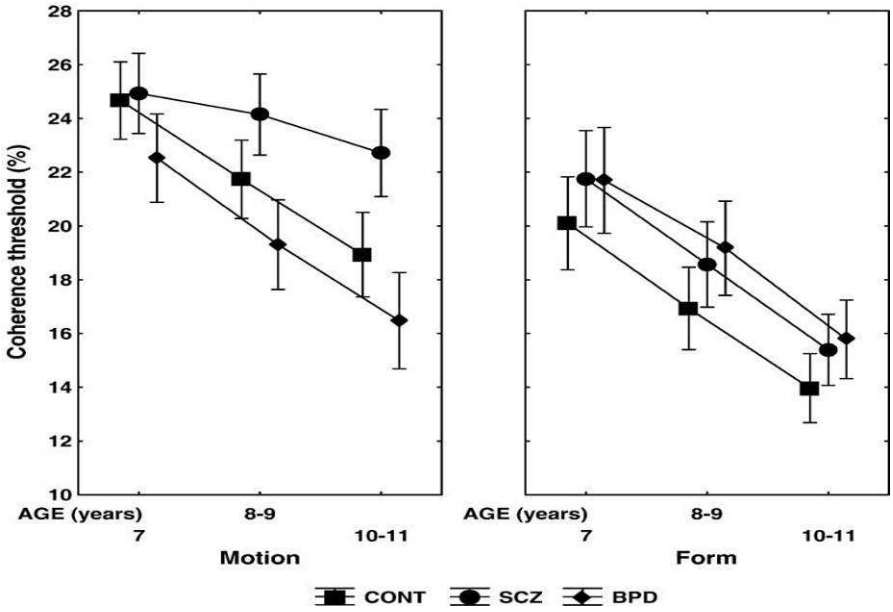


Figure 8. Mean coherence thresholds from the motion and form tasks. CONT—control children (n = 30), SCZ—children of mothers with schizophrenia (7 years: n = 36, 8–9 years: n = 31, 10–11 years: n = 28), BDP—children of mothers with bipolar disorder (7 years: n = 28, 8–9 years: n = 25, 10–11 years: n = 23). Error bars indicate 95% confidence intervals. The ANOVA indicated significant main effects of group ($F(2, 78) = 3.92$, $p < 0.05$), coherence task type ($F(1, 78) = 52.56$, $p < 0.0001$), and age ($F(2, 156) = 244.30$, $p < 0.0001$). There were significant two-way interactions between group and coherence task type ($F(2, 78) = 8.79$, $p < 0.001$), group and age ($F(4, 156) = 2.74$, $p < 0.05$), and coherence task type and age ($F(2, 156) = 4.28$, $p < 0.05$). Critically, the three-way interaction among group, coherence task type, and age was also significant ($F(4, 156) = 3.80$, $p < 0.05$).

The three-way interaction was further explored by using F tests. When the children of mothers with schizophrenia were compared with controls, the interaction was significant ($F(1, 78) = 6.79$, $p < 0.05$) in contrast to the comparison between children of mothers with bipolar disorder and controls ($p = 0.73$). When the children with mothers with schizophrenia and bipolar disorder were directly compared, the critical interaction among group, coherence task type, and age was again significant ($F(1, 78) = 7.72$, $p < 0.05$). Motion coherence thresholds were higher in children of mothers with schizophrenia than that in controls at 8–9 years of age ($t(59) = -2.21$, $p < 0.05$) and at 10–11 years of age ($t(56) = -3.00$, $p < 0.005$). There were no differences in form coherence thresholds ($p > 0.1$). When compared with children of mothers with bipolar disorder, children of mothers with schizophrenia showed higher motion coherence threshold at all ages (7 years: $t(62) = 2.59$, $p < 0.05$; 8–9 years: $t(54) = 4.05$, $p < 0.0005$; 10–11 years: $t(49) = 4.66$, $p < 0.0001$). Again, there were no differences in form coherence thresholds ($p > 0.6$) (*Figure 8*).

Separate ANOVAs revealed no significant differences between boys and girls ($p > 0.1$) and between children living with and without the affected parent ($p > 0.5$).

V.4. ASSOCIATION BETWEEN EXECUTIVE FUNCTION AND EMOTIONAL DECISION-MAKING IMPAIRMENT IN MDD, MEASURED BY DIFFERENT NEUROPSYCHOLOGICAL TEST METHODS

MDD patients were characterized by impaired executive function as measured by the WCST and showed suboptimal decision-making strategies in experimental game situations

We found that the median number of categories completed in the WCST was 4.0 (range: 0–6) in the MDD group and 6.0 (range: 4–6) in the controls ($Z = -3.11$, $p < 0.005$). The median number of perseverative errors was 11.0 (range: 8–30) in the MDD patients and 8.0 in the controls (range: 5–18) ($Z = 3.07$, $p < 0.005$). These values are generally used for the measurement of executive function, category-learning and set-shifting in this task.

When examining IGT performance ANOVA revealed significant main effects of group ($F(1, 49) = 22.52$, $p < 0.001$), IGT type ($F(1,49) = 16.43$, $p < 0.001$), and trials ($F(4, 196) = 35.57$, $p < 0.001$). The two-way interactions between group and IGT type ($F(1, 49) = 5.18$, $p < 0.05$) and between group and trials ($F(4, 196) = 12.53$, $p < 0.001$) were also significant. Finally, the three-way group by IGT type by trials interaction also reached the level of statistical significance ($F(1, 49) = 6.54$, $p < 0.001$). Student's *t*-tests revealed that the patients with MDD made fewer advantageous decisions than the controls in the ABCD version after 41–60, 61–80, and 81–100 trials ($t < -3.0$, $p < 0.001$, power > 0.90). There were no significant between-group differences in the EFGH version (*Figure 9.*).

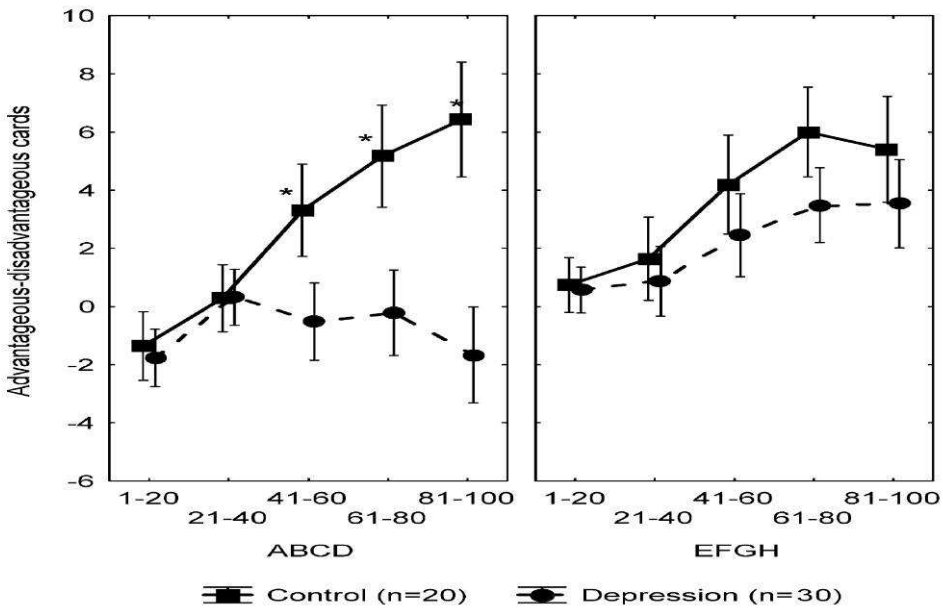


Figure 9. Mean number of cards selected from advantageous minus disadvantageous decks. Positive scores reflect advantageous strategy (overall gain), whereas negative scores reflect disadvantageous strategy (overall loss). Error bars indicate 95% confidence intervals. *p < 0.001, t-test.

Correlation and linear regression analysis have been performed when analyzing the results. We found that the WCST, IGT, and HAM-D measures did not correlate ($R < 0.2$). The HAM-D scores inversely correlated with the EFGH performances after 41–60 trials ($r = -0.39$, $p < 0.05$, power = 0.73), 61–80 trials ($r = -0.50$, $p < 0.05$, power > 0.90), and 81–100 trials ($r = -0.48$, $p < 0.05$, power = 0.89). No such correlations were found in the case of the ABCD version ($r < 0.3$). The linear regression analysis revealed that the HAM-D scores (beta = −0.48, $p < 0.001$, power > 0.90) but not the WCST perseverative errors predicted EFGH performances after 100 trials. No such effect was found in the case of the ABCD version. The HAM-A scores did not correlate with test performances ($r < 0.2$) and did not predict test performances (*Figure 9.*).

V.5. THE REMARKABLE INFLUENCE OF PERSONALITY TRAITS AND GENETIC VARIATIONS ON DECISION-MAKING STRATEGIES

MDD patients with the ss variant of the 5-HTTLPR achieved lower persistence scores on the TCI and selected more disadvantageous decks in the ABCD version of the IGT which measures hypersensitivity to reward

Our results revealed that genotype frequencies did not deviate from Hardy–Weinberg equilibrium ($p > 0.1$). MDD patients with the ss variant of the 5-HTTLPR achieved lower persistence scores on the TCI compared with patients with the ’ll’ variant; patients with the ’ls’ variant scored between ’ll’ and ’ss’ patients. No other TCI parameters showed significant differences as a function of 5-HTTLPR genetics.

Table 5. Demographical and clinical data of the patients, TCI and IGT results as a function of 5-HTTLPR

	ll (n = 31)	**ls (n = 58)**	**ss (n = 35)**	**p**
Age (years)	42.3 (8.5)	43.6 (9.2)	41.0 (7.7)	0.82
Education (years)	14.3 (4.8)	15.2 (5.0)	15.5 (6.3)	0.86
Duration of illness (years)	12.4 (4.2)	11.0 (9.5)	13.4 (7.6)	0.72
HAM-D	22.3 (7.5)	21.5 (8.4)	23.0 (6.3)	0.57
HAM-A	4.5 (4.7)	4.9 (3.2)	4.9 (3.8)	0.84
Harm avoidance	23.9 (7.4)	23.3 (8.8)	24.8 (9.9)	0.69
Reward dependence	15.0 (2.9)	15.0 (3.2)	15.1 (2.8)	0.99
Novelty seeking	17.3 (6.1)	16.5 (6.1)	15.8 (4.9)	0.64
Persistence	4.5 (1.6)	3.7 (1.9)	3.0 (1.6)	0.01
Self-directedness	25.9 (5.7)	26.1 (6.0)	25.1 (5.3)	0.82
Cooperativeness	28.0 (5.8)	28.4 (5.9)	27.1 (6.5)	0.73
Transcendence	13.8 (7.1)	14.7 (7.0)	15.1 (6.5)	0.53

Data are mean (standard deviation). One-way ANOVA: $F(1,122) = 4.62$, $p = 0.01$; ’ll’ > ’ss’: $t(64) = 3.21$, $p < 0.005$.

In the ABCD version of the Iowa Gambling Test, patients with the ’ss’ variant selected less advantageous decks compared with patients carrying the ’ll’ variant; the value of ’ls’ patients was between the scores of the ’ss’ and ’ll’ patients (*Figure 10*.). The genetic variant of the 5-HTTLPR accounted for 10.8% of variance in the ABCD task (beta = 0.33, $p < 0.05$), whereas persistence accounted for 1.9% of variance (beta = − 0.14, $p = 0.26$). In the case of the EFGH

version, there was no such relationship ($p > 0.1$). This differential deficit was confirmed by a MANOVA test, including task type as a within-subject factor (ABCD vs. EFGH). This test revealed a significant genotype by task type interaction ($F(2,122) = 4.58$, $p < 0.05$).

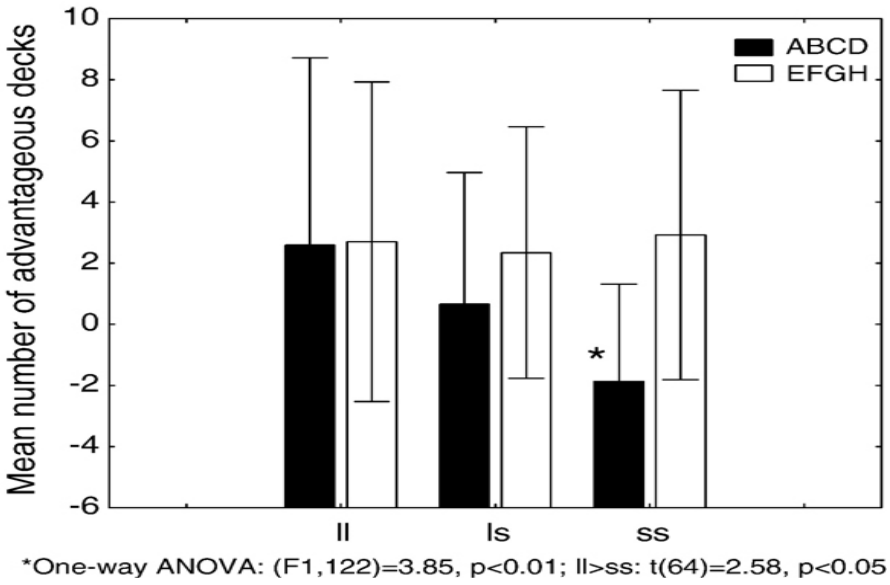


Figure 10. Mean number of advantageous decks selected in the ABCD and EFGH versions of the Iowa Gambling Test in patients with 'll', 'ls', and 'ss' versions of the 5-HTTLPR. Error bars indicate standard deviation of the mean.

There was a negative relationship between harm-avoidance and performance on the EFGH task ($r = -0.40$, $p < 0.05$), whereas the relationship between persistence and ABCD performance was positive ($r = 0.35$, $p < 0.05$). Depressive symptoms did not correlate with performance on the ABCD task ($p > 0.1$), but showed inverse correlation with EFGH performance ($r = -0.47$, $p < 0.05$). All other correlations were not significant ($p > 0.1$). Finally, male and female patients did not differ in any measure ($p > 0.1$).

VI. DISCUSSION

The relationship between the magno and parvocellular pathways was investigated with a contrast categorization task studying low level perception, memory and abstraction. We aimed to find out if deficits in memory, attention and perceptional function can also be detected in healthy first-degree biological relatives, in our case siblings of schizophrenia patients and if one of these measures might be considered a genetic marker of the illness and called an endophenotype. Contrast categorization deficit in schizophrenia subejcts was measurable in all contrast ranges of our interest. This perfectly lines up with prior findings of our laboratory (Keri et al., 1999, Keri et al., 2000). However, in the group of healthy relatives, the contrast categorization deficit was found in the 10% to 15% range only, which is exactly the transition zone between the specific receptive fields of the M and P pathways. This finding lets us conclude that the perceptual component of the categorization task might be a marker independent from the development of the disease, in other words, a possible endophenotype. We may also conclude that working memory impairments and deficiencies in abstract thinking are linked to contrast categorization deficits in schizophrenia.

Visual perception disturbances in schizophrenia, which could be described using the contrast categorization task, might also be related to impaired neuronal connections in the primar visual cortex of schizophrenia patients. Kapadia and his colleagues measured contrast threshold in humans in parallel with single cell recordings from monkey V1. They found that the observer's contrast threshold was 40% improved by a second collinear bar with a similar localization to that of the lateral flankers in our study. Consistent with the feature specificity of V1, the effect was eliminated when the bars were separated along their axis, were displaced from co-linearity or if their relative orientation was changed. Recordings from monkey V1 revealed that neurons showed a similar facilitation effect for a second collinear bar outside their receptive field with a high location and orientation specificity (Kapadia et al., 1995). These results support the view that the flanker facilitation effect is a reliable method to investigate low-level visual processing. Using a slightly different method with Gabor patches, we have demonstrated that these early feature-specific interactions in the visual cortex are specifically impaired in highly functioning schizophrenia patients. Although visual perception has been intensively studied in schizophrenia, targeted and specific testing of early visual areas is still difficult. Centrally presented Gabor patches, surrounded by two collinear or

orthogonal flankers are ideal stimuli for this purpose. Healthy subjects are described to show lower contrast thresholds for central Gabor patches when collinear flankers are presented. We found this effect to be significantly reduced in unmedicated highly functioning schizophrenia patients who performed well on other neuropsycholgical test methods. We found no correlation with the positive and negative symptoms either. The fact that the patients performed less well during the condition which was easier for the controls indicates that the findings cannot be explained by task difficulty effects. Another confounding factor may be that because of the short exposure time, the patients were unable to encode stimuli. However, two facts are at odds with this possibility. First, the patients showed normal degraded CPT performance, suggesting that they were able to encode briefly presented stimuli. The finding that reduced flanker facilitation was associated with normal CPT performance may reflect different sensitivities of these tests to detect visual abnormalities. Second, Slaghuis showed that increased exposure time did not lead to performance improvements during contrast detection tasks in schizophrenia patients (Slaghuis, 1998).

Since we controlled general intellectual and attention/ stimulus encoding problems, our results suggest that lateral connections in early visual cortex of schizophrenia patients are specifically impaired. This is consistent with neuropathological findings revealing disordered neuronal connectivity in the occipital cortex of schizophrenia patients (Selemon, 2001). The present data also are in accordance with studies demonstrating dysfunctions in perceptual organization in schizophrenia, that is, a failure to integrate local features into global objects (Cox and Leventhal, 1978, Silverstein et al., 2000). These results are also closely related to backward masking and smooth pursuit eye movement abnormalities described in schizophrenia. As a neurobiological basis of these phenomena, *N*-methyl-D-aspartate (NMDA) glutamate receptors and integrated synaptic networks may be of special relevance. However, we have to mention the limitations of these studies caused by confounding factors such as medication effects, attention impairment and general task difficulty.

Recent research work focusing on schizophrenia vulnerability claims that motion-sensitive areas in the dorsal occipito-parietal visual system are vulnerable to genetic and environmental factors, which affect brain maturation and development. These might begin prenatally and persist through childhood. In our prospective follow-up study we tried to identify developmental abnormalities which might be related to major psychiatric disorders due to genetic factors. We directly measured motion and form perception in order to gain information about visual processing deficits in children of affected mothers. Results revealed

that the rate of development in the motion task was less pronounced in children of mothers with schizophrenia than that in children of mothers with bipolar disorder and in age-matched controls. The development of form perception was spared. Children of mothers with bipolar disorder showed an intact development in both motion and form perception tasks. These results suggest that the progressive developmental abnormality of motion-sensitive visual areas may be a characteristic feature of schizophrenia-vulnerability. Motion coherence data from children of mothers with schizophrenia were qualitatively different from that observed in childhood autism (Spencer et al., 2000), but were similar to that observed in childhood hemiplegic cerebral palsy due to prenatal and perinatal developmental malformations and hypoxic lesions (Gunn et al., 2002). Children with autism showed a normal decrease of motion coherence threshold with increasing age, but in each age group (7, 8–9, 10–11 years), their performance was uniformly poorer than that of the age-matched controls (Spencer et al., 2000). In contrast, a decrease in motion coherence threshold with increasing age was less pronounced in children of mothers with schizophrenia than that in age-matched controls. This suggests a progressive developmental abnormality instead of a stable deficit, which would be fully present even at 7 years of age and would remain stable during childhood. This highlights the need to investigate critical developmental periods in children at risk of psychosis. There is no general agreement about the neuronal correlates of motion perception deficits in schizophrenia. Lencer and co-workers (Lencer et al., 2005) found that impairments in the tracking of a moving target were significantly correlated with a focal decrease of the hemodynamic response in the motion-sensitive V5 complex. In contrast, Hong and his group (Hong et al., 2005) published that patients had reduced pursuit-related activation in several motion processing areas including frontal and supplemental eye fields, medial superior temporal cortex, and anterior cingulate. The comparison of form and motion coherence allows the specific assessment of non-frontal visual motion areas, with a special reference to the V5 complex, which is specifically activated during the motion task relative to the form task (Braddick et al., 2000). Since we observed a selective deficit in the motion task, our data suggest that the developmental abnormality related to schizophrenia-vulnerability affects non-frontal motion areas. Contrary to our findings, Chen and colleagues (Chen et al., 2005) reported normal motion coherence threshold in biological relatives of schizophrenia patients, suggesting that directional motion processing does not reflect schizophrenia-vulnerability in contrast to velocity discrimination, which is closely related to the deficit of smooth pursuit eye movements even in non-affected biological relatives. However, in the (Chen et al., 2005) study, relatives of both schizophrenia and schizoaffective patients were included using a

cross-sectional design, whereas in our study, children of mothers with schizophrenia were followed-up, the sample being special because only mothers were affected in these families. The proportion of children who later develop schizophrenia is unknown and therefore it can be that directional motion perception abnormalities predict the later appearance of psychosis. The most important limitation of this study is that, due to the limited follow-up period, the number of children who later develop schizophrenia or bipolar disorder is not known.

The other main topic of the thesis is related to MDD. Contrary to our hypothesis, patients with MDD performed poorly on the ABCD version, whereas they showed a normal learning rate on the EFGH version of the IGT. Although executive functions were also impaired, these did not account for decision-making problems during the IGT. These results suggest that patients showed an increased sensitivity to reward, leading to disadvantageous choices from decks with high immediate reward but even higher future loss. Furthermore, immediate high punishment did not prohibit the patients to continue selecting cards from these decks, similarly to the controls. We also found that less depressed patients more frequently neglected high punishment than did more depressed patients. Confounding conditions prior associated with disadvantageous decision-making might be substance abuse (Bechara et al., 2001, Bechara et al., 2002), obsessive-compulsive disorder (Cavallaro et al., 2003), and cluster B personality disorders (Rogers, 2003), which were excluded in this study. We may further speculate that the pattern of IGT performance in patients with MDD was due to a general blunting of emotional reactivity. In this sense, patients may select from decks with higher immediate emotional valence, regardless of rewarding or punishing quality, in order to compensate their reduced reactivity to emotional stimuli. Another possibility is that failure in the ABCD version reflects behavioral impulsivity, which may be related serotonergic disturbances (Tanaka et al., 2004). However, the inter-trial interval was long resulting in a reduced pace of the task. This may have prevented the participants to execute premature impulsive responses. Furthermore, it is possible that punishment in the EFGH version was not especially aversive for the patients. However, the finding that less depressed patients more often ignored high immediate punishment is against this possibility.

Recent evidence using fMRI methods raises the possibility that the same brain structures are involved in the mediation of reward and punishment contingency based learning mechanisms, the only difference would be in the activation pattern of these structures during different emotional biases. Thus, potential loss would cause a decrease in the activation of the striatum, the ventromedial prefrontal cortex (VMPFC), the ventral anterior cingulate cortex (ACC) and

the medial orbitofrontal cortex, whereas structures involved in the processing of negative emotional stimuli, e.g. the amygdale and the anterior insula show an increased activity during this context. Potentional gain however causes an increased activity of the mentioned brain structures, the striatum, the VMPFC, the ventrolateral prefrontal cortex (VLPFC), AC, OFC but also the mesolimbic dopaminergic regions (Tom et al., 2007) (*Figure 11*.).

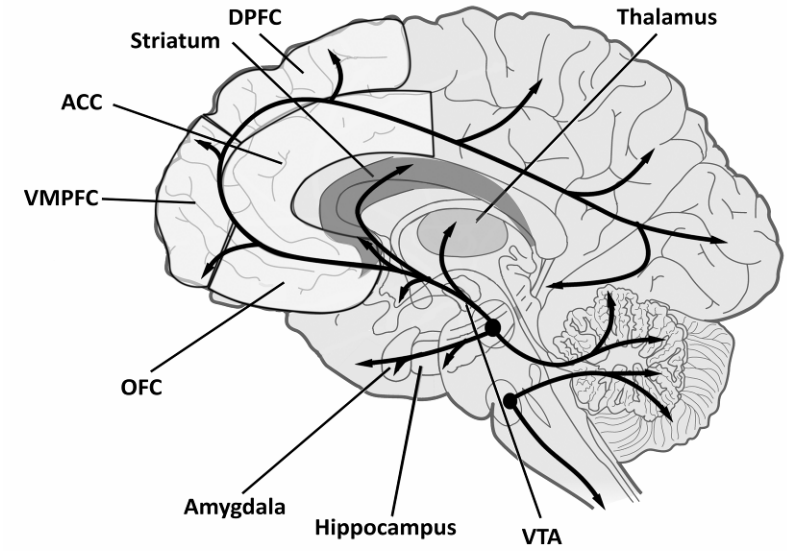


Figure 11. Regions involved in human decision-making and their relation to the serotonergic pathways. DPFC: dorsolateral prefrontal cortex; ACC: anterior cingulated cortex; VMPF: ventromedial prefrontal cortex; OFC: orbitofrontal cortex; VTA: ventral tegmental area

Steele and his colleagues performed further investigations measuring reaction time differences during emotional decision making and using fMRI methods comparing the group of patients with major depression to healthy controls. Control subjects responded to negative feedback by increased reaction time and increase of anterior cingulum (AC) activity, while positive feedback resulted in a decrease of the reaction time and increased activity of the ventral striatum. However, depressed patients failed to show any of these changes. The reaction time changes directly correlated to subjectively reported anhedonia feelings in both groups (Steele et al., 2007). Using positron emission tomography (PET), (Elliott et al., 1998) found that response to feedback in depressed patients was associated with an abnormal activation in the medial caudate and ventromedial PFC. Together with evidence from other approaches (Drevets, 2001, Mayberg, 2003, Hasler et al., 2004), all this data suggests that the brain structures related to the regulation of mood and the acquisition of reward–punishment

contingencies is dysfunctional in MDD. We may assume that in MDD altered sensitivity to reward and punishment or behavioral impulsivity may stand behind decision-making abnormalities, which, according to our data, were not a pure consequence of executive dysfunction.

MDD patients with the ’ll’ version of the 5-HTTLPR displayed higher persistence and performed better on the ABCD task compared with patients with the ’ss’ variant. Less persistence may be associated with a reduced ability to acquire or to maintain a decision-making strategy that did not lead to immediate high reward. The EFGH task investigated the possibility that decision-making problems were due to the failure of high reward to outweigh immediate punishment (Bechara et al., 2000) If the patient was too heavily influenced by immediate punishment, the decision-making strategy would have not been optimal. Patients with high trait anxiety, harm-avoidance, and depressive symptoms may have shown such enhanced sensitivity to punishment. Several studies demonstrated that Cloninger's temperament factors are associated with depression (e.g. (Cloninger et al., 2006). In our sample, the frequency of the ss genotype was high comparing to other European populations, which may indicate its role in depression (Lesch and Mossner, 1998).

Surprisingly, our data indicated that the genetic variants of the 5-HTTLPR did not influence trait anxiety and sensitivity to punishment. This is consistent with the recent meta-analysis (Munafo et al., 2005) which found that the association between 5-HTTLPR polymorphism and anxiety traits, if present, is weak. However, it depends on the instrument used for the personality assessment (Sen et al., 2004). It is of our interest and planned to extend the investigation to a larger sample size and to include healthy controls, which can be considered the main limitation of this study. Our next approach will also include the assessment of personality traits and decision-making using multiple questionnaires and neurocognitive tasks. We would consider the special relevance of impulsivity, suicidal attempts and behaviour on one hand and working memory and sustained attention on the other hand related to decision-making abnormalities in major depressive disorder.

Decision-making paradigms may offer a unique opportunity to investigate functional changes in MDD. In our study, we showed that medicated patients with MDD display disadvantageous choices at immediate large rewards, whereas immediate large punishment did not prohibit associated responses. This latter effect was more pronounced in the case of less severe depressive symptoms. To investigate whether these results might be related to medication

effects, further studies are necessary including patients on and off medication. These studies should also take into consideration individual personality style and cognitive, motivational, and response sources which have a significant effect on decision-making behaviour (Busemeyer and Stout, 2002). Another important point which has to be taken into account is the exact diagnosis of affective disorders with special regard on identifying mixed depression with co-occuring hypomanic states and impulsivity (Benazzi, 2008).

To briefly conclude, our data suggests the functional involvement of the different regions of the prefrontal cortex, the VMPFC, the OFC and the DLPFC in major depression. However, we could not find significant correlation between the function of these different cortical areas as measured by different neuropsychological test methods focusing on the 'speciality' of each area. Contrary to this stands the main criticism on the IGT claiming that the decision-making in the task clearly involves executive functions besides affective components (Maia and McClelland, 2004). Consistent with our findings, there is evidence suggesting the lack of connection between emotional biased decision making and cognitive strategies in other main psychiatric disorders (e.g. schizophrenia) as well (Lee et al., 2007). Our results support the separability of the rather flexible use of cognitive strategies in decision making and emotionally driven contingencies. We have to emphasize on the role of the 5-HTTLPR polymorphism in decision-making performance, which seems to be a stronger predictor of these strategies compared to the clinical symptoms of the disorder. However, the clinical signs might then have a more accentuated role than the executive dysfunction does. When studying a large, comorbid clinical sample of psychiatric patients, Jollant and his colleagues described the role of impulsivity and the therapeutic effect of affective modulation in order to improve altered decision-making strategies (Jollant et al., 2007).

VII. BRIEF SUMMARY

Our purpose was to investigate genetic vulnerability associated with clinical symptoms, functional alterations and neurocognitive deficits found in psychiatric disorders. We focused on low-level visual perceptual deficits and abnormalities in schizophrenia patients using methods and tasks relying on contrast detection. According to our findings, schizophrenia vulnerability might also be characterized by developmental abnormalities of motion-sensitive visual areas, detected in children of mothers with schizophrenia. Our interest also focused on cognitive deficits in major depressive disorder. We performed the Wisconsin Card Sorting Test in order to measure executive functions, set shifting mainly related to dorsolateral PFC and two versions of the Iowa Gambling Task, based on decision making strategies influenced by the cumulative effect of monetary reward and punishment. Surprisingly, but consistently, we found that depressed patients performed poorly on the task variant measuring reward sensitivity, which seems to be a paradoxical decision making strategy. Our results suggest that depressed patients tend to be influenced by high immediate reward, which could be explained by personality traits, especially persistence, and genetic factors, with special focus on the serotonin system associated with depression vulnerability.

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X. CONTENTS

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