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Molecular Imaging of Serotonergic Biomarkers and Impulsivity

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POPULAR REVIEW

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Serotonin (5-HT), known by popular culture as the happiness molecule, stands for much more than just that. Although researchers have found this neurotransmitter to be heavily involved in happiness, depression, anxiety, aggression, and the list goes on, a new method has uncovered the truth about serotonin's role in impulse control. Its influence on impulse control has been hinted at for the last forty years of metabolite, postmortem, animal models, and genetic research and intensive research in psychiatric disorders, violent suicide attempts, impulsive outrage, substance abuse and sexual aggression but no one has been able to exactly quantify its significance, until recently with the use of in vivo Pet imaging. PET imaging with the use of in vivo biomarkers is a highly advanced, expensive, and yet extremely selective method for quantifying the neurotransmitter of interest.

In the present thesis quantification of the 5-HT1A receptor and 5-HTT transporter was performed with the radioactive tracers, or radioligands, [^{11}C]WAY and [^{11}C]MADAM in the brains of healthy individuals with no psychiatric history or drug abuse history. The radioligands have a high affinity and selectivity for serotonin 5-HT1A receptor and transporter, 5-HTT, respectively. Binding potential (BP) of the radioligand to serotonin 5-HT1A receptor and 5-HTT transporter allowed for the quantification of the density in each region of interest for each subject. BP was compared to level of impulsivity through a Pearson Correlation.

Personal impulsivity for each subject was measured in personality tests. Personality inventory test include many facets of behavior, impulsivity and impulsivity like characteristics are just one of many facet evaluated, and therefore subjects were blind to what was being extracted from the tests.

In concordance with past research there seems to be a putative relationship between the serotonergic system and impulsivity. We found significant correlations with high density in the serotonin receptor in the temporal cortex, hippocampus, amygdala, and orbital frontal cortex and high density of serotonin transporter in the frontal cortex and the neocortex associated with impulsiveness in healthy individuals. We also found significant correlations with low density of serotonin transporter in the caudatus, putamen, and thalamus in association with impulsiveness.

The future of in vivo PET imaging technique leads to open doors not only in research but even more importantly treatment. Studying healthy subjects uncovers the biological bases for our unique, individual differences in personality and behavior. While imaging psychiatric patients provides methods for understanding, intervention, and treatment. The history of serotonin research has lead science here, beginning with metabolites in cerebral spinal fluid and genetic alterations in transporters and receptors, all good clues to serotonins influence on behavior but the beauty of PET lies in the actual imaging of the brain and its mechanics. It is our belief that the future of in vivo molecular imaging will be a revolutionary innovation in psychotherapy, psychology, psychiatry, medicine, and so much more.

ABSTRACT
Serotonin metabolite found in the cerebral spinal fluid has been linked to suicidality, alcohol consumption, aggression, and anxiety. Furthermore animal models, post mortem research, and genetic studies allude to the same conclusion, that serotonin influences personality. In this study we, for the first time, used an in vivo Positron Emission Tomography technique, to investigate the association between impulsivity and serotonin neuro-transmission in healthy humans. To do this we used radioactive tracer molecules, or radioligands, with high affinity and selectivity to the serotonergic proteins in questions. [^{11}C]WAY-100635 and [^{11}C]MADAM binds with high affinity and selectivity to serotonin 5-HT1A receptor and serotonin transporter, 5-HTT, respectively. Impulsivity was measured in personality inventories, including Karolinska Scale of Personality (KSP), NEO-PI-R, and Temperament and Character Inventory (TCI). There were significant correlations between impulsivity and [^{11}C]WAY -100635 binding potential in temporal cortex, orbital frontal cortex hippocampus, and amygdala. There were also significant correlation between impulsivity and binding potential of [^{11}C]MADAM in the frontal cortex, neocortex, caudatus, putamen and thalamus. In summation, the putative results lead us to believe that the regulation of the serotonergic system influences impulsiveness and further investigation is paramount.

ABBREVIATIONS

- 5-HIAA: 5-hydroxyindoleactic acid
- 5-HT: 5- hydroxyl tryptamine, serotonin
- 5-HTP: 5- hydroxyl tryptophan
- 5-HTT: Serotonin transporter, SERT
- 5-HTTLPR: Polymorphism linked to 5-HTT
- BP: Binding potential
- CSF: Cerebral spinal fluid
- DRN: Dorsal raphe nucleus
- Htr2b: Gene that transcribes 5-HT2B
- KSP: Karolinska Scale of Personality
- MADAM: 5-HTT Radioligand, N,NDimethyl-2-(2-amino4methylphenyl)methyl]-N-2-(4fluorophenylethyl)-piperdine
- MRI: Molecular Resonance Imaging
- NEO-PI-R: Revised version of NEO Personality Inventory
- p: significance
- PET: Positron emission tomography
- r: Pearson's correlation coefficient
- ROI: Region of interest
- SPECT: Single-positron emission tomography
- SRTM: simplified reference tissue model
- SSRI: selective serotonin reuptake inhibitors
- TCI: Temperament and Character Inventory
- WAY: 5-HT1A radioligand, N-[2-(4-(2-metoxyphenyl)-1-piperazin)ethyl]-N-(2-pyridinyl)- cyclohexanecarboxamide trihydrocloride

INTRODUCTION

Serotonin is a pertinent hormone and monoamine neurotransmitter, encompassing vast roles within the gastrointestinal tract and central nervous system (CNS) of many species: including fungi, plants, and animals.

Animal models, post mortem, genetic, and clinical studies have proven serotonin's expansive influence both physiologically and psychologically. Its influence on pain, appetite, sexual behavior, sleep regulation, perception, emotion, and cognition are as complex and expansive as the neurotransmitter itself. The serotonergic system is said to be one of the most complex and specific systems of neurotransmission within the human brain. This is one of the reasons that much of the serotonin research has led to false and inconclusive results about its regulation because within its complexity lies its diversity. For example serotonin has roughly fifteen different receptors. The variation in receptors alone, leads to many different roles for the neurotransmitter and different locations of affect. Impulsivity is a behavioral trait in which an individual acts without forethought or planning and without thought of the consequences of their actions. It is known that the regulation of serotonin influences impulsivity but the complexity of the neurotransmitter is responsible for making the exact relationship of serotonin and impulsivity elusive. Although there was early and strong evidence in serotonin metabolite concentration and its influence on personality, it is speculative and not very scientific to draw vast conclusion from such research. The same can be said of made of post mortem research. However, we believe PET images can be a positive outlet to investigate the connection between impulsivity and serotonin where these other methods falter, due to PET's specificity and use of radioligands to bind to the exact protein in question. Our aim is to investigate the density of serotonin receptor and transporter in the brains of healthy individuals in association with their impulsivity level.

The serotonergic system

The serotonergic pathway

Serotonin is present in many non neuronal cells, including mast cells, platelets and enterochromaffin cells. In fact only about 2% of serotonin is present in the central nervous system, about 8% is present in the blood platelets and the remaining 90% present in the GI system.

The majority of serotonin originates from a family of nuclei called the raphe nuclei which lie in the reticular formation of the brain. The raphe nuclei that project rostrally are the caudal linear, dorsal raphe nucleus (DRN) and the medial raphe nucleus. The raphe nuclei that project caudally are the raphe magnus, raphe obscurus, raphe pallidus nuclei and parts of the adjacent lateral reticular formation (Hornung, 2003). The caudal raphe nuclei supply serotonin to the cerebellum, brainstem and spinal cord. The DRN supply serotonin to the prefrontal cortex, basal forebrain, striatum, nucleus accumbens, thalamus, hypothalamus, amygdala, hippocampus, and cerebellum. (*Figure 1)*

The DRN supplies almost all the serotonin in the brain. It encompasses about 250,000 neurons, which stretch their axons all over the brain in two major pathways. One road, a medial pathway that supplies the amygdala, basal forebrain, hypothalamus, and hippocampus and a second road, the lateral pathway, running through the capsula interna and supplying the lateral cerebral cortex.

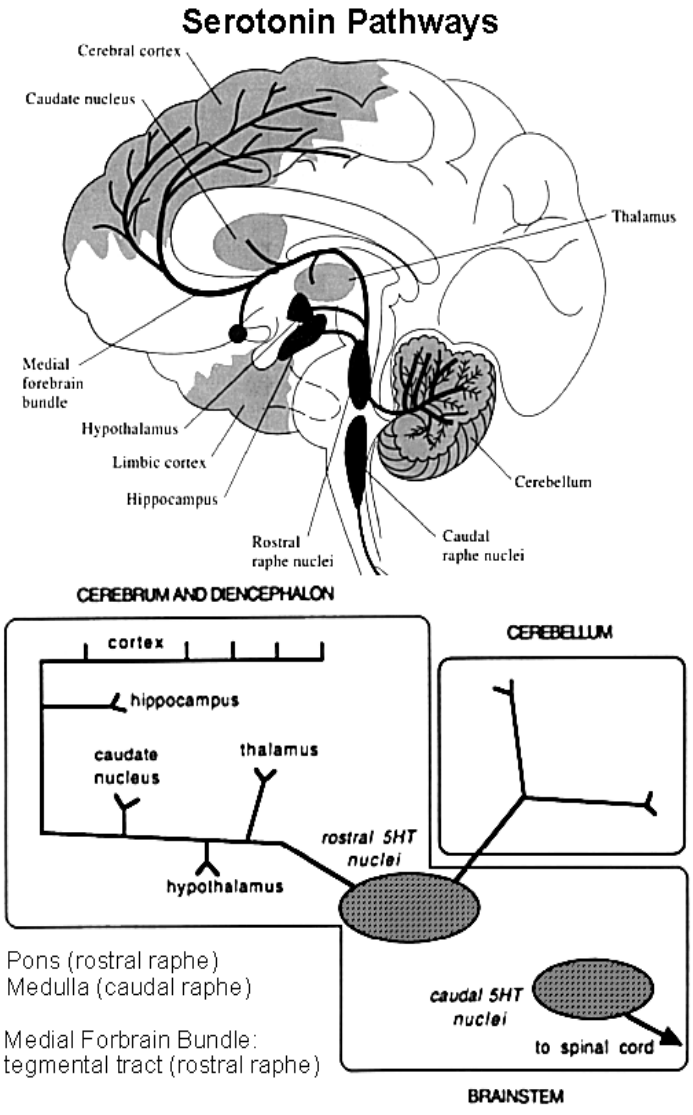

Figure 1: Shows the two pathways from the raphe nuclei to supply the Central Nervous System with Serotonin.

Synthesis and Degradation

Serotonin is synthesized from the amino acid tryptophan. Once tryptophan is imported into the brain there are two enzymes which help in the conversion form tryptophan to serotonin, first tryptophan hydroxylase which converts tryptophan to 5-hydroxy-

tryptophan (5HTP), and secondly aromatic amino acid decarboxylase coverts 5HTP to serotonin (5HT). Serotonin is packed into vesicles within the presynaptic neuron by the aid vesicular monoamine transporter.

Serotonin is degraded by the enzyme monoamine oxidase and converted to serotonin metabolite, most commonly 5-hydroxyindoleactic acid (5-HIAA). Degraded 5-HT in the synaptic cleft is transported by serotonin transporter (5-HTT) back into the presynaptic cleft.

Serotonergic Neurotransission- Structure and Function

Biomarkers and radioligand

A biomarker allows for the measurement of a biological substance for the quantification of behavioral traits, pathology, and for pharmacological purposes. Serotonin has multiple different proteins that aid in neurotransmission and sequentially help to study the activity of serotonergic transmission. The two biomarkers that will be used in the present thesis are 5-HT1A receptor and serotonin transporter (5-HTT).

Serotonin subreceptors

There are about 15 known receptors with different functions and characteristics which lend to the complexity of serotonin. Among the many different serotonin receptors there are seven families (Borg, 2007), thirteen are G- protein coupled receptors (GPCR) and one ligand gated ion channel protein (Hoyer & Hannon, 2002; Hannon &Hoyer, 2008; Borg 2007; & Stahl 2008;). Presynaptic 5HT receptors are autoreceptors, meaning they work in a negative feedback manner, when 5- HT is present they reduce or cease the release of serotonin. Examples of such presynaptic autoreceptors are terminal autoreceptors, like 5HT1B/D and somatodendritic atutoreceptors, like 5HT1A. 5HT1B/D monitor serotonin in the synaptic cleft and the regulation of additional serotonin. Presynaptic 5HT1A will be discussed in further detail below. Postsynaptic 5HT receptors allow for the communication of the neurotransmission. For example, 5HT1A regulate the inhibition of 5HT2A. It is believed to elicit and regulate anxiety, cognition, and depression. While 5HT2A works in opposition, it excites pyramidal neurons thus eliciting glutamate release and the inhibition of dopamine. Appetite, mood, and cognition seem to be regulated by the receptor 5HT2C, which also interacts with dopamine and, in addition, norepinephrine release. Within the cortex 5HT3 elicit inhibition of interneurons. Further examples such as 5HT6 and 5HT7 are under investigation still.
(Stahl, 2008).

5HT1A

5HT1A is one of the greatest studied receptors within the serotonergic receptor family. In the presynaptic neuron 5HT1A is a somatodendritic autoreceptor most dense in DRN. Its role is to recognize 5HT in the cell body and dendrites. When 5HT is recognized it slows the neuronal impulse through the neuron. As a postsynaptic neuron, 5HT1A inhibits pyramidal neurons and accelerates the release of dopamine by disinhibiting 5HT2A. The two receptors work in opposition; one accelerates dopamine and the other acts as a break

(Stahl, 2010). Postsynaptic 5HT1A are located throughout the brain, yet they are most densely located on the hypothalamus, limbic, and cortical regions. Where they can be found on cells types, including granule cells, in addition to pyramidal cells and GABAergic inhibitory interneurons.

5HT1A is recognized to be involved in many psychiatric disorders as well as behavioral variations. PET studies in primate models have shown the binding of psychoactive drugs, like pindolol and busipirone, to the binding site of 5-HT1A receptor (Andree & Halldin, 2000). Pindolol has a very high affinity to 5HT1A receptor, where it acts as a β-adrenoreceptor antagonist. In combination with SSRIs it appears to be a plausible treatment for depression.

5HTT

From both a pharmalogical, physiological, and therapeutic standpoint 5-HT1A and 5-HTT relationship seems to reflect in their density. Bose and Mehta see a congruent low level of the receptor and transporter in both the limbic region and dorsal raphe nucleus (2011). This adds further reason to use receptor and transporter as biomarkers in the present thesis.

5-HTT greatest density lies in the raphe, putamen, hippocampus, cingulate cortex, and frontal cortex.

Serotonin transporter (5-HTT) contributes to the concentration of serotonin in the synaptic cleft. It transports the 5-HT in the synaptic cleft back to the presynaptic neuron, where it is then packaged back into synaptic vesicles, by vesicular monoamine transporter 2 (VMAT2). Serotonin transporter (SERT or 5HTT) is a unique transporter to serotonin and is said to be one of the key regulators of all monoamines, in this case serotonin, the other being COMT. Furthermore, genetic alterations in either cause problems with information processing (Stahl, 2010). Likewise, the distribution and density of serotonin in the brain seem to be linked to cognition and behavior, furthermore anxiety and impulsivity (Carver & Johnson, 2011). Therapeutic treatment, seen in depression and bipolar disorder, has targeted 5-HTT, with use of selective serotonin reuptake inhibitors (SSRI), which allow for increase amount of serotonin to remain in the synaptic cleft. Studies on animal models have shown the reduction in alcohol uptake when given SSRIs. SSRIs are an effective treatment for Obsessive Compulsive Disorder and Premenstrual Dysphoric Disorder, which are both disorders characterized by impulse control impairments. Furthermore, SSRIs, have been given to individuals with anxiety, as an antidepressant, and continues to be tested pharmacologically. 5-HTTLPR is a polymorphism in the serotonin transporter that has gained more and more popularity as a predictor for psychiatric disorders. Yet, with much research focused on pharmacology, the biological mechanism of 5-HTT still remains elusive.

PET studies will allow for a deeper understanding between behavior and concentration of serotonin, as well as the effect of the 5-HTT densities on 5-HT1A densities.

Personality and Serotonin's Role

Personality

Personality is a branch in psychology that evaluates the variation in human behavior in the way they react emotionally, perceptually and cognitively to different stimuli. Since the early theories of Hippocrates (460- 370 BC) and Galen (130- 200 AD) there has been speculation that the human body plays an intimate role in behavior (Chamorro- Premuzic, 2011). The development of exactly how and where this mind-body process takes place has becomes more specific with every theorist. When evaluating scholars such as Eysenck who hypothesized that variation in behavior was due to individualistic activation of reticulocortical and limbic formation when stimulated by stress and anxiety (Ref), we see that Hippocrates was at the forefront of behavioral science (Chamorro- Premuzic, 2011). Biology and psychology are joining hands and reevaluating the combat of the centuries whether nature or nurture, biological or psychological. We now know credit goes to all sides and as more knowledge unravels, scientists and psychologists alike realize how intertwined the subjects of biology and behavioral science truly are. The associations between personality and biology and the influence they have on one another should therefore be greatly investigated and appreciated.

Since the birth of personality theory many psychologist have battled to find a schematic way to analyze and quantify personality. Such scales are called personality inventory. Personality inventory consists of many statements called items, which assess a person's thoughts, emotions and behavior. Answers consist of true/false, or a scale from 1- 4 or 1- 5 with increasing agreement to the statement or question. There is a rubric that pertains to the personality inventory, which list all the items that belong to the construct. For example, Impulsiveness items, item 8) I have a tendency to act on spur of the moment without really thinking ahead; item 20) When I have to make a decision, I "sleep on it" before I decide. Each construct/facet is similar in layout to the examples given. All items are merged together to give a total score for that individual construct, in the last examples for Impulsiveness.

The most common models of personality Eysenck's Gigantic Three factor model and Goldberg's et al. Big Five factor model. Eysenck's gigantic three, which includes extroversion/ introversion, neuroticism and psychotocism believes that all personality traits fall into one of the three major factors. Costa and McCrea believed a five factor model including openness, consciousness, extravertedness, agreeableness, and neuroticism (Chamorro- Premuzic, 2011; John & Richard, 2010) encapsulated all personality traits. Today the Big Five Personality scale is the most widely accepted and used in personality psychology and science (John & Richard, 2010). The NEO-PI-R (Costa & McCrae, 1992) scale of personality is used globally to evaluate the Big Five factors. There are many personality tests with different numbers of personality subscales that have been developed for the same purpose of evaluating and predicting personality. Such examples are Temperament and Character Inventory (TCI), Karolinska Scale of Personality (KSP), Swedish Scale of Personality (SSP), Chinese Personality Inventory (CPAI) and many others that have been developed by individuals and institutions. The

above theories, models and scales allow for scientists and psychologist to quantify a personality, as well as subsets of personality, for example aggression or impulsivity.

Impulsivity

Impulsivity is the inability to control impulses or the lack of foresight prior to action; it is often characteristic of psychiatric disorders, such as suicidality, violent behavior and addiction (Bevilacqua & Doly, 2010). When studying impulsivity often the subject tested are those that fall into the above extremes because they exhibit impulse disorders and therefore easier to identify a trend between behavior and neurotransmitter. Although, in the present thesis, individuals with no history of psychiatric disorders or alcohol/ drug abuse are examined and assumed to have a variation in their impulse control. We include analysis/es that evaluate impulsivity specifically as well as those that evaluate aggression, anxiety, and violence because impulsivity studied in healthy subjects is not well investigated and such personality traits overlap and can provide knowledge about one another.

In the present thesis impulsivity is defined and measured by the following personality tests: Temperament and Character Inventory (TCI), Karolinksa Scale of Personality (KSP), and NEO.

Karolinska Scale of Personality

Karolinska Scale of Personality (KSP) is a self reported personality inventory used to assess personality traits using 135 items and categorizes 15 different personality facets. We looked specifically at Impulsivity and Monotony Avoidance, Verbal Aggression, and negative scores in Inhibition of Aggression. Furthermore, KSP is an inventory used in pharmacology, biochemistry, and medicine both internal and social, in addition to psychology and psychiatry (Schalling, 1986). Quantification of individual personality is obtained by evaluating habitual behaviour, individual preferences, cognition, and situational reactivity (Schalling, 1986). Although, KSP has been critiqued like most personality inventories, most of the critique has been overstated, Nunally (1978).

Temperament and Character Inventory

Temperament and Character Inventory (TCI) is also, a self- report, personality inventory used to assess personality traits. Novelty seeking and negative scores in Harm Avoidance were evaluated specifically in the TCI inventory to evaluate individual impulsivity. TCI includes 238 true/ false statements. The dimensions of temperament: including novelty seeking, harm avoidance, reward dependence, and persistence and the character dimension including: self-transcendence, cooperation, and self directedness, reflect both inherited and environmental influenced dimensions respectively (Schalling, 1986).

NEO-PI-R

NEO-PI-R is the revised version of the NEO Personality Inventory, which uses the Big Five Factors including: Openness, Consciousness, Extraversion, Agreeableness, and Neuroticism, as a construct to assess personality traits. The 240 items in the NEO-PI-R inventory measure the Big Five, and in addition to that, six subsets or facets within each

of the five factors. The facets evaluated in the present thesis were Impulsiveness and Excitement Seeking, which are found respectively as subsets in Neuroticism and Extraversion.

The Beginning: Preclinical Research including: Serotonin Metabolite in Humans, Animal Models, and Post Mortem Studies.

In the late 1970's the first research on the serotoninergic system and its influence on personality began. Quantifying serotonin metabolite (5-HIAA) concentration in the cerebral spinal fluid (CSF) has paved the pathways for the expansive research between serotonin and personality. In 1976 Åsberg and Träskman, studied suicidal acts in depressed patients. Individuals who had attempted suicide more times had a lower 5-HIAA concentration than those who attempted fewer times or attempts were less violent. Furthermore, those individuals who managed to kill themselves had a very low 5-HIAA concentration in there CSF (Åsberg and Träskman, 1976). Here it was hypothesized that the serotonin metabolite was an indication of the amount of serotonin present in the brain.

Although CSF concentration does provide a piece of evidence to the role of serotonin in the brain, it is false to jump to such vast conclusions. Further research on suicide as well as violence, hypoglycaemia, and early alcoholism came to the same conclusion that such individuals had low levels of 5-HIAA (Linnoila & Virkkunen, 1992). Linnoila & Virkkunen in 1993 studied impulse control in individuals with unipolar depression, violent marines, and those that had multiple violent suicidal attempts. All of which had a lower level concentration of 5-HIAA in their CSF. In addition, individuals with a history of violence, fire arsonists, and obsessive compulsive disorder showed a negative correlation between concentrations of 5-HIAA and impulsivity. When comparing males who had an early onset of alcoholism, Type II, to late onset alcoholics, Type I, they had a lower concentration of 5-HIAA (Linnoila & Virkkunen, 1993).

Higley and Linnoila took this one step further. Type II Cloninger's alcoholism is characterized by decreased impulse control and thus as a default in serotonin regulation. They believed the low amount of 5-HIAA was do to the concentration of serotonin in the brain and tested their hypothesis using (selective serotonin reuptake inhibitors) SSRIs (Higley& Linnoila, 1997). Animal models showed long term effects on 5-HIAA concentrations in monkeys that were peer- reared rather than mother- raised. Peer-raised monkeys showed high aggression, impulsivity, low social ranking, and high alcohol consumption, similar to what is characterized in humans. When given specific serotonin reuptake inhibitors (SSRI) it reduced the level of alcohol uptake in the monkeys who consumed high amounts of alcohol, while it had no effect on those monkeys who consumed low levels of alcohol (Higley & Linnoila, 1997).

Returning once again to human models, violent offenders with paternal alcoholism showed a lower 5-HIAA than those without paternal alcoholism (1993) as well as violent offenders who committed impulsive crimes rather than non impulsive crimes, for example fire starters who were not normally violent, had a lower concentration of 5-HIAA. Yet, still the lowest concentration is in those individuals who attempted suicide (1993).

Linnoila and Virkkunen (1993) hypothesized that the frontal cortex may be associated with the amount of 5-HIAA turnover. They found a very low 5-HIAA concentration in the frontal cortex of the lumbar spine of cadavers who had injures to their frontal temporal brain regions. The frontal cortex role in executing decision and impulse control is clearly relevant, yet it is important to remember that the metabolite found in the CSF is the accumulation of all the serotonin within the serotonergic system and to jump to such specific conclusions should be done with caution.

Although such findings were replicated and did influence further research, measuring serotonin metabolite in the CSF only allows for the hypothetical predictions about serotonin in the brain and does not allow for the exact quantification of specific serotonin proteins or allow for the quantification of markers within specific regions of interest. To draw such conclusions one must look further at genetic markers and most importantly at brain imaging, such as PET, which allows for the precise tagging through the use of radioligands and examination of serotonin biomarkers in specific regions of interest. Brain imaging examples and methods will be given in more detail following genetic evidence.

Preclinical Research including Genetic Markers

Genetic studies have allowed for the identification of serotonergic markers and perhaps "candidate endophenotypes" in the assessment of individuals with impulsivity, anxiety suicide attempts, and violence. The role of serotonin in such behavior types is relevant and will be discussed in brief detail from a genetic point of view. There are many reviews and research that have identified and studied both serotonin receptors and transporters in the impulsivity, anxiety, and aggression. It is widely believed that the most significant is serotonin transporter polymorphism, 5-HTTLPR, and serotonin receptor, 5HT1A.

In Mann's review he states that further investigation should be made in finding an endophenotype for the identification of suicidal individuals, those with impulse control disorders, including aggression and violence. In Anguelova and Benkelfats (2003) META- analysis of multiple publications on 5-HT polymorphism they were unable to find conclusive data on 5-HT receptor and increased aggression/ impulsivity but they did find significant data on 5-HTTLPR and increased depression, suicide, aggression, and impulsivity.

More recently, in Mann's review (2009) he states, that there is an upregulation of 5-HT2A gene within the Brodmann region 11 in suicide individuals when compared to control individuals. Mann identifies "candidate endophenotypes" as a high density of serotonin receptors, 5-HT1A and 5-HT2A, and low binding potential to serotonin transporter. Although, 5-HT1A influence on impulsivity is yet to be clearly identified and results replicated, the regulation of 5-HT1A should share a coinciding relationship with the upregulation of 5-HT2A because 5-HT2A and 5-HT1A interact with one another postsynaptically. If 5HT1A inhibits serotonin release, then 5HT2A signal to dopamine receptors is disinhibited, meaning the inhibition is turned off and dopamine is released (Stahl, 2008). These two receptors work in opposition. Like, stated previously one would expect to find upregulation of 5-HT1A where there is upregulation of 5-HT2A and this

may correctly identify an individual with high impulsivity or aggression. Although, one must be critical of speculating about one receptor because of the theoretical relationship with another receptor.

Agreeably, a much supported candidate endophenotype are low concentrations of 5-HIAA serotonin metabolite, found in the CSF, says Mann (2009), Higley and Linnoila, (1997), Linnoila and Virkkunen, M. (1992), Linnoila, and Virkkunen (1993), Åsberg and Schalling (1987), and Åsberg and Träskman (1976).

A recent study looking for genetic markers in a highly impulsive group of Finns found a stop codon in the Finnish population, labeled Q20*, that blocks the transcription of the 5-HT2B, one of the serotonin receptors (Bevilacqua & Doly, 2010). Individuals with Q20* allele seem to be more likely to have lower impulse control, seen in increased alcoholism, violence, and arsonism than those that are homozygous Q20. Most importantly the attacks by the Q20* allele criminals were not premeditated. Such individuals also scored higher on novelty seeking and harm avoidance test. Htr2b knockout mice showed an increase in impulsivity giving further credit to genetics, yet such an allele was only found in Finnish people.

Furthermore, previous studies have been correlated to negative actions of impulse control, as seen in violent suicide attempts, for example, drowning and hanging versus less violent attempts including drug overdose (Åsberg, Träskman, et al.,1976), arsonists who are normally not violent individuals (Linnoila, Virkkunen, et al., 1993), as well as in psychiatric disorders such as borderline personality disorders and bipolar disorders (Mallow- Diniz, L., Neves, F., & de Morales, P. 2011). We believe, although a majority of previous research has been elicited on such extreme groups, such trends in serotonin and impulsivity can also be found in normal subjects and this is exactly what the most recent research has investigated. 5-HTTLPR polymorphism has been studied in individuals with no history of psychiatric disorders or alcohol abuse. Such studies are closer in line with the present thesis, although here they use a genetic technique rather than in vivo biomarker PET imaging. Furthermore the polymorphism seems to play a role in normal individuals behavior, furthermore in aspects of personality, such as agreeableness, aggression, novelty seeking, and consciousness (Carver, Johnson, & Joorman, 2010). Carver and Johnson (2010) studied the role of 5-HTTLPR polymorphism, in both positive and negative emotional reactivity, as well as the cognitive implications of impulsivity. They saw that 5-HTTLPR polymorphism, S allele, is a significant marker for normal individuals who show lack of control, or impulsivity although they shed doubt on whether it is impulsivity itself or the susceptibility to emotion. Thus studying the diverse sides of impulsivity is paramount (Carver, Johnson, & Joorman, 2010).

The genetic data surrounding serotonin is as elusive as it is expansive and challenging. Some genetic findings are in contradiction with the known role of the receptor (Mann, 2009) and polymorphism in different proteins seem to play similar roles in behavioural outcome (Bevilacqua & Doly, 2010; Carver, Johnson, & Joorman, 2010). A multitude of

genetic finding point to many different results and controversial conclusions, thus we turn to in vivo brain imaging.

Clinical research including in vivo markers, SPECT, and PET

The previous findings linking impulsivity and aggression with serotonin variations were found in preclinical studies including cerebral spinal fluid metabolite, animal models, and genetic markers in psychiatric and nonpsychiatric subjects. Preclinical studies, although the elder of the two models, have developed simultaneously with clinical studies. The present thesis uses PET imaging to study impulsivity, thus the following research using brain imaging techniques is of paramount significance.

Single-photon emission tomography (SPECT) is a molecular imaging technique much like PET, but with lower spatial resolution and less sensitivity and specificity. Tiihonen and Kuikka used SPET in 1997 to image 5-HTT in the brain, with radioligand ([123I]beta-CIT). Clinical studies, such as Tiihonen and Kuikka found that violent offenders had a lower density of serotonin transporter than in normal controls.

We continue with examples of brain imaging in individuals with no history of psychiatric disorders, or drug and alcohol abuse. PET imaging like SPET is a method for imaging in vivo biomarkers. PET imaging is highly specific to the biomarker in question. Parsey and Oquendo (2007) used PET analysis to study the relationship between aggression and 5-HT1A. They used the Goodwin Aggression History scale to measure lifetime aggression in the healthy controls. In which they found a lower binding of [11C]WAY radioligand to serotonin receptor, thus assuming lower density 5-HT1A receptor in aggressive individuals.

Soloff and Price (2010), like Parsey and Oquendo (2002) found gender differences between serotonin receptor in normal controls, although they evaluated serotonin 2A receptor binding using radioligand [18F]altanserin and PET imaging. There results were not identical to 5-HT1A findings (Pasey and Oquendo, 2002). Male specific regions of interest (ROIs) for aggression and 5-HT2A binding potential (BP) included left orbital frontal cortex and left medial frontal cortex in males, while correlation for both sexes were only significant in the medial temporal cortex. Soloff and Price (2010) investigated a few other constructs of personality including novelty seeking, harm avoidance, and reward dependence in the TCI personality scale, all of which were not deemed significant in concordance to BP.

Although, brain imaging is probably the most reliable method for quantifying biomarkers it is difficult to replicate results purely due to the availability and expense of PET centers. This makes the present thesis very fortunate because of the PET resources available.

Summary

There is a clear relationship between impulsivity and serotonin regulation but the exact nature is still unclear. The accumulation of evidence drawn from the previous findings touch on and support the present thesis. Yet, the novelty of this present thesis lies within the PET imaging technique and the assessment of impulsivity traits within non

psychiatric individuals. In vivo PET imaging is very specific and allows for the examination and quantification of serotonin biomarkers. The serotonergic system is a very rich and complex system of neurotransmission, much more than dopamine. PET imaging allows for the specificity that is needed.

AIMS

The aim of the present thesis is to examine the role of the serotonergic system in the regulation of impulsivity and impulse control using in vivo biomarker PET imaging and analysis. More specifically:

The first aim is to evaluate the receptor density of 5-HT1A in individuals with low impulsivity when compared to individuals with high impulsivity (Study I).

The second aim is to evaluate the transporter density, 5-HTT, in individuals with low impulsivity when compared to individuals with high impulsivity (Study II).

Furthermore, which regions of interest (ROI) in the brain have a greater density of receptors and transporters in those exhibiting impulse control (Study I & II).

Hypothesis

Our hypothesis is that impulsivity is influenced by the regulation of serotonin. Furthermore, individuals who exhibit high impulsivity, when compared with those with low impulsivity, will show hyporegulation of their serotoninergic system. Individuals with high impulsivity, when compared to individuals with low impulsivity, will have a lower serotonin receptor density as well as a lower density of serotonin transporters. This will be evaluated by a lower binding potential of the respective radioligands to serotonin receptors and a lower binding potential in serotonin transporters in high impulsivity individuals.

My second hypothesize is that binding potential will vary in intensity and correlate with different regions of the brain because serotonin is region specific and highly complex.

MATERIALS & METHODS

Positron Imaging Tomography (PET)

PET-is a non-invasive brain imaging method that measures the spatial distribution between radiolabeled markers. A tracer, marked with positron emitting radionuclide, known as a radioligand, is injected intravenously where it then travels across the blood brain barrier, into the brain. Once in the brain it binds to the specific high affinity target molecules. PET system is unique because it allows for the quantification of low density molecules, like receptors and transporters.

PET measures the spatial distribution by the decay of the radioactive isotope. When it decays it emits a positron, which travels a short distance before it annihilates with an electron. The annihilation indirectly causes a pair 511 keV gamma particles (photons) to be emitted in approximately opposite direction (180 degrees +/- 1degree). The gamma particles (photons) are then detected by the PET system. *(Figure 2).* Thus allowing for an estimation of where the annihilation occurred. The spatial distribution of radioactivity uptake over time allows for a series of images to be gathered and reconstructed.

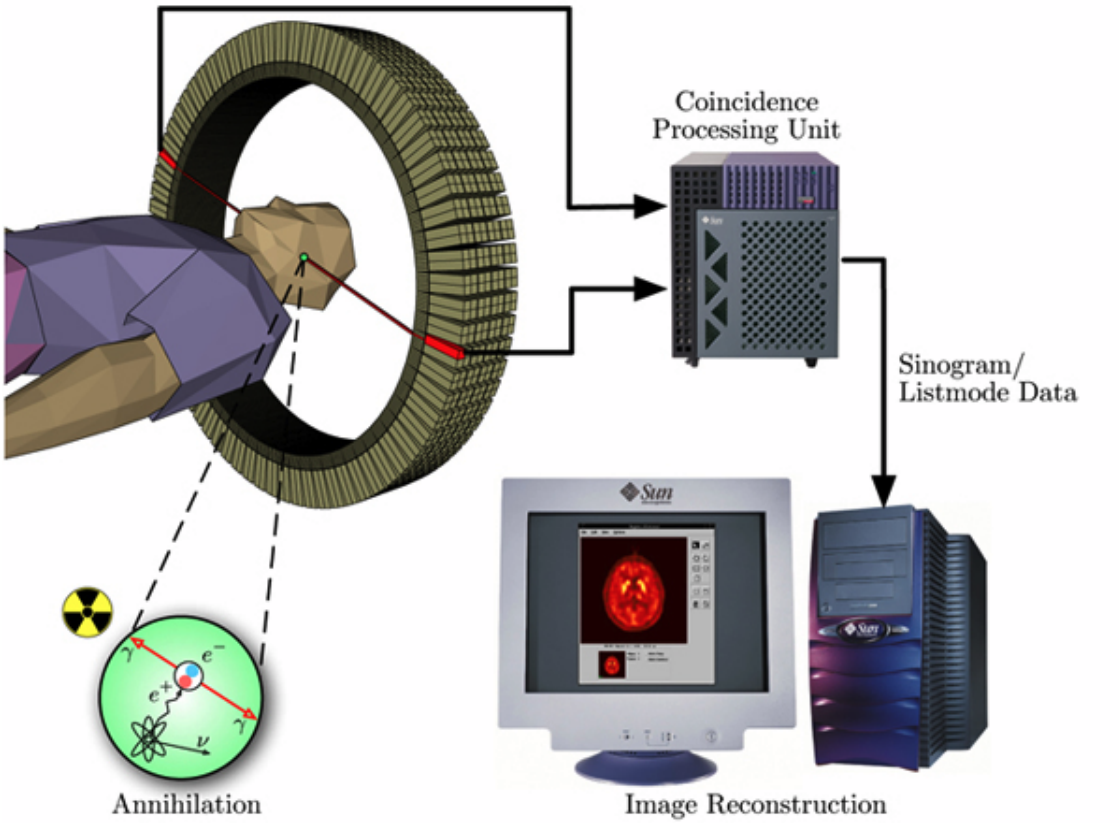

Figure 2: The radioligand bound to the receptor annihilates and causes an indirect emission of gamma particles or photons to be emitted. Which are then detected by the PET system. In courtesy of Dr Simon Cervenka.

Specific Radioligands for Serotoninergic Receptor and Transporter

Radioligands are a radioactive molecule that binds to the receptors, transporters, and enzymes in the body or, like in the present thesis, the brain. The radioactive decay of the biochemical substance is measured to quantify the affinity or availability of the protein in question.

[carbonyl-(11)C]WAY-100635

[^{11}C]WAY -100635 is a highly selective radioligand to the 5-HT1A receptor in both humans and non- human primates (Andree & Halldin, 2000). [^{11}C]WAY-100635 acts as an antagonist to 5-HT1A receptors.

[carbonyl-^{11}C]MADAM

N,N-dimethyl-2-(2-amino-4-methylphenylthio)benzylamine or MADAM is a radioligand with high affinity and selectivity to the serotonin transporter (5-HTT). It acts as a 5-HTT inhibitor. The recent development of [^{11}C]MADAM began with Chalon, who synthesized and used [^{11}C]MADAM in rat models and saw a 1000- fold affinity to the serotonin transporter than to other transporters present in the brain (2003). The same high affinity, selectivity, and stability in rat brains have also been seen in non- human primates, post mortem, as well as in living humans (Lundberg & Odano, 2005).

Subjects

There were Ninety-three subjects total, nineteen female and seventy- four male, for [^{11}C]WAY-100635 PET analysis ranging in age from twenty-four to sixty-one. Thirty subjects participated in [^{11}C]MADAM PET analysis ranging in age from twenty to fifty-five, with a two to one ration, respectively. The participants had no history of psychiatric disorder, alcohol abuse, or drug abuse.

MRI and PET procedures

Magnetic Resonance Imaging (MRI)

All subject underwent MRI scanning prior to PET scans. This allowed for the delineation of regions of interest (ROI). The MRI that was used to image all subjects was a Signa Advantage 1.5 Tesla GE with a four second repetition time (TR) 256x256 matrix. Both spatial and high sensitivity resolution was obtained with two different weights, one proton density and the other, T2 weighted images. Head movement was retrained during images and maintained the same position for both MRI and PET.

Positron Emission Tomography (PET)

Following MRI procedure, all subjects underwent PET imaging by the PET system ECAT Exact HR 47. The scanner was run in a 3D mode.

Analyses of PET data: ROI and Binding Potential

ROIs were delineated individually on the MRI using Human Brain Atlas and then transferred to their respective PET image. All ROIs were delineated with the exception of the dorsal raphe nucleus, which had to be delineated on the PET images because it is unable to be detected on the MRI. The radioactivity for each individual ROI were corrected for decay and plotted against time, to elicit a time activity curve (TAC). The absence of 5-HT1A receptors and 5-HTT transporters in the cerebellum, enables its use as a reference. The Simplified Reference Tissue Model (SRTM) can be used if the following two assumptions are met. First assumption, non- specific bound ligand must be the same volume in both the tissue of interest and the reference tissue, and secondly, the reference tissue is not influenced by the pathology at hand (Lammertsma & Hume, 1996). SRTM allowed for the measurement of binding potential (BP) in each ROI. For analysis, SPM2 software was used obtain BP for each region of interest.

ROIs for serotonin receptor, 5-HT1A, were the temporal cortex, insula, hippocampus,

amygdala, anterior cingulate, raphe nucleus, and the orbital frontal cortex. ROI for serotonin transporter, 5-HTT, were similar, including frontal cortex, temporal cortex, insula, anterior cingulate, hippocampus, raphe nucleus, caudatus, putamen, thalamus, and neocortex.

Personality Test Procedure
Extensive evidence has shown that parts of people's personality is modulated by the regulation of the serotonergic system. Recent evidence has pointed to psychiatric problems, characterized by impulsivity, being linked to serotonin receptor, 5-HT1A and serotonin transporter, 5-HTT. We hypothesized that impulsivity in normal subjects (non-psychiatric/ non- alcohol drug abuse subjects) would also show variation in their serotonergic system. Impulsivity was measured by evaluating impulsivity and impulse control in the following personality tests: KSP, TCI and NEO.

Statistics
SPSS Student Version 18 was the statistical software used. We correlated the individual BP in each region of interest with the individual impulsivity score. We ran a Pearson Correlation Coefficient for each ROI with association to each of the eight impulsivity inventory facets and correlated the two variables, each ROI and each impulsivity score, in a scatter plot. If pairwise information was not present both ROI BP and impulsivity inventory score was not included in the correlation.

RESULTS
Studies

Study I: An explorative study on serotonin receptor, 5-HT1A, and impulsivity and impulsive like characteristics.
Study I was made for the purpose of exploring the regulation of serotonin in different regions of the brain and quantifying the receptor density in relation to individual impulsivity.

There were ninety-three subjects, ages ranging from 24 to 61 at time of PET scan, although not all ages were accurately recovered. Subjects had no history of psychiatric illness or drug abuse. Each subject underwent MRI prior to PET scan. Radioligand [^{11}C]WAY was injected intravenously prior to PET. The binding potential between [^{11}C]WAY and serotonin receptor, 5-HT1A, was assessed and assumed to be a quantification of 5-HT1A density in the following regions of interest: frontal cortex, temporal cortex, insula, hippocampus, amygdala, anterior cingulate, raphe nucleus, and the orbital frontal cortex. Impulsivity was measured in KSP, TCI, and NEO-PI-R. KSP. We compared 5-HT1A binding potential in each regions of interest to the score in each facet of impulsivity using a Pearson Correlation. See *Table 1*.

There was a positive significant correlations between, high [^{11}C]WAY-100635 binding potential in temporal cortex and orbital frontal with high scores in KSP's Verbal Aggression. Furthermore there was a highly significant positive correlation, with high

scores in KSP's Impulsivity in association with high binding potential in the hippocampus and a positive significant correlation in the amygdala *(figure 3)*. Thus, we conclude there is a greater 5-HT1A density in the above brain regions in high impulse individuals.

Table 1. Pearson correlation coefficients (r) between 5-HT1A binding potential and Impulsivity facets in KSP, NEO, and TCI personality inventory.

WAYBP	Frontal cx	Temporal cx	Insula	Hippoc	Amygdala	Ant cing	Raphe	Orbital Fcx
KSP_I	0.117	0.151	0.086	0.275**	0.250*	0.155	0.049	0.309
KSP_M	0.079	0.079	0.103	0.136	0.039	0.045	0.139	0.220
KSP_VA	0.192	0.211*	0.188	0.164	0.170	0.144	0.127	0.338*
KSP_InhA	-0.023	-0.016	-0.021	-0.098	-0.052	0.032	-0.006	-0.139
NEO_I	0.014	-0.007	-0.022	0.124	0.108	-0.028	-0.147	0.044
NEO_ES	0.055	0.035	0.091	0.182	0.177	0.033	0.119	0.103
TCI_NS	0.075	0.082	0.056	0.152	0.149	0.096	0.102	0.198
TCI_HA	-0.012	-0.047	-0.049	-0.125	-0.074	-0.032	-0.054	-0.101
*p<0.05	**p<.01							

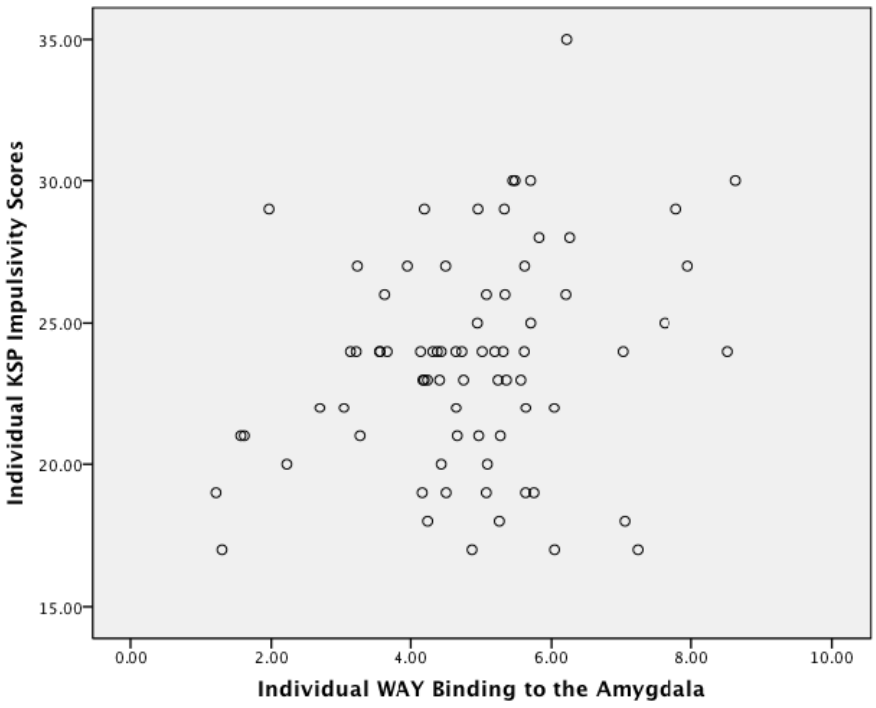

Figure 3: Individual binding potential values for [^{11}C]WAY in the amygdala in respect to individual subject KSP Impulsivity scores [r=.250, n=76 p<.05].

Study II: An explorative study on serotonin transporter, 5-HTT, and impulsivity and impulsive like characteristics.

The purpose of Study II was for explorative measures of serotonin transporter, 5-HTT, density and its influence on impulsivity and impulsive like characteristics including verbal aggression, novelty seeking, and negative scores in harm avoidance.

A total of 30 subjects, ranging in age from twenty to fifty- five underwent both MRI and PET scans as well as three Personality inventories. Prior to PET scan they were injected intravenously with the radioligand [^{11}C]MADAM , which has a high selectivity and affinity for 5-HTT. PET system measures radioactivity and the information is transformed into binding potential of the radioligand [^{11}C]MADAM to the serotonin transporter, 5-HTT, and thus assumed to elicit the density of serotonin in the specific regions of interest. Such regions of interest included: frontal cortex, temporal cortex, insula, anterior cingulate, hippocampus, raphe nucleus, caudatus, putamen, thalamus, and neocortex. The binding potential in each ROI was than correlated, using a Pearson correlation, to each facet of the three personality inventories mentioned previously in Study I.

There were both positive and negative significant correlation found between [^{11}C]MADAM and impulsivity *(Table 2).* Due to the explorative nature of the study there were numerous regions of interest, like in the first study, including: frontal cortex, temporal cortex, insula, anterior cingulate, hippocampus raphe nucleus, caudatus, putamen, thalamus, and neocortex. There were significant positive correlations between high binding potential in the frontal cortex and neocortex with high scores in TCI Novelty Seeking. There were also significant positive correlation, which agreed with our own hypothesis, between high binding potential in the caudatus, putamen, and thalamus with high scores in TCI Harm Avoidance *(Figure 4).* There were significant negative correlations, which agreed with our original hypothesis, between high binding potential in the caudatus and low scores in KSP Monotony Avoidance. Thus, in summation, leading us to believe there is a putative role between serotonin transporter, both in upregulation and downregulation depending on the area of the brain, and impulsivity.

Table 2. Pearson correlation coefficients (r) between 5-HTT binding potential and Impulsivity constructs in KSP, NEO-PI-R, and TCI personality inventory.

MADAMBP	*Frontal cx*	*Temporal cx*	*Insula*	*Ant cing*	*Hippoc*	*Raphe*	*Caudatus*	*Putamen*	*Thalamus*	*Neocx*
KSP_I	*0.363*	*0.143*	*0.29*	*0.345*	*0.128*	*0.221*	*-0.036*	*0.075*	*0.04*	*0.297*
KSP_M	*0.028*	*0.071*	*-0.03*	*-0.211*	*-0.334*	*-0.232*	*-.393**	*-0.357*	*-0.271*	*0.063*
KSP_VA	*0.178*	*-0.274*	*-0.048*	*0.109*	*0.056*	*0.095*	*0.081*	*-0.028*	*0.114*	*-0.08*
KSP_InhA	*0.102*	*0.257*	*0.213*	*-0.053*	*0.138*	*0.241*	*0.01*	*0.119*	*-0.041*	*0.227*
TCI_NS	*.462**	*0.246*	*0.198*	*0.172*	*-0.26*	*-0.053*	*-0.286*	*-0.035*	*-0.315*	*.412**
TCI_HA	*0.291*	*0.052*	*.396**	*0.229*	*0.253*	*0.053*	*.411**	*.456**	*.470**	*0.192*
NEO_I	*-0.047*	*-0.023*	*0.203*	*0.08*	*-0.284*	*-0.292*	*0.38*	*0.249*	*0.131*	*-0.039*
NEO_ES	*-0.062*	*0.296*	*0.198*	*-0.29*	*-0.18*	*-0.284*	*0.066*	*-0.054*	*0.045*	*0.226*
**p<0.05*	***p<.01*									

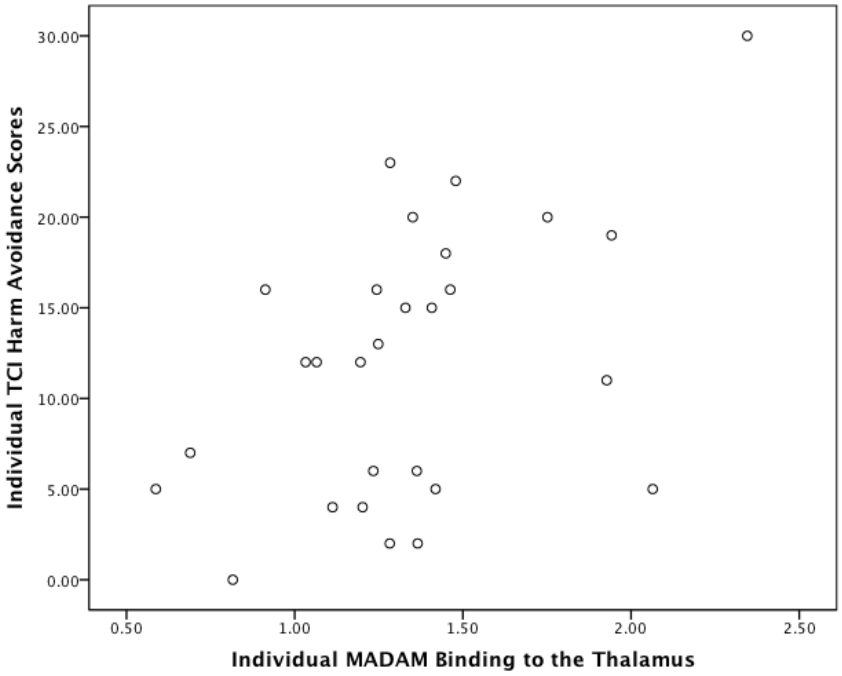

Figure 4. Individual binding potential of [^{11}C]MADAM in the thalamus in respect to TCI Harm Avoidance scores [r=.470, n=28, p= .012].

DISCUSSION

Summary

Serotonin's influence on impulsivity has been hinted at for the last forty years through the extensive preclinical and clinical investigations in psychiatric disorders, highly aggressive, extremely violent, and alcoholic subjects, whose behaviours were characterized by impulsivity. Furthermore animal studies, including non-human primates and genetic studies, in both humans and knockout mice, have investigated both polymorphisms in 5-HTT, as well as, other receptors in the serotoninergic family. The previous results have been both replicated and refuted, the question of serotonin's regulation of impulsive behaviour is an elusive one, yet the significance we found in the present in vivo PET study is remarkable. The novelty of the present study lies within the in vivo PET imaging of healthy subjects and the personality construct in question, impulsivity. Our hope was that it would help to create a better foundation for further molecular imaging studies in personality and more specifically, impulsivity. We hypothesized a lower receptor and transporter density in individuals with higher impulsivity. We partially refute our original hypothesis, due to high 5-HT1A BP in the amygdala, hippocampus, temporal cortex, and orbital frontal cortex, as well as, high 5-HTT BP in the frontal cortex and neocortex in relation to high impulsivity. We accept our original hypothesis, with our results of low 5-HTT BP in the insula, caudatus, putamen, and thalamus in relation to high impulsivity. The hypothesis was originally formulated

from the very few previous molecular imaging studies on aggression as well as receptor, 5HT2A, and the overconfidence in serotonin metabolite in the cerebral spinal fluid to report specific function of serotonin.

However, we are reminded by the results that the serotoninergic system is one of great complexity and specificity. Furthermore, explorative studies like the present one, can be critiqued for the multiple correlations and its liberal measures in significance. Yet it is irrefutable that what we have found is a clear influence between the regulation of the serotonergic system and impulsivity in healthy individuals. Due to the novelty of the present study, our methods and thus our results are not an identical replication of any past research, yet there are similarities and they will be discussed in detail.

Serotonin

We begin with the many serotonin metabolite studies. The founders of serotonin personality research were very accurate when they identified the neurotransmitter serotonin as a biological marker influencing aggression, suicide, and furthermore impulsivity (Higley & Linnoila, 1997; Linnoila, & Virkkunen, 1992; Linnoila & Higley 1993; Åsberg & Thorén, 1976). Although they attributed those behaviours to lower levels of serotonin in the brain, our results hint at a more elaborate system. There is both upregulation, seen in all regions of 5HT1A significant BP and in 5-HTT frontal cortex and neocortex significant BP, and downregulation of 5-HTT in the insula, putamen, caudatus, and thalamus, in individuals with high impulsivity levels. These findings further underline the fact that the serotonin-personality system is a complex and multifaceted one.

First in 1993 Higley and Linnoila suspected that the frontal cortex was responsible for the turnover of serotonin, seen in the measurement of serotonin metabolite, 5HIAA in the cerebral spinal fluid of cadavers who had injured their frontal cortex. In 1997, they found that individuals with damaged frontal cortex had lower impulse control and they hypothesized more specifically, that a lower orbital frontal receptor level would lead to lower impulse control. Although we did not replicate lower receptor levels for 5-HT1A, we do support the association between receptor density in the orbital frontal cortex as well as other ROIs influence on individual impulsivity. We found a significant correlation between 5-HT1A BP in the orbital frontal cortex and verbal aggression, as well as 5-HTT BP in the frontal cortex and Novelty Seeking. Furthermore, the frontal cortex is not solely responsible for impulsivity, but it does contribute to the regulation of impulsivity.

5-HT1A

Although PET studies are very infrequent, Parsey & Oquendo (2002) and Soloff & Price (2010) have used in vivo molecular imaging in association with personality. Yet their observations vary slightly. Parsey and Oquendo (2002) studied serotonin and lifetime aggression. They looked at 5-HT1A and found there was lower BP in aggressive individuals. The results presented in this thesis do not agree entirely. Although we did not study aggression per se, we looked at KSP Verbal Aggression as a measure of controlling ones impulses when speaking, we found a high BP in the temporal cortex and orbital

frontal cortex, while Parsey and Oquendo (2002) found lower BP in association with higher lifetime aggression scores. It is possible that such discrepancy could be due to the lower number of subjects (twenty-five subjects total) participating in their study, the personality inventory they used or the difference between two aggression types examined: lifetime aggression versus impulsive aggression. However, when looking at Mann's (2009) review, eight years after Parsey and Oquendo's PET analysis, Mann did not include downregulation 5-HT1A gene, as Parsey and Oquendo (2002) suggested, rather upregulation, as a "candidate endophenotype," for suicidality. Mann believes aggressive traits are genetically correlated to suicide, as well as co-segregation between impulsivity/aggression and suicide. Furthermore, due to the consistency we saw in our results we can not make the same conclusions from the results that Parsey and Oquendo (2002) did for aggression, or apply them to impulsivity.

Mann (2009) believed candidate endophenotypes for suicidal behaviour characterized by aggression and impulsivity would be high BP in 5-HT1A, 5-HT2A, and low BP serotonin transporter. Our results of high 5-HT1A BP with high impulsivity supported Mann's findings although his regions were slightly different maybe due to his more elaborate specificity in defining regions. He reported high 5-HT1A BP in the dorsolateral prefrontal cortex and in the brain stem dorsal raphe nucleus in the post mortem brains of suicide victim, while our results reflected high BP in the temporal cortex and orbital frontal cortex, in addition to amygdala and hippocampus, we had no significant BP in the dorsal raphe nucleus. This thesis does support Mann's (2009) candidate endophenotypes, although we also believe serotonin is region specific and studies should be mindful of region specific BP, especially for serotonin transporter.
We see little variation in the binding potential of [^{11}C]WAY to 5-HT1A through out the brain, yet we find variance in BP significance between regions. For example, there is no significance in the dorsal raphe nucleus, which has the highest density of 5HT1A receptors in the brain. This first came as a surprise, but in fact it further supported the specific region by region distribution of 5HT1A dependent influence on impulsivity. Impulsivity is not regulated by the whole brain, rather it is more dependent on some regions than others , and thus is the argument for measuring serotonin metabolite, which is merely the accumulation of serotonin within the entire system. Yet with molecular imaging such as PET, the exact identification and quantification of biomarker by region can be identified. Therefore, we conclude that our results are more valid and question the ability of the previous research to clearly capture the complexity of serotonin.

5-HTT
In concordance with past findings there appears to be a definite correlation between the serotonergic regulation and impulsivity. Our finding with serotonin transporter (5-HTT) agree with those found in Anguelova and Benkelfats (2003) META- analysis, which showed a positive correlation between the polymorphism 5-HTTLPR and suicide, aggression, depression and impulsivity. Furthermore, Carver and Johnson (2010) who studied 5-HTTLPR in normal individuals, like in the present study, found an association between the polymorphism and impulse control. We thus agree with the significance of 5-HTT regulation of impulsivity, but how exactly it functions in the brain is discussed in more detail below.

In concordance with Tiihonon and Kuikka (1997) SPECT study investigating 5-HTT in violent offenders, we replicated the lower BP in the midbrain. Our results showed lower BP in the putamen, caudatus, thalamus, and insula. Although we are hesitant to agree with Tiihonen and Kuikka's overall conclusion that lower BP is associated with impulsive aggression, which they found in suicide behaviour and impulsive violence. Furthermore, we did not study such extremes as suicide and violence, but rather looked at normal healthy subjects and found not only low BP in impulsive individuals but also high BP in the cortical areas, including frontal cortex and neocortex. We believe 5-HTT is region specific and although we are supportive of the multiple studies that have associated low BP with impulsivity (Mann 2009; Tiihonon & Kuikka, 1997) We do not feel comfortable drawing the same vast conclusion for all regions about serotonin transporter.

Limitations

Due to the exploratory measures of this experiment one can be critical about the amount of significant figures found. A Bonferroni correction would be a good solution for further research methods because there were so many correlations run. However, due to fact that this was an exploratory study this use of liberal p-values is in my opinion excusable. Furthermore due to the excessiveness of significant values in specific personality facets such as Verbal Aggression and Impulsivity in KSP for the WAY group and Harm Avoidance in TCI it provides further validity to the significant values found, and denies just by chance findings. When looking in more detail at WAY, all significant values are positive, which is important to show consistency especially because of its consistency as a receptor through out the brain. Yet with further testing it would be best advised to use a Bonferroni correction and act more conservatively about such significant values.

NEO-PI-R personality inventory was not correlated to any of the significant figures in BP. We believe that having no significance in NEO-PI-R personality inventory is not a surprising outcome because previous research of NEO-PI-R scales shows no, to little significance in serotonin as well as dopamine. Although Soloff and Price (2010) found significant correlation in vulnerability of NEO-PI-R and 5-HT2A BP, they found none for impulsivity. Other research groups at PET Center Karolinska Institute have found little or no correlation with NEO-PI-R (Borg, 2007; Sigray, 2010).

Future Endeavours

The present study-is a novel prototype. For such reasons its exploratory nature can be criticized but also paramount. In vivo molecular imaging research, furthermore on healthy subjects, is extremely scarce due to the resource available and expense. Yet with in vivo PET analyses neuroscience, personality psychology, pharmacology, and so much more become fields of endless discovery.

Future investigations should look into gender differences as well. Furthermore, it is believed there are such gender differences in personality; including behaviors such as impulsivity, aggression, anorexia, bulimia, and obesity, and attempted/ executed suicide. Research is looking for the answers within serotonin biomarkers (Soloff & Price, 2010;

Parsey, & Oquendo, 2002). 5-HT1A and 5-HTT should be investigated in each gender in association to different aspects of impulsivity.

Future research should compare cognitive measures of impulsivity with those found in the personality inventory. Self- tests can be criticized for falsification, and for this purpose we provided many measures of impulsivity. It would be interesting to test variation within the significance found in personality inventory and BP and cognitive tests.

Furthermore, serotonin transporter polymorphism, 5-HTTLPR, plays a putative role in bipolar disorder, anxiety, and suicide (Malloy & Neves, 2011) and acts as a biomarker for low impulse control in healthy individuals (Carver and Johnson, 2010). Thus it would be extremely relevant and interesting to see the association between 5-HTT BP and the genetic biomarker and polymorphism, 5-HTTLPR. Also, knockout mice, with no 5htr2b have been shown to be more impulsive. Future research could use in vivo PET analyses with the biomarker 5-HT2b and subsequent radioligand to see if there is the same association seen in the PET studies as in the knockout mice and group of highly impulsive Finns (Bevilacqua & Doly, 2010).

We believe that the most basic importance for this research and future projects is the putative biological bases of who we are and how we act and react as individuals, known as our personality psychology. Such research bridges the relationship between psychology and biology. Impulsivity is a characteristic of many psychiatric disorders as well as alcohol and drug abuse and if we can find ways to identify these individuals with biomarkers, genetically but even better through the use of PET, rather than merely assessing their phenotype we improve our method for classifying, treating and medicating. Research on neurotransmitters for some, may seem like a waste of time like picking through a couple hundred hay stacks for a needle. Why should the public care about something that can not even be seen by the naked eye, why not use the same method of counseling and self report, that has worked for decades in psychology and medicine? Why go to all this work to know what exactly is going on the brain? Well we are all humans and false diagnostics happen more than often within psychology and the medical field, if we can identify “candidate endophenotypes” (Mann, 2009) we can lower the risk of individuals taking there problems into their own hands, for example suicide and self medicating, we don’t have to rely on self reports which are not always honest, we can evaluate criminal minds and find justification and most importantly a solution. Clinical work will never be replaced but with in vivo Pet research we can revolutionize our method for treating psychiatric disorders, medical syndromes, criminal behavior, and we take a huge step forward in unraveling the mystery of who we as individuals.

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