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PET STUDIES OF THE SEROTONIN SYSTEM IN RELATION TO BEHAVIORAL PHENOTYPES IN PSYCHIATRY

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PET studies of the serotonin system in relation to behavioral phenotypes in psychiatry

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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“Major breakthroughs often come after major breakdowns”

– Matshona Dhliwayo

ABSTRACT

Behavioral phenotypes beyond core symptoms of diagnoses have become an area of high interest in psychiatric research. All major psychiatric diagnoses are associated with deficits in cognitive function, including impairments in social abilities, which contribute to great suffering and have a negative impact on the everyday life. Aberrations in the central serotonin system has been demonstrated in several psychiatric disorders. However, treatment targeting cognitive impairment is lacking due to limited understanding of neurobiological mechanisms in psychiatry. The overall aim of this thesis is to investigate associations between cognitive ability and serotonin transporter and serotonin receptor 5-HT_{1B} in major depressive disorder (MDD), autism spectrum disorder (ASD) and in non-psychiatric control subjects.

In **Study I**, ten patients with MDD were examined with cognitive tests and positron emission tomography (PET) and the radioligand [^{11}C]AZ10419369 binding to 5-HT_{1B} receptor before and after Internet-based cognitive behavioral therapy (ICBT) and for comparison with ten matched control subjects. The results showed improvements in verbal fluency from baseline to follow-up in the patient group. Correlations were found between improvement in verbal fluency and changes in 5-HT_{1B} binding in ventral striatum and amygdala as well as between cognitive flexibility and dorsal brainstem, amygdala and hippocampus. In the control group when controlled for age and education level, an association between visuo-constructive memory and 5-HT_{1B} availability in dorsal brainstem was demonstrated. The finding implicates a positive association between improvement in executive function and change in 5-HT_{1B} binding in the MDD group.

Study II investigated cognitive performance and the serotonin transporter (5-HTT) availability with PET and the radioligand [^{11}C]MADAM in fifteen adults with ASD and fifteen matched control subjects. Analyses revealed lower 5-HTT availability in several brain regions in the ASD group compared to the controls. Also, positive associations between social cognition and 5-HTT binding were demonstrated. These results are in line with the hypothesis of lower brain 5-HTT binding in individuals with ASD, and further supports the theory of serotonin involvement in ASD neurodevelopment.

In **Study III**, cognitive ability and 5-HT_{1B} receptor binding with PET and the radioligand [^{11}C]AZ10419369 were examined in 43 healthy control subjects. Our aim were to replicate parts of Study I as well as explore if other cognitive domains were associated with 5-HT_{1B}.

The findings between visuo-constructive performance and 5-HT_{1B} receptor binding in the dorsal brainstem from Study I could not be replicated. Exploratory analyses when not controlled for age, revealed positive associations between visuo-constructive memory and 5-HT_{1B} binding in several brain regions as well as negative correlations between 5-HT_{1B} binding in numerous brain regions and cognitive flexibility and reaction time. When controlling for age effects, negative correlations between reaction time and 5-HT_{1B} availability remained. Since a negative correlation between reaction time and amount of errors was found, implying faster reaction time and poorer impulse inhibition, these findings suggest that 5-HT_{1B} receptors are involved in impulsive behavior.

In **Study IV**, we investigated autism-related cognitive functions and the serotonin transporter (5-HTT) as well as serotonin receptor 5-HT_{1B} with PET and the radioligands [^{11}C]MADAM and [^{11}C]AZ10419369 in a sample of healthy participants. In the 5-HTT sample, positive correlations between social cognition and standardized 5-HTT binding in striatum and putamen, as well as a negative correlation between social cognition and standardized 5-HTT binding in brainstem, were demonstrated. In the 5-HT_{1B} sample, a significant correlation between central coherence and 5-HT_{1B} binding in thalamus was found, but after controlling for age effects the correlation did not remain significant. The results of 5-HT_{1B} binding in autism-like cognition do not support an association. Together with our finding of brain 5-HTT binding in relation to social-cognitive ability in neurotypical controls, and previous literature of individuals with ASD, a neurobiological and behavioral phenotype continuously distributed in the population is suggested for social ability.

LIST OF SCIENTIFIC PAPERS

I. **Tangen, Ä**., Borg, J., Tiger, M., Varnäs, K., Sorjonen, K., Lindefors, N., Halldin, C., & Lundberg, J. (2017). Associations between cognition and serotonin 1B in patients with major depressive disorder – a pilot study. *Psychiatry Research: Neuroimaging,* 267, 15-21. Doi: 10.1016/j.pscychresns.2017.06.001

II. Andersson, M., **Tangen, Ä**., Halldin, C., Farde, L., Borg, J., & Lundberg, J. Lower serotonin transporter binding in adult subjects with high-functioning autism as measured with [^{11}C]MADAM. *Molecular Psychiatry* (in print). Doi: 10.1038/s41380-020-00868-3

III. **Tangen, Ä**., Veldman, E., Svensson, J., Tiger, M., Nord, M., Sorjonen, K., Andersson, M., Plavén-Sigray, P., Varrone, A., Halldin, C., Varnäs, K., Borg, J., & Lundberg, J. Associations between cognition and serotonin receptor 1B binding in control subjects – A [^{11}C]AZ10419369 Positron Emission Tomography study (in manuscript).

IV. **Tangen, Ä**., Veldman, E., Svensson, J., Tiger, M., Nord, M., Andersson, M., Sorjonen, K., Plavén-Sigray, P., Varrone, A., Halldin, C., Varnäs, K., Borg, J., & Lundberg, J. Associations between autism-related cognitive functioning and regional binding of 5-HTT and 5-HT$_{1B}$ receptor in neurotypical control subjects (in manuscript).

ADDITIONAL LIST OF SCIENTIFIC PAPER

Horder, J., Andersson, M., Mendez, MA., Singh, N., **Tangen, Ä**., … Borg, J. (2018). GABA$_A$ receptor availability is not altered in adults with autism spectrum disorder (ASD) or in ASD mouse models. *Science Translational Medicine,* 10, eaam8434.

CONTENTS

Abbreviations

Abbreviation	Term
5-HT	serotonin, 5-hydroxytryptamine
5-HT_{1A}	serotonin receptor 1A
5-HT_{1B}	serotonin receptor 1B
5-HTT	serotonin transporter
ACC	anterior cingulate cortex
ADOS	Autism diagnostic observation schedule
ASD	autism spectrum disorders
BP_{ND}	non-displaceable binding potential
CBT	cognitive behavioral therapy
CNS	central nervous system
CPT	continuous performance test
DBS	dorsal brainstem
D-KEFS	Delis-Kaplan executive function system
DSM	Diagnostic and statistical manual of mental disorders
EFT	embedded figure test
FPT	fragmented picture test
GABA	gamma-aminobutyric acid, γ-aminobutyric acid
HR	high resolution
HRRT	high resolution research tomograph
ICBT	internet-based cognitive behavioral therapy
MADRS	Montgomery–Åsberg depression rating scale
MASC	movie for the assessment of social cognition
MDD	major depressive disorder
MINI	Mini international neuropsychiatric interview
MRI	magnetic resonance imaging

OCD	obsessive compulsive disorder
OFC	orbitofrontal cortex
PCC	posterior cingulate cortex
PET	positron emission tomography
PTSD	posttraumatic stress disorder
RCFT	Rey´s complex figure test
ROI	region of interest
SGPFC	subgenual prefrontal cortex
SPM	statistical parametric mapping
SRTM	simplified reference tissue model
SSRI	selective serotonin reuptake inhibitor
S-WAPI	stationary wavelet-aided parametric imaging
TCFT	Taylor´s complex figure test
TMT	trailmaking test
WAIS	Wechsler adult intelligence scale
WCST	Wisconsin card sorting test
WHO	World Health Organization

1 BACKGROUND

1.1 INTRODUCTION

Psychiatric disorders are associated with great suffering influencing cognitive, behavioral and social aspects, reduced quality of life, and higher risk of mortality and suicide (Beautrais et al., 1996; Rapaport et al., 2005; Van Heijst and Geurts, 2015). Literature to date reveals high prevalence, with psychiatric disorders accounting for nearly thirteen percent of the global burden of disease, exceeding both cardiovascular diseases and cancer (World Health Organization, 2004; Collins et al., 2011). Nevertheless, development of existing psychiatric treatments as well as discovery of new options addressing clinical core symptoms have remained relatively unchanged over the past 30 years.

Besides clinical core symptoms, psychiatric disorders are also associated with cognitive impairment. Patients report cognitive deficits of varying severity, including attention, different aspects of memory, learning, processing speed, visuospatial ability, and executive functions with verbal fluency, planning, decision-making and cognitive flexibility as well as impairments in central coherence and social cognition with theory of mind. Within the spectrum of psychiatric disorders, cognitive deficits were initially mainly associated with schizophrenia. However, such impairments have also been acknowledged in other disorders, including anxiety disorders, bipolar disorder, obsessive compulsive disorder (OCD), posttraumatic stress (PTSD), anorexia nervosa, borderline personality disorder, major depressive disorder (MDD) and autism spectrum disorders (ASD)(Jolliffe and Baron-Cohen, 1997; Millan et al., 2012; Lang et al., 2014; Goueli et al., 2019).

Hence, cognitive deficits are widespread within the psychiatric field. However, treatment of this domain has proven to be difficult. Pharmacological interventions targeting cognitive symptoms are lacking due to limited understanding of neurobiological underpinnings.

Psychiatric neuroimaging research implicates a role of the neurotransmitter serotonin in several mental disorders, such as schizophrenia (Rasmussen et al., 2010), OCD (Perani et al., 2008), MDD (Gryglewski et al., 2014), anorexia nervosa (Bailer et al., 2007) and ASD . Moreover, associations between serotonergic markers, mainly the serotonin transporter, and the serotonin receptor subtypes 5-HT_{1A} and 5-HT_{2A}, and cognitive functions have been demonstrated. However, despite slowly growing body of evidence, the neurobiological mechanisms are still elusive.

1.2 MAJOR DEPRESSIVE DISORDER

Major depressive disorder (MDD) is a highly prevalent (lifetime prevalence of 4-10%) and burdensome condition (Kessler et al., 2009) considered to be the leading cause of disability worldwide (World Health Organization, 2017). The gender distribution in MDD is skewed with approximately twice as many affected women than men. Studies have showed that this gender difference accumulates during late adolescence, and is relatively constant into old age (Kuehner, 2017).

The diagnosis of MDD is based on nine symptom criteria of persistent low mood, loss of interest and/or energy, sleep problems, weight change, psychomotor agitation, rumination, cognitive impairment and suicidal ideation (American Psychiatric Association, 1994). To fulfill the diagnosis, at least five criteria are required, where at least one of these five is low mood or loss of interest. Hence, it is a clinically heterogeneous disorder with high variation in symptom profiles within the same diagnosis (Fried and Nesse, 2014). It has been implicated that some MDD criteria add unnecessary diversity to the diagnosis and are not specific enough. However, when investigating the psychometric properties of MDD criteria, all nine criteria have been shown to significantly contribute to MDD with highest odds ratio for low mood (OR: 61.2) and loss of interest (OR: 29.7) and lowest odds ratio for suicidal thoughts (OR: 8.2)(Zimmerman et al., 2006).

Besides clinical core symptoms, cognitive deficits are also important and common. Individuals with MDD show a broad range of impairment across different cognitive domains, including attention, memory, visuo-spatial ability, processing speed, and executive function with verbal fluency, inhibition, reasoning, and cognitive flexibility (Fossati et al., 2003; Porter et al., 2007; Ahern and Semkovska, 2017). Some of these abilities normalize after a depressive episode, including memory, processing speed, learning, shifting ability, and general intellectual ability (Behnken et al., 2010; Ahern and Semkovska, 2017), whereas others are more persistent, such as executive function with verbal fluency and inhibition (Ahern and Semkovska, 2017). A longitudinal study showed persistent impairments in verbal fluency and inhibition at nine months follow-up as depressive symptoms declined when compared to a control group (Schmid et al., 2011). Moreover, a meta-analysis including 27 studies, demonstrated residual cognitive difficulties of attention, working and verbal memory, processing speed and executive function after clinical remission (Bora et al., 2013). Recent findings suggest that residual cognitive impairments increases with number of depressive episodes (Semkovska et al., 2019)

Available treatment for MDD involves both psychological and pharmacological interventions. There are various psychological interventions for MDD treatment, including cognitive behavioral therapy (CBT), which has been shown to be highly effective (Hofmann et al., 2012). CBT refers to a set of interventions focusing on maladaptive emotions, thoughts and behaviors. The treatment consists of techniques, including behavioral activation, cognitive restructuring and exposure, in order to reduce depressive symptoms and improve level of everyday functioning. Also, pharmacological treatment options are available, where selective serotonin reuptake inhibitor (SSRI) is a widespread and well-used antidepressive drug reducing depressive symptoms (Jakobsen et al., 2017), but however, fails in treating cognitive deficits. Existing, but however limited, pharmacological research of antidepressant effects on cognition in MDD patients suggests improvements in some cognitive functions, such as processing speed, delayed recall and verbal learning (Rosenblat et al., 2015; Bennabi et al., 2019). Nevertheless, the exact underlying neurobiological mechanisms are still partly unknown, which hampers the progress of developing successful treatment targeting cognitive impairment in MDD.

1.3 AUTISM SPECTRUM DISORDERS

Autism spectrum disorders (ASD) are heterogeneous, heritable, complex and life-long neurodevelopmental conditions with a prevalence of approximately 1.5% (Baxter et al., 2015). The disorder is defined by impairments in social interaction and communication as well as stereotypic, restricted behaviors and interests from early childhood.

Autism-like traits are considered to be continuously distributed in the population, where clinical ASD symptoms represent extremes on the continuum (Lundström et al., 2012). A high proportion of autistic-like symptoms have been identified in the psychiatric population, including schizophrenia (Frith and Corcoran, 1996), bipolar disorder (Santos et al., 2017) and eating disorder (Carton and Smith, 2014). Psychiatric comorbidity in ASD is high. The overlap between ASD and other neurodevelopmental disorders including attention deficit hyperactivity disorder (ADHD) and intellectual disability is common and well-described (Lai et al., 2014). Also, co-occurring mood and anxiety disorders are highly prevalent in the ASD population (Hofvander et al., 2009; Mannion and Leader, 2013; Lai et al., 2014). A study examining psychiatric comorbidity in young adults with Asperger syndrome, demonstrated that 70% av the participants had experienced at least one MDD episode, and 50% had experienced several MDD episodes (Lugnegård et al., 2011), which can be compared to the lifetime prevalence of 4-10% in MDD (Kessler et al., 2009). Possible explanations to the high MDD overlap may be an increased vulnerability in

individuals with ASD than the general population, with suggestions of secondary depression due to growing up with ASD, overlapping diagnostic symptoms or shared genetic and familial vulnerability. Neurobiological findings point also to neural aberrations in ASD, including the serotonin system.

Concerning cognitive aspects in ASD, there are in particular three domains where impairments have been found – executive function, theory of mind and central coherence. Individuals with ASD tend to perform worse on executive function tasks when compared to neurotypical controls (Demetriou et al., 2018) as well as in comparison to subjects with ADHD in tests measuring executive functions of cognitive flexibility, but also processing speed (Fried et al., 2016). When comparing the cognitive construct of theory of mind, findings frequently demonstrate that individuals with ASD have difficulties in recognizing others mental state when compared to neurotypical controls (Baron-Cohen et al., 1985). This decreased ability to interpret and predict social situations leads to social challenges, consistent with core symptoms of ASD. However, the concept of theory of mind does not capture the difficulties with non-social cognition. Individuals with ASD show difficulties in getting caught in details and making the details cohere within the context, which is a cognitive style called weak central coherence (Frith and Happé, 1994). On the other side, weak central coherence could also be beneficial, where individuals with ASD show superior performance in tasks where local processing is advantageous (Shah and Frith, 1983, 1993).

Behavioral interventions for ASD are available, such as social skills training (low to moderate effect) or vocational intervention focusing on work-related support (insufficient effect)(Lai et al., 2014). Other treatment options are psychotherapy or pharmacotherapy addressing comorbid disorders, such as MDD or anxiety, which show positive effects (Sizoo and Kuiper, 2017). Also, medications can be used to alleviate specific symptoms, such as SSRI for reducing repetitive behaviors in children (Soorya et al., 2008). However, pharmacological options targeting the core symptoms of social communication in ASD are still lacking.

1.4 COGNITIVE AND SOCIAL BEHAVIORAL PHENOTYPES IN PSYCHIATRY

Cognitive deficits are not only very common across most psychiatric disorders, it is also important in predicting treatment response (Park et al., 2020), course of illness (Vicent-Gil et al., 2018) and treatment outcome (Bannour et al., 2013). A tremendous amount of cognitive measurements are available. The tests described below are used in this thesis and

are included based on existing literature on well-established tests investigating cognitive domains associated with MDD, ASD and serotonin.

Executive function is an umbrella term and refers to a set of complex processes of planning, inhibition control, decision-making, cognitive flexibility, creativity and effective performance (Jurado and Rosselli, 2007). These are important abilities with high impact on everyday life functioning, and can be assessed by using several different tests.

The Continuous Performance Test (CPT), developed by Conners and derived from the original Rosvold with colleagues in 1956, initially for investigating patients with brain injuries (Rosvold et al., 1956). It is a popular tool, both in clinical assessment as in psychiatric research, and is designed to evaluate attention and vigilance/response inhibition of executive control. However, the performance also relies on other cognitive abilities including maintenance of task instructions, visual perception of stimuli and manual response. CPT is a computerized test, where the participant monitors a continuous presentation of stimuli in various time intervals with the instructions to react as fast as possible to the occurrence of a target. An analysis of the performance includes fifteen variables, where detectability (d`) is acknowledged as the primary outcome measure.

Another well-established and often used test is Verbal fluency. Several versions are available with various combinations of letters and categories, but the most commonly used version is perhaps the letter production task FAS (Bechtoldt et al., 1962). The instruction is to produce as many items starting with a certain letter (F, A, S) within one minute. The Verbal fluency test has later been extended with tasks also in category production and semantic flexibility. In the former, the participant is asked to produce as many words as possible for a particular category within one minute, for instance animals or fruits, and in the subtest semantic flexibility, the task is to switch between two categories that are not naturally associated with each other within one minute, such as fruits and furniture. Total number of correct items or switches produced within one minute in each subtest is used to examine abilities of attention, semantic and long-term memory, information processing speed as well as executive functions of initiation and strategic retrieval (Ruff et al., 1997).

The Trailmaking test is another frequently used instrument and consists of two subtests. In Trailmaking test A (TMT A), the instruction is, by pen and paper or on a computer, to draw a line connecting numbers in chronological order. In Trailmaking test B (TMT B), the participant is asked to draw a line connecting alternating numbers and letters in sequence. Performance is assessed by the time taken to complete each test. Although both tests are

used to measure attention, motor speed and working memory, TMT B requires additional cognitive effort in cognitive flexibility and set shifting due to the instruction to alternate between two sets of categories (numbers and letters)(Kortte et al., 2002).

Another common cognitive flexibility and set shifting measurement is the Wisconsin card sorting test (WCST), which nowadays is a computer-based test and involves sorting cards by different task rules, such as color, number or shape of figure based on feedback (Berg, 1948; Grant and Berg, 1948). More specifically, the participant is required to maintain or shift a strategy due to positive or negative feedback given after each set and based on an unknown sorting rule that changes without warning. The responses are interpreted by the program providing fifteen outcome measures. One frequently used measure is perseverative errors, which is the number of failures to shift a set in response to negative feedback, where a high score indicates lower performance with reduced set shifting ability.

At date, several tower tests of executive function are available, such as the Tower of London (Shallice, 1982), the Tower of Hanoi (Simon, 1975) and Delis-Kaplans Tower test (Delis et al., 2001). The tests share similar principles of planning and problem-solving skills, but are not completely comparable due to different instructions, task structure, reliability as well as that they have been suggested to measure different constructs within the executive function domain (Humes et al., 1997; Larochette et al., 2009). In our studies, D-KEFS Tower test has been used (however, named Tower of Hanoi in Study III). In this test, the participant is instructed to move disks of varying sizes on three pegs to a specified ending position in as few moves as possible. The performance is scored according the sum of completion times for all nine trials (Delis et al., 2001).

Rey´s complex figure test (RCFT) was developed by Rey in 1941 for initially investigating brain damages in adults (Rey, 1941). It was later standardized by Osterrieth (Osterrieth, 1944) and is nowadays used in several fields for investigating visuospatial and visuo-constructive memory. Similar versions but with different designs have been developed for comparison with RCFT of pre- and post-treatment, including Taylor Complex Figure Test (TCFT). The traditional administration of the test uses an incidental procedure divided into two parts, the first one requires the participant to copy a complex geometric figure while viewing it, the second part requires the participant to reproduce the figure from memory after a time interval of, usually, 3 and 30 minutes respectively. The most well-used scoring system involves placement and accuracy scoring, which ranges from 0 to 36. The copy trial is used to assess perceptual analytic strategy and is a parameter of the visuo-constructive

ability, and the recall trials are used to assess the amount and the quality of information retained, which evaluates visuospatial memory within declarative memory.

Social cognition is a multi-dimensional construct, which includes cognitive processes underlying social behavior, such as to understand and reason about others and ones' own feelings, thoughts and intentions. One such aspect is the theory of mind (ToM), which refers to a meta-cognitive ability in understanding and attributing thoughts, beliefs and intentions of others (Baron-Cohen et al., 1985). In this thesis, social cognition have been measured by using the Movie for the assessment of social cognition, Reading the mind in the eyes and Faux pas. The test of Movie for the assessment of social cognition (MASC) was developed by Dziobek and colleagues (2006) as an alternative for assessment of ToM. The intention was to resemble realistic and socially high-demanding situations. MASC is a computerized test, showing a fifteen minutes long movie of four characters at a dinner party with multiple-choice questions for the participant to answer concerning thoughts, beliefs and intentions of the characters. Performance is scored as the sum of total correct answers, which ranges from 0 to 44. The Reading the mind in the eyes test is a well-established and nowadays computerized test measuring ToM in adults (revised version)(Baron-Cohen et al., 2001). The instruction is to define the expressed emotion when viewing only the eye region displayed on a computer screen. The participant chooses one of four alternatives, and total sum of correct answers (total 36 items) is used as outcome variable. The Faux pas test for adults was developed by Stone and colleagues (Stone et al., 1998)(based on the version for children (Baron-Cohen et al., 1999)) and measures the ability to recognize social rule violations when presented with stories describing social situations and unintentionally social rule violations, such as that one character unintentionally makes an inappropriate comment resulting in negative feelings in another character. Administration of the test consists of reading the stories aloud to the participant while the participant is provided also with a written version. In total, 20 stories are presented. Ten faux pas stories are randomly interleaved with ten control stories without a faux pas. For each story, six questions are asked covering aspects of detection of a faux pas, person identification, explanation, false belief, empathy as well as a control question. Performance is assessed by the total score of 60 possible points from the questions in the stories containing a faux pas.

Central coherence refers to the ability to derive overall meaning from details (Frith and Happé, 1994), where strong central coherence implies a cognitive style to combine details into a global meaning, to use the context for an overall understanding and to switch between details and global strategy when necessary. Contrarily, weak central coherence

indicates a focus on details or local processing and failure to extract global meaning. Tests used to measure this cognitive ability are, among a few others, the Embedded figure test (EFT) and Fragmented picture test (FPT). EFT involves detection of a geometric figure hidden within a complex background (Witkin et al., 1971; Shah and Frith, 1993). In detail, the participant is presented with a complex background and asked to describe it. A geometric figure is then presented while the complex background is removed. Lastly, the complex background is again presented while the geometric figure is removed, where the participant is to locate the geometric figure within the complex background. Performance is assessed for reaction time to complete the task, with a total of twelve tasks. FPT, developed in 1987 (Snodgrass et al., 1987) from the original Gollin figures (Gollin, 1960), is designed to measure visual coherence by identification of common objects, such as pig or shoe, from partially completed (fragmented) pictures. Herein, the subject is presented with a picture that frame-by-frame forms over ten levels, and is instructed to verbally respond to what the picture might represents as soon as possible. If the answer is incorrect, the task continues. The outcome measure is the summarized reaction time to complete the, in total, ten pictures included in the test.

1.5 THE SEROTONIN SYSTEM

Serotonin (5-hydroxytryptamine, 5-HT) is a widely distributed neurotransmitter in the human body (Dahlström and Fuxe, 1964; Steinbusch, 1981). A majority of the serotonin is located in the gut (synthesized in enterochromaffin cells) regulating digestion through intestinal movements (Gershon and Tack, 2007), and a smaller part of serotonin can be found in blood platelets involved in hemostasis facilitation (Berger et al., 2009).

Less than one percent of all serotonin in the human body is located in the brain (Hornung, 2003). The serotonergic neurons originate from brainstem raphe nuclei, where serotonergic cell bodies are found, synthesizing serotonin from tryptophan, and project via axonal connections throughout the brain. Serotonin is essential for a wide range of functions, including temperature regulation, appetite, sleep, sexual behavior as well as aggression and cognition (Buhot, 1997; Lucki, 1998; Buhot et al., 2000).

The serotonin system includes a transporter and several receptors regulating homeostasis in different ways. The serotonin transporter (5-HTT) has been intensively examined since the development and progress of the antidepressant drugs with selective serotonin reuptake inhibitor (SSRI) activity in the 1990`s. The main role of 5-HTT, located on pre-synaptic serotonergic neurons, is to transport released serotonin from the extracellular space back to

the presynaptic neuron. Regarding the serotonin receptors, fourteen subtypes have been identified and classified into seven families (5-HT_1-5-HT_7). Further, within the serotonergic receptor family, the 5-HT_{1A} and 5-HT_{2A} are perhaps the most studied serotonergic receptors. The interest for the 5-HT_{1B} was initially low, partly because it was initially claimed to exist only in animals, and partly because of difficulties in separating 5-HT_{1B} from 5-HT_{1D} (Sari, 2004; Ruf and Bhagwagar, 2009), but the interest has since clarity in classification greatly increased. The 5-HT_{1B} receptor is perhaps best known for its role in aggression and impulsivity, but is suggested to also be involved in drug-abuse reinforcement, anxiety, depression, as well as migraine. The 5-HT_{1B} receptor is an inhibitory G-protein coupled receptor. High distribution of the receptor has been found in basal ganglia, striatum and neocortex, and lower levels have been demonstrated in the amygdala and hippocampus. The function of the 5-HT_{1B} receptor depends on its location. The presynaptic autoreceptor on serotonergic terminals regulates serotonergic levels via a negative feedback system, whereas the postsynaptic heteroreceptor on other neurons is involved in regulation of other neurotransmitters, including dopamine, acetylcholine, glutamate and GABA (Chenu et al., 2005). Hence, the role of serotonin is very much significant and diverse, and thus not a specific effect, but more of a modulatory function with sophisticated interactions with other neurotransmitter systems.

Hypotheses of the relationship between serotonin and the psychiatric disorders MDD and ASD have existed since 1960´s. For MDD, Schildkraut and Coppen implicated the involvement of serotonin in affective disorder, resulting in the monoamine hypothesis of depression (Schildkraut, 1965; Coppen, 1967). Other studies have demonstrated reduced serotonin metabolite levels in the cerebrospinal fluid of MDD patients compared to controls (Asberg et al., 1976), acute tryptophan depletion resulted in increased MDD symptoms in remitted patients (Ruhé et al., 2007) as well as positive pharmacological effects of SSRI targeting 5-HTT on MDD (Mace and Taylor, 2000), which also have been suggested to improve cognitive function in MDD patients (Rosenblat et al., 2015). Neuroimaging studies with positron emission tomography (PET) have shown significant differences in 5-HTT availability between MDD cases and controls, making a deviation in 5-HTT expression the most replicated molecular imaging finding in MDD (Savitz and Drevets, 2013). Findings of 5-HT_{1B} receptor in preclinical MDD models are inconclusive. Selective 5-HT_{1B} knockout in mice has shown antidepressant-like behavior (Nautiyal et al., 2016) and overexpression of 5-HT_{1B} has been associated with antidepressant-like effects (McDevitt et al., 2011). In humans, neuroimaging research shows an involvement of 5-HT_{1B} in psychiatry. For example, higher 5-HT_{1B} binding was associated with higher levels of psychopathic traits (da

Cunha-Bang et al., 2016), decreased 5-HT_{1B} binding was found in subjects with cocaine-dependency (Matuskey et al., 2014) and decreased 5-HT_{1B} binding was reported in PTSD and also associated with greater symptom severity (Murrough et al., 2011a). Molecular imaging literature related to MDD is very limited, but is nevertheless indicating a tendency of low 5-HT_{1B} availability in patients with MDD (Murrough et al., 2011b; Tiger et al., 2016, 2018).

Since the discovery of elevated whole blood serotonin in a subsample of children with ASD (Schain and Freedman, 1961), a large number of studies have been performed investigating serotonin in ASD. Findings indicate central serotonin alterations in ASD, both preclinical observations linking serotonin deviations to autistic traits (Veenstra-VanderWeele et al., 2012) as well as tryptophan depletion studies showing exacerbate repetitive behavior and unpleasant emotions in adults with autism (McDougle et al., 1996). Also, findings of recognition of emotion and response inhibition have been associated with serotonin level abnormalities in individuals with ASD (Daly et al., 2012). Neuroimaging studies of adults with ASD have primarily focused on 5-HTT and the serotonin receptors 5-HT_{1A} and 5-HT_{2A} within the serotonin system. Studies of 5-HTT have demonstrated lower binding in children and adolescents with ASD (Makkonen et al., 2008) and in adults with ASD (Nakamura et al., 2010), which also found a positive correlation between 5-HTT binding in cingulate cortex and Faux pas test. Girgis et al (2011) found no significant change in 5-HTT availability in adult participants with ASD compared to controls. For the serotonin receptors, disparate or lack of findings have been reported, where one study showed lower 5-HT_{2A} availability in subjects with ASD using single-photon emission computed tomography (SPECT)(Murphy et al., 2006), whereas others could not find a difference in 5-HT_{2A} binding using PET (Girgis et al., 2011). A recent study investigating 5-HT_{1A} receptor binding, found no difference between the ASD group and the control group (Lefevre et al., 2018). Taken together, the results are supportive of suggested serotonergic differences in individuals with ASD compared to neurotypical controls, but the details are still unknown.

Table 1. A short and non-exhaustive historical summary of important events due to serotonin

1868	Studies of vasoconstriction
1937	Italian scientist Ersparmer discovers Enteramine in enterochromaffin cells and performs the first isolation of Enteramine
1948	The American scientists Page, Green and Rapport introduce serotonin
1949	The molecular structure (5-HT) is reported by Rapport. In many ways, this is the true discovery of serotonin for now it can be truly identified and studied
1950´s	First antidepressive drug
1952	The name of serotonin is widely accepted and Enteramine is no longer used
1953	Serotonin is found in the human brain/CNS by Betty Twarog (USA), leading to the establishment of serotonin as a neurotransmitter
1954	Suggestions about the relation between brain chemistry with serotonin and behavior and mental disorders are made, partly based on Hoffmann´s (Switzerland) discovery of the properties of LSD in 1943
1965	Schildkraut (USA) suggests that affective states are the consequence of altered brain catecholamine levels
Monoamine theories of depression	
1967	Coppen (U.K) implicates that serotonin is involved in depression
1974	Hoffman and Phelps (USA) develops the PET system
1977	First commercial PET examination is executed and hence, the first PET study is published
1979	Development of radioligand binding technology with 5-HT_1 and 5-HT_2 binding sites
1981	5-HT_{1B} is characterized by Pedigo and colleagues (USA)
Late 1980´s	The antidepressive drug SSRI (Fluoxetine) hits the market
	A substantial number of PET studies are investigating potential biomarkers in relation to psychiatric and neurological disorders
Today	

1.6 POSITRON EMISSION TOMOGRAPHY

Positron emission tomography (PET) is a molecular imaging method for visualization and quantification of physiological and biochemical activity *in vivo*. Scientifically, PET is used in brain research for drug development as well as quantification of receptors, transporters and more recently, synapse availability in relation to psychiatric disorders.

The principle of PET is that the injected radioligand reaches and binds the target tissue in the brain. At decay of radionuclide, a positron is emitted. The positron travels a short distance in the brain tissue where it eventually collides with an electron. Since the positron is the anti-particle of the electron, they convert into two oppositely directed photons and thus, generate a pair of gamma-rays, which is detected by the highly sensitive PET system surrounding the participant. During a PET examination, a large number of such simultaneous activities of gamma-rays are collected within a time limit and used to reconstruct three-dimensional images of the radioactivity distribution by calculations of collision occurrences and by that, identify regions of high target density. After definition of specific regions with MR images, and generation of time activity curves, the outcome measure is calculated, and PET images are created for visualization. The radioligands used in our four studies are [^{11}C]MADAM binding to the 5-HTT (Halldin et al., 2005) and [^{11}C]AZ10419369 binding to the 5-HT$_{1B}$ receptor (Andersson et al., 2011), and non-displaceable binding potential (BP_{ND}) was used, which is a measure of radioligand binding in the region of interest relative to that in a reference region lacking the target.

1.7 SUMMARY

Within psychiatry, MDD and ASD are complex disorders with heterogeneous phenotypes and great variation in symptom profiles. Further, overlapping symptoms occur. Cognitive difficulties are evident for both disorders, where some are disorder-mutual, including executive dysfunction, and others may be more disorder-specific, such as that impairments in visuospatial ability and memory are more associated with MDD, and weak central coherence is primarily associated with ASD.

Treatments focusing on core symptoms of MDD as well as related symptoms in ASD (for instance anxiety and sleeping problems) are available, both psychological/behavioral interventions and pharmacotherapy. A role for serotonin in the pathophysiology of MDD and ASD has been suggested, where neuroimaging studies have demonstrating deviations in the serotonin system, especially the serotonin transporter, for both MDD and ASD. However, treatment focusing on cognitive impairment is hampered due to limited

understanding of neurobiological aspects of cognitive functioning, why the overall aim of this thesis was to contribute to this limited field focusing on serotonin in relation to cognitive function in MDD and ASD.

2 AIMS

In order to contribute to the limited research field of cognitive impairment in relation to neurobiological markers in psychiatric disorders, the overall aim of this thesis was to explore associations between dimensional cognitive ability and two different markers of the serotonin system.

The aim of **Study I** was to explore cognitive ability in depressed patients before and after treatment. Also, to investigate correlations between 5-HT_{1B} binding and cognitive functions in patients with MDD before and after treatment and, in comparison to healthy control subjects.

In **Study II**, we aimed to investigate cognitive ability and 5-HTT binding in an ASD group and, in comparison to a neurotypical control group. We hypothesized lower 5-HTT binding among the ASD subjects compared to the controls as well as a correlation between performance on the social-cognitive test of Faux pas and 5-HTT availability, as reported by Nakamura and colleagues (2010). A further aim was to explore putative associations between other relevant cognitive functions and 5-HTT binding.

The first aim of **Study III** was to replicate the results from Study I, which demonstrated a significant correlation between visuo-constructive memory and availability of 5-HT_{1B} receptors in the dorsal brainstem in the control group. The second aim was to explore other cognitive domains in relation to 5-HT_{1B} availability in a larger group of healthy participants.

Based on the continuous distribution of autism-like traits in the population, we aimed in **Study IV** to explore a possible link between autism-related cognitive abilities of both social cognition and central coherence, and markers of the serotonergic 5-HT_{1B} and 5-HTT in a sample of neurotypical subjects.

3 METHODS, RESULTS AND CONCLUSIONS

3.1 STUDY I. ASSOCIATIONS BETWEEN COGNITION AND SEROTONIN 1B IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER – A PILOT STUDY

3.1.1 Methods

3.1.1.1 Participants and procedure

In Study I, ten patients with MDD (according to diagnostic and statistical manual of mental disorders, DSM-IV) were recruited by advertisements in press or by the Internet Psychiatry unit at Psychiatry Southwest, Karolinska University Hospital, Southern Campus in Stockholm, Sweden. The patients were healthy according to medical history, physical examination with negative urine toxicology, blood analysis, had an ongoing MDD episode according to Mini International neuropsychiatric interview (MINI) of moderate type (score of 20-35 in Montgomery-Åsberg depression rating scale (MADRS)) and over the age of 18. The control subjects were recruited by newspaper advertisement or from a website designed for recruiting research participants. This group of 10 subjects had no psychiatric history and were otherwise healthy according to interviews with MINI or structured clinical interview for the diagnostic and statistical manual of mental disorders (DSM, fourth edition), and matched the patients in terms of gender and age (±3 years (±4 years for one pair). Exclusion criteria for both groups were bipolar disorder, current substance abuse, organic brain disorder, current psychopharmacological treatment and magnetic resonance imaging (MRI) abnormalities, and pregnancy.

The procedure consisted of a magnetic resonance imaging (MRI) scan, where examinations with cognitive tests and PET and [^{11}C]AZ10419369 were preferably executed on the same day, and within two weeks after the MRI scan. For the patient group, Internet-based cognitive behavioral therapy (ICBT) was initiated on the same day as the first PET examination (treatment duration: 11.9 ±1.4 weeks) and 14 ±2.2 weeks after treatment initiation, a second examination with cognitive tests and PET was performed. Also, a depression questionnaire was administered, both clinician-rated MADRS at each PET experiment (mean baseline: 26; mean follow-up: 7.4) and self-rated MADRS-S which was completed weekly by the patients throughout the study. The controls were examined with cognitive tests and PET and [^{11}C]AZ10419369 at baseline, and only cognitive tests approximately twelve weeks later. The control group did not receive ICBT. Parts of the results have previously been published (Tiger et al., 2014, 2016).

3.1.1.2 Cognitive behavioral therapy

Cognitive behavioral therapy (CBT) is a structured treatment intervention aiming to modify maladaptive thoughts, behaviors and emotions, and the interaction them between by different modules or techniques, including cognitive restructuring, behavior activation and exposure. Internet-based CBT (ICBT) is based on traditional CBT protocol, but is delivered online via a platform with digital guidance from a therapist (Hedman et al., 2012). The patient gets weekly access to modules and homework assignments to complete.

3.1.1.3 Assessment of behavioral phenotypes

Examinations of cognitive ability were executed for all participants at baseline and follow-up. The tests were chosen based on existing literature on cognitive deficits in MDD (Blanco et al., 2013; Snyder, 2013; Rock et al., 2014). Hence, visuo-constructive memory ability was estimated by Rey complex figure test (RCFT) at baseline (Shin et al., 2006) and Taylor complex figure test (TCFT) at follow-up to minimize learning effects. Executive function was assessed with Verbal fluency subtests letter production and category production (Tombaugh et al., 1999) as well as Trailmaking test A and B (TMT A; TMT B) (Tombaugh, 2004). Also, general intellectual ability was estimated by Wechsler adult intelligence scale, third version (WAIS-III) subtest vocabulary.

3.1.1.4 Image acquisition

The MRI (Signa 1.5T or 3.0T, GE Healthcare) scan was executed for exclusion of structural pathology (T2-weighted images) and for co-registration with PET data (T1-weighted images), and later segmented into gray matter, white matter and cerebrospinal fluid using SPM5 (statistical parametric mapping, Wellcome Trust Centre for Neuroimaging, United Kingdom). The patient group was examined twice with PET (ECAT HRRT, Siemens Molecular Imaging) and the radioligand [^{11}C]AZ10419369 for 5-HT$_{1B}$ receptor availability, synthesized as previously described (Pierson et al., 2008). The patient was placed recumbent with the head in the PET system, where a plastic helmet for minimizing head movements was used (Bergström et al., 1981). Brain radioactivity was measured for 93 minutes ranging from 20 seconds to 6 minutes (mean injected radioactivity: 385.7 ±30.9 MBq). Regions of interest were selected based on literature of deviating serotonin marker densities in MDD (Drevets, 2000; Savitz and Drevets, 2009; Murrough et al., 2011b); orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), subgenual prefrontal cortex (SPC), amygdala, hippocampus, ventral striatum and dorsal brainstem (DBS). The regions were manually defined on individual MRI images and then transferred into PET images as

previously described (Varnäs et al., 2011). Due to insignificant levels of 5-HT_{1B} receptors (Varnäs et al., 2001), the cerebellar cortex was used as a reference region (Table 3) for quantification of the outcome measure of binding potential (BP_{ND}) using S-WAPI (stationary wavelet transform-based parametric mapping framework) implemented in Matlab R2007b for Windows (Turkheimer et al., 2003; Cselényi et al., 2006; Schain et al., 2013).

Table 3. Mean [^{11}C]AZ10419369 binding.

	Controls BP_{ND} ±SD	Patients BP_{ND} ±SD (PET1)	Patients BP_{ND} ±SD (PET2)	Change in BP_{ND} ((PET2-PET1)/PET1)
OFC	1.08 ± 0.16	0.99 ± 0.36	0.93 ± 0.23	-0.05 ± 0.17
ACC	1.03 ± 0.25	0.80 ± 0.27	0.81 ± 0.18	0.01 ± 0.21
SPC	0.90 ± 0.11	0.71 ± 0.24	0.74 ± 0.19	0.05 ± 0.17
Ventral striatum	2.03 ± 0.40	1.79 ± 0.43	1.71 ± 0.31	-0.05 ± 0.20
Amygdala	0.91 ± 0.20	0.81 ± 0.38	0.73 ± 0.26	-0.15 ± 0.47
Hippocampus	0.33 ± 0.12	0.26 ± 0.12	0.21 ± 0.10	-0.31 ± 0.53
DBS	0.45 ± 0.28	0.56 ± 0.25	0.38 ± 0.20	-0.76 ± 1.02

Note. BP_{ND} = binding potential; SD= standard deviation; PET= positron emission tomography; OFC=orbitofrontal cortex; ACC=anterior cingulate cortex; SPC=subgenual prefrontal cortex; DBS=dorsal brainstem.

3.1.1.5 Statistics

Parametric paired samples t-tests were used for comparisons of cognitive performance from baseline to follow-up as well as between the matched groups. Mixed effect modeling were executed to investigate differences over time as this model integrates time-varying factors, but also takes missing values into consideration. Pearson´s correlations were applied to explore relationships between cognitive performance and 5-HT_{1B} binding. For significant correlations from the initial analyses, a second step with multiple linear regression analyses at baseline were applied. Also, Pearson´s correlations were used to explore differences in cognitive performance in relation to differences in 5-HT_{1B} binding in the patient group. The relative change in cognition and 5-HT_{1B} binding from baseline to follow-up was calculated by each cognitive test and 5-HT_{1B} binding in each brain region (cognitive performance follow-up – cognitive performance baseline)/cognitive performance follow-up = ΔCP; (BP_{ND} follow-up – BP_{ND} baseline)/BP_{ND} follow-up) = ΔBP_{ND}).

3.1.2 Results

The patient group was examined twice with PET, and all study subjects were examined twice with cognitive tests. However, due to missing data parts of the results from the

cognitive tests could not be retrieved (Table 4). No statistically significant difference between the groups in age, intellectual ability or education were found (Table 5).

Table 4. Results for the different subjects in RCFT/TCFT (Rey´s Complex Figure Test, Taylor´s Complex Figure Test), Verbal fluency letter and category production, TMT A and B (Trailmaking Test) and WAIS-III (Wechsler Adult Intelligence Scale, version III).

	Controls		Patients	
	Baseline	Follow-up	Baseline	Follow-up
RCFT/TCFT 1	20.1 (7.8)[8]	24.5 (3.2)[6]	22.4 (7.2)[10]	26.7 (6.1)[7]
RCFT/TCFT 2	17.4 (6.6)[7]	24.1 (4.3)[6]	21.4 (8.5)[10]	27.7 (5.2)[7]
Letter production	33.9 (9.9)[9]	38.8 (13.6)[6]	46.4 (15.5)[10]	55.6 (18.2)[7]
Category production	43.2 (12.0)[9]	54.5 (6.9)[6]	50.8 (13.4)[10]	61.3 (13.9)[7]
TMT A	36.6 (12.0)[9]	35.2 (12.6)[6]	36.2 (11.0)[9]	29.0 (13.2)[7]
TMT B	93.1 (29.6)[9]	66.5 (19.8)[6]	75.1 (29.2)[9]	61.1 (31.0)[7]
WAIS-III	-	46.5 (9.4)[8]	-	49.0 (6.8)[7]

Note. RCFT (Rey´s complex figure test) at baseline and TCFT (Taylor´s complex figure test) at follow-up; superscript= number of participants in each test (max=10).

Table 5. Patient and matched control subject characteristics.

	Patients						Matched controls		
Nr	Age	Gender	Education	Hand	Episodes	MADRS	Age	Gender	Education
1	25	Male	13	Right	2	20	29	Male	15
2	51	Female	17	Right	10	35	54	Female	13,5
3	46	Female	15	Right	3	28	46	Female	20
4	68	Female	16	Right	3	24	69	Female	7
5	66	Male	19	Right	3	28	64	Male	15
6	37	Female	15.5	Right	>10	26	36	Female	18
7	66	Male	16.5	Right	>10	25	69	Male	13
8	24	Female	14	Right	3	26	25	Female	16
9	57	Male	20	Right	2	24	54	Male	13
10	38	Female	18	Right	2	24	41	Female	15
M	47.8		16.4			26	48.7		14.6
SD	±16.97		±2.2			±3.9	±16.0		±3.5

Note. Education = years of education; Hand= handedness; Episodes= number of major depressive episodes; MADRS = Montgomery Åsberg Depression Rating Scale at baseline; *M* = mean; *SD* = standard deviation.

3.1.2.1 Cognitive performance from baseline to follow-up

The patient group showed significant improvement in verbal fluency, both letter production (t= –3.14; p= 0.02) and category production (t= –2.66; p= 0.038), but not in the other tests. The control group demonstrated a significant improvement only in verbal fluency, category production (t= –2.76; p= 0.04).

3.1.2.2 Associations between cognitive performance and 5-HT$_{1B}$ binding

In the patient group at baseline, moderate and positive correlations were found between RCFT, immediate recall (named delayed recall in the published version) and 5-HT$_{1B}$

binding in amygdala (r_{xy}= 0.65; p= 0.041), ventral striatum (r_{xy}= 0.69; p= 0.027) and DBS (r_{xy}= 0.69; p= 0.028). Similar findings were shown in RCFT, delayed recall (named delayed recognition in the published version) and 5-HT_{1B} binding in amygdala (r_{xy}= 0.66; p= 0.04), ventral striatum (r_{xy}= 0.71; p= 0.022) and DBS (r_{xy}= 0.74; p= 0.015). Multiple linear regression analyses were performed for significant findings in the initial correlation analyses. However, in the patient group at baseline, no correlation survived when controlling for age and years of education. In the patient group at follow-up, no significant correlations between cognitive ability and 5-HT_{1B} binding were found.

In the control group at baseline, strong and positive correlations were demonstrated between RCFT, immediate recall (named delayed recall in the published version) and 5-HT_{1B} binding in the OFC (r_{xy}= 0.89; p= 0.003) and amygdala (r_{xy}= 0.81; p= 0.015) as well as between RCFT, delayed recall (named delayed recognition in the published version) and 5-HT_{1B} binding in the OFC (r_{xy}= 0.96; p= 0.001) and DBS (r_{xy}= 0.83; p= 0.021). When controlling for age and years of education by multiple regression analyses, the relationship between RCFT, delayed recall and 5-HT_{1B} binding in DBS remained (β= 10.62; p= 0.026). Also, the age effect on RCFT, delayed recall was significant (β= –0.30; p= 0.013).

3.1.2.3 Group differences in cognitive performance at baseline

The patient group performed significantly better than the control group in RCFT, delayed recall (named delayed recognition in the published version)(t= 3.62; p= 0.011).

3.1.2.4 Group differences in cognitive performance at follow-up

The patient group performed significantly better than the control group in verbal fluency, letter production (t= 8.14; p= 0.001). No significant differences in general intellectual ability estimated with WAIS-III Vocabulary task were found.

3.1.2.5 Effect of time and group on cognitive performance

Significant time effects on cognitive performance in RCFT/TCFT, delayed recall (F(1, 26)= 6.96, p= 0.014) and verbal fluency, category production (F(1, 28)= 6.11, p= 0.02) were found. Also, a significant group effect on cognitive performance, verbal fluency, letter production (F(1, 28)= 7.84, p= 0.009) was demonstrated. No significant interaction effects (time*group) were shown.

3.1.2.6 Difference in cognitive performance and 5-HT$_{1B}$ binding before and after treatment

A relative change (ΔCP and ΔBP$_{ND}$) was calculated to explore putative correlations between differences in cognition abilities and 5-HT$_{1B}$ binding from baseline to follow-up, and demonstrated significantly positive correlations between improvement in verbal fluency, letter production and difference in 5-HT$_{1B}$ binding in ventral striatum (r_{xy}= 0.79; p= 0.033), between improvement in verbal fluency, category production and 5-HT$_{1B}$ binding in amygdala (r_{xy}= 0.76; p= 0.049) as well as between improvement in TMT B and 5-HT$_{1B}$ binding in DBS (r_{xy}= 0.85; p= 0.032), amygdala (r_{xy}= 0.87; p= 0.024) and hippocampus (r_{xy}= 0.89; p= 0.017)(Table 6; Fig. 1-2).

Table 6. Correlations (r) between the difference in cognitive test performance and difference in BP$_{ND}$ in the patient group

	ΔTCFT/RCFT, delayed recall r (p)	ΔTCFT/RCFT, delayed recognition r (p)	ΔLetter production r (p)	ΔCategory production r (p)	ΔTMT A r (p)	ΔTMT B r (p)
ΔOFC	0.15 (0.75)	0.09 (0.84)	0.59 (0.16)	0.29 (0.52)	-0.37 (0.94)	0.54 (0.27)
ΔACC	0.26 (0.58)	0.23 (0.63)	0.55 (0.21)	0.14 (0.76)	-0.50 (0.25)	0.30 (0.57)
ΔSPC	-0.04 (0.94)	-0.19 (0.68)	-0.07 (0.89)	0.15 (0.75)	-0.19 (0.68)	0.24 (0.65)
ΔVST	0.31 (0.51)	0.32 (0.49)	0.86 (0.01)*	0.29 (0.52)	-0.15 (0.74)	0.24 (0.65)
ΔAMY	0.17 (0.72)	0.02 (0.96)	0.32 (0.49)	0.53 (0.22)	0.60 (0.16)	0.89 (0.02)*
ΔHIP	-0.01(0.98)	-0.15 (0.75)	0.10 (0.82)	0.23 (0.61)	0.18 (0.70)	0.95 (0.00)**
ΔDBS	-1.01 (0.83)	-0.32 (0.48)	-0.02 (0.96)	0.16 (0.73)	-0.14 (0.77)	0.92 (0.00)**

Note. RCFT=Rey´s Complex Figure Test; TCFT=Taylor´s Complex Figure Test; TMT A= Trailmaking test A; TMT B= Trailmaking test B; ACC=anterior cingulate cortex; OFC=orbitofrontal cortex; SPC=subgenual prefrontal cortex; VST= ventral striatum; DBS=dorsal brainstem; AMY=amygdala; HIP=hippocampus; *= p<0.05; **=p<0.001.

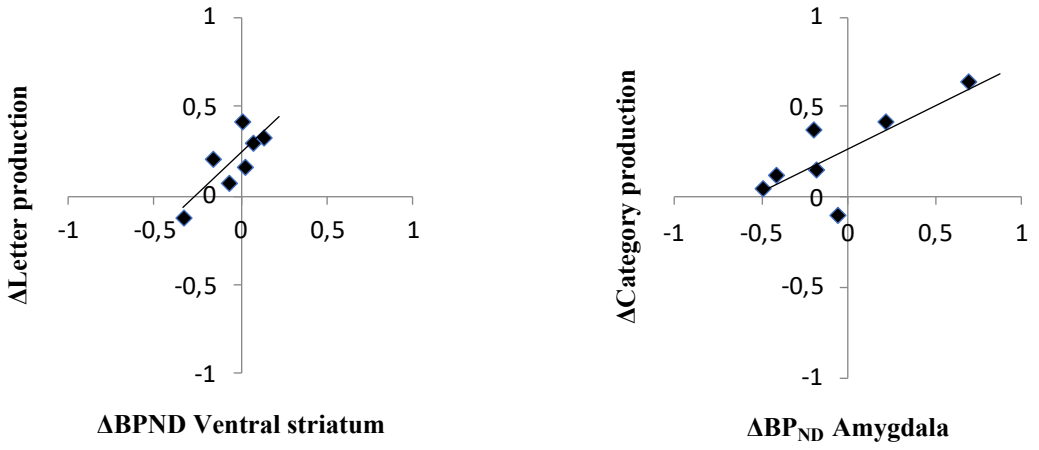

Fig 1. Scatter plot illustrating the association between the relative difference in letter production and binding potential (BP$_{ND}$) in ventral striatum as well as between category production and binding potential (BP$_{ND}$) in amygdala.

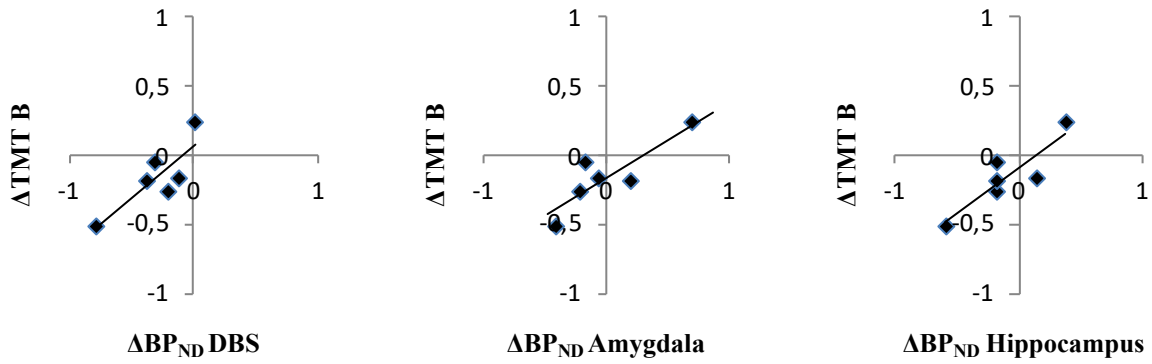

Fig. 2. Scatter plot illustrating the association between relative difference in Trailmaking Test B (TMT B) performance and binding potential (BP_{ND}) in dorsal brainstem (DBS), amygdala and hippocampus.

3.1.2.7 Difference in cognitive performance and clinical change before and after treatment

In the patient group, no significant correlation was found between difference in cognitive performance (ΔCP) and difference in clinical change (ΔMADRS) from baseline to follow-up.

3.1.3 Conclusions

The main finding showed that cognitive ability in executive function improved in depressed patients from baseline to follow-up, and that this improvement was associated with changes in 5-HT_{1B} binding in several brain regions. Also, in the control group when controlling for age, a significant association was found between visuo-constructive memory and dorsal brainstem. In sum, these results implicate a role of the 5-HT_{1B} receptor in cognition, both in healthy subjects as well as in MDD.

3.2 STUDY II. LOWER SEROTONIN TRANSPORTER BINDING IN ADULT SUBJECTS WITH HIGH-FUNCTIONING AUTISM AS MEASURED WITH [^{11}C]MADAM

3.2.1 Methods

3.2.1.1 Participants and procedure

Study II consisted of 15 subjects with ASD that were recruited through specialized healthcare clinics and 15 control subjects that were recruited by advertisement in local newspapers in the Stockholm region. The inclusion criteria for the ASD group were a clinical diagnosis of autism or Asperger syndrome according to International classification of diseases (ICD-10)/DSM-IV and over the age of 18. The clinical diagnosis was supported by the result of the Autism diagnostic observation schedule, second edition (ADOS-2), module 4. The control subjects did not have an ASD diagnosis and was individually matched to each participant with ASD based on gender (11 males, 4 females), age (±3 years) and estimated general intellectual intelligence quotient (IQ) (±1 *SD*) by Wechsler adult intelligence scale, fourth version (WAIS-IV), subtest Matrix reasoning (Table 7). Exclusion criteria for all participants were current psychiatric disorder according to DSM-IV, IQ< 70, central nervous system related disorder, psychopharmacological treatment within six months, nicotine use, substance abuse or other major health problems, and pregnancy. The sample of the present study was the same as the one described in a previous published article (Horder et al., 2018).

The screening procedure contained a psychiatric interview with MINI and medical history, and somatic examination with blood analysis and urine toxicology, electrocardiogram as well as MRI. All participants were examined with cognitive tests and a PET examination with the radioligand [^{11}C]MADAM for 5-HTT binding.

3.2.1.2 Assessment of behavioral phenotypes

All participants were assessed with an extensive cognitive test protocol. Social cognition was examined by Movie for assessment of social cognition (MASC)(Dziobek et al., 2006), Reading the mind in the eye (EYE)(Baron-Cohen et al., 2001), and Faux pas (Baron-Cohen et al., 1999). Executive function was assessed by using Verbal fluency, subtest letter production, category production and semantic flexibility, Continuous performance test-II (CPT) as well as the Tower test from the broader Delis-Kaplan executive function system

(Delis et al., 2001). Central coherence was estimated by Embedded figure test (EFT)(Almeida et al., 2010) and Fragmented picture test (FPT)(Snodgrass et al., 1987).

Table 7. Demographics, imaging and behavioral sample characteristics.

	ASD					Control					
	n	mean	SD	min	max	n	mean	SD	min	max	*p*
Demographic											
Age	15	33.0	9.1	19.4	48.0	15	33.1	9.4	22.1	49.1	.92
Education (years)	15	13.7	3.4	9	20	15	16.3	4.0	11	25	.02
WAIS matrix (sp)[1]	15	12.5	4.0	4	18	15	12.2	3.4	5	17	.72
Height (cm)	15	177.3	9.6	161	189	15	179.1	8.6	167	194	.50
Weight (kg)	15	75.8	17.0	50.6	107.7	15	73.7	12.4	51	109	.59
Imaging											
Injected activity (MBq)	15	366.5	62.6	253	464	15	372.0	55.1	247	440	.79
Molar activity (GBq/µmol)	15	228.1	85.8	73	403	15	241.3	73.6	106	373	.71
Injected mass (µg)	15	0.54	0.34	0.24	1.36	15	0.46	0.19	0.20	0.99	.51
Ref. Region AUC (SUV)[2]	15	12.1	1.96	7.8	14.4	15	11.7	1.51	10.0	15.9	.38
Behavioral											
EYE	15	24.13	5.53	13	30	15	29.60	2.67	24	33	.005
MASC	15	29.20	5.66	18	37	15	36.13	2.85	28	40	<.001
Faux Pas	15	43.87	10.51	21	57	15	53.13	5.22	41	60	.005
VF lp	15	35.13	11.40	10	52	15	49.67	15.15	24	83	.01
VF cp	15	43.00	10.74	26	69	15	50.67	10.27	31	70	.06
VF sf	15	12.27	3.22	4	16	15	15.87	2.97	10	20	.004
Tower	15	519.5	275.9	205	1024	15	453.3	178.5	222	744	.56
CPT	15	0.60	0.42	0.11	1.87	15	0.87	0.44	0.22	1.8	.06
EFT	15	726.2	693.9	46	2353	15	468.3	198.4	151	810	.30
FPT	15	226.3	80.4	131	394	15	213.9	93.4	80	460	.72

Group mean and standard deviation (SD). Paired samples t-test. Reading the mind in the eye (EYE), Movie for assessment of social cognition (MASC), Faux pas, Verbal fluency letter production (VF lp), Verbal fluency category production (VF cp), Verbal fluency semantic flexibility (VF sf), Tower test (Tower), Conner's continuous performance test II (CPT), Embedded figure test (EFT), Fragmented picture test (FPT). [1]Scalar points. [2]Standardized uptake value.

3.2.1.3 Image acquisition

An MRI scan (3T GE Discovery MR750, GE Milwaukee WI) was conducted for all subjects, where T1-weghted images were used for co-registration with PET data (Statistical parametric mapping 5 (Department of Cognitive Neurology, University College London)) in Matlab 2007b for Windows (MATLAB version 7.5, Natick, Massachusetts; The Mathworks Inc.). Regions of interest were delineated using Freesurfer software (version 5.0, http://surfer.nmr.mgh.harvard.edu), where brain region anatomy was defined by the cortical atlas of Desikan-Killany (Desikan et al., 2006). During the examination, the

participant was placed recumbent with the head in the PET system (ECAT Exact HR 47 PET system (CTI/Siemens, Knoxville, TN)) while using a head fixation device for minimizing head movements (Bergström et al., 1981) with an acquisition time of 93 minutes. The radioligand [^{11}C]MADAM for 5-HTT availability was synthesized as previously described (Halldin et al., 2005). Brain regions were selected based on anatomical and functional properties of the serotonin system and putative relevance to ASD with a total of 20 regions including total gray matter, where cerebellar cortex was used as a reference region. For 5-HTT quantification, the simplified reference tissue model (SRTM) was used (Lammertsma and Hume, 1996).

3.2.1.4 Statistics

Normality of data was evaluated, which showed a normal distribution in 5-HTT binding, but not in cognitive performance. Hence, parametric paired samples t-tests were used for descriptive statistics and investigations of tracer administration, size of brain regions and differences in 5-HTT binding in total gray matter as well as the other 19 regions between the ASD group and controls. Non-parametric Wilcoxon signed-rank test was used to examine differences in cognitive performance between the ASD group and the control group. Also, non-parametric Spearman´s correlations for analyzing putative associations between cognitive ability and 5-HTT binding were investigated in the whole data set (n= 30) based on the assumption that ASD represents the extreme end of a continuous distribution of traits rather than categorical symptoms. Corrections for multiple comparison were performed using the false discovery rate (FDR) method (Benjamini and Hochberg, 1995).

In addition, differences in 5-HTT binding between male and female sample were performed using paired samples t-test. Due to previous findings which demonstrated associations between Faux pas and 5-HTT availability (Nakamura et al., 2010), an exploratory voxel-based analysis was executed.

Power analysis showed that 15 subjects were required for a power of 0.8 when assuming a mean effect size of 0.78 (Girgis et al., 2011) and alpha value of 0.05. For outlier identification, Grubb´s test was used. No subject was identified as an outlier, but however, 10 datapoints were outliers in Grubb´s test, of which 7 of these were classified as outliers after normalizing 5-HTT to gray matter binding according to Grubb´s test (1 in the ASD group; 6 in the control group). Hence, for all analyses involving 5-HTT data, outliers were

excluded. The statistical analyses were two-tailed and executed using R software (version 3.4.1, R Foundation).

3.2.2 Results

The groups did not differ in terms of gender, age or level of intellectual ability, but the control subjects had significantly higher level of education (p= 0.02). No significant difference between the groups in imaging data of injected or molar activity, or in [^{11}C]MADAM uptake in the reference region of cerebellum (Table 7).

3.2.2.1 Assessment of behavioral phenotypes

Non-parametric Wilcoxon signed-rank test showed that the ASD group had significantly lower performance in all three social-cognitive tests compared to the control group (p< 0.005). Also, a larger variability in social-cognitive performance in the ASD group was observed. Moreover, the ASD group had a numerically lower performance in all executive functioning tests, but significant differences were found in verbal fluency, lp (n= 15, Z= 103.5, p= 0.01) and verbal fluency, sf (n= 15, Z= 111.5, p= 0.003). In the central coherence tests, a numerically but not significantly, lower performance was shown in the ASD group for FPT (n= 15, Z= 53, p= 0.72) and EFT (n= 15, Z= 41, p= 0.30) (Table 7).

3.2.2.2 5-HTT availability

In total gray matter, 5-HTT binding was significantly lower in the ASD group compared to the control group (14.6%)(Fig. 3). 5-HTT binding was numerically lower in all nineteen specific brain regions in the ASD group, where 10 were significantly lower, including neocortex, frontal cortex, parietal cortex, rostral middle frontal, insular cortex, anterior cingulate cortex, posterior cingulate cortex, nucleus accumbens, and putamen (Table 8; Fig. 4). When correcting for multiple comparisons, all findings remained significant.

Exploration of differences in 5-HTT binding between male and female sample did not demonstrate gender-specific effects. The *post hoc* exploratory voxel-based analysis of the findings of Nakamura and colleagues (2010) showed two significant clusters in left posterior cingulate cortex and left middle frontal cortex.

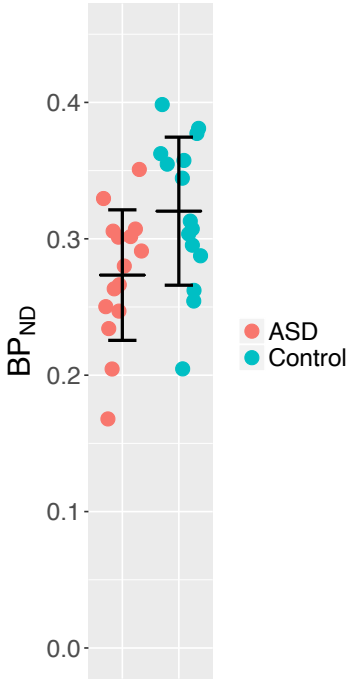

Fig 3. 5-HTT availability in total gray matter (BP_{ND}). Individual values and group mean. Error bars show ± 1 SD. Subjects with ASD and control subjects. ASD BP_{ND} mean [SD] 0.27 [0.05], control BP_{ND} 0.32 [0.05], p= 0.004, paired samples t-test.

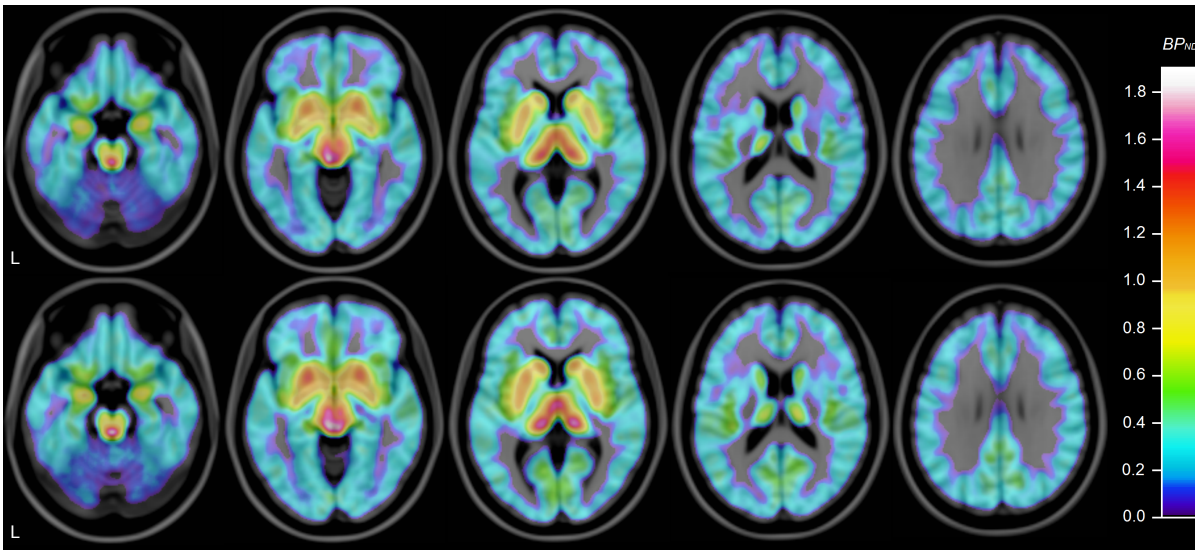

Fig 4. Mean 5-HTT availability in ASD and control group. Subjects with ASD above and control subjects below, “L” indicates left.

Table 8. Differences in regional 5-HTT availability.

	ASD			Control				
Region of interest	n	mean	SD	n	mean	SD	*p*	Difference
Neocortex	15	0.18	0.04	15	0.22	0.05	.02*	-16.4%
Frontal cortex	15	0.16	0.04	15	0.20	0.06	.02*	-19.2%
Occipital cortex	14	0.23	0.06	14	0.26	0.06	.13	-11.2%
Parietal cortex	15	0.19	0.04	15	0.23	0.05	.02*	-16.8%
Temporal cortex	15	0.21	0.07	15	0.24	0.06	.08	-15.7%
Orbitofrontal cortex	13	0.20	0.08	13	0.23	0.10	.48	-11.4%
Rostral middle frontal cx	14	0.09	0.04	14	0.12	0.05	.02*	-27.4%
Fusiform cortex	15	0.27	0.08	15	0.31	0.09	.08	-13.9%
Insular cortex	15	0.55	0.08	15	0.62	0.11	.03*	-11.7%
Anteror cingulate cortex	15	0.37	0.06	15	0.46	0.09	.008*	-19.7%
Posterior cingulate cortex	14	0.30	0.08	14	0.36	0.08	.02*	-17.1%
Amygdala	14	1.00	0.19	14	1.02	0.18	.79	-1.8%
Hippocampus	15	0.53	0.13	15	0.57	0.15	.46	-6.9%
Nucleus accumbens	14	1.03	0.21	14	1.18	0.25	.03*	-13.1%
Caudate	15	0.63	0.12	15	0.71	0.11	.12	-11.4%
Putamen	15	1.07	0.15	15	1.23	0.16	.02*	-12.5%
Pallidum	15	1.20	0.27	15	1.22	0.22	.80	-1.6%
Thalamus	15	1.05	0.14	15	1.13	0.15	.10	-7.5%
Brainstem	15	0.73	0.17	15	0.86	0.15	.008*	-15.0%

5-HTT availability (BP_{ND}) in 18 subregions of grey matter and brainstem. Group mean and standard deviation (SD). Paired samples t-test. Presented numbers are not corrected for multiple comparisons. *Significant after correction for multiple comparisons.

3.2.2.3 Associations between behavioral phenotypes and 5-HTT availability

In social cognition, Spearman´s correlation demonstrated significant and positive associations between all three social-cognitive tests and 5-HTT binding in nucleus accumbens (range in *rho* was 0.40 to 0.48, $p < 0.034$). In comparison to all 10 test variables presented in this study, Reading the mind in the eyes test was significantly and moderately correlated with the highest number of brain regions (9 regions, range in *rho* was 0.38 to 0.68). MASC was positively correlated with 5-HTT binding in putamen (*rho*= 0.38, *p*= 0.04), and Faux pas was positively correlated with 5-HTT binding in ACC (*rho*= 0.38, *p*= 0.04) and putamen (*rho*= 0.38, *p*= 0.04).

In executive function, significant and positive correlations were found between 5-HTT availability in nucleus accumbens and verbal fluency, both letter production (*rho*= 0.39, *p*= 0.04) and category production (*rho*= 0.38, *p*= 0.05). Among the five test variables of executive function, the highest amount of significant correlations were found in Verbal fluency, semantic flexibility, which correlated positively with three regions of interest;

rostral middle frontal cortex (*rho*= 0.39, *p*= 0.04), caudate (*rho*= 0.40, *p*= 0.03) and thalamus (*rho*= 0.48, *p*= 0.01). CPT correlated significantly with thalamus (*rho*= 0.38, *p*= 0.04). No significant correlations were found between the Tower test and 5-HTT binding in any region.

In central coherence, two positively significant correlations were shown between EFT and 5-HTT binding in nucleus accumbens (*rho*= 0.42, *p*= 0.03) and insula (*rho*= 0.38, *p*= 0.04). No correlations were significant between FPT and 5-HTT binding (Fig. 5).

When correcting for multiple comparisons, only the correlation between Reading the mind in the eyes and 5-HTT binding in anterior cingulate cortex (ACC) remained significant (M_{eff}= 129.89).

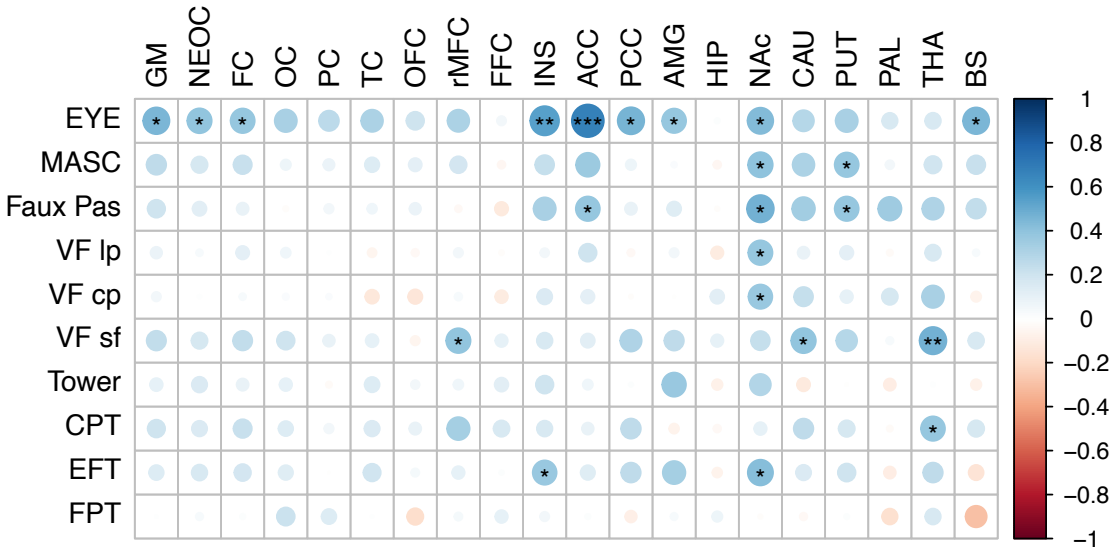

Fig 5. Correlations between 5-HTT availability and performance in behavioral phenotype assessments. Spearman´s correlation coefficient. GM= total gray matter; NEOC= neocortex; FC= frontal cortex; OC= occipital cortex; PC= parietal cortex; TC= temporal cortex; OFC= orbitofrontal cortex; rMFC= rostral middle frontal cortex; FFC= fusiform cortex; INS= insular cortex; ACC= anterior cingulate cortex= PCC= posterior cingulate cortex; AMG= amygdala; HIP= hippocampus; NAc= nucleus accumbens; CAU= caudate; PUT= putamen; PAL= pallidum; THA= thalamus; BS= brainstem; EYE= reading the mind in the eyes; MASC= movie for the assessment of social cognition; VF lp= verbal fluency, letter production; VF cp= verbal fluency, category production; VF sf= verbal fluency, semantic flexibility; Tower= tower test; CPT= continuous performance test; EFT= embedded figure test; FPT= fragmented picture test. In tests of Tower, EFT and FPT, a higher score is indicative of lower performance. For visualization purposes, the sign of Spearman´s correlation for these tests has been changed in the figure to reflect the positive relationship between 5-HTT availability and cognitive performance (**p*< 0.005, ***p*< 0.01; ****p*< 0.001, uncorrected for multiple comparisons).

3.2.3 Conclusions

Significantly lower 5-HTT binding in total gray matter in the ASD group compared to a matched neurotypical group was found. Numerically lower performance in all tests in the ASD group was demonstrated. Also, associations were found between cognitive abilities of social cognition, executive function, central coherence and 5-HTT availability in several brain regions, however, when correcting for multiple comparisons, only the association between social cognition and 5-HTT availability in ACC remained significant. In addition, we replicated a previous correlation between social cognition and regional 5-HTT binding. Hence, these findings are in line with the theory of serotonin involvement in ASD neurodevelopment and further endorse the involvement of serotonin in the physiology and cognitive aspects of ASD.

3.3 STUDY III. ASSOCIATIONS BETWEEN COGNITION AND SEROTONIN RECEPTOR 1B BINDING IN CONTROL SUBJECTS – A [^{11}C]AZ10419369 POSITRON EMISSION TOMOGRAPHY STUDY

3.3.1 Methods

3.3.1.1 Participants and procedure

The sample of Study III is a collection of healthy subjects from previous studies at PET center, Karolinska Institutet, Stockholm examining cognitive ability and the 5-HT$_{1B}$ receptor with PET and the radioligand [^{11}C]AZ10419369 at baseline (Nord et al., 2013, 2014b; Svensson et al., in manuscript; Tiger et al., 2014, 2016). Out of 54 controls examined with PET, 43 subjects were included in further analyses (Table 9). The remaining 11 participants were excluded due to no available cognitive data (10 subjects) or segmentation failure within the MRI image (1 subject).

The group was healthy according to the screening procedure with psychiatric interview and somatic examination, negative urine toxicology and MRI was performed. The participants had been investigated with cognitive tests and PET and [^{11}C]AZ10419369 for 5-HT$_{1B}$ availability. Parts of the results have previously been reported (Nord et al., 2013, 2014; Tiger et al., 2014, 2016; Tangen et al., 2017).

3.3.1.2 Assessment of behavioral phenotypes

All participants had been examined with cognitive tests selected to measure domains associated with serotonin and MDD. Visuo-constructive memory was assessed with Rey complex figure test (RCFT) on immediate recall and delayed recall. Verbal fluency and cognitive flexibility were examined with verbal fluency subtests letter production, category production and semantic flexibility. Task-switching ability, processing speed and cognitive flexibility were investigated with Trailmaking test A and B (TMT A; TMT B) with outcome measure of seconds spent to complete the task. Attention and vigilance were examined with Continuous performance test-II (CPT) outcome measures of detectability (d′), reaction time and number of omissions and commissions. Cognitive flexibility were assessed with Wisconsin card sorting test (WCST) with outcome measures of perseverative errors, total errors and reaction time to positive feedback to unambiguous correct response, and planning ability was examined with Tower of Hanoi with outcome measure of seconds to complete the task. Also, the general intellectual ability was examined

Table 9. Demographic data and descriptive statistics for the replication sample and the exploratory sample, where the replication sample is a subsample of the exploratory sample.

	Replication sample (total *n*= 38)			Exploratory sample (total *n*= 43)		
	n	Range	*M (SD)*	*n*	Range	*M (SD)*
Age	38	20–75	34.5 (14.7)	43	20–75	35.3 (14.2)
Gender	38	22 males; 16 females		43	23 males; 20 females	
Education	34	9–25	15.5 (3.5)	39	9–25	15.6 (3.4)
Handedness	37	33 right, 4 left		42	38 right, 4 left	
WAIS vb	30	24–58	42 (8.0)	35	24–58	43 (8.1)
WAIS mr	17	11–25	20.3 (4.3)	17	11–25	20.3 (4.3)
RCFT, ir	34	9–34	23.0 (6.3)	39	9.5–34	22.5 (6.2)
RCFT, dr	34	9.5–34	23.1 (6.3)	39	10–34	22.5 (6.4)
VF, lp	38	20–73	45.3 (12.0)	43	20–73	44.3 (12.2)
VF, cp	38	30–93	52.7 (12.7)	43	30–93	52.4 (12.4)
VF, fl	24	10–21	14.5 (2.8)	26	10–21	14.4 (2.8)
CPT	30	0.1–1.9	0.9 (0.4)	35	0.1–1.9	0.8 (0.4)
TMT A	33	15–63	29.5 (10.8)	38	15–63	30.0 (11.0)
TMT B	33	34–283	80.4 (47.2)	38	34–283	80.3 (44.1)
ToH	17	205–1383	519.5 (315.6)	17	205–1383	519.5 (315.6)
WCST	24	4–56	16.4 (14.7)	29	4–56	17.4 (14.9)

Note. *n*= number of participants; *M*= mean; *SD*= standard deviation; Education = years of education; WAIS vb = Wechsler adult intelligence scale, vocabulary, raw score; WAIS mr = Wechsler adult intelligence scale, matrix reasoning, raw score; RCFT, ir= Rey´s complex figure test, immediate recall; RCFT, dr= Rey´s complex figure test, delayed recall; VF lp= Verbal fluency, letter production; VF, cp= Verbal fluency, category production; VF, fl= Verbal fluency, flexibility; CPT= Continuous performance test-II, detectability (d´); TMT A= Trailmaking test A, seconds; TMT B= Trailmaking test B, seconds; ToH= Tower of Hanoi, seconds; WCST= Wisconsin card sorting test, perseverative errors.

with Wechsler adult intelligence scale (WAIS, third or fourth version), subtests vocabulary and matrix reasoning with raw scores as outcome measure.

3.3.1.3 Image acquisition

All subjects underwent an initial MRI scan (3.0T, GE Healthcare), where MR images were segmented (SPM5, Wellcome Trust Centre for Neuroimaging, U.K) and co-registered with PET data. The participants were examined with PET (High Resolution Research Tomograph, Siemens Molecular Imaging) (Wienhard et al., 2002) and the radioligand [^{11}C]AZ10419369, which was synthesized as previously described (Pierson et al., 2008). Due to different protocols in the original studies, radioactivity was measured in a series of consecutive time-frames for 63 minutes (Nord et al., 2013, 2014) or 93 minutes (Svensson et al., in manuscript; Tiger et al., 2014, 2016). Hence, the first 63 minutes were used for quantification in the present study, and data reconstruction from one study (Svensson et al., in manuscript) was executed to ensure matching frame definitions of all the data. Moreover, all PET data from the original studies were re-analyzed due to different definition methods of regions of interest.

Based on literature of assumed clinical relevance and 5-HT$_{1B}$ distribution, relevant brain regions were chosen for further analyses (Ruf and Bhagwagar, 2009; Tangen et al., 2017; Tiger et al., 2018), including gray matter, frontal cortex (FC), orbitofrontal cortex (OFC), dorsolateral frontal cortex (DLFC), occipital cortex (OC), anterior cingulate cortex (ACC), ventral striatum, hippocampus, amygdala, thalamus, insula, limbic lobe and dorsal brainstem (DBS). Binding potential relative to non-displaceable binding (BP_{ND}) quantification was calculated using SRTM with cerebellum as reference region (Varnäs et al., 2001). Moreover, ventral striatum, hippocampus, amygdala and DBS were predefined due to noise reduction using an algorithm for wavelet-aided parametric imaging (WAPI)(Cselényi et al., 2006), since SRTM performs less optimal for smaller brain regions.

Most brain regions were automatically defined using Freesurfer (5.0.0, http://surfer.nmr.mgh.harvard.edu/). However, for DBS and gray matter, definition was based on [^{11}C]AZ10419369 PET template data (Veldman et al., in manuscript) or SPM segmentation. The cerebellar region was automatically adjusted as described elsewhere (Matheson et al., 2017) in order to avoid spill-over from OC, cerebrospinal fluid and cerebellar vermis.

3.3.1.4 Statistics

The statistical analyses were performed in two steps; replication and exploratory. To replicate the finding from Study I, the replication sample (*n*= 38) was a subgroup of the exploratory sample (*n*= 43) but without participants included in Study I (*n*= 5). Tests with Shapiro-Wilk revealed that cognitive data did not meet the assumption of normal distribution, hence, non-parametric tests were used for all variables. For investigation of inter-regional 5-HT_{1B} binding as well as associations between regional 5-HT_{1B} availability and age and level of education, Spearman´s correlations were used. A partial Spearman´s correlation was executed between RCFT, delayed recall and 5-HT_{1B} binding in DBS controlled for age in the control group at baseline due to the finding in Study I showing a significant association between the visuo-constructive memory test RCFT, delayed recall (named RCFT, delayed recognition in the published version) and 5-HT_{1B} binding in DBS in the controls. Exploratory, investigations of possible links between cognitive ability and 5-HT_{1B} binding in brain regions adjusting for age effects were executed. Regression analyses investigating dfBeta for identifying outliers that could affect the results were performed, due to the skew age distribution in the present sample with 63% between 20-37 years of age. Also, Spearman´s correlations when not controlling for age were investigated (*n*= 43) for comparison with baseline data in Study I. All tests were two-tailed except the replication analysis which was one-tailed, with significance level at ≤ 0.05 and SPSS (version 26) for Windows was used for the statistical analyses.

3.3.2 Results

Inter-regional correlations in 5-HT_{1B} availability were positive and mostly strong in all regions but amygdala and hippocampus. When investigating age effects, correlations were found with RCFT, immediate recall (*rho*= –0.40, *p*= 0.05), RCFT, delayed recall (*rho*= –0.48, *p*= 0.02), CPT, reaction time (*rho*= 0.46, *p*= 0.01) and WCST, reaction time (*rho*= 0.51, *p*= 0.01). Also, 5-HT_{1B} binding in all brain regions (range in *rho* was –0.30 to –0.80) but hippocampus correlated significantly with age. Level of education was not significantly correlated with cognitive ability or 5-HT_{1B} binding.

The replication analysis (*n*= 38) of RCFT, delayed recall and 5-HT_{1B} binding in DBS did not remain significant in this sample (*rho*= –0.075, *p*= 0.68).

The exploratory analyses (*n*= 43) not controlling for age revealed positive and moderate correlations between RCFT, immediate recall and 5-HT_{1B} binding in gray matter (*rho*= 0.32, *p*= 0.05), occipital cortex (*rho*= 0.53, *p*= 0.00), limbic lobe (*rho*= 0.33, *p*= 0.04) and

DBS (*rho*= 0.35, *p*= 0.03) as well as between RCFT, delayed recall and 5-HT_{1B} binding in gray matter (*rho*= 0.33, *p*= 0.04), occipital cortex (*rho*= 0.53, *p*= 0.00), limbic lobe (*rho*= 0.32, *p*= 0.04) and DBS (*rho*= 0.36, *p*= 0.03). Moreover, negative and moderate correlations were demonstrated between CPT, reaction time and 5-HT_{1B} binding in all brain regions (range in *rho* was –0.36 to –0.59) but hippocampus and thalamus as well as between TMT B and amygdala (*rho*= –0.38, *p*= 0.02), and between WCST, reaction time and 5-HT_{1B} binding in all brain regions (range in *rho* was –0.40 to –0.64) but ventral striatum, hippocampus and thalamus (Table 10).

Table 10. Spearman´s correlation (*rho*) between cognitive performance and 5-HT_{1B} availability in brain regions of interest, not controlled for age (*n*= 43).

	RCFT, ir	RCFT, dr	VF, lp	VF, cp	VF, fl	CPT, d´	CPT, rt	TMT A	TMT B	ToH	WCST, pe	WCST, rt
Gray matter	0.32*	0.33*	0.16	-0.03	0.16	-0.29†	-0.59*	-0.10	-0.29†	0.08	-0.26	-0.53*
Frontal cortex	0.23	0.23	0.17	0.05	0.18	-0.25	-0.56*	-0.03	-0.23	-0.09	-0.16	-0.43*
OFC	0.24	0.24	0.14	0.00	0.18	-0.24	-0.56*	-0.00	-0.22	-0.09	-0.24	-0.46*
DLFC	0.23	0.24	0.17	0.05	0.15	-0.25	-0.55*	-0.05	-0.22	0.05	-0.11	-0.40*
Occipital cortex	0.53*	0.53*	0.03	-0.15	0.05	-0.17	-0.51*	-0.20	-0.32†	-0.04	-0.37†	-0.64*
ACC	0.18	0.18	0.20	0.08	0.20	-0.25	-0.53*	-0.03	-0.21	0.16	-0.21	-0.41*
Ventral striatum	0.15	0.14	0.10	0.10	0.04	-0.18	-0.37*	-0.08	-0.25	-0.01	-0.18	-0,27
Hippocampus	0.13	0.13	-0.02	-0.15	0.00	-0.24	-0.27	-0.11	-0.25	0.19	-0.05	-0,22
Amygdala	0.18	0.20	0.15	0.03	0.32	-0.09	-0.36*	-0.14	-0.38*	-0.01	-0.29	-0.47*
Thalamus	0.31†	0.29†	0.07	-0.30†	-0.02	-0.00	-0.10	0.11	-0.03	0.39	0.14	-0.08
Insula	0.25	0.24	0.21	0.02	0.17	-0.25	-0.54*	-0.01	-0.21	-0.07	-0.20	-0.42*
Limbic lobe	0.33*	0.32*	0.16	0.01	0.14	-0.27	-0.56*	-0.08	-0.31†	-0.02	-0.31	-0.54*
DBS	0.35*	0.36*	0.20	0.02	0.21	-0.17	-0.41*	-0.07	-0.24	0.11	-0.22	-0.56*

Note. RCFT, ir= Rey´s complex figure test, immediate recall; RCFT, dr= Rey´s complex figure test, delayed recall; VF lp= Verbal fluency, letter production; VF, cp= Verbal fluency, category production; VF, fl= Verbal fluency, flexibility; CPT, d´= Continuous performance test-II, detectability; CPT, rt= Continuous performance test-II, reaction time; TMT A= Trailmaking test A, seconds; TMT B= Trailmaking test B, seconds; ToH= Tower of Hanoi, seconds; WCST, pe= Wisconsin card sorting test, perseverative errors; WCST, rt= Wisconsin card sorting test, reaction time; OFC= orbitofrontal cortex; DLFC= dorsolateral frontal cortex; ACC= anterior cingulated cortex; DBS= dorsal brainstem; *= $p< 0.05$; †= $p< 0.10$.

In exploratory analyses controlling for age effects, negative and moderate correlations remained significant between CPT, reaction time and 5-HT_{1B} binding in total gray matter (*rho*= –0.42, *p*= 0.02), frontal cortex (*rho*= –0.39, *p*= 0.03), OFC (*rho*= –0.38, *p*= 0.04), DLFC (*rho*= –0.37, *p*= 0.04), insular cortex (*rho*= –0.37, *p*= 0.04) and limbic lobe (*rho*= –0.38, *p*= 0.03), as well as between WCST, reaction time at and 5-HT_{1B} availability in occipital cortex (*rho*= –0.46, *p*= 0.02)(Table 11). Additional *post hoc* correlation analyses showed a strong negative correlation between CPT, reaction time and CPT, amount of commissions (*rho*= –0.79, *p*= 0.00) and moderate correlations between WCST, reaction time and WCST, total errors (*rho*= 0.63, *p*= 0.00) and perseverative errors (*rho*= 0.66, *p*= 0.00). No statistical multivariate outlier was detected using dfBeta in regression analysis.

3.3.3 Conclusions

The result from Study I between visuo-constructive memory and 5-HT_{1B} availability in the control group could not be replicated. Exploratory analyses showed positive associations between visuo-constructive memory, cognitive flexibility and 5-HT_{1B} availability as well as negative associations between reaction time and 5-HT_{1B} binding in brain regions. Moreover, that the faster reaction time was correlated to higher number of errors. When controlling for age, the negative correlations between reaction time and 5-HT_{1B} availability in several brain regions remained. These findings are in line with previous research supporting the involvement of 5-HT_{1B} receptors in impulsive behavior.

Table 11. Spearman´s correlation (*rho*) between cognitive performance and 5-HT_{1B} availability in brain regions of interest, controlled for age (n= 43).

	RCFT, ir	RCFT, dr	VF, lp	VF, cp	VF, fl	CPT, d´	CPT, rt	TMT A	TMT B	ToH	WCST, pe	WCST, rt
Gray matter	-0.07	-0.07	-0.01	0.12	0.09	-0.34†	-0.42*	0.02	-0.15	0.27	-0.04	-0.32
Frontal cortex	-0.20	-0.20	0.02	0.21	0.12	-0.28	-0.39*	0.11	-0.06	0.01	0.09	-0.18
OFC	-0.21	-0.21	-0.04	0.15	0.12	-0.25	-0.38*	0.16	-0.05	0.04	-0.01	-0.21
DLFC	-0.19	-0.19	0.01	0.22	0.09	-0.27	-0.37*	0.08	-0.06	0.23	0.16	-0.14
Occipital cortex	0.22	0.21	-0.26†	-0.05	-0.13	-0.19	-0.26	-0.14	-0.18	0.16	-0.12	-0.46*
ACC	-0.24	-0.24	0.06	0.24	0.15	-0.27	-0.35†	0.10	-0.06	0.34	0.00	-0.17
Ventral striatum	-0.02	-0.04	0.03	0.16	0.01	-0.16	-0.24	-0.03	-0.18	0.06	-0.03	-0.07
Hippocampus	0.01	0.01	-0.10	-0.11	-0.07	-0.22	-0.12	-0.07	-0.20	0.27	0.02	-0.11
Amygdala	-0.13	-0.11	0.03	0.13	0.30	-0.06	-0.12	-0.06	-0.29†	0.15	-0.09	-0.24
Thalamus	0.10	0.07	-0.02	-0.22	-0.13	0.02	0.13	0.19	0.17	0.48†	0.26	0.16
Insula	-0.17	-0.19	0.07	0.17	0.12	-0.26	-0.37*	0.13	-0.05	0.02	0.01	-0.19
Limbic lobe	-0.06	-0.07	-0.23	0.16	0.07	-0.31†	-0.38*	0.05	-0.18	0.17	-0.11	-0.33†
DBS	-0.07	-0.07	0.06	0.16	0.16	-0.15	-0.15	0.05	-0.09	0.44†	-0.04	-0.37†

Note. RCFT, ir= Rey´s complex figure test, immediate recall; RCFT, dr= Rey´s complex figure test, delayed recall; VF lp= Verbal fluency, letter production; VF, cp= Verbal fluency, category production; VF, fl= Verbal fluency, flexibility; CPT, d´= Continuous performance test-II, detectability; CPT, rt= Continuous performance test-II, reaction time; TMT A= Trailmaking test A, seconds; TMT B= Trailmaking test B, seconds; ToH= Tower of Hanoi, seconds; WCST, pe= Wisconsin card sorting test, perseverative errors; WCST, rt= Wisconsin card sorting test, reaction time; OFC= orbitofrontal cortex; DLFC= dorsolateral frontal cortex; ACC= anterior cingulated cortex; DBS= dorsal brainstem; *= $p< 0.05$; †= $p< 0.10$.

3.4 STUDY IV. ASSOCIATIONS BETWEEN AUTISM-RELATED COGNITIVE FUNCTIONING AND REGIONAL BINDING OF 5-HTT AND 5-HT_{1B} RECEPTOR IN NEUROTYPICAL CONTROL SUBJECTS

3.4.1 Methods

3.4.1.1 Participants and procedure

In this study, both 5-HTT binding and 5-HT_{1B} receptor binding were investigated in relation to autism-related cognitive ability, why the sample consisted of two groups. However, some of the subjects (*n*= 17) have been examined with both radioligands and thus, occur in both groups. In the 5-HTT group, 32 participants were examined with PET and the radioligand [^{11}C]MADAM and cognitive tests. This group (15 males, 17 females) had a mean age of 40.16 (±13.85 *SD*) and mean years of education of 16.10 (±4.04 *SD*). In the 5-HT_{1B} group, 33 subjects were examined with PET and the radioligand [^{11}C]AZ10419369 and cognitive tests. This group with 13 males and 20 females had a mean age of 38.27 (±14.91) and mean years of education of 15.43 (±3.53 *SD*).

Subjects were included if they were healthy according to psychiatric assessment with clinical interview with MINI as well as a physical examination and negative urine toxicology. Main exclusion criteria for participation were history of psychiatric chronic disorders, substance abuse, head trauma and other major health problems as well as contraindications for MRI, or pregnancy. A subset of the data has previously been published (Nord et al., 2014; Tiger et al., 2014, 2016), and some of the participants (*n*= 15) occur also in Study II.

3.4.1.2 Assessment of behavioral phenotypes

Tests measuring dimensional autism-related cognition were performed for all participants. The domain of social cognition contained the Movie for assessment of social cognition (MASC)(Dziobek et al., 2006), Reading the mind in the eye (Baron-Cohen et al., 2001) and Faux pas (Baron-Cohen et al., 1999). In central coherence, Embedded figure test (EFT) and Fragmented picture test (FPT)(Snodgrass et al., 1987) were included.

3.4.1.3 Image acquisition

All subjects were scanned with MRI (3.0T, GE Healthcare) for exclusion of structural pathology (T2-weighted images) and anatomical co-registration of relevant brain regions (T1-weighted images) as previously described using SPM5 or SPM12 (Wellcome

Department of Cognitive Neurology, University College, London, U.K.). In all PET examinations, the subject was placed recumbent with the head inside the PET system using a plastic fixation device for minimizing head movements (Bergström et al., 1981) injected with the radioligands [^{11}C]MADAM or [^{11}C]AZ10419369, which were synthesized as previously described (Halldin et al., 2005; Pierson et al., 2008).

In the 5-HTT group (*n*= 32), fifteen participants were examined with PET High Resolution system (ECAT Exact HR 47 PET system (CTI/Siemens, Knoxville, TN)) and [^{11}C]MADAM binding with an acquisition time of 93 minutes (Andersson et al., 2020). Freesurfer (version 5.0, http://surfer.nmr.mgh.harvard.edu)(Fischl, 2012) was used for brain region delineation, and a cortical atlas of Desikan-Killany was used for brain region anatomy definition (Desikan et al., 2006). The 5-HTT binding outcome measure of BP_{ND} was calculated with SRTM model (Lammertsma and Hume, 1996) with cerebellar cortex as reference region. The additional seventeen subjects were examined with PET High Resolution Research Tomograph system (ECAT HRRT PET system (Siemens Molecular Imaging)) and [^{11}C]MADAM with an acquisition time of 93 minutes (Svensson et al., in manuscript). Freesurfer (version 6.0, http://surfer.nmr.mgh.harvard.edu)(Fischl, 2012) was used for brain region delineation. The 5-HTT binding outcome measure of BP_{ND} was calculated with Logan reference tissue method (Logan et al., 1996) with cerebellum as reference region. Relevant brain region were chosen based on existing literature of autism-related cognition and 5-HTT distribution; gray matter, frontal cortex, OFC, occipital cortex, parietal cortex, temporal cortex (TC), ACC, posterior cingulate cortex (PCC), hippocampus, amygdala, thalamus, insula, striatum, caudate, pallidum, putamen, ventral diencephalon (VDC), accumbens, limbic lobe and brainstem.

In the 5-HT_{1B} group, 33 participants were examined with PET HRRT and [^{11}C]AZ10419369. Due to different PET protocols with time lengths between 63 and 93 minutes in the original studies, the first 63 minutes were used for quantification to enable pooling of data. Thus, this required raw data reconstruction from one study (Svensson et al., in manuscript) to ensure matching frame definitions of all the data. Freesurfer (5.0, http://surfer.nmr.mgh.harvard.edu/)(Fischl, 2012) was used for definition of all brain regions but DBS and gray matter, where a [^{11}C]AZ10419369 PET template data was used (Tiger et al., 2020; Veldman et al., in manuscript) or by SPM segmentation. SRTM (Lammertsma and Hume, 1996) was used for BP_{ND} quantification with cerebellar cortex as reference region as it has negligible 5-HT_{1B} densities (Varnäs et al., 2001). The cerebellum was automatically adjusted as previously described (Matheson et al., 2017) to avoid spill-

over from OC, cerebrospinal fluid and cerebellar vermis. Also, since SRTM performs better with bigger brain regions than smaller, ventral striatum, hippocampus, amygdala and DBS were predefined for noise reduction using an algorithm for wavelet-aided parametric imaging (WAPI)(Cselényi et al., 2006). Analyzed brain regions were gray matter, frontal cortex, orbitofrontal cortex (OFC), occipital cortex, dorsolateral frontal cortex (DLFC), anterior cingulate cortex (ACC), hippocampus, amygdala, thalamus, insula, ventral striatum, limbic lobe and dorsal brainstem (DBS).

3.4.1.4 Statistics

Descriptive statistics are presented in Table 12. In the 5-HTT group, since two different PET system and quantification methods were used (fifteen subjects with HR and seventeen subjects with HRRT) BP_{ND} values were standardized to z-scores and pooled for further analyses. The Shapiro-Wilk test showed that most variables and approximately half of the z-transformed 5-HTT data were not normal distributed, why non-parametric tests were applied. Non-parametric Spearman´s correlation was executed to examine inter-regional associations as well as associations of cognitive ability in relation to age and years of education and serotonin binding in relation to age and years of education, in each sample. Spearman´s correlation was used to examine potential associations between autism-related cognition and z-transformed BP_{ND} values for 5-HTT and 5-HT_{1B}. Since significant associations were found between age and 5-HT_{1B} binding, partial Spearman´s correlations controlling for age were performed between cognitive ability and 5-HT_{1B} binding. No associations were found between age and standardized 5-HTT binding, why age was not corrected for in further analyses involving 5-HTT data. Moreover, because of the exploratory and hypothesis-driven approach of this study, the results are presented uncorrected for multiple comparisons, but additional corrections for multiple comparisons were executed using the false discovery rate method (FDR)(Benjamini and Hochberg, 1995). The level of significance was ≤ 0.05 and all tests were two-tailed and performed with SPSS 26 for Windows or R software (version 3.4.1, R Foundation).

3.4.2 Results

Inter-regional correlations showed positive associations in both z-transformed 5-HTT and 5-HT_{1B} binding. In the 5-HTT group, no significant correlation was found between age and cognitive ability, or age and standardized 5-HTT binding in any brain region. The variable years of education was significantly correlated with the cognitive test EFT (*rho*= –0.50, *p*=

0.003) and standardized 5-HTT binding in ACC (*rho*= –0.37; *p*= 0.036) and accumbens (*rho*= –0.47; *p*= 0.007). In the 5-HT$_{1B}$ group, no significant correlation was found between

Table 12. Descriptive statistics for the sample examined with PET and [^{11}C]MADAM binding to the serotonin transporter (5-HTT) and the sample examined with PET and [^{11}C]AZ10419369 binding to 5-HT$_{1B}$ receptor

	Serotonin transporter sample (total *n*= 32)			5-HT$_{1B}$ receptor sample (total *n*= 33)		
	n	Range	*M (SD)*	*n*	Range	*M (SD)*
MASC	32	27-42	35 (4.07)	33	25-42	34 (4.34)
EYE	32	20-33	28 (3.30)	32	20-32	28 (3.24)
Faux pas	32	41-60	54 (4.90)	17	46-60	55 (4.55)
EFT	32	31-1509	473 (322.24)	33	31-1509	514 (330.44)
FPT	32	80-460	185 (79.77)	33	87-538	197 (87.59)

Note. MASC= movie for assessment of social cognition; EYE= reading mind in the eyes; EFT= embedded figure test, seconds; FPT= fragmented picture test, seconds; *n*= number of participants; *M*= mean; *SD*= standard deviation.

age and cognitive ability. Correlations between age and 5-HT$_{1B}$ binding were significant for all the brain regions (range in *rho*: –0.36 to –0.84; *p*< 0.05). The variable years of education was significantly correlated with the cognitive test EFT (*rho*= –0.66, *p*< 0.001), but not with 5-HT$_{1B}$ binding.

In the 5-HTT group, Spearman´s correlation demonstrated significant associations between the cognitive test MASC and standardized 5-HTT availability in striatum (*rho*= 0.37, *p*= 0.042), putamen (rho= 0.49, *p*= 0.005) and brainstem (*rho*= –0.42, *p*= 0.02)(Table 13). Similar strength of the correlation in both the HR and HRRT group was demonstrated when analyzing them separately. In the 5-HT$_{1B}$ group, Spearman´s correlation not controlled for age, showed that EFT was significantly correlated with 5-HT$_{1B}$ binding in thalamus (*rho*= 0.42; *p*= 0.02)(Table 14). However, when controlling for age, this correlation was no longer significant (Table 15). Additional analyses of multiple comparison in the 5-HTT group were executed, where no findings remained statistically significant.

Table 13. Spearman´s correlations (*rho*) between performance in tests of autism-related cognitive functions and regional standardized 5-HTT binding (*n*= 32).

	MASC	EYE	Faux pas	EFT	FPT
Gray matter	-0.22	-0.08	0.16	0.19	0.17
Frontal cortex	0.02	0.00	0.09	0.10	0.17
OFC	0.02	-0.06	0.04	-0.08	0.13
Occipital cortex	-0.28	-0.17	0.03	0.25	0.24
Parietal cortex	-0.31†	-0.09	-0.04	0.17	0.20
Temporal cortex	-0.13	-0.05	0.13	0.22	0.23
ACC	0.08	0.07	0.12	-0.01	0.22
PCC	-0.23	0.07	-0.11	-0.17	0.19
Hippocampus	-0.17	-0.04	0.21	0.14	0.15
Amygdala	0.18	-0.05	0.28	0.06	-0.06
Thalamus	-0.03	-0.01	0.26	0.20	0.06
Insula	-0.07	-0.01	0.07	0.03	0.24
Striatum	0.37*	-0.06	0.14	-0.14	-0.02
Caudate	0.11	0.07	-0.05	-0.16	0.03
Pallidum	0.23	0.11	0.34	0.14	0.15
Putamen	0.49**	-0.04	0.26	-0.10	0.07
VDC	-0.08	-0.14	0.25	0.08	0.17
Accumbens	0.06	-0.08	0.31†	0.23	0.11
Limbic lobe	-0.16	0.03	0.11	-0.10	0.17
Brainstem	-0.42*	0.06	0.24	0.30†	0.31†

Note. MASC= movie for assessment of social cognition; EYE = reading mind in the eyes; EFT= embedded figure test; FPT= fragmented picture test; OFC = orbitofrontal cortex; ACC= anterior cingulate cortex; PCC= posterior cingulate cortex; VDC= ventral diencephalon; **= $p< 0.01$; *= $p< 0.05$; †=$p< 0.1$.

3.4.3 Conclusions

The results demonstrated positive association between 5-HTT binding in striatum and putamen and social cognition as well as a negative correlation between 5-HTT binding in brainstem and social cognition in neurotypical subjects. Moreover, a positive correlation between 5-HT_{1B} availability and central coherence was found, but when controlling for age effects, the correlation did not remain significant. The present study did not support an association between 5-HT_{1B} and social cognition, but our significant findings of 5-HTT binding in relation to social cognition support previous literature of ASD and suggest a dimensional approach of neurobiological and behavioral phenotype for social functioning in neurotypical subjects as well as individuals with ASD.

Table 14. Spearman´s correlations (*rho*) between performance in tests of autism-related cognitive functions and regional 5-HT_{1B} binding, not controlled for age (n= 33).

	MASC	EYE	Faux pas	EFT	FPT
Gray matter	-0.05	0.25	0.12	0.06	0.13
Frontal cortex	0.00	0.31†	0.16	0.12	0.14
OFC	-0.04	0.24	0.10	0.03	0.17
Occipital cortex	-0.04	0.09	0.10	0.12	0.14
DLFC	0.00	0.28	0.21	0.13	0.14
ACC	-0.06	0.28	0.22	0.17	0.12
Hippocampus	-0.26	0.30†	0.17	0.06	0.23
Amygdala	-0.11	0.19	0.22	-0.16	0.02
Thalamus	-0.16	-0.31†	0.00	0.42*	-0.02
Insula	-0.08	0.28	0.16	0.13	0.16
Ventral striatum	-0.03	0.04	-0.13	0.14	-0.03
Limbic lobe	-0.05	0.25	0.25	0.08	0.10
DBS	-0.14	0.12	0.23	0.10	0.11

Note. MASC= movie for assessment of social cognition; EYE = reading mind in the eyes; EFT= embedded figure test; FPT= fragmented picture test; OFC= orbitofrontal cortex; DLFC= dorsolateral frontal cortex; ACC= anterior cingulate cortex; DBS= dorsal brainstem; *= p<0.05; †=p<0.1.

Table 15. Spearman´s correlations (*rho*) between performance in tests of autism-related cognitive functions and regional 5-HT_{1B} binding, controlled for age (n= 33).

	MASC	EYE	Faux pas	EFT	FPT
Gray matter	-0.17	-0.13	-0.13	0.15	0.06
Frontal cortex	0.02	0.03	-0.04	0.13	-0.22
OFC	-0.10	-0.11	-0.18	0.02	-0.07
Occipital cortex	-0.11	-0.33	-0.25	0.13	0.06
DLFC	0.04	-0.07	0.02	0.32	-0.11
ACC	-0.14	-0.17	0.04	0.28	-0.23
Hippocampus	-0.37	0.12	0.07	0.18	0.40
Amygdala	0.04	-0.20	0.01	-0.23	-0.18
Thalamus	-0.34	-0.45†	-0.12	0.49†	0.24
Insula	-0.16	-0.13	-0.01	0.08	-0.15
Ventral striatum	-0.12	-0.36	-0.27	0.06	0.05
Limbic lobe	-0.12	-0.11	0.04	0.12	-0.22
DBS	-0.26	-0.42	-0.03	0.23	0.18

Note. MASC= movie for assessment of social cognition; EYE = reading mind in the eyes; EFT= embedded figure test; FPT= fragmented picture test; OFC= orbitofrontal cortex; DLFC= dorsolateral frontal cortex; ACC= anterior cingulate cortex; DBS= dorsal brainstem; †=p<0.1.

3.5 LIMITATIONS

There are some limitations that need to be addressed in relation to the studies herein included.

Participants included in medical research tend to have higher education than the general population (Tambs et al., 2009). Hence, this is a common problem, including in our studies, and has been addressed by using years of education as a controlling variable in the analyses. In sum, high education has in our studies been shown to have none to small impact on the findings. Further, neuroimaging studies do in general have low power due to small sample in comparison to other research fields, such as psychology. In light of this, also in combination of an often exploratory approach with several brain regions of interest and other variables to consider, it is essential to take into account the risk of false positive findings as well as false negative findings due to underpowered studies, when interpreting the results.

Based on current PET methodology, the results in this thesis cannot answer questions of number of available serotonergic neurons or serotoninergic level in the brain, nor if higher 5-HT_{1B} binding entails an up-regulation of the receptor or higher amount of 5-HT_{1B} receptors per synapse or neuron. Moreover, it is also not possible to draw any conclusions of lower 5-HTT availability in relation to down-regulation of 5-HTT or fewer 5-HTT containing neurons.

Study I suffered from cognitive data loss, a variation in time aspect for cognitive testing as well as that the results were not corrected for multiple comparisons. Also, some of the results may have been driven by age as the multiple linear regression analyses controlling for age implied. In sum, all conclusions should be interpreted with caution.

In **Study II**, the ASD group was cautiously selected, in where the results may not be representable for the whole ASD population with intellectual disability and high occurrence of comorbidity. However, this study design has also made it possible to measure ASD-specific phenotypes with reduced risk of confounding factors.

In **Study III**, age was shown to be a possible confounding factor affecting the results with a skewed age distribution. The majority of the sample was in the younger section (20-37 years of age), and moreover, in particular one young subject had unproportionally large impact on the analyses. However, the analyses were controlled for putative age effects and further, dfBeta regression analysis was performed to analyze possible influence from

statistical outliers, which did not identify multivariate outliers. Yet, due to unexpected and absent correlations between age and cognitive tests known to be influenced by age, this could indicate atypical characteristics in the sample. For four of the subjects, there was an approximately 1.5 year long time interval between PET examination and cognitive testing. This could have effects on the results, but in the healthy population, the decline in 5-HT_{1B} availability density and cognition is expected to be minor within this time interval. Also, since the examinations in PET were performed during different seasons, and seasonal variability in binding of other serotonin markers has been shown (Matheson et al., 2015), such effects cannot be excluded.

The sample in **Study IV** is partly identical to the control group in Study II, which may affect the result in this study. However, comparison analyses between the whole 5-HTT sample and only the HR sample did not indicate that the HR sample was driving the association. Also, the 5-HTT sample had been examined with two different PET systems (HR and HRRT), which may have influenced the results. However, a study compared high-resolution HRRT with the lower-resolution HR with the radioligand [^{11}C]MADAM for 5-HTT binding and demonstrated higher binding potential values for HRRT than HR (23% on average), but when correcting for partial volume effect, comparisons between the two systems could be possible (Schain et al., 2012).

4 DISCUSSION

4.1 STUDY I. ASSOCIATIONS BETWEEN COGNITION AND SEROTONIN 1B IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER – A PILOT STUDY

In the patient group, we found that improvement in executive functions of verbal fluency and task-switching cognitive flexibility was associated with changes in 5-HT_{1B} availability in amygdala, ventral striatum and hippocampus as well as DBS. Also, cognitive performance in the patient group improved at follow-up, where this improvement was significant for verbal fluency, both letter production and category production. However, the control group did also improve in verbal fluency, category production, which may indicate a learning effect in this specific test. Moreover, the patients performed better at cognitive tests than the control subjects at baseline. No interaction effects of time or group were found, which gives reason for cautious interpretation of the results. Our finding of positive associations between cognitive ability and 5-HT_{1B} binding is in line with a previous study examining creativity and 5-HT_{1B} availability (Varrone et al., 2015). However, the result of significant associations between changes in cognition and 5-HT_{1B} binding are partly novel.

Available, but however limited, literature demonstrates involvement of serotonergic 5-HT_{1B} binding in MDD (Murrough et al., 2011b; Tiger et al., 2014, 2016). Further, serotonin has also been implicated in cognitive abilities known to be affected in MDD. For instance, verbal fluency is associated with idea fluency or creativity, which has been reported to be positively related to 5-HT_{1B} availability in total gray matter in control subjects (Varrone et al., 2015). Also, improvements in cognitive flexibility have been shown after successful MDD treatment targeting serotonin (SSRI)(Blier et al., 1990; Rosenblat et al., 2015).

4.2 STUDY II. LOWER SEROTONIN TRANSPORTER BINDING IN ADULT SUBJECTS WITH HIGH-FUNCTIONING AUTISM AS MEASURED WITH [^{11}C]MADAM

The findings showed lower 5-HTT binding among the individuals with ASD. Also, several correlations were found between behavioral phenotypes and 5-HTT binding. After correcting for multiple comparisons, the positive association between social cognition and 5-HTT availability in ACC remained.

The hypothesis of globally lower 5-HTT binding in individuals with ASD was further supported, and may reflect reductions of serotonergic connections and changes in expressions of 5-HTT, reductions in 5-HTT expression with unchanged serotonergic

connections. This finding of lower 5-HTT binding in brainstem as well as cortical and subcortical regions in comparison to that serotonergic neuronal soma and dendrites are located in the raphe nucleus in the brainstem and that axons project to other areas of cortical and subcortical regions, may indicate functional differences in serotonergic soma, dendrites and axons in ASD. In light of this, these results are in line with studies demonstrating reductions in somatodendritic and axonal development in serotonergic neurons in ASD models of neurodevelopmental hyperserotonemia (Whitaker-Azmitia, 2001), showing changes in the central serotonin system in ASD.

We found a significant positive correlation between 5-HTT binding in ACC and the social-cognitive test of Reading the mind in the eye. This study supports the idea that the Reading the mind in the eye test represent an implicit or automated form of social cognition developed in infancy (Baron-Cohen et al., 2001; Oniski and Baillargeon, 2005), whereas MASC and Faux pas have been suggested to measure a more explicit or deliberate form of social cognition developed later in childhood (Heyes and Frith, 2014; Happé et al., 2017). As ASD has been suggested to mainly be associated with implicit social cognition alterations (Frith, 2004), our significant finding of 5-HTT binding in Reading the mind in the eyes test would be expected as a biomarker of etiological significance.

Taken together, these results implicate a role of 5-HTT in behavioral phenotypes of adult ASD and, encourage research to replicate as well as to further explore aspects of the serotonin system in ASD to obtain a more comprehensive understanding of the involvement of serotonin in the neurodevelopment and ASD.

4.3 STUDY III. ASSOCIATIONS BETWEEN COGNITION AND SEROTONIN RECEPTOR 1B BINDING IN CONTROL SUBJECTS – A [^{11}C]AZ10419369 POSITRON EMISSION TOMOGRAPHY STUDY

The results revealed negative associations between reaction time and 5-HT_{1B} binding in several brain regions controlling for age. Since reaction time was negatively correlated with amount of errors, this could be interpreted as poorer impulse inhibition, and may indicate an association of 5-HT_{1B} availability in measures of impulsivity. This finding is in line with the results from an earlier study reporting reduced reaction time and increased number of errors after administration of 5-HT_{1B} agonists to a healthy sample of volunteers. More specifically, decreased reaction time and increased number of errors were observed in a cognitive task of complex word recognition after administration of 5-HT_{1B} enhancing drugs (van der Post et al., 2002). These results suggest a connection between 5-HT_{1B} agonists and

high 5-HT_{1B} binding and increased impulsivity. The relation between low levels of brain serotonin and high impulsivity and aggression is well-established (Coccaro, 1992; Duke et al., 2013), and emerging evidence suggests that the 5-HT_{1B} receptor is important in modulation of impulsivity and aggression (Bouwknecht et al., 2001; da Cunha-Bang et al., 2016). A study investigating a selective 5-HT_{1B} knockout model of response inhibition showed that mice without 5-HT_{1B} receptors were unable to inhibit responses, and moreover, that the impulsive phenotype was reversed by rescue of receptors expression in adulthood (Nautiyal et al., 2015).

Our study showed an asymmetrical age distribution, where most participants were between 30-37 years old. Even though regression analysis did not demonstrate any statistical multivariate outliers, age was correlated with several cognitive variables and 5-HT_{1B} binding in most brain regions, and hence, age may be a confounding factor in 5-HT_{1B} binding and a statistical noise variable in cognitive ability. However, when controlling for age effects, the association between reaction time and 5-HT_{1B} binding in total gray matter and specific regions remained. This indicates a direct relationship and further supports an important role of -HT_{1B} receptors in the impulsive phenotype.

4.4 STUDY IV. ASSOCIATIONS BETWEEN AUTISM-RELATED COGNITIVE FUNCTIONING AND REGIONAL BINDING OF 5-HTT AND 5-HT_{1B} RECEPTOR IN NEUROTYPICAL CONTROL SUBJECTS

This study demonstrated positive associations between social-cognitive ability of MASC and z-transformed 5-HTT binding in striatum and putamen, as well as a negative correlation between MASC and z-transformed 5-HTT binding in brainstem. Nakamura and colleagues (2010), demonstrated that reduction in 5-HTT binding was correlated with poor performance in social cognition. A positive correlation between central coherence with EFT and 5-HT_{1B} availability in thalamus was shown, but when correcting for age, the correlation was no longer significant.

The present study contribute to the hypothesis of a role of the serotonin transporter in social cognition in neurotypical as continuously distributed, but not serotonin receptor 1B in social cognition.

4.5 ETHICAL CONSIDERATIONS

All studies were approved by the Regional Ethics Committee, Stockholm and the Radiation Safety Committee of the Karolinska University Hospital and were performed according to the guidelines of the Declaration of Helsinki. All participants were examined at PET center, Karolinska Institutet, Stockholm, Sweden.

There are several ethical issues to consider in clinical neuroimaging studies like these. Participating in a study with multilevel and highly demanding assessments is challenging. Depressed individuals with severe type and/or suicidality according to scores higher than 35 and/or a score higher than four on item 10 in MADRS, were excluded from participation (Study I). These individuals were informed and referred to a polyclinic for further assessments and follow-up. Also, included patients were informed that treatment would still be offered if they at some point during the study refused to participate. Excluded patients were also offered ICBT. Individuals with ASD that were excluded during the screening procedure (mostly because of comorbidity) had ongoing contact with healthcare services and/or Habilitation, why no further contact was taken (Study II). Healthy control subjects were not contacted after study completion. All participants were offered individual feedback on their study results.

All participants did undergo a thorough screening, MRI and PET examinations, and a comprehensive cognitive test procedure, where these assessments were executed twice in one study (Study I). Precaution had been taken in order to protect the health and rights of the participants, such as give both verbal and written information about the study before written informed consent, including the possibility to withdraw at any time from the study without reprisal. Moreover, all subject-related information was handled confidentially and according to research routine practice at Karolinska Institutet, such as that each participant was given a specific code which was used throughout the study for anonymity reasons and that data was stored in locked metal cabinets and on specific password-protected servers via Karolinska Institutet. The study results were exclusively presented at group level for integrity protection of individual participants.

The radioactive isotope that was used (^{11}C) for radioligand labelling decays rapidly and disappears from the body approximately two hours after injection. The amount of radioactivity that is injected during a PET examination is comparable to background radiation from the environment during one year in Stockholm.

5 FINAL CONCLUSIONS AND FUTURE DIRECTIONS

This thesis is exploring the serotonergic markers 5-HT_{1B} and 5-HTT in relation to cognitive abilities. The studies are based on adult individuals with MDD and ASD as well as subjects without a psychiatric disorder.

The main findings in all four studies showed significant associations between cognitive ability and binding in serotonergic markers of the 5-HT_{1B} receptor and 5-HTT in psychiatric samples from baseline to follow-up, in comparison to matched non-psychiatric samples as well as in larger control samples. More specifically, Study I demonstrated positively significant associations between 5-HT_{1B} binding and cognitive performance in MDD patients before to after treatment as well as between 5-HT_{1B} binding and cognitive performance in control subjects. Also, 5-HT_{1B} binding in healthy controls was negatively correlated with reaction time, which is an inverse cognitive measure where lower scores represents better performance (Study III). Study II showed positive correlations between 5-HTT binding and social-cognitive performance in ASD. In Study IV, positively significant associations were found between 5-HTT binding and social-cognitive performance as well as between 5-HT_{1B} binding and cognitive performance in control subjects. One correlation was found to be negatively significant (5-HTT binding in brainstem and social-cognitive performance).

The conclusions drawn from our studies are to some extent in line with previous research, but to note, existing literature of serotonergic markers in relation to cognitive ability in psychiatric disorders is inconclusive. For instance, animal studies have shown better learning performance in complex cognitive tasks in 5-HT_{1B} knockout mice compared to a control group (Wolff et al., 2003) as well as antidepressant-like effects when overexpressing the 5-HT_{1B} autoreceptor (McDevitt et al., 2011). An antidepressant-like effects was also demonstrated in another study when stimulating the receptor with a 5-HT_{1B} agonist (Chenu et al., 2008), whereas the opposite result have been found where the same agonist caused impaired performance in contextual memory but improved performance when inhibiting 5-HT_{1B} receptors (Eriksson et al., 2008). In healthy humans, studies have shown positive associations between 5-HTT binding and intellectual ability when controlled for age and gender (Tseng et al., 2015), between 5-HTT binding and memory, cognitive flexibility and logical reasoning (Madsen et al., 2011) as well as between 5-HT_{1B} binding and creative ability (Varrone et al., 2015) and between 5-HT_{1A} receptor binding and verbal memory (Penttilä et al., 2016). Whereas other have demonstrated negative

correlations between 5-HT_{1A} binding and memory (Yasuno et al., 2003), between 5-HT_{1B} binding and impulsivity (van der Post et al., 2002) or lack of association between 5-HT_{1A} availability and cognitive ability (Borg et al., 2006, 2009). Psychiatric research investigating 5-HTT have shown reduced 5-HTT availability in OCD (Reimold et al., 2007), ASD (Nakamura et al., 2010) and in MDD (Selvaraj et al., 2011; Gryglewski et al., 2014) with comorbid anxiety (Reimold et al., 2008), but also increased 5-HTT binding in MDD (Ichimiya et al., 2002; Reivich et al., 2004) and lack of association in MDD (Meyer et al., 2004) and ASD (Girgis et al., 2011) when compared to a control group. The role of 5-HT_{1B} in psychiatric disorders is less well studied, but literature has demonstrated decreased 5-HT_{1B} binding in MDD (Murrough et al., 2011b; Tiger et al., 2016), posttraumatic stress (Murrough et al., 2011a) and substance-dependency (Matuskey et al., 2014) compared to control subjects. Also, a positive correlation between 5-HT_{1B} receptor binding and anger and psychopathy in violent offenders as well as reduction of 5-HT_{1B} binding after treatment for MDD (Tiger et al., 2014). In sum, most studies implicate an involvement of serotonin in cognitive and psychiatric aspects, but how such associations looks like, whether it is good or bad to have high or low amounts of 5-HT_{1B} receptors and 5-HTT, are not completely understood.

Well-established findings are, however, the occurrence of cognitive impairments in psychiatric disorders. Impairments of similar cognitive domains seem to occur in several disorders, suggesting an overlapping cognitive phenotype within the psychiatric field, varying in the population with clinical phenotypes in the more extreme ends of the continuum. It is suggested that cognitive impairment might serve as a transdiagnostic phenotype across psychiatric disorders (McIntyre et al., 2019), and thus, representing an overlapping and dimensional approach varying along a spectrum in the population. The clinical neuroscientific research field is in great need of studies exploring neurobiological markers in relation to cognitive impairment in the psychiatric context. Pharmacological interventions targeting serotonin has been widely used in treating clinical symptoms, but are still lacking in effect on cognitive impairment, both during an active psychiatric episode as well as residual symptoms after clinical remission.

Overall, the results support existing literature that cognitive deficits may serve as overlapping transdiagnostic phenotypes within the psychiatric field, varying in the population with clinical phenotypes in the more extreme ends of the continuum. Consequently, our findings highlight and emphasize the importance of further exploration

of serotonergic markers involved in behavioral phenotypes in relation to psychiatric disorders.

Hence, future directions are needed and herein suggested. Firstly, the discussion of pros and cons with current diagnostic systems in psychiatry could be a thesis of its own. However, the use of only categorical symptom cut-offs hampers scientific progress due to significant symptom overlap between psychiatric disorders (e.g. MDD and generalized anxiety disorder) and diagnosis heterogeneity (Fried and Nesse, 2014), leading to uncertain results with confounding factors and possible noise. Instead, moving towards a more dimensional-based approach focusing on aspects of behavioral and neurobiological phenotypes can be helpful (McIntyre et al., 2019). Second, the importance of multi-center studies have been highlighted in many previously published studies and theses. Hence, for an important reason – to overcome the problem with low power due to not big enough sample sizes, and continue the development of existing as well as discovery of new neurobiological targets (which has somewhat lagged since the breakthrough of SSRI). Third, scientifical studies in general and neuroimaging studies in particular, have become more complex in its nature making it difficult to replicate previous findings (Nørgaard et al., 2019). Transparency through pre-registration and sharing data through, for example, supplementary material, protect against publication bias and may encourage further replication studies and meta-analyses. Fourth, variability in methodology has likely contributed to disparate findings, which further limits generalizability. A greater consensus in terms of method, protocol, variable measurements, assessment of behavioral phenotypes and outcome variables is required. In sum, a large number of different factors exist that may hamper the development in the field, but this may be improved by a dimensional, systematic and transparent approach.

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