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Impulsivity and its biomarkers: a focus on the tryptophan pathways and the moderating effects of physical exercise

Doctoral thesis approved for the degree

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by

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Affidavits following §7 section 2 No. 4 and 5 of the doctoral regulations from the German Sport University Cologne, February 20th 2013:

Hereby I declare:

The work presented in this thesis is the original work of the author except where acknowledged in the text. This material has not been submitted either in whole or in part for a degree at this or any other institution. Those parts or single sentences, which have been taken verbatim from other sources, are identified as citations.

I further declare that I complied with the actual “guidelines of qualified scientific work” of the German Sport University Cologne.

Date, Signature

Ordo ab chaos

Order out of chaos

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Special thought is given to my grandfather that left too early but continues to be a source of inspiration and an example.

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Acronyms

5-HIAA: 5-hydroxyindoleacetic acid

5-HT: serotonin

5-HTP: 5-hydroxytryptophan

5-HTT: Serotonin Transporter

5-HTTLPR: Serotonin Transporter-Linked Polymorphic Region

AA: amino acid

a: adenine

ANOVA: analysis of variance

ANCOVA: analysis of covariance

BMI: Body Mass Index

BBB: Blood Brain Barrier

CFI: Comparative Fit Index

CMS: Common Mode Sense

CNS: Central Nervous System

CSF: cerebrospinal fluid

DLR: Drive Right Leg

DNA: deoxyribonucleic acid

ELISA: Enzyme-Linked ImmunoSorbent Assay

g: guanine

GFI: Goodness of Fit Index

HIIT: High-Intensity Interval Training

HR: heart rate

iAPF: individual Alpha Peak Frequency

IDO: indoleamine 2,3-dioxygenase

IFN-γ: interferon-gamma

IL: interleukin

ISTD: internal standards

KAT: kynurenine aminotransferase

KMO: kynurenine 3-monooxygenase

KYN: kynurenine

KYNA: kynurenic acid

L: long *(when talking about alleles)*

mRNA: messenger ribonucleic acid

MAO-A: monoamine oxidase A

PCR: Polymerase Chain Reaction

QA: quinolinic acid

RMSEA: Root Mean Square Error of Approximation

S: short *(when talking about alleles)*

S100B: calcium-binding protein B

STin2: Serotonin Transporter intronic region 2

TDO: tryptophan 2,3-dioxygenase

TRP: tryptophan

UPPS: Urgency, Premeditation, Perseverance, and Sensation seeking

VNTR: Variable Number Tandem Repeats

Abstract

Impulsivity represents a complex multidimensional psychological construct that is difficult to accurately conceptualise, affects many facets of daily life, and is accepted as a transdiagnostic risk factor for a broad range of psychopathologies. Considering the robust ties existing between emotion-related impulsivity, psychopathologies, and problematic behaviours (e.g., pathological gambling, drug use, aggression, and suicide), a growing body of research has focused on the distinction between emotion-related and non-emotion-related impulsivity.

Multiple physiological, genetic, and imaging studies suggest a neurobiological basis concordant to the psychological construct of impulsivity. Although several biological markers of impulsivity (e.g., systemic levels of serotonin, monoaminergic polymorphisms, markers of cortical activity, peripheral inflammation, and circulating levels of tryptophan) have been found, the neurobiology of this construct is still not fully understood. Moreover, few attempts have been made to combine comprehensive approaches that include psychological and biological markers. Therefore, this PhD thesis considers emotion-related and non-emotion-related impulsivity from psychological, genetic, physiological, and electrophysiological perspectives in order to better understand the underlying mechanisms of these impulsivity dimensions.

Once the predictors and mediators of impulsivity have been understood, measures to reduce impulsivity in individuals can be developed and evaluated. Physical exercise has been shown to modulate several neurobiological markers of impulsivity including peripheral inflammation and the tryptophan pathways. It is, therefore, reasonable to assume that physical exercise may have an effect on impulsivity itself. This hypothesis has been confirmed in seminal research on attention-deficit/hyperactivity disorder showing that physical exercise training significantly reduces the impulsivity levels of participants. Thus, this thesis also examines the effect of exercise on physiological markers of impulsivity while differentiating between its emotion-related and non-emotion-related forms.

Three articles were included in the core of this thesis and one additional article was used for introductory purposes. The first article presents the validation of the German version of the Three-Factor Impulsivity index examining emotion-related and non-emotion-related impulsivity as well as seminal links between physical exercise and impulsivity (see Article 2). The second article used an endophenotypic approach to describe impulsivity based on the polymorphisms of genes involved in serotonin neurotransmission and markers of cortical activity (see Article 3). Finally, in the third article,

the effects of an exercise intervention study on psychological and physiological markers of impulsivity in highly emotionally impulsive individuals were investigated (see Article 4).

The results of this thesis show that emotion-related and non-emotion-related impulsivity are likely to rely on slightly different biological mechanisms. Most of the biological markers of impulsivity tested in this thesis were, actually, related to emotion-related impulsivity (i.e., serotonin transporter-linked polymorphic region, monoamine oxidase A, prefrontal alpha asymmetry, individual alpha peak frequency, tryptophan levels, and kynurenic acid/kynurenine). Furthermore, it appears that the tendencies to engage in regrettable behaviours in response to emotions might rely more on the assessed serotonergic markers while cognitive and motivational responses to emotions might be more related to changes in the kynurenine pathway. Finally, the results of this thesis suggest that exercise is a very promising technique to decrease the levels of physiological impulsivity markers. High-intensity interval training in particular shows the most favourable results, decreasing a broad range of impulsivity biomarkers and all forms of impulsivity. These results are very encouraging and motivate the development of further studies to transfer this research approach to clinical samples.

Zusammenfassung

Impulsivität ist ein komplexes, multidimensionales psychologisches Konstrukt, welches schwer zu konzeptualisieren ist, viele Facetten des täglichen Lebens beeinflusst und als transdiagnostischer Risikofaktor für ein breites Spektrum von Psychopathologien gilt. In Anbetracht der robusten Zusammenhänge zwischen emotionsbezogener Impulsivität, psychopathologische Befunde und Verhaltensweisen (z. B. pathologisches Glücksspiel, Drogenkonsum, Aggression und Suizid) hat sich ein wachsender Teil der Forschung auf die Differenzierung emotionsbezogener und nicht-emotionsbezogener Impulsivität konzentriert.

Mehrere physiologische, genetische und bildgebende Studien deuten auf eine neurobiologische Grundlage hin, die mit dem psychologischen Konstrukt der Impulsivität übereinstimmt. Obwohl mehrere biologische Marker für Impulsivität (z. B. systemische Serotoninspiegel, monoaminerge Polymorphismen, Marker für kortikale Aktivität, periphere Entzündungen und zirkulierende Tryptophankonzentrationen) gefunden wurden, ist die Neurobiologie des Konstrukts noch immer nicht vollständig verstanden. Darüber hinaus wurden bisher nur wenige Versuche unternommen, umfassende Ansätze zu kombinieren, die psychologische und biologische Marker umfassen. Daher wird in dieser Dissertation die emotionsbezogene und die nicht-emotionsbezogene Impulsivität aus psychologischer, genetischer, physiologischer und elektrophysiologischer Sicht betrachtet, um die zugrunde liegenden Mechanismen der Dimensionen besser zu verstehen.

Sobald die Prädiktoren und Mediatoren von Impulsivität bekannt sind, können Maßnahmen zur Verringerung der Impulsivität bei Einzelpersonen entwickelt und bewertet werden. Es hat sich gezeigt, dass körperliche Betätigung mehrere neurobiologische Marker von Impulsivität moduliert, darunter die periphere Entzündung und Verstoffwechselung von Tryptophan. Daher liegt die Vermutung nahe, dass sich körperliche Betätigung auch auf Impulsivität selbst auswirken kann. Diese Hypothese wurde in bahnbrechenden Forschungsarbeiten zur Aufmerksamkeitsdefizit-/Hyperaktivitätsstörung bestätigt. Diese zeigten, dass körperliches Training die Impulsivität der Teilnehmer signifikant reduziert. Demzufolge wird in dieser Arbeit auch die Wirkung von körperlicher Betätigung auf physiologische Marker der Impulsivität untersucht. Hierbei wird zwischen den emotionsbezogenen und nicht-emotionsbezogenen Formen von Impulsivität unterschieden.

Drei Veröffentlichungen wurden in den Kern dieser Doktorarbeit aufgenommen. Eine zusätzliche Veröffentlichung wurde für einführende Zwecke verwendet. Die erste Veröffentlichung stellt die Validierung der deutschen Version des Drei-Faktoren-Impulsivitäts-Indexes vor. Der Index untersucht emotionsbedingte und nicht-emotionsbedingte Impulsivität, sowie zukunftsträchtige

Zusammenhänge zwischen körperlicher Bewegung und Impulsivität (siehe Artikel 2). In der zweiten Veröffentlichung wurde ein endophänotypischer Ansatz zur Beschreibung der Impulsivität verwendet, der auf den Polymorphismen von Genen, die an der Serotonin-Neurotransmission beteiligt sind, und auf Markern der kortikalen Aktivität beruht (siehe Artikel 3). Schließlich wurden in der dritten Veröffentlichung die Auswirkungen einer Trainingsinterventionsstudie auf psychologische und physiologische Marker der Impulsivität bei hoch emotional impulsiven Personen untersucht (siehe Artikel 4).

Die Ergebnisse dieser Arbeitlegen dar, dass emotionsbezogene und nicht-emotionsbezogene Impulsivität vermutlich auf leicht unterschiedlichen biologischen Mechanismen beruhen. Die meisten der in dieser Arbeit getesteten biologischen Marker für Impulsivität standen tatsächlich mit emotionsbezogener Impulsivität in Zusammenhang (d. h. Serotonintransporter-verknüpfte polymorphe Region, Monoaminoxidase A, präfrontale Alpha-Asymmetrie, individuelle Alpha-Peak-Frequenz, Tryptophanspiegel und Kynurensäure/Kynurenin). Darüber hinaus scheint es, dass die Tendenz zu später bereuenden Verhaltensweisen als Reaktion auf Emotionen eher von den erfassten serotonergen Markern abhängt, während kognitive und motivationale Reaktionen auf Emotionen eher mit Veränderungen in dem Kynurenin-Stoffwechsel zusammenhängen können. Schließlich deuten die Ergebnisse dieser Arbeit darauf hin, dass Sport eine vielversprechende Methode ist, um die Konzentration physiologischer Impulsivitätsmarker zu senken. Insbesondere hochintensives Intervalltraining zeigt die vielversprechendsten Ergebnisse, da es die Konzentration von einem breiten Spektrum von Impulsivitäts-Biomarkern und alle Formen von Impulsivität senkt. Diese Ergebnisse motivieren zur Entwicklung weiterer Studien, um diesen Forschungsansatz auf klinische Populationen zu übertragen.

Publications included in this PhD thesis

The present work is a cumulative doctoral thesis that contains two published articles, one in press, and one currently submitted in a peer-reviewed journal. Of these four articles, one is used to support the introduction while the three others form the core of the thesis. All articles presented within this PhD thesis have been adapted in order to ensure uniformity in abbreviations, citation style, figures, tables, and languages (English - United Kingdom, proofread by Matthew Watson). Hence, the originally published articles may slightly differ from the chapters of this thesis. References were cited using the APA guidelines. Each article is presented with its references section. An additional section is presented at the end of this PhD thesis including all other references. Finally, I would like to clarify that when using the pronoun "I" throughout this thesis it is only to reflect the fact that I initiated the work conducted and is by no means an attempt to disregard the precious help of my colleagues and co-authors. Any help related to the realisation of this PhD thesis is mentioned in the section "Acknowledgements" (page 4-5).

Article 1: Javelle, F., Lampit, A., Bloch, W., Häussermann, P., Johnson, S., Zimmer, P., (2019) 'Effects of 5-hydroxytryptophan on distinct types of depression : a systematic review and meta-analysis', *Nutrition Reviews*, pp. 1–12. doi: 10.1093/nutrit/nuz039. (Impact Factor in 2019: 6.500)

Article 2: Javelle, F., Wiegand, M., Joormann, J., Timpano, K., Zimmer, P., Johnson, S., (2020) 'The German Three-Factor Impulsivity Index: Confirmatory factor analysis and ties to demographic and health-related variables', *Personality and Individual Differences*, 171(110470), pp. 1–12. doi: 10.1016/j.paid.2020.110470. (Impact Factor in 2020: 2.311)

Article 3: Javelle, F., Löw, A., Bloch, W., Hosang, T., Jacobsen, T., Johnson, S., Schenk, A., Zimmer, P., (no date) 'Unravelling the contribution of serotonergic polymorphisms, pre-frontal alpha asymmetry, and individual alpha peak frequency to the emotion-related impulsivity endophenotype', *Submitted*

Article 4: Javelle, F., Bloch, W., Knoop, A., Guillemin, G., Zimmer, P., (2021) 'Toward a neuroprotective shift: eight weeks of high-intensity interval training reduces the neurotoxic kynurenine activity concurrently to impulsivity in emotionally impulsive humans – A randomised controlled trial', *Brain, Behavior, and Immunity [in press].*
doi: 10.1016/j.bbi.2021.04.020. (Impact Factor in 2021: 6.633)

In the following sections of this thesis, the articles mentioned above will be referred to using the terms "Article 1", "Article 2", "Article 3", and "Article 4" respectively, instead of using the citations.

Publicity and awards related to this thesis

- **June 15th 2020:** TV report aired on WDR Lokalzeit (realized in September 2019) about my exercise intervention study, *NoSTRESS* (partly presented in Articles 3 and 4).
- **December 2018:** Awarded the "Hochschulinternen Forschungsförderung" grant for research funding (€4,780), an annual grant from the German Sport University.
- **February 2018**: Awarded the "Studienstiftung des deutschen Volkes"scholarship grant from the German Academic Scholarship Foundation, an organisation that awards scholarships to outstanding students, irrespective of their political, ideological, or religious convictions and affiliation (€50,750).

Preface

One says that it is at the end that we think back to the beginning... Four years ago, in April 2017, I was arriving in Germany, ready to embark on this PhD journey. I was not thinking that I was about to enter one of the most challenging periods of my life. Yet, today, I can say that it was so full of learning experiences and incredible people that I would not be willing to see it differently.

Impulsivity, tryptophan, and me, it is a long story (when considering my time in research) that began, while I was studying in New Zealand, on the 10th of July 2015. That was my 23rd birthday. After a videoconference with Prof. Dr. Sheri Johnson and Jordan Tharp from the University of California, Berkeley, I got the great news that we could collaborate and build a study based on tryptophan supplementation to reduce impulsive traits in humans. Long story short, I had the chance to go to Berkeley, but the ethical committee did not allow us to implement the tryptophan supplementation in our study. Nonetheless, the work I did and the people I met over there have greatly developed my interest in research.

Still looking to pursue this aim, when I planned my PhD project, I designed a study using physical exercise and 5-hydroxytryptophan supplementation to treat major depressive disorder. Unfortunately, once again the project could not be realised due to ethical and financial challenges. Considering these drawbacks, I then began to reflect with more interest on the interplay between biology (my background) and psychology. From my perspective, these two fields were measuring the same things using different tools. But considering the limits of each field and of our technology, it was also clear that one field should not be considered without the other. Consequently, the idea of considering the psychobiological foundations of impulsivity, a trait strongly tied to psychopathologies and problematic behaviours, arose.

I got very lucky to integrate a team where the leader, Prof. Dr. Dr. Zimmer, trusted me and introduced me to different experts from whom I have learnt and sharpened my skills. Additionally, through the "foreigners' gang" at the German Sport University, I met incredible scientific researchers that I am very pound to call my friends. Interacting with all these persons helped me to fulfil the ground rule I set myself when I began my PhD, which was to be able to run all tests and analyses autonomously. I have learnt multiple techniques from various disciplines. From lab work (e.g., blood draw, blood analysis, ELISA test, genotyping), to advanced statistical analyses (e.g., meta-analysis, confirmatory factor analysis, mixed models analysis), from electroencephalography and electrocardiography record/analyses to cardiopulmonary exercise testing and physical exercise training, it has been a very

complete and extensive learning period. In the end, what I have earned during this PhD journey has to me more value than a degree: I have earned my scientific independence.

Now, follow me into the scientific journey of that PhD period, and let me unravel the psychobiological secrets of impulsivity for you.

1. Introduction

Impulsivity represents a complex multidimensional construct that is difficult to accurately conceptualise given the heterogeneity of its manifestations and measures. It can be defined as acting on a moment to moment basis without precognition or prior consideration of adverse repercussions (Whiteside & Lynam, 2001). The psychological trait impulsivity is recognised to affect many facets of daily life and is accepted as a transdiagnostic risk factor for a broad range of psychopathologies (S. L. Johnson, Tharp, Peckham, Carver, & Haase, 2017) such as personality disorder (Mulder, Joyce, Sullivan, Bulik, & Carter, 1999), aggression (Corruble, Damy, & Guelfi, 1999), attention-deficit/hyperactivity disorder (Guerrero et al., 2019), bipolar disorder (Swann, Anderson, Dougherty, & Moeller, 2001), substance abuse disorder (Perry & Carroll, 2008), addiction (Whiteside & Lynam, 2003), depression (Carver, Johnson, & Joormann, 2008), and suicide (Corruble et al., 1999).

To date, the psychological dimensions of impulsivity are very often only evaluated using self-report questionnaires, interviews, and behavioural tasks (e.g., delay discounting task). Nevertheless, various genetic and imaging studies suggest a concordant neurobiological basis (Canli & Lesch, 2007; Carver, Johnson, Joormann, Kim, & Nam, 2011; Hariri et al., 2002; B. T. Lee & Ham, 2008). Although several biological markers have been detected, the neurobiology of this multidimensional construct is still unclear. In line with the endophenotype concept (Gottesman & Shields, 1973; John & Lewis, 1966), it is not only important to properly define biomarkers of impulsivity, but also necessary to integrate them with the psychological dimensions of impulsivity to generate a better understanding of this construct. However, it is rare to find such instances of combined approaches. Promoting a psycho-physiological understanding of impulsivity in healthy and clinical conditions is of major importance to prevent and properly treat subsequent impulsivity-related disorders. Indeed, a very large majority of pharmacological treatments that are administered are based solely on psychological symptoms, even though the prescribed medication is operating on a physiological level. This approach, recognised as functional in many cases, can also lead to misdiagnosis and allocation to improper treatment (or no treatment) that can sometimes worsen the clinical condition (J. Johnson, Morris, & George, 2021). Therefore, this PhD thesis considers impulsivity not only from psychological but also from genetic, physiological, and electrophysiological perspectives. Drawing from the past twenty years of research in the field, this work aimed to point out the neurobiological sources of the impulsivity dimension most strongly associated with psychopathologies, and therefore the most clinically relevant, emotion-related impulsivity.

Knowing the biological causes of impulsivity is interesting, but what if we could modulate them at will? A simple therapeutic technique used to treat impulsivity-related psychopathologies might give us this opportunity: physical exercise. It has been demonstrated that physical exercise can modulate

several neurobiological markers of impulsivity including peripheral inflammation and tryptophan (TRP) pathways (Mathur, Pedersen, & Mathur Neha, 2008; Phillips & Fahimi, 2018). It is therefore reasonable to think that physical exercise may have an effect on impulsivity itself. This hypothesis has been confirmed in seminal research on attention-deficit/hyperactivity disorder showing that physical exercise can significantly reduce impulsivity levels in humans (Cerrillo-Urbina et al., 2015; Cho, Baek, & Baek, 2014). Thus, this thesis also considers the effect of physical exercise on physiological markers while evaluating psychological symptoms of impulsivity.

To achieve this aim, I have included three articles in the core of my thesis (see Figure 1) and one additional article that illustrate the introduction section *"2.2.3.2 Serotonin deficiency and 5-hydroxytryptophan supplementation"*. These articles consider emotion-related and non-emotion-related impulsivity from a psychological and biological perspective (see Figure 1). The first article presents the validation of the German Three-Factor Impulsivity index examining emotion-related and non-emotion-related impulsivity as well as seminal links between physical exercise and impulsivity.

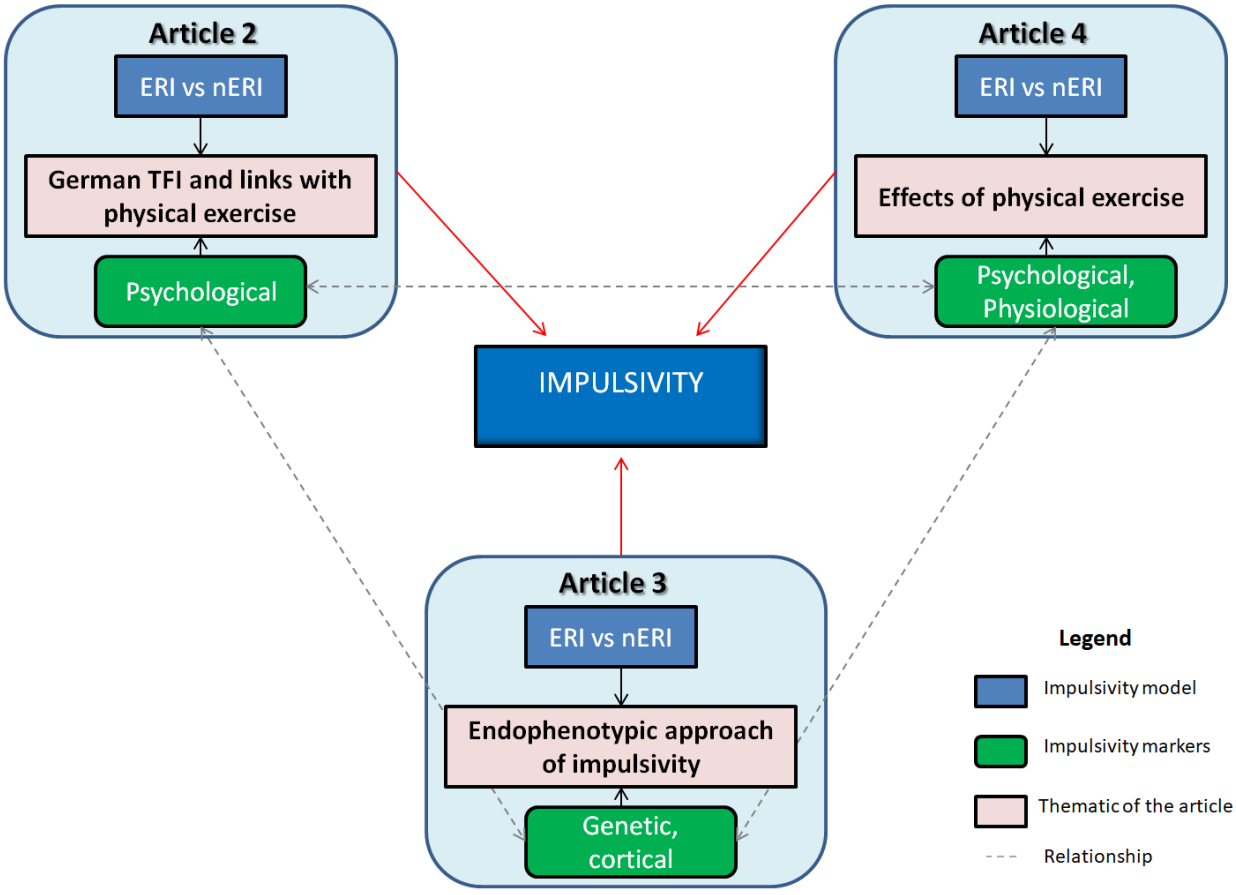

Figure 1: Overview of the objectives from the three articles included in the core of this PhD thesis. ERI: Emotion-Related Impulsivity; nERI: non-Emotion-Related Impulsivity; TFI: Three-Factor Impulsivity index.

Then, I introduce an endophenotypic approach of impulsivity based on the polymorphisms of genes involved in the serotonin (5-HT) neurotransmission. Finally, I demonstrate the effects of an exercise intervention on psychological and physiological markers of impulsivity in highly emotionally impulsive individuals.

2. Scientific Background

2.1 Impulsivity from a psychological perspective

2.1.1 Early models of impulsivity

One of the oldest and most influential conceptualizations of impulsivity was developed by Ernest Barratt (1965) who focused on defining and measuring impulsivity as orthogonal to anxiety and separable from extraversion, sensation seeking, risk-taking, and emotional factors (Barratt, 1965). Further developments of this scale (Patton, Stanford, & Barratt, 1995) captured three general factors of impulsiveness, including attentional (i.e., making quick decisions), motor (i.e., acting without thinking), and non-planning impulsiveness (i.e., lack of forethought). To date, the Barratt Impulsiveness Scale (1995), is the most widely used and cited questionnaire assessing impulsivity (Patton et al., 1995, on April 26th 2021, has 7545 citations). This preliminary view of impulsivity as a multi-dimensional construct had a significant impact on the research field. Nevertheless, even though the Barratt Impulsiveness Scale reflects specific expressions of impulsivity, it does not take into account the conditions that trigger impulsive behaviour (Carver & Johnson, 2018).

Another attempt to define this multi-faceted construct comes from Dickman (1990) who differentiates between functional and dysfunctional impulsivity and developed the Dickman Impulsivity Inventory (Dickman, 1990) to capture them. These two factors can simply be defined either as considering impulsivity as an asset (i.e., functional) or as a source of difficulty (i.e., dysfunctional). Dickman demonstrated that these two tendencies are not highly correlated and therefore bear different relations both to other personality traits and to how certain basic cognitive processes are executed (Dickman, 1990).

Even though these first models of impulsivity are crucial to the understanding of impulsivity, they only partially evaluate this trait. Indeed, these two approaches fail to consider stimuli that may strongly trigger impulses: emotions.

2.1.2 Emotion-related impulsivity

Although older impulsivity scales tend to focus on problems with planning, deliberation, and attention (Barratt, 1965; Dickman, 1990), more recent research documents the importance of impulsivity that occurs in response to states of high emotion, including both negative and positive

emotions (Carver et al., 2011; S. L. Johnson et al., 2017; Whiteside & Lynam, 2001; Zorrilla & Koob, 2019). The relevance of this distinction resides mainly in the more robust ties that exist between emotion-related impulsivity, psychopathologies, and problematic behaviours such as suicidality, physical assault, and aggression than with other forms of impulsivity (Carver & Johnson, 2018; Kulacaoglu & Kose, 2018).

Whiteside and Lynam (2001) were the first to gather a factor analytic model of impulsivity from measures of impulsivity already used in research including an emotion-related parameter. They called it the Urgency, Premeditation, Perseverance, and Sensation seeking (UPPS) impulsive behaviour scale. It distinguishes the tendency to act impulsively due to negative emotions (i.e., urgency) from other forms of impulsivity that are not influenced by emotions (i.e., sensation seeking, lack of planning, lack of perseverance).

This work was followed by the development of the Positive Urgency scale, which covers impulsive responses to positive emotions (Cyders & Smith, 2008). Multiple studies suggest that the Positive and Negative Urgency scales are distinct from other self-rated forms of impulsivity (Cyders & Smith, 2008; Cyders et al., 2007; S. L. Johnson, Tharp, Peckham, Sanchez, & Carver, 2016). Because the scales form one higher-order factor without regard to valence (Carver et al., 2011; Cyders & Smith, 2008), researchers have used the phrase emotion-related impulsivity (Carver et al., 2008, 2011; Zorrilla & Koob, 2019). A theoretical model of emotion-related impulsivity focuses on failures of top-down control over emotion as a possible mechanism driving emotion-related impulsivity (Carver et al., 2008). Within this model, researchers define emotion-related impulsivity as reflexive responding to strong emotions of either positive or negative valence (Carver et al., 2008). These reflexive responses are theorised to differ for different types of emotion. While reflexive responses to anger may encompass impulsive aggression; reflexive, unconstrained responses to sadness may involve passivity and loss of motivation (Carver et al., 2008).

In support of this theory, Carver et al. (2011) assembled a broad set of items assessing reflexive and unconstrained responses to positive and negative emotions. Exploratory and confirmatory factor analyses revealed three distinct factors. “Feelings Trigger Action” reflects rash and regrettable speech and behaviour in response to positive and negative emotions (mostly items from the Positive and Negative Urgency scales; Cyders & Smith, 2008). “Pervasive Influence of Feelings”, though, is more unique among impulsivity scales, in that it reflects the tendency for one’s (mostly negative) emotions to influence motivation, self-views, and cognitions about the world in an unconstrained manner. “Lack of Follow-Through” covers impulsive responding without regard to emotion, including being distracted easily and failing to complete tasks. Both emotion-related factors have been validated as related to early trauma, a polymorphism of the Serotonin Transporter (5-HTT) gene, internalizing disorders,

externalizing disorders, suicidality, and aggression (Auerbach, Stewart, & Johnson, 2017; Carver et al., 2011; S. L. Johnson et al., 2017).

Despite the increased use of this Three-Factor Impulsivity index, no German version is available. Although other scales assessing impulsivity already exist in German (e.g., UPPS) (Babayan et al., 2019), the Three-Factor Impulsivity index offers unique added value. It combines a broader range of emotion-related impulsivity phenomena, including reflexive responses to emotions and poor control over the motivational and cognitive influences of one's emotional state. Therefore, the Three-Factor Impulsivity index offers a more complete report on emotion-related impulsivity, and also a robust non-emotional impulsivity evaluation. Given that this PhD was to be realised in Germany, the development of a German version of the Three-Factor Impulsivity index appeared to be a necessary first step to evaluate impulsivity in participants.

2.2 Impulsivity from a biological perspective

So far, I have defined impulsivity from a psychological perspective. In the following sections, I will introduce biological markers that can be qualified as determinants of impulsivity levels in healthy and clinical conditions and that can be used to follow the development of impulsivity-related disorders. From genetic variability to brain activity and passing by circulating biological compounds, the underlying markers of impulsivity are numerous and complex (see Figure 2). Therefore, this PhD thesis targets the main biological processes associated with impulsivity (see Figure 2).

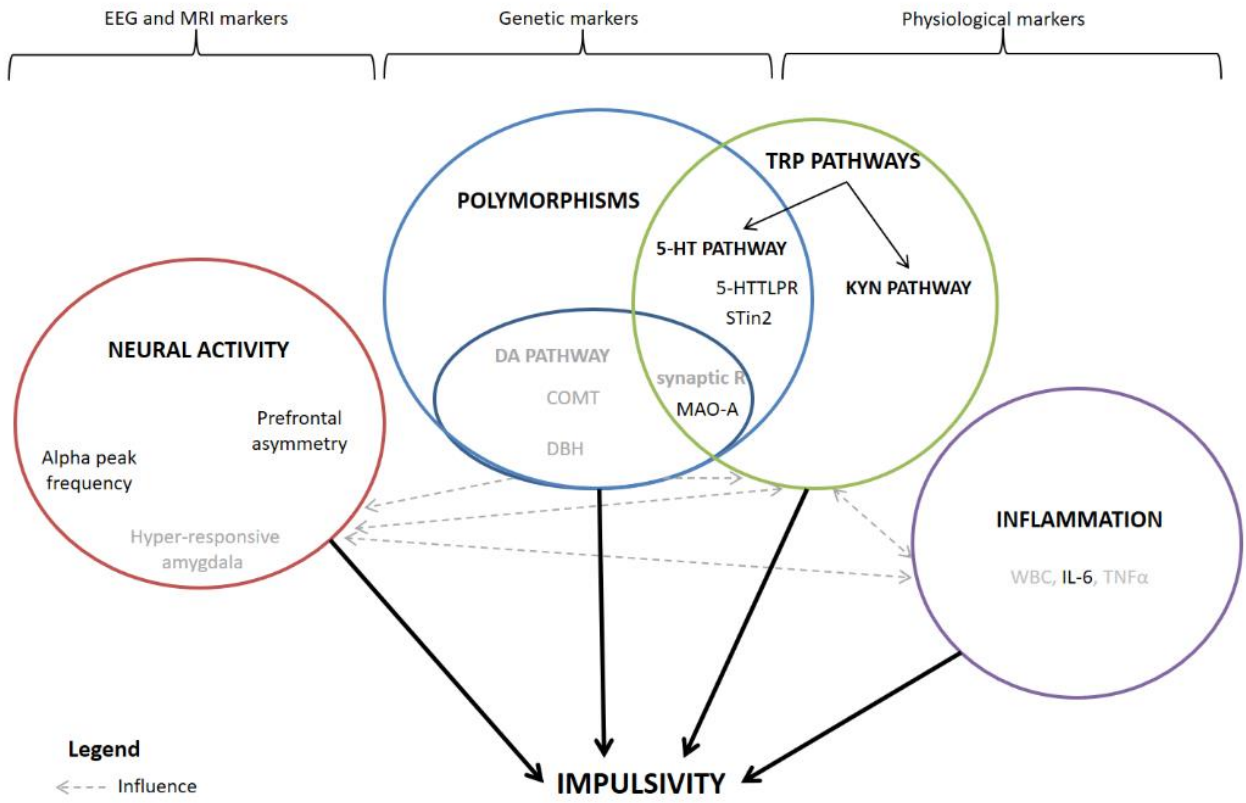

Figure 2: Main biomarkers of impulsivity. Markers not evaluated in this thesis are displayed in grey. DA: dopamine. COMT: catecholamine-O-methyltransferase. DBH: Dopamine Beta-Hydroxylase; 5-HT: serotonin; 5-HTTLPR: Serotonin Transporter-Linked Polymorphic Region; STin2: Serotonin Transporter intronic region 2; MAO-A: monoamine oxidase A; TRP: tryptophan; KYN: kynurenine; WBC: White Blood Cells; IL-6: interleukin 6; TNFα: Tumor Necrosis Factor alpha; synaptic R: synaptic receptors.

2.2.1 Polymorphisms involved in the serotonin neurotransmission

5-HT is an important neurotransmitter in the Central Nervous System (CNS) that is involved in the regulation of different brain functions and behaviours, particularly mood and emotions (Trickelbank & Daly, 2018). Two key regulators of this neurotransmission are 5-HTT, which removes 5-HT released into the synaptic cleft, and monoamine oxidase A (MAO-A), which catabolises monoamines with a strong affinity for 5-HT and catecholamines (Canli & Lesch, 2007; Trickelbank & Daly, 2018; Williams et al., 2009). The activity level differences in these monoamine genes result in phenotypic distinctions perceptible when noticing the existence and/or the development of some psychological traits (e.g., impulsivity)(Canli & Lesch, 2007; Williams et al., 2009).

The 5-HTT protein is encoded by a single gene, SLC6A4 (chromosome 17 – q11.1 – q12).

Transcriptional activity of the human SLC6A4 gene is modulated by several variations, including a repeating sequence called the Serotonin Transporter-Linked Polymorphic Region (5-HTTLPR). There is a short and a long version (S versus L) of 5-HTTLPR eliciting different expression levels of 5-HTT (Canli & Lesch, 2007; Trickelbank & Daly, 2018). Indeed, the short 5-HTTLPR variant produces significantly less 5-HTT messenger ribonucleic acid (mRNA) and protein than the long variant (Heils et al., 1996; Lesch et al., 1996) (see Figure 3 and Table 1). Fifteen years ago, a single nucleotide adenine (a) / guanine (g) polymorphism (rs25531) was found within the long allele indicating that the 5-HTTLPR is functionally triallelic (S/Lg/La)(Kraft, Slager, McGrath, & Hamilton, 2005). The Lg variant is associated with a reduced 5-HTT transcriptional efficacy comparable to the S allele (see Table 1) (Kraft et al., 2005). A wide range of studies has shown that several psychological traits including impulsivity (Carver et al., 2011), neuroticism (for a review see Canli & Lesch, 2007), anxiety (Lesch et al., 1996), and emotional instability (for a review see Canli & Lesch, 2007) might occur more frequently in people carrying the low 5-HTTLPR activity phenotype (S and Lg variants).

Another important variation that modulates the activity of the SLC6A4 gene is the Serotonin Transporter intronic region 2 (STin2) Variable Number Tandem Repeats ([VNTR], rs57098334) (for a review see Iurescia et al., 2017). STin2 has four known alleles consisting of 12, 10, 9, and 7 repeats, with 12 and 10 being the most frequently occurring (Lesch et al., 1994) (see Figure 3). The functional influence of the 12 and 10 VNTR was tested in a transgenic embryonic mouse model and the longest sequence was shown to act as a stronger transcriptional inducer than the shorter sequence (see Table1)(Niesler et al., 2010). Oades et al., (2008), in a large-scale study (n=1180), found this polymorphism to be associated with cognitive impulsivity. Other studies have found the shortest repetitive sequences to be associated with elevated anxiety scores (Evans et al., 1997), major depressive disorders (Ogilvie et al., 1996), the early development of bipolar disorders (Bellivier et al., 2002), and suicide attempts (De Lara et al., 2006) to a greater extent than the longest VNTR (12 repeats).

The genetic variability of the MAO-A gene is as frequent as that of the SLC6A4 gene. Indeed, the VNTR polymorphism of the MAO-A gene on the chromosome X (p11.23) has 5 known alleles (2, 3, 3.5, 4, and 5) that produce low and high transcriptional activity MAO-A phenotypes (see Table 1)(Y. Y. Huang et al., 2004; Sabol, Hu, & Hamer, 1998). The low transcriptional activity alleles elicit lower expression of MAO-A and therefore less effective degradation of the 5-HT, while the opposite is true for the high transcriptional activity allele (Sabol et al., 1998)(see Figure 3). The scientific community has investigated the relationship between the MAO-A gene and psychological disorders for decades.

Table 1

Phenotype categorisation based on the transcriptional activity levels of genes. The phenotype categorisation is based on the following references: Canli & Lesch, 2007; Iurescia et al., 2017; Kraft et al., 2005; Niesler et al., 2010; Williams et al., 2009.

Polymorphic region	**Low activity**	**Moderate activity**	**High activity**
	Alleles	*Alleles*	*Alleles*
5-HTTLPR	SS – SLg	SLa - LaLg	LaLa
STin2 - VNTR	10/10 – 9/10	10/12 -12/9	12/12
MAO-A VNTR	4/3 – 3/3 – 5 - 3	-	4/4 – 3.5/4 – 4 – 3.5 – 3.5/3.5

S: short; L: long; a: adenine; g: guanine; VNTR: Variable Number Tandem Repeats; Serotonin Transporter-Linked Polymorphic Region; MAO-A: monoamine oxidase A; STin2: Serotonin Transporter intronic region 2.

Links with antisocial behaviour (Williams et al., 2009), emotional instability (Rodríguez-Ramos, Moriana, García-Torres, & Ruiz-Rubio, 2019), impulsivity (Brunner, Nelen, Breakefield, Ropers, & Van Oost, 1993), bipolar disorder (Furlong et al., 1999) and violent aggression (Stetler et al., 2014) have been found.

Although it would be logical to relate the transcriptional activity levels of these genes to monoamine rates within neurons and synapses, research suggests that the relationship between serotonergic polymorphisms and monoamine levels is more complex. In fact, serotonergic gene polymorphisms are more likely to relate to the activity of certain brain regions potentially influenced by circulating monoamine levels during foetal life. Indeed, several studies have shown that carriers of the low transcriptional activity of 5-HTTLPR and MAO-A have hyper-responsive amygdalae and anterior cingulate cortices during the display of negative emotional stimuli (Hariri et al., 2002; B. T. Lee & Ham, 2008; Meyer-Lindenberg et al., 2006; Pezawas et al., 2005). This primed response may predispose an individual toward stress-related psychopathology (Hariri et al., 2002; B. T. Lee & Ham, 2008; Meyer-Lindenberg et al., 2006; Pezawas et al., 2005). Researchers working on 5-HTTLPR polymorphisms have explained this deregulation of the amygdala by demonstrating a decreased functional connectivity between the amygdala and anterior cingulate cortex in the low compared with the high transcriptional activity phenotype (Pezawas et al., 2005). This decreased functional connectivity might come from differences in foetal neurodevelopment. Indeed, a more recent study assessing placenta MAO-A and 5-HTT proteins found that low transcriptional activity 5-HTTLPR and MAO-A phenotypes have, respectively, less 5-HTT and MAO-A mRNA levels (Zhang, Smith, Liu, & Holden, 2010).

The multidimensional nature of the impulsivity construct, along with the variety of definitions and

measurements it engenders, hinders the attempt to develop a comprehensive understanding of its neurogenetic basis. Therefore, it appears to be important to evaluate genetic markers of serotonergic neurotransmission altogether while differentiating between clinically relevant parts of impulsivity. Nonetheless, identifying intervening variables that are sensitive to the effects of genetic variation (endophenotype approach) can provide a higher level of understanding of the impulsivity construct.

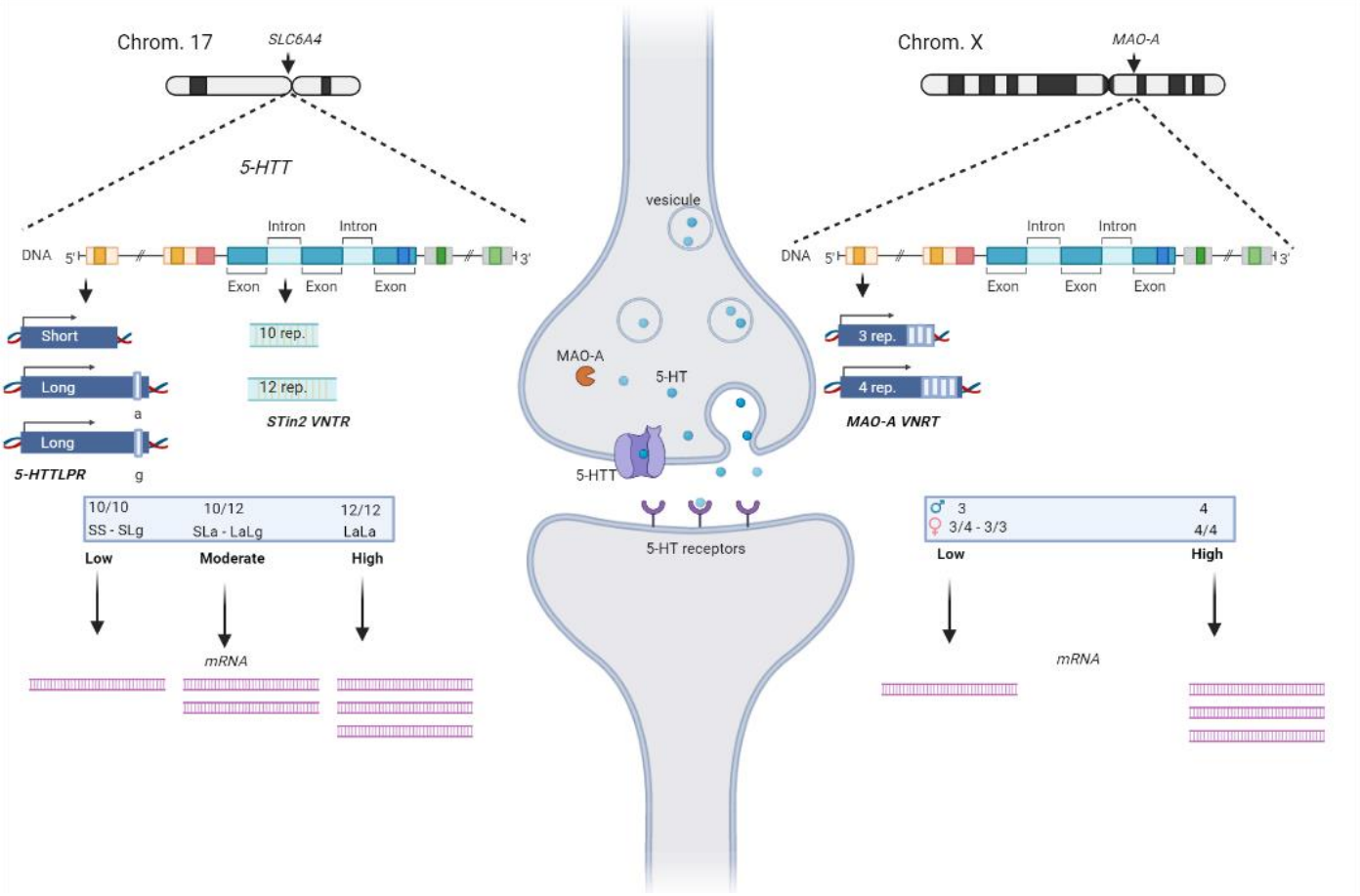

Figure 3: Allelic variation for Serotonin Transporter-Linked Polymorphic Region (5-HTTLPR), Serotonin Transporter intronic region 2 (STin2) and monoamine oxidase A (MAO-A) leading to different transcriptional activity phenotypes. Chrom.: Chromosome; 5-HTT: Serotonin Transporter; 5-HT: serotonin; rep.: repeats; VNTR: Variable Number Tandem Repeats. This figure has been created using BioRender.com

2.2.2 Cortical activity

Cortical activity is a partially genetically modulated parameter that is widely assessed in order to characterise psychological traits and is sometimes associated with polymorphism analyses (Papousek et al., 2013). High levels of emotional instability have often been associated with lateralisation of frontal alpha activity (Gable, Mechin, Hicks, & Adams, 2015; Harmon-Jones, Gable, & Peterson, 2010;

Muhlert & Lawrence, 2015; Neal & Gable, 2017; Papousek et al., 2013). Indeed, for much of the past century, research has demonstrated that the left and right-frontal cortical regions are asymmetrically related to approach, avoidance, motivational and emotional tendencies. Specifically, the left-frontal cortex is associated with emotional processes related to approach, whereas the right-frontal cortex is associated with emotional processes related to withdrawal (Goldstein, 1939; Rosadini & Rossi, 1967). Resting alpha asymmetrical activity with a greater right frontal activity has more recently been associated with impulsivity in various studies (Gable et al., 2015; Harmon-Jones et al., 2010; Neal & Gable, 2017).

Following on from the previous section, prefrontal asymmetry has also been found to exist in the low transcriptional activity 5-HTTLPR phenotype (Papousek et al., 2013) and to be linked to amygdala activity (Davidson, 2000, 2002; Jackson, Malmstadt, Larson, & Davidson, 2000; Ochsner, Bunge, Gross, & Gabrieli, 2002). In his reviews, Davidson has suggested that regions of the left prefrontal cortex might play an important role in inhibiting the amygdala (Davidson, 2000, 2002). Another functional magnetic resonance imaging study (Ochsner et al., 2002) reported strong inverse relations between activation in the left ventrolateral prefrontal cortex and the amygdala when subjects were requested to voluntarily downregulate their negative affect. Research has shown that greater right prefrontal activity is associated with greater negative affect (Tomarken, Davidson, Wheeler, & Doss, 1992), lower positive affect (Tomarken et al., 1992), avoidance motivation (Gable, Neal, & Threadgill, 2018), behavioural inhibition (Sutton & Davidson, 1997), repressive defensiveness (Tomarken & Davidson, 1994), and reactivity to positive and negative emotion elicitors (Tomarken, Davidson, & Henriques, 1990; Wheeler, Davidson, & Tomarken, 1993) in adults.

Furthermore, other cortical activity characteristics, such as individual Alpha Peak Frequency (iAPF), are highly heritable and thus appear to be under substantial genetic control (Anokhin, Müller, Lindenberger, Heath, & Myers, 2006; Anokhin et al., 2001; Smit, Wright, Hansell, Geffen, & Martin, 2005). Specifically, iAPF show high stability over test-retest intervals in healthy and clinical conditions (Gasser, Bächer, & Steinberg, 1985; Salinsky, Oken, & Morehead, 1991). Given the high stability of inter-individual differences in iAPF, it is not surprising that it is considered to be a valuable marker for monitoring differences in psychological traits such as impulsivity (Grandy et al., 2013).

2.2.3 The tryptophan pathways

TRP is an essential amino acid (AA), meaning it is derived from dietary proteins rather than being synthesised by the human body. Once ingested, 90% of the TRP is transformed to kynurenine (KYN) while the rest is allocated to the 5-HT pathway and protein synthesis. In the following sections, I will

first discuss the 5-HT pathway and its links to impulsivity. I will then describe the KYN pathway and its potential involvement in the underlying mechanisms of the impulsivity construct.

2.2.3.1 The serotonin pathway

Several studies suggest an association between impulsivity and low serotonergic function in healthy or at-risk samples in animal (Dalley, Mar, Economidou, & Robbins, 2008; Evenden, 1999; Fairbanks, Melega, Jorgensen, Kaplan, & McGuire, 2001) and human models (Brown et al., 1982; Cherek & Lane, 1999; Murphy, Smith, Cowen, Robbins, & Sahakian, 2002; Nelson, 2005; Walderhaug, Nordvik, & Landrø, 2002). For example, previous findings have shown that forebrain 5-HT depletion is related to higher impulsivity levels in rodents (Dalley et al., 2008). Lower concentrations of 5-hydroxyindoleacetic acid (5-HIAA), the main metabolite of 5-HT, have also been detected in the cerebrospinal fluid (CSF) of violent criminals (Nelson, 2005) and individuals committing impulsive suicides (Brown et al., 1982). Furthermore, serotonergic dysfunction has been suggested in several impulsivity-related disorders, especially depressive disorders (see Article 1). In contrast, elevated concentrations of 5-HT are associated with decreased impulsivity (Cherek & Lane, 1999)

Synthesis of 5-HT depends on the availability of the AA precursor, TRP. Circulating TRP can be found in two forms; free (10%) or bound to the protein albumin (90%) (Badawy, 2017; Mcmeeamy & Oncley, 1958). When bound to albumin, TRP can be considered as in storage. In contrast, only free TRP can be transformed into further metabolites, used in protein synthesis, or pass through the Blood Brain Barrier (BBB). Free TRP must cross the BBB to be transformed into 5-HT in the brain, a process that depends on large neutral AA transporters (Fernstrom, 2013; Fernstrom & Faller, 1978; Fernstrom & Wurtman, 1972). However, TRP competes with other large neutral AAs (i.e., tyrosine, valine, phenylalanine, leucine, and isoleucine) for the use of large neutral AA carriers (Fernstrom, 2013; Fernstrom & Faller, 1978; Fernstrom & Wurtman, 1972) such as that increase of large neutral AAs diminishes transporters availability for TRP (Fernstrom, 2013; Fernstrom & Faller, 1978; Fernstrom & Wurtman, 1972). Consequently, the ratio of TRP to other large neutral AAs in the peripheral blood is decisive for central 5-HT synthesis.

Once in the brain, TRP is mainly transformed to 5-HT in serotonergic neurons because they express higher rates of two limiting enzymes, TRP hydroxylase and aromatic amino acid decarboxylase (AAAD) (Bach-Mizrachi et al., 2006; Eaton et al., 1993). Serotonergic neurons originate in the raphe nuclei of the pons and upper medulla, from which they have both ascending and descending projections (Kaufman, Delorenzo, Choudhury, & Parsey, 2016). The ascending projections arise in the median and dorsal raphe nuclei and project to the forebrain, the hippocampus, the limbic system, the basal ganglia, and the hypothalamus (Kundu et al., 2012). Logically, descending projections arise in the

spinal cord and influence various somatosensory, motor, and autonomic functions (e.g, nociceptive inputs)(Bowker, Westlund, Sullivan, & Coulter, 1982). Furthermore, 14 synaptic receptors have been described for 5-HT, of which some have opposite actions (Köhler, Cierpinsky, Kronenberg, & Adli, 2016; Yohn, Gergues, & Samuels, 2017). Therefore, it is apparent that the serotonergic system is a very complex system that acts throughout the brain.

Yet, as is the case for 5-HT, the deficiency of TRP can result in higher impulsivity (Javelle, Li, Zimmer, & Johnson, 2019; Walderhaug et al., 2002) and altered attention (Schmitt et al., 2000) in healthy subjects. Although the efficacy of TRP supplementation for increasing brain 5-HT levels is limited by important barriers (e.g., a. transporters are required to go through the BBB, b. limiting enzymes, c. not the main stream of TRP transformation), a broad range of studies have used it to treat high level of impulsivity and impulsivity-related disorders (Lindseth, Helland, & Caspers, 2015; Shaw, Turner, & Del Mar, 2002; Turner, Loftis, & Blackwell, 2006; Young, 2013). The results were, however, mediocre because the 5-HT pathway is not the main direction of TRP transformation in healthy and clinical conditions. Additionally, a supraphysiologic concentration of TRP increases the activity of tryptophan 2,3-dioxygenase (TDO; 5 to 6 times in mice model), the first enzyme of the KYN pathway (S. A. Smith & Pogson, 1980). As a result, the transformation of TRP to KYN is elevated. Therefore, it is very likely that should TRP supplementation increase central 5-HT levels, it is only by a very small amount.

Subsequent studies addressed these issues by using 5-hydroxytryptophan (5-HTP), which is one metabolite further into the 5-HT pathway (the product of TRP once hydroxylated by TRP hydroxylase) (Hinz, Stein, & Uncini, 2012; Meyers, 2000). Supplementation with 5-HTP has major advantages over TRP when it comes to increasing 5-HT levels. (1) It can freely cross the BBB to be converted to 5-HT without feedback inhibition. (2) 5-HTP has only one limiting enzyme; AAAD (Hinz et al., 2012; Meyers, 2000). (3) Unlike TRP, 5-HTP cannot be metabolised within the KYN pathway (Schwarcz, Bruno, Muchowski, & Wu, 2012) (for more details see Article 1).

A very high 5-HT level is, however, not as healthy as one might believe and can lead to health issues and pathologies (Chouinard et al., 2017; Gressler, Hammond, & Painter, 2017). Neurotransmitters activity can be viewed as a web of parameters, reciprocally influencing each other. Accordingly, the acute increase of one might also lead to the decrease of another (Hinz, Stein, & Uncini, 2011; Hinz et al., 2012). For example, a bilateral influence between 5-HT and dopamine synthesis has been widely acknowledged (Hinz, Stein, and Uncini 2012; Meeusen et al. 1996; Strüder and Weicker 2001). Considering that dopamine is also a potential biomarker of impulsivity (not discussed in this PhD thesis), understanding the biological source of impulsivity-related symptoms in a patient before treating him/her appears to be of major importance in order to achieve a proper therapeutic effect

without worsening the pathology. In the next section, I will discuss the effect of increasing 5-HT synthesis via 5-HTP supplementation on impulsivity-related disorders through the example of depression.

2.2.3.2 Serotonin deficiency and 5-hydroxytryptophan supplementation: Article 1

To illustrate this section, I am taking the example of the first meta-analysis I conducted, which displays the effects of 5-HTP supplementation implemented in treatments of an impulsivity-related disorder, namely depression. To avoid too much overlap between the article and the thesis, only the abstract is presented. The complete article can be found using the following reference:

> **Article 1**: Javelle, F., Lampit, A., Bloch, W., Häussermann, P., Johnson, S., Zimmer, P., (2019) 'Effects of 5-hydroxytryptophan on distinct types of depression : a systematic review and meta-analysis', *Nutrition Reviews*, pp. 1–12. doi: 10.1093/nutrit/nuz039. (Impact Factor in 2019: 6.500)

Effects of 5-hydroxytryptophan on distinct types of depression: a systematic review and meta-analysis

Florian Javelle [a], Amit Lampit [b, c], Wilhelm Bloch [a], Peter Häussermann [d], Sheri L. Johnson [e], and Philipp Zimmer [a, f]

Abstract

Context: Serotonergic dysfunction, including reduced central 5-HT levels, is associated with different psychiatric syndromes, including depression. As a 5-HT precursor, 5-HTP has long been used as a non-pharmacological treatment for depression.

Objective: A systematic review and meta-analysis were conducted to determine the antidepressant effects of 5-HTP in depressed patients.

Data sources: MEDLINE (via PubMed) and Google Scholar were searched from inception to May 2018.

Data extraction: Thirteen investigations were included in the systematic review (using PRISMA guidelines), and seven in the full meta-analysis (pre-registered on PROSPERO: CRD42018104415). The data extraction process is presented in the flow diagram in Figure 4.

Data analysis: Analyses revealed a depression remission rate of 0.65 (95% confidence interval [CI], 0.55–0.78; remission rate [k] = 13; see Figure 5), and this was confirmed by the questionnaire results, which revealed a large Hedges' g (1.11; 95% CI, 0.53–1.69; see Figure 6). Methodological variability (in treatment duration, type of depression studied, experimental design, 5-HTP dosage) contributes to heterogeneity in the results (I^2= 76%, τ^2 = 0.379). In addition, the Office of Health Assessment and Translation risk of bias rating tool suggested that, on the whole, current studies are relatively weak (few include placebo groups).

Conclusion: Further trials should overcome these limitations by using placebo-controlled studies that include patients with well-defined depression diagnoses, along with a strong characterisation of psychological and physiological patient characteristics.

2.2.3.3 A new target: the kynurenine pathway

The KYN pathway accounts for over 90% of the TRP metabolism, the rest being allocated to 5-HT transformation and protein synthesis (Schwarcz et al., 2012). The conversion of TRP to KYN is initiated by the liver-specific TDO and the inflammation-mediated indoleamine 2,3-dioxygenase (IDO) enzymes (Badawy, 2017). Then, regarding neuromodulation, the KYN pathway can be summarised by two branches, one that is neurotoxic and one that is neuroprotective. The neurotoxic branch (B2.1 and B2.2 in Figure 7) is mostly driven by the activity of the inflammation-mediated enzyme kynurenine 3-monooxygenase (KMO). The branch produces several neurotoxic metabolites including quinolinic acid (QA), which has multiple neurotoxic mechanisms including deregulation of the glutamate release/uptake, lipid peroxidation, and oxidative stress due to its N-methyl-D-aspartate receptor agonist properties (Guillemin, 2012; Vécsei, Szalárdy, Fülöp, & Toldi, 2013). Furthermore, by the same token as chronic inflammation, pathological levels of QA and its precursor, 3-hydroxykynurenine, are associated with neuronal damages and BBB permeability markers (e.g., calcium-binding protein B [S100B], neurofilament light protein)(Darlington et al., 2007; Forrest et al., 2011; Tarasov et al., 2020). By contrast, the neuroprotective branch is driven by the activity of the kynurenine aminotransferase (KAT) enzymes (Schwarcz et al., 2012) producing kynurenic acid (KYNA). Due to its polar structure, KYNA, like QA, cannot cross the BBB (Fukui et al., 1991). Thus, brain KYNA is predominantly derived from brain KYN. KYNA acts as an antagonist of all three ionotropic glutamate receptors, including N-methyl-D-aspartate receptors, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors, and kainate receptors (Schwarcz et al., 2012). Given its capacity to block neuronal excitation and scavenge free radicals, KYNA is widely considered to have neuroprotective and anticonvulsant properties (Plitman et al., 2017; Schwarcz et al., 2012).

Furthermore, it is worth noting that a new direction of TRP to KYNA transformation was found very recently. Sadik et al. (2020) showed, using polyarteritis nodosa tissue, that an upregulated level of interleukin 4 induced 1 can transform TRP to indole-3-pyruvic acid and then to KYNA (see Figure 7)(Sadik et al., 2020). However, as this TRP catabolism direction is activated in tumour cases (e.g, human glioblastoma), it is of little importance for the samples used in this study.

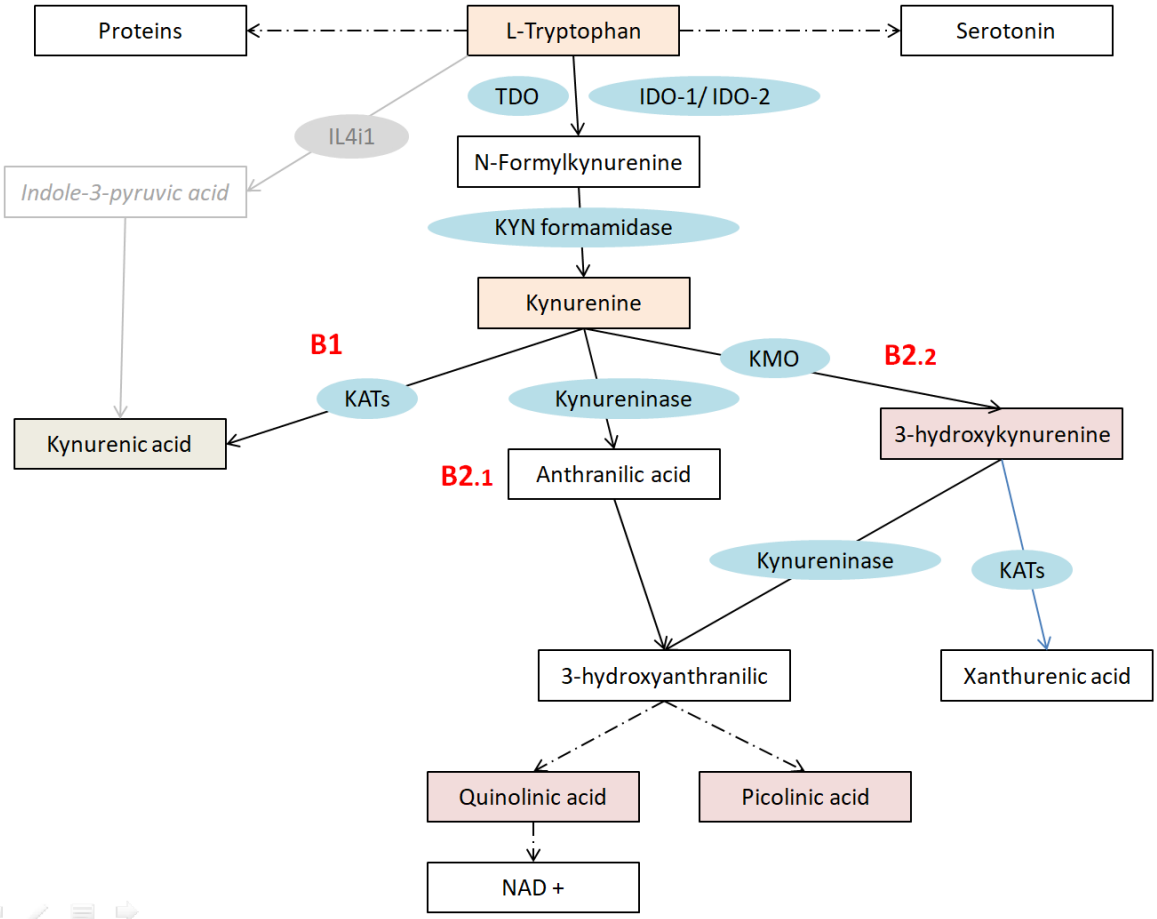

Figure 4: The kynurenine (KYN) pathway – extended version. TRP is oxidised to N-formylkynurenine by one of three enzymes: indoleamine 2,3-dioxygenase 1 (IDO1), IDO2, or tryptophan 2,3-dioxygenase (TDO). Next, N-formylkynurenine is metabolised by formamidase producing KYN. The KYN pathway can then continue through three distinct branches (B1, B2.1, and B2.2). KYN can be irreversibly transaminated to kynurenic acid (KYNA) by four kynurenine aminotransferases (KAT, KATII being the most active in humans). KYN can also be oxidised by kynurenine 3-monooxygenase (KMO) to produce 3-hydroxykynurenine. Lastly, KYN can undergo oxidative cleavage by kynureninase to form anthranilic acid (for more details see reviews of Dounay, Tuttle, & Verhoest, 2015; Schwarcz et al., 2012; Vécsei, Szalárdy, Fülöp, & Toldi, 2013). The route illustrated in grey, driven by the interleukin 4 induced 1 (IL4i1), is activated only in tumour cases. Figure adapted from Article 4 (Javelle, 2021).

2.3 Inflammation

The relationship between inflammation and psychological disorders has been recognised by the scientific community for almost a century (Julius Wagner-Jauregg - Nobel Prize in 1927 for his observation of the psychiatric manifestations of fever). Nevertheless, interest in the underlying neurophysiological mechanisms only exponentially grew in the past two decades. Accordingly, recent work suggests that healthy impulsive individuals already have chronic low-grade inflammation at cellular and humoral levels (Gassen et al., 2019; Sutin et al., 2012, 2010).

Indeed, Sutin et al. (2012) showed in their large scale study (n= 5652) that impulsivity-related traits were linked to higher white blood cells (WBC) counts. This complements other findings showing that high impulsive traits, impulsive decisions, and high levels of neuroticism are associated with elevated levels of pro-inflammatory interleukin 6 (IL-6) and tumour necrosis factor-alpha (Gassen et al., 2019; Sutin et al., 2012, 2010).

Chronic inflammation has been found to trigger several biological compounds to a pathological level. One of the most striking examples is the pronounced activity of the KYN pathway in various diseases such as cancer (Platten, Nollen, Röhrig, Fallarino, & Opitz, 2019) or multiple-sclerosis (Lovelace et al., 2016) and in impulsivity-related psychological pathologies including major depressive disorder (Arnone et al., 2018), schizophrenia (Marx et al., 2020), bipolar disorder (Bartoli *et al.*, 2020), attention-deficit/hyperactivity disorder (Evangelisti et al., 2017), and attempted suicide (Bryleva & Brundin, 2017). Nevertheless, no research assessing the KYN pathway activity and emotion-related impulsivity levels in healthy samples has yet been conducted.

2.4 The effects of physical exercise on impulsivity

Physical exercise is defined as a "physical activity that is planned, structured, repetitive, and purposive in the sense that improvement or maintenance of one or more components of physical fitness is an objective" (Caspersen, Powell, & Christenson, 1985). It is a subcategory of physical activity, which is "any bodily movements produced by skeletal muscles that result in energy expenditure" (Caspersen, Powell, & Christenson, 1985).

Physical activity has also been positively linked to areas of cognition that are associated with impulse control, including sustained attention, emotion regulation, and working memory (Donnelly et al., 2016; Minear, Brasher, McCurdy, Lewis, & Younggren, 2013). Pilot studies show an effect of physical activity on delay discounting tasks (often used to assess impulsivity) and attribute these changes to improved executive control (Sofis, Carrillo, & Jarmolowicz, 2017). Furthermore, seminal research on attention-deficit/hyperactivity disorder has shown that physical exercise can significantly reduce the impulsivity levels of participants (Cerrillo-Urbina et al., 2015; Cho et al., 2014). Thus, physical activity and physical exercise may be viable methods for promoting improved inhibitory control and reducing impulsivity. However, research on this topic is relatively sparse and the underlying mechanisms still need to be clarified.

The behavioural benefits of exercise might be tied to the underlying physiological effects of the KYN pathway. Previous findings have shown that physical exercise leads to the transformation of KYN to KYNA, which subsequently blunt the central synthesis of further neurotoxic metabolites (Agudelo et al., 2014; Allison et al., 2019; Małkiewicz et al., 2019; Phillips & Fahimi, 2018; Schlittler et

al., 2016). Studies suggest that this shift might be due to an upregulation of skeletal muscle-derived transcriptional coactivators promoting KAT expression (Agudelo et al., 2014; Allison et al., 2019). Furthermore, Agudelo et al. (2014) also suggest, in their murine model, that endurance exercise training reduces KMO activity, which subsequently leads to a higher synthesis of neuroprotective versus lower neurotoxic KYN metabolites.

It has previously been demonstrated that some enzymes of the KYN pathway can be up-regulated by inflammation and stress (see Figure 8). Indeed, IDO is enhanced by pro-inflammatory cytokines such as interferon-gamma (IFN-y) or IL-6 (Fuchs *et al.*, 1990), while high glucocorticoid levels increase the activity of TDO (Yiquan Chen & Guillemin, 2009). Even though acute bouts of physical exercise lead to an increase in glucocorticoids (Duclos & Tabarin, 2016) and a transient inflammatory state (Perdersen et al., 2001; Walsh et al., 2011), this is the complete opposite for exercise training. Indeed, long-term physical exercise training decreases the overall inflammation (Agudelo et al., 2014; Alizadeh et al., 2019; Euteneuer et al., 2017) and stress marker levels (Clow et al., 2006; Filaire, Ferreira, Oliveira, & Massart, 2013; Hakkinen, Pakarinen, Alen, Kauhanen, & Komi, 1988; C. J. Huang, Webb, Zourdos, & Acevedo, 2013; Kraemer et al., 1999), resulting in a reduction of KYN metabolism activity (see Figure 8).

Physical exercise not only helps to reduce visceral fat mass (a major source of inflammation) but also increases the body's anti-inflammatory potential. Agudelo et al. (2014) have shown that hippocampus inflammation is decreased in a sample of stress-induced-depression mice after nine weeks of exercise. This is likely due to the acute increase in peripheral KYNA after exercise that also has anti-inflammatory potential. Indeed, KYN and KYNA are ligands of the aryl hydrocarbon receptors, which enhance the differentiation of naive T-cells to regulatory T-cells, the main producers of anti-inflammatory cytokines (e.g., IL-10, TGF-ß). Correspondingly, Weinhold et al. (2016) indicated that endurance capacity in a large cohort of athletes is positively correlated with numbers and proportions of circulating regulatory T-cells. Other studies have reported a peripheral anti-inflammatory effect of physical exercise with a significant increase in anti-inflammatory cytokine levels (Alizadeh et al., 2019; Euteneuer et al., 2017; Hajizadeh Maleki, Tartibian, & Chehrazi, 2017; Li et al., 2018; Lira et al., 2017; Nunes et al., 2019; Steckling et al., 2016; Vella, Taylor, & Drummer, 2017). Nevertheless, not all studies report the same effects, which suggests that not all exercise paradigms are equivalent. When considering studies leading to the highest rate of metabolic changes in animal (Freitas et al., 2018; Li et al., 2018) and human models (Alizadeh et al., 2019; Hajizadeh Maleki et al., 2017; Nunes et al., 2019; Steckling et al., 2016), it appears that High-Intensity Interval Training (HIIT) may represent an optimum mode of training.

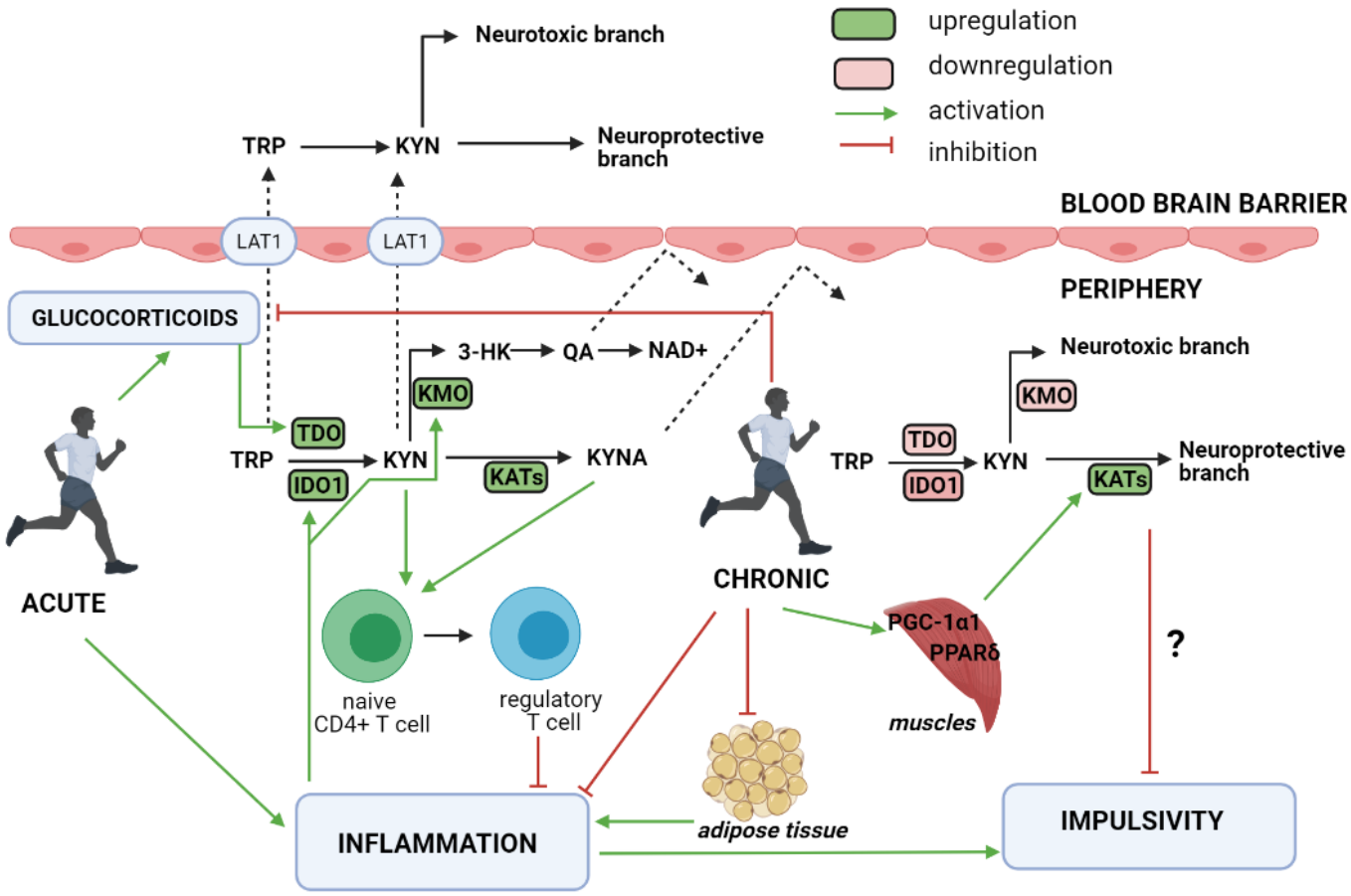

Figure 5: Potential effects of acute and chronic exercise on the kynurenine pathway and inflammation. 3-HK: 3-hydroxykynurenine; IDO: indoleamine 2,3-dioxygenase 1; KYNA: kynurenic acid; KMO: kynurenine 3-monooxygenase; KYN: kynurenine; QA: quinolinic acid; TDO: tryptophan 2,3 dioxygenases; TRP: tryptophan; PPARδ: peroxisome proliferator-activated receptor-delta transcription factor; PGC-1α1: peroxisome proliferator-activated receptor-γ co-activator 1-alpha1.This figure has been created using BioRender.com

3. Research question and hypotheses

To sum up, no validated German tools currently exist that assess together the behavioural (i.e. tendencies to engage in regrettable behaviours when facing emotion) and cognitive (unconstrained cognitive or motivational responses when facing emotions) forms of emotion-related impulsivity, despite these forms of impulsivity being increasingly seen as the most clinically relevant. Furthermore, even though the current state of research has reported numerous potential biomarkers of impulsivity, there is a lack of studies that use an endophenotypic approach to understand the underlying mechanisms of the impulsivity construct. Finally, the previous seminal findings that suggest a relationship between physical exercise and impulsivity are primarily relying on correlational analyses or assess only psychological symptoms. Properly controlled, randomised intervention studies that investigate the effect of physical exercise on impulsivity and its circulating biomarkers are urgently needed.

This thesis has been designed to address these gaps. **It focuses on the psychological and biological markers of impulsivity before testing whether physical exercise can concordantly modulate circulating biomarkers and impulsivity itself.** To achieve this purpose three articles are presented.

In Article 2, ***the aim is to develop and validate a German Three-Factor Impulsivity index allowing evaluating emotion-related impulsivity in a German sample***. To do so, the index was first translated and back-translated. Then, the factor structure of the translated scale was analysed via confirmatory factor analysis. Moreover, the scale has been validated against variables known to relate to impulsivity (i.e., gender, Body Mass Index [BMI], age, sleep disturbance, drugs use, and psychological disorders). Finally, novel links between emotion-related impulsivity and fitness level were tested. I hypothesised that people that report higher impulsivity would report less engagement in physical exercise. This article is important to validate a German version of the Three-Factor Impulsivity index that will later be used in the two other articles included in this PhD thesis.

In Article 3, ***the aim is to assess the variance of emotion-related and non-emotion-related impulsivity scores using an endophenotypic approach combing genetic serotonergic polymorphisms, lateralisation of the prefrontal alpha activity, and iAPF.*** I hypothesised that low transcriptional activity in serotonergic polymorphisms and high resting right alpha pre-frontal lateralisation score would relate to higher impulsivity, in particular the emotion-related form. Considering the inexistent work investigating the relationship between impulsivity and iAPF in healthy individuals, iAPF was

considered in an explorative manner. This article is important to understand the effects of genetic (related to 5-HT neurotransmission) and cortical markers of impulsivity on inter-individual differences.

Then, in Article 4***, the aim is to evaluate the physiological effects of physical exercise on impulsivity levels and the accompanying alterations of inflammatory-mediated changes of the KYN pathway in a sample of highly emotionally impulsive humans using an eight-week intervention of supervised HIIT in comparison to an active control group***. I hypothesised that the HIIT intervention would decrease impulsivity along with inflammation markers and neurotoxic KYN metabolites levels after eight weeks of training. The corresponding values in the control group would not change. This is the first article to investigate the effect of physical exercise on impulsivity and its circulating biomarkers in a sample of healthy humans at risk.

In the following sections, I will present the three experiments carried out within the present PhD thesis and subsequently provide a general discussion, that summarises the main findings, highlights relevant limitations, and outlies promising directions for future research.

4. Article 2

In the following pages, only the highlights and the abstract of Article 2 are presented (copyright issue). The full article can be found using the following reference:

Javelle, F., Wiegand, M., Joormann, J., Timpano, K. R., Zimmer, P., & Johnson, S. L. (2020). 'The German Three-Factor Impulsivity Index: Confirmatory factor analysis and ties to demographic and health-related variables'. *Personality and Individual Differences*, *171*(110470), 1–12. doi: 10.1016/j.paid.2020.110470 (Impact factor 2020: 2.311)

Highlights

•Fit indices for the confirmatory factor analysis of the German Three-Factor Impulsivity index replicate the original work.

•Correlations between the three factors are higher than in the original article.

•All communalities surpassed 0.75.

•Correlations between the physical exercise and the impulsivity scores were observed.

The German Three-Factor Impulsivity Index: Confirmatory factor analysis and ties to demographic and health-related variables

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4.1 Abstract

Context: A growing body of research has focused on the differentiation of emotion-related versus non-emotion-related impulsivity, assessed by the Three-Factor Impulsivity index.

Objective: The goal of this study is to develop a German Three-Factor Impulsivity index, and to validate the emotion-related impulsivity subscales against indices of substance abuse, physical or psychological disorder, physical exercise, BMI, and hours of sleep.

Methods: 395 native-German speakers completed the German Three-Factor Impulsivity index and questions on validity indicators online. Factor analyses supported the three-factor structure, including Pervasive Influence of Feelings, Lack of Follow-Through, and Feelings Trigger Action.

Results: Correlations between factors were higher than in the original work. Both emotion-related impulsivity subscales correlated significantly with psychological disorder, engagement in, and minutes of physical exercise per week. When included in multivariate regression models, the three factors explained 3.1%, and 29.2% of the variance in the amount of exercise per week and psychological disorder, respectively.

Conclusion: In sum, findings indicated that the German Three-Factor Impulsivity index has a robust three-factor structure that showed expected links to validity indicators, and novel effects in relation to physical exercise

5. Article 3

In the following pages, only the highlights and the abstract of Article 3 are presented (copyright issue). The full article can be found using the following reference:

Javelle, F., Löss, A., Bloch, W., Hosang, T., Jacobsen, T., Johnson, S., Schenk, A., & Zimmer, P. (no date) 'Unravelling the contribution of serotonergic polymorphisms, pre-frontal alpha asymmetry, and individual alpha peak frequency to the emotion-related impulsivity endophenotype.' *Submitted*

Highlights

- In univariate analyses, iAPF correlated with both forms of emotion-related impulsivity.
- Multiple regression models displayed that only the low transcriptional activity 5-HTTLPR phenotype was associated with iAPF.
- In univariate analyses, carriers of the low transcriptional activity 5-HTTPLR and MAO-A phenotypes obtained higher emotion-related impulsivity scores than others did.
- In multiple linear regression models, 5-HTTLPR polymorphism, iAPF, and prefrontal alpha asymmetry scores were significant, and the variables explained 21%-32% of the variance in Feelings Trigger Action scores.
- Both emotion-related factors might rely on slightly different biological mechanisms.

Unravelling the contribution of serotonergic polymorphisms, pre-frontal alpha asymmetry, and individual alpha peak frequency to the emotion-related impulsivity endophenotype

Running Title: The emotion-related impulsivity endophenotype

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5.1 Abstract

Context: The unique contribution of 5-HTTLPR, STin2, and MAO-A genes to individual differences in personality traits has been widely explored, and research has shown that certain forms of these polymorphisms relate to impulsivity and impulsivity-related disorders. Humans showing these traits are also described as having an asymmetrical pre-frontal cortical activity when compared to others.

Objective: In this study, we examine the relationship between serotonergic neurotransmission polymorphisms, cortical activity features (pre-frontal alpha asymmetry, iAPF), emotion-related and non-emotion-related impulsivity in humans.

Methods: 5-HTTLPR, MAO-A, and STin2 polymorphisms were assessed in blood taken from 91 participants with high emotion-related impulsivity. 66 participants completed resting electroencephalography and a more comprehensive impulsivity index.

Results: In univariate analyses, iAPF correlated with both forms of emotion-related impulsivity. In multiple linear regression models, 5-HTTLPR polymorphism, iAPF, and prefrontal alpha asymmetry scores were significant, and the variables explained 21%-32% of the variance in emotion-related impulsivity. Carriers of the low transcriptional activity 5-HTTPLR and MAO-A phenotypes obtained higher emotion-related impulsivity scores than others did. No significant results were detected for non-emotion-related impulsivity, or for a form of emotion-related impulsivity involving cognitive/motivational reactivity to emotion.

Conclusions: Our findings support an endophenotypic approach to impulsivity, showing that tri-allelic 5-HTTLPR polymorphism, iAPF, and pre-frontal alpha asymmetry are robust predictors of one form of emotion-related impulsivity.

Keywords: 5-HTTLPR - MAO-A – STin2 – emotion-related impulsivity – iAPF – alpha asymmetry

6. Article 4

In the following pages, only the highlights and the abstract of the article are presented (copyright issue). The full results and their discussion can be found using the following reference:

Javelle, F., Bloch, W., Knoop, A., Guillemin, G.J., & Zimmer, P. (2021). Toward a neuroprotective shift: eight weeks of high-intensity interval training reduces the neurotoxic kynurenine activity concurrently to impulsivity in emotionally impulsive humans – A randomised controlled trial. *Brain Behavior and Immunity [in press]* doi: 10.1016/j.bbi.2021.04.020.

Highlights

- HIIT increased participants' VO_{2peak} and produced physiological changes whereas stretching did not.
- HIIT reduced pro-inflammatory IL-6 levels.
- HIIT reduced the activity of the neurotoxic branch of the KYN pathway.
- HIIT decreased levels of emotion-related and non-emotion-related impulsivity.
- Changes in impulsivity were correlated to changes in KYNA/KYN.

Toward a neuroprotective shift: eight weeks of high-intensity interval training reduces the neurotoxic kynurenine activity concurrently to impulsivity in emotionally impulsive humans – A randomised controlled trial

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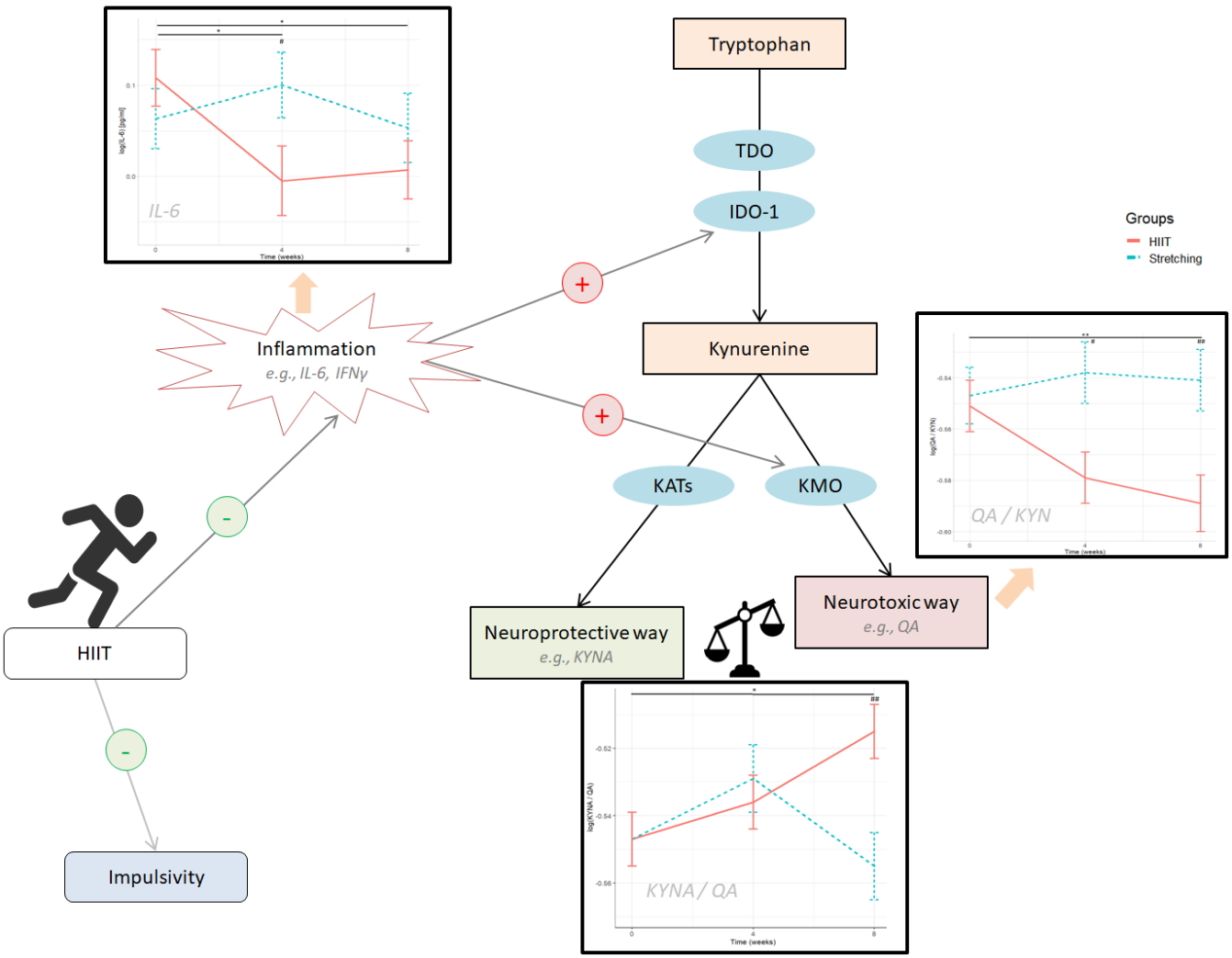

Figure 6 : Graphical Abstract - Eight weeks of High-Intensity Interval Training (HIIT) reduces the neurotoxic kynurenine (KYN) activity concurrently to impulsivity in emotionally impulsive humans IDO-1: indoleamine 2,3-dioxygenase-1; TDO: tryptophan 2,3-dioxygenase; KATs: kynurenine aminotransferases; KMO: kynurenine 3-monooxygenase; IL-6: interleukin 6; IFN-γ: interferon-gamma; QA: quinolinic acid; KYNA: kynurenic acid.

6.1 Abstract

Context: Previous findings suggest that impulsivity is related to chronic low-grade inflammation. Inflammation is known to trigger the KYN pathway to a pathological level in various impulsivity-related disorders. Nonetheless, murine models and recent human studies have shown that physical exercise, in particular HIIT, could counterbalance the negative effects of inflammation on the KYN pathway.

Objective: This study evaluates the effects of eight weeks of HIIT versus an active control group on impulsivity levels and accompanying alterations of inflammatory-mediated changes of the KYN pathway in a sample of emotionally impulsive humans.

Methods: Participants were randomly allocated to either HIIT or stretching conditions (three trainings per week for eight weeks). Fitness level was evaluated via VO_2peak values at the beginning at end of the intervention. KYN metabolites, pro-inflammatory cytokines, and impulsivity levels were evaluated at T0, T4, and T8 weeks. Statistical analyses were performed using mixed models.

Results: Fifty-three participants were included in the modified Intention To Treat analysis (45 finished the intervention). The HIIT group (n=28) largely increased the aerobic fitness of its participants and produced physiological changes while the stretching group (n=25) did not. HIIT reduced IL-6 levels (small to moderate interaction) and reduced the activity of the neurotoxic branch of the KYN pathway (small to moderate interaction for KYNA/QA and KYN/QA) after eight weeks of training while the active control did not change. Both interventions were effective to decrease emotion-related impulsivity, however only the HIIT group decreased participants' non-emotion-related levels. Changes in emotion-related and non-emotion-related impulsivity were moderately correlated to changes in KYNA/KYN.

Conclusion: This study demonstrated that HIIT was able to switch the KYN pathway from its neurotoxic branch to its neuroprotective one. This shift was associated with a decrease in impulsivity. Based on these findings, future work may consider investigating more intensively the effect of HIIT on impulsivity-related disorders.

7. General discussion

7.1 Discussion

Given the evidence that impulsivity is a multidimensional construct that relies on a wide spectrum of psychological and biological markers, **the general aim of this thesis was to determine how important these main biomarkers are in explaining emotion-related and non-emotion-related impulsivity levels. Thereafter, the goal was to test if repetitive high-intensity physical exercise can concordantly modulate circulating biomarkers (e.g., inflammation and KYN metabolites) and different forms of impulsivity themselves.**

In Article 2, a German version of the Three-Factor Impulsivity index was developed and validated, allowing the assessment of behavioural (i.e., Feelings Trigger Action) and cognitive (i.e., Pervasive Influence of Feelings) forms of emotion-related impulsivity in a German sample. Moreover, given the ties between both impulsivity and fitness and the serotonergic and dopaminergic systems, I tested novel links of emotion-related impulsivity with fitness levels (Cho et al., 2014; Heijnen, Hommel, Kibele, & Colzato, 2016). I hypothesised that people who report higher impulsivity levels would report less engagement in physical exercise. The results provided support for my hypothesis, showing that all three impulsivity factors were related to a lower likelihood of engagement in exercise and less time exercising per week.

In Article 3, I assessed the variance of emotion-related and non-emotion-related impulsivity levels in highly emotionally impulsive humans using an endophenotypic approach that combines serotonergic polymorphisms, lateralisation of the prefrontal alpha activity, and iAPF. I hypothesised that low transcriptional activity in serotonergic polymorphisms and high right alpha pre-frontal lateralisation score would relate to higher impulsivity, particularly the emotion-related form. Considering the scarcity of work on impulsivity and iAPF, I had no specific directional hypothesis for this parameter. When included in multiple regression models, 5-HTTLPR polymorphism, iAPF, and prefrontal alpha asymmetry were robust predictors of behavioural emotion-related impulsivity. Moreover, my results show that carriers of the low transcriptional activity 5-HTTPLR and MAO-A phenotypes have higher behavioural emotion-related impulsivity levels than other phenotypes. Cognitive emotion-related and non-emotion-related impulsivity might rely on other higher-order predictors. Nonetheless, iAPF was the only predictor significantly that influenced both emotion-related factors in the same manner.

Finally, in Article 4, I evaluated the physiological effects of physical exercise on impulsivity levels and accompanying alterations of inflammatory-mediated changes of the KYN pathway in a sample of highly emotionally impulsive humans using an eight-week intervention of supervised HIIT

versus an active control group. I hypothesised that participation in the HIIT program would both decrease impulsivity and reduce the levels of inflammation markers (i.e., pro-inflammatory cytokines) and neurotoxic KYN metabolites (i.e., QA, KMO activity) after eight weeks of training while the control group would not change. My results validated this hypothesis, showing that HIIT significantly reduced pro-inflammatory cytokines IL-6 levels and the activity of the neurotoxic branch of the KYN pathway. Furthermore, HIIT had a general effect on all impulsivity factors, whilst changes in the control group only occurred in emotion-related factors. Finally, correlational analysis of delta values displayed that the changes in impulsivity were associated with a change in the activity in the neuroprotective branch of the KYN pathway.

The discussions of these findings are presented in their respective articles. In the following section, I will take a broader perspective and bring these different results together to display the bigger picture and its relevance.

The first study, which developed the German version of the Three-Factor Impulsivity index, was a major step forward from a methodological standpoint. Indeed, all impulsivity assessments included in this thesis, as well as some independent articles (Javelle, Borges, et al., *Submitted*; Javelle, Vogel, et al., *Submitted*), were realised using this newly-validated German Three-Factor Impulsivity index. In the original validation article, three-factor scores were drawn from an oblique factor analysis of the subscale scores in a large scale sample, and the factor structure was confirmed using structural equation modelling (Carver et al., 2011). In agreement with the English validation of the Three-Factor Impulsivity index (Carver et al., 2011), three distinct factors were detected and validated via confirmatory factor analysis in Article 2. These results strengthen the validity of the Three-Factor Impulsivity index modelling across languages. The between-factor correlations were consistent with the English scale in the three articles presented here, with a small exception existing in Article 2 (slightly stronger correlations between emotion-related and non-emotion-related impulsivity factors than in the other articles).

These results are in line with the past 20 years of research on the topic. Impulsivity triggered by positive or negative emotions has been shown to be more clinically relevant than other forms that are not related to emotion (Carver, Johnson, & Timpano, 2017; Peters, Eisenlohr-Moul, Walsh, & Derefinko, 2019). Despite the overlap in the validity of the emotion-related impulsivity factors (i.e., Pervasive Influence of Feelings and Feelings Trigger Action), both are important and potentially operate through different biological mechanisms. Past studies have suggested that it may be important to distinguish between these two factors in order to fully understand impulsivity-related psychopathologies (Carver et al., 2017; Peters et al., 2019). There is some evidence that Pervasive Influence of Feelings is more relevant for internalizing conditions such as depressive symptoms,

whereas Feelings Trigger Action is more robustly related to externalizing conditions and hypomanic symptoms (Auerbach et al., 2017; S. L. Johnson, Carver, Mulé, & Joormann, 2013). Carver and colleagues have even suggested that impulsive reactivity to emotion might underlie the general factor of psychopathology (p factor) (Carver et al., 2017), described as intercorrelations among psychological dysfunctions existing in many forms of psychopathology (for a review see G. Smith, Atkinson, Davis, Riley, & Oltmanns, 2020). A later review, however, states that emotion-related impulsivity cannot explain all variables that load onto the p factor (e.g., anhedonia) and therefore might not be the core of p (G. Smith et al., 2020).

Furthermore, across the articles presented in this thesis, it was shown that Pervasive Influence of Feelings and Feelings Trigger Action might rely on the same biological basis but also have clear differences. Firstly, the two emotion-related impulsivity factors shared more biomarkers with each other than with the non-emotion-related factor (i.e., Lack of Follow-Through). Both emotion-related factors were inversely correlated to baseline levels of circulating serum TRP and positively correlated to iAPF. On the contrary, non-emotion-related impulsivity was the factor that was least connected to all evaluated biomarkers in the presented articles. These findings suggest a common biological basis for the two emotion-related factors while the non-emotion-related factor might be more distinct than initially expected. Nevertheless, behavioural and cognitive forms of emotion-related impulsivity also have slightly different underlying biological mechanisms.

The results of the multiple regression models show that 5-HTTLPR polymorphism, iAPF, and prefrontal alpha asymmetry (evaluated via the F4/F3 score) are robust predictors of tendencies to engage in regrettable behaviours when facing emotions (i.e., Feelings Trigger Action). Nevertheless, even though the model created for the cognitive form of emotion-related impulsivity (i.e., Pervasive Influence of Feelings) explained 17.7% of the total variance in our sample, it was not significant, which suggests that other higher-order predictors exist that were not evaluated in Article 3. However, we can note tendencies that show higher Pervasive Influence of Feelings scores in low transcriptional activity serotonergic polymorphisms phenotypes. This suggests that the tested predictors may also have a small influence on the cognitive form of emotion-related impulsivity, but one that was too weak to be detected by our experiment. In the field of psychology, impulsivity as a trait (high stability over time) is differentiated from impulsivity as a state (induced by an endogenous or exogenous stimulus, and can easily change over test-retest intervals)(Wingrove & Bond, 1997; Zuckerman, 1983). From this perspective and considering the different levels of stability amongst impulsivity biomarkers, one might speculate that psychological trait impulsivity relates more to genetic markers while state impulsivity could be more easily explained by circulating biomarkers. In Article 3, genetic markers explained emotion-related impulsivity as a trait but were only significant for the form involving regrettable

behaviour. It is possible that stimuli exogenous to the experiment may have affected impulsivity as a state. If this was the case, thoughts are more easily affected than action and therefore the evaluation of Pervasive Influence of Feelings would have been the first factor altered. Consequently, one might speculate that even in a neutral situation, the neurogenetic basis of Pervasive Influence of Feelings is more complicated to evaluate than that of Feelings Trigger Action.

Article 4 also showed that Pervasive Influence of Feelings was correlated to changes in circulating levels of KYN, KYN/TRP, and QA/KYN whereas other impulsivity factors were not. It is therefore possible that, while both forms of emotion-related impulsivity are linked to TRP pathways, the cognitive form might relate more to changes in the KYN pathway, whereas the behavioural form relates more to the serotonergic pathway. Further studies are required to confirm that statement. Indeed, uncertainty arises upon closer consideration of this aspect. Firstly, no circulating serotonergic marker was evaluated in Articles 3 and 4. Moreover, as explained in the introduction, due to foetal neurophysiological processes, the serotonergic transcriptional activity phenotypes are more strongly linked to the activity of specific brain regions (i.e., amygdala, anterior cingulated cortex, and prefrontal cortex) than to central 5-HT circulating levels. Therefore, I can only ascertain that the behavioural form of emotion-related impulsivity relates more to serotonergic polymorphisms (not the serotonergic pathway) than the cognitive form. Additionally, the relationship between Pervasive Influence of Feelings and changes in KYN markers might be more complex than a simple linear relationship because no significant correlations between baseline levels of KYN markers and impulsivity were detected.

So far, I have described biomarkers that are distinct for each of the three impulsivity factors, but there are others that are shared by all three factors. Indeed, the findings of Article 4 show that all impulsivity factors might vary inversely with changes in the neuroprotective branch (KYNA/KYN) of the KYN pathway (moderate effect sizes; Figure 20). This strengthens the idea that the KYN pathway might be another TRP transformation that influences impulsivity levels. The KYNA/KYN ratio could potentially be more clinically relevant than other biomarkers because it correlates with changes in all impulsivity factors. Nonetheless, this finding should be interpreted with caution. Indeed, the KYN pathway has been shown to be inflammation-mediated and to drastically change in several severe clinical conditions that are not necessarily impulsivity-related (e.g., cancer, multiple sclerosis)(Yiquan Chen & Guillemin, 2009). Furthermore, in some specific impulsivity-related disorders such as schizophrenia, very high central levels of KYNA have been detected, which suggests that KYNA may also be implicated in the pathophysiology of the disease (for a review, see Marx et al., 2020; Plitman et al., 2017). Thus, in some clinical conditions, the central overactivity of the neuroprotective KYN branch might be tied to psychological impairments. Therefore, the KYNA/KYN ratio might not always be a good marker of impulsivity. Further exercise interventions with impulsivity-related and non-emotion-related clinical

samples that assess conjoint changes in the KYN pathway and impulsivity levels are required. It would help to determine in the clinical conditions and disease stage in which the hypoactivity of the neuroprotective branch of the KYN pathway (KYNA/KYN) can be declared as a new biomarker of impulsivity.

Let's now consider the potential neurobiological link between impulsivity and physical exercise. Exercise has been shown to influence the serotonergic and the catecholaminergic pathways (Heijnen et al., 2016; Małkiewicz et al., 2019; Zouhal, Jacob, Delamarche, & Gratas-Delamarche, 2008). Given the ties between the monoamine pathways and impulsivity (Hennig, Netter, & Munk, 2021; Pardey, Kumar, Goodchild, & Cornish, 2013)(Articles 3 and 4), physical exercise has been suggested to be a potential moderator of impulsivity. As shown in Article 2, all three impulsivity factors were related to a lower likelihood of engagement in exercise and to less time exercising per week. These results were confirmed in a study independent of this thesis that used a large sample size (n=773) (Javelle et al., *Submitted*). Engaging in regular physical exercise requires commitment and so the link with perseverance is intuitive. Interestingly, though, high emotion-related impulsivity was also related to less exercise time, and low Pervasive Influence of Feelings scores were related to a higher intensity of exercise.

Article 4 showed that participants with high levels of emotion-related impulsivity tolerated eight weeks of HIIT or stretching well. Both interventions led to a significant decrease in emotion-related impulsivity scores. Furthermore, HIIT increased aerobic fitness in all participants and triggered positive physiological changes, whereas stretching did not (Figure 17A and 17B). This indicates that both interventions achieved their purpose. Seminal research in persons suffering from attention-deficit/hyperactivity disorder has already shown that regular aerobic exercise training is likely to decrease impulsivity levels (Cerrillo-Urbina et al., 2015; Den Heijer et al., 2017). Extending these findings, our results suggest that HIIT and stretching (active control) are efficient to moderately decrease emotion-related impulsivity levels in highly emotionally impulsive individuals. Interestingly, even though the HIIT group had greater effect sizes (in both Pervasive Influence of Feelings and Feelings Trigger Action) than the stretching group, no significant differences were detected. These results suggest that the intensity of exercise might not be the major moderator of exercise-induced benefits on emotion-related impulsivity levels. Social interaction and a feeling of accomplishment in the performed activity have been shown to be strong predictors of the intensity of symptoms in impulsivity-related disorders (especially internalizing disorders)(Jorge, 2015; Miller et al., 2019; Snowden et al., 2015). It is, therefore, reasonable to think that they might be essential contributing factors. To confirm this, further studies with different active control groups of the same level of social exposure (e.g., stretching, cards, and low-intensity exercise) and evaluation of the perceived self-

efficacy in each performed activity are required. Nonetheless, the questionnaire-based indices from Article 2 suggest that individuals that report doing high-intensity exercise have lower Pervasive Influence of Feelings scores. Thus, even though it was not the major moderator of emotion-related impulsivity levels, physical exercise intensity may have some influence that was too weak to be detected in Article 4.

The HIIT group was, however, the only group to show lower levels of Lack of Follow-Through after the intervention (large time and group differences after post-hoc tests). As suggested in Article 2, the commitment (three sessions per week) required for the exercise intervention of Article 4 may have played an important role in reducing the lack of perseverance. Moreover, the required intensity level of HIIT is likely to be more psychologically demanding than stretching and could partly explain the detected interaction in non-emotion-related impulsivity levels. Correspondingly, previous research has shown that HIIT increases the motivation to exercise, even compared to other modes of exercise (Knowles, Herbert, Easton, Sculthorpe, & Grace, 2015; Wilke et al., 2019).

Finally, even though the work presented in this thesis has successfully shown the involvement of the KYN pathway in impulsivity levels, it does not provide sufficient empirical data to confirm seminal research that links impulsivity with inflammation (Gassen et al., 2019; Sutin et al., 2012, 2010). Indeed, in Article 4, no baseline correlation between IL-6 and IFN-γ and emotion-related or non-emotion-related impulsivity was detected. Furthermore, despite the results showing that eight weeks of HIIT reduced IL-6 levels, these changes were not correlated with impulsivity changes. Therefore, the reduction in the levels of all three impulsivity factors in the HIIT group does not seem to be associated with the anti-inflammatory effects of exercise. Nevertheless, we cannot make any definite conclusions on this point. Indeed, no anti-inflammatory markers were assessed across the intervention reported in Article 4 (IL-6 and IFN-γ are pro-inflammatory cytokines). Additionally, the impulsivity spectrum of participants included in Article 4 was reduced, and thus small correlations could have been easily missed.

7. 2 Limitations and perspectives

Despite important findings, the results of this thesis should be interpreted within the context of its limitations. Firstly, across all the articles included in this thesis, only the Three-Factor Impulsivity index was used to measure impulsivity. Although this makes it possible to compare findings across studies, we cannot exclude the possibility that other impulsivity assessment tools may have elicited slightly different results. Future studies might consider including clinician interviews and cognitive tests of inhibition (e.g., Go/No-Go test) to obtain deeper insights into the biomarkers of impulsivity and how exercise modulates them.

Secondly, no clinical samples were used in the three core papers of this thesis. Further studies are warranted that replicate these findings in clinical conditions. Applying these experiments and replicating these findings in impulsivity-related disorders (e.g., depression, bipolar disorders) might provide valuable information about the maximum boundary of the impulsivity spectrum, whilst they may also have important clinical applications (e.g., treatment, supporting treatment). Indeed, the biomarkers of impulsivity evident in this thesis might help to develop and select better treatments. Additionally, exercise is thought to be a potentially beneficial treatment for impulsivity-related disorders. With this in mind, integrating a full spectrum of impulsivity levels would provide a more accurate idea of effect sizes from the results reported in Articles 3 and 4.

Thirdly, this thesis focused on the main biomarkers of impulsivity. Nevertheless, as displayed in Figure 1, other biomarkers exist that were left out because of a lack of focus, time, and financial resources. For example, dopamine is an important neurotransmitter involved in the modulation of emotional and reward responses, behaviour, and cognitive functions (Robbins, 2005) and thus thought to influence impulsivity (Congdon & Canli, 2005; B. Lee et al., 2009). Lee and colleagues (2009) showed using positron emission tomography, that inadequate activity of D2-like receptors induces impulsive responses. Additionally, work with impulsivity-related disorders has shown potential relationships between impulsivity and dopamine transporter, dopaminergic receptor type 4, catecholamine-O-methyltransferase, and dopamine beta-hydroxylase (Daly, Hawi, Fitzgerald, & Gill, 1999; Dougherty et al., 1999; Esposito, 2006; Krause, Dresel, Krause, Kung, & Tatsch, 2000; Rangel-Barajas, Coronel, Floran, C., & I., 2015; Smalley et al., 1998). Therefore, dopamine would be a valuable add-on for further studies, especially when considering polymorphisms. Furthermore, Article 4 showed that not only the serotonergic pathway but also the TRP pathways overall are involved in impulsive traits. Thus, it might be worth assessing other polymorphisms from TRP catabolism (i.e., TRP hydroxylase) and within the KYN pathway (e.g., KMO). With deeper resources, we could even go further and consider the sequencing of all monoamine-related genes, which would provide a more precise and complete understanding of genetic information that potentially explains impulsivity. Nevertheless, the explorative character of both suggestions and the expected inter-individual variability would require larger sample sizes.

Fourthly, future studies might consider assessing the interaction between all the investigated biomarkers. In the presented articles, I have first investigated the interaction between genetic (i.e., serotonergic polymorphisms) and cortical (i.e., prefrontal asymmetry and iAPF) impulsivity biomarkers, and then the interaction between circulating impulsivity biomarkers (i.e., KYN pathway and inflammation). However, it is possible that these genetic and cortical impulsivity biomarkers also interact with some of the circulating ones. For example, seminal research has shown in healthy and

clinical conditions that 5-HTTLPR mediates behavioural responses due to acute circulating TRP depletion (Neumeister et al., 2006; Walderhaug et al., 2007, 2002). Future studies with deeper resources might consider analysing all these biomarkers within the same sample of participants.

Fifthly, other variables such as childhood adversity and drug use might be worth examining. As explained in the introduction, the transcriptional activity levels of serotonergic genes likely relate to the activity of specific brain regions that were potentially influenced by circulating monoamine levels during foetal life. Nevertheless, other factors might be involved in the re-wiring of these brain regions. Previous work has shown that the 5-HTTLPR polymorphism also interacts with childhood adversity (Carver, 2011). It is, therefore, possible that the carriers of the low transcriptional activity phenotype are more sensitive to childhood adversity, leading to a rewiring of the limbic system and, in turn, with prefrontal alpha asymmetry and hyper-sensitivity of the amygdala. This may then explain the up-regulation of emotion-related impulsivity levels in low transcriptional activity phenotype carriers when facing strong emotions. This mechanism might be the same for intense stimuli such as drug use/abuse. Thus, variables such as childhood adversity or abuse and drug use might be important to consider, especially in clinical conditions.

Finally, even though Article 3 revealed useful insights into the underlying biological mechanisms of impulsivity by investigating serotonergic neurotransmission polymorphisms, it did not fully consider the interaction between psychological traits and the environment. Integrating epigenetic techniques into the assessment of impulsivity might bring a more dynamic understanding of this relationship. For example, assessing the DNA methylation in each of the presented polymorphisms in Article 3 might provide valuable insights that integrate the relationship between genes and the environment. Indeed, DNA methylation is one of several epigenetic mechanisms (e.g., histone acetylation, micro RNA, chromatin packing) that cells use to control gene expression (to lock the gene in the “off” position)(Domschke et al., 2014; Philibert et al., 2007; Reuter et al., 2020). In most cases, high methylation levels relate to lower transcriptional activity (Domschke et al., 2014; Philibert et al., 2007; Reuter et al., 2020). Additionally, this technique has real potential to demonstrate the genetic effects of lifestyle interventions (e.g., exercise intervention or diet) on impulsivity levels.

7.3 Conclusion

The present PhD thesis aimed to determine the importance of the main biomarkers of impulsivity while distinguishing between the emotion-related and non-emotion-related forms of this construct. Thereafter, the goal was to investigate whether physical exercise can concordantly modulate circulating biomarkers and different forms of impulsivity themselves. One meta-analysis and three studies were conducted with a complete spectrum of individuals (Article 2), encompassing emotionally impulsive adults (Article 3 and 4) and persons suffering from depression (Article 1).

Overall, my results show that emotion-related and non-emotion-related impulsivity are likely to rely on slightly different biological mechanisms. Most of the biological markers of impulsivity tested in this thesis were actually related to emotion-related impulsivity (i.e., 5-HTTLPR, MAO-A, prefrontal asymmetry, iAPF, TRP levels, and KYNA/KYN). Furthermore, it was shown that the behavioural emotion-related impulsivity might rely more on the assessed serotonergic markers while the cognitive form might be more strongly linked to changes in the KYN pathway. Finally, physical exercise was shown to be a very promising technique to influence the biomarkers of impulsivity itself. HIIT provided the most promising results and significantly decreased a broad range of impulsivity biomarkers and all forms of impulsivity. My results, however, do not display one of the latter as being the cause of the other. These results are extremely promising and are encouraged to be tested in clinical populations that express extreme levels of impulsivity (e.g., depression, bipolar disorder, schizophrenia, substance abuse disorder).

8. References

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9. Supplementary Materials

9.1 Three-Factor Impulsivity index – German Version

Jeder der folgenden Punkte ist eine Aussage, mit der eine Person entweder einverstanden oder nicht einverstanden sein kann. Geben Sie für jede Aussage an, inwiefern diese auf Sie zutrifft. Bitte versuchen Sie, auf alle Aussagen zu antworten und wählen Sie nur eine Antwort pro Aussage. Bitte seien Sie so genau und ehrlich wie möglich. Reagieren Sie auf jede Aussage, als wäre es die einzige. Machen Sie sich also keine Sorgen, dass Sie in Ihren Antworten "konsistent" sind.

1 = trifft überhaupt nicht zu

2 = trifft eher nicht zu

3 = trifft teils/teils zu

4 = trifft eher zu

5 = trifft voll und ganz zu

	(1)	(2)	(3)	(4)	(5)
Es fällt mir schwer Impulse zu kontrollieren. (1)	○	○	○	○	○
Es fällt mir schwer meinen Verlangen zu widerstehen (z.B. nach Essen, Zigaretten). (2)	○	○	○	○	○
Ich werde oft in Situationen verwickelt, aus denen ich später gerne wieder herauskommen würde. (3)	○	○	○	○	○
Wenn ich mich schlecht fühle, tue ich oft Dinge, um mich kurzfristig besser zu fühlen, die ich später aber bereue. (4)	○	○	○	○	○
Manchmal, wenn ich mich schlecht fühle, kann ich einfach nicht aufhören mit dem, was ich gerade tue, auch wenn es mir dadurch nur noch schlechter geht. (5)	○	○	○	○	○
Wenn ich aufgeregt bin, handle ich oft unüberlegt. (6)	○	○	○	○	○

Wenn ich mich abgelehnt fühle, sage ich oft Dinge, die ich später bereue. (7)	○	○	○	○	○
Es fällt mir schwer, mich daran zu hindern, nach meinen Gefühlen zu handeln. (8)	○	○	○	○	○
Oft mache ich etwas nur noch schlimmer, weil ich unüberlegt handle, wenn ich aufgeregt bin. (9)	○	○	○	○	○
In der Hitze eines Wortgefechts sage ich oft Dinge, die ich später bereue. (10)	○	○	○	○	○
Ich bin immer in der Lage meine Gefühle unter Kontrolle zu halten. (11)	○	○	○	○	○
Manchmal tue ich aus einem Handlungsimpuls heraus Dinge, die ich später bereue. (12)	○	○	○	○	○
Andere reagieren schockiert oder besorgt auf die Dinge, die ich tue, wenn ich sehr aufgeregt bin. (13)	○	○	○	○	○
Wenn ich überglücklich bin, kann ich mich schwer zurückhalten, nicht über das Ziel hinauszuschießen. (14)	○	○	○	○	○
Wenn ich sehr aufgeregt bin, neige ich dazu, nicht über die Konsequenzen meines Verhaltens nachzudenken. (15)	○	○	○	○	○
Ich neige zum Handeln ohne Nachdenken, wenn ich sehr aufgeregt bin. (16)	○	○	○	○	○
Wenn ich sehr glücklich bin, finde ich mich selbst oft in Situationen wieder, in denen ich mich normalerweise eher unwohl fühlen würde. (17)	○	○	○	○	○
Wenn ich sehr glücklich bin, fühlt es sich okay an meinem Verlangen völlig freien Lauf zu lassen. (18)	○	○	○	○	○
Ich bin überrascht über das, was ich tue, wenn ich außerordentlich gut gelaunt bin. (19)	○	○	○	○	○
Ich handle in der Regel unmittelbar nach meinem Gefühl. (20)	○	○	○	○	○
Meine Emotionen wandeln sich schnell in Handlungen um. (21)	○	○	○	○	○
Wenn ich etwas will, hole ich es mir direkt. (22)	○	○	○	○	○
Stichprobenartige Antwortkontrolle: Bitte wählen Sie "trifft eher zu" (23)	○	○	○	○	○

Wenn ich ein Verlangen in mir spüre, handle ich sofort danach. (24)	○	○	○	○	○
Bei einer emotionalen Reaktion auf etwas handle ich oft unüberlegt. (25)	○	○	○	○	○
Ich reagiere impulsiv auf meine Gefühle. (26)	○	○	○	○	○
Wenn ich voller Begeisterung für etwas bin, setze ich mich in Bewegung. (27)	○	○	○	○	○
Wenn eine einzelne Sache schief geht, fange ich an, daran zu zweifeln, ob ich überhaupt irgendetwas gut kann. (28)	○	○	○	○	○
Ich lasse nicht zu, dass die Unzufriedenheit mit etwas Bestimmtem sich auch auf meine Gefühle in anderen Lebensbereichen auswirkt. (29)	○	○	○	○	○
Wenn ich an mir einen Fehler entdecke, denke ich unweigerlich auch über weitere Schwachstellen nach. (30)	○	○	○	○	○
Ein einziger Fehltritt reicht aus, um mich von einer guten Ausgangsstimmung in große Selbstzweifel zu stürzen. (31)	○	○	○	○	○
Wenn ich traurig bin, fühle ich mich wie gelähmt. (32)	○	○	○	○	○
Wenn ich mich traurig fühle, höre ich einfach auf, weiterzumachen. (33)	○	○	○	○	○
Von meinen Gefühlen bin ich schnell überwältigt. (34)	○	○	○	○	○
Wie ich meine Umwelt wahrnehme, wird stark von meinen Gefühlen beeinflusst. (35)	○	○	○	○	○
Emotionale Erfahrungen beeinflussen meine Sicht auf das Leben stark. (36)	○	○	○	○	○
Ich führe Dinge im Allgemeinen gerne zu Ende. (37)	○	○	○	○	○
Ich neige dazu, leicht aufzugeben. (38)	○	○	○	○	○
Unbeendete Aufgaben sind mir sehr unangenehm. (39)	○	○	○	○	○
Bin ich erst einmal in eine Tätigkeit vertieft, höre ich nur äusserst ungern wieder damit auf. (40)	○	○	○	○	○

Es fällt mir leicht, mich auf etwas zu konzentrieren. (41)	○	○	○	○	○
Was ich einmal angefangen habe, bringe ich auch zu Ende. (42)	○	○	○	○	○
Ich verstehe es ziemlich gut, mich so zu organisieren, dass Arbeiten rechtzeitig erledigt werden. (43)	○	○	○	○	○
Ich bin ein produktiver Mensch, der seine Arbeit immer erledigt. (44)	○	○	○	○	○
Wenn ich erst einmal mit einem Projekt beginne, so führe ich es fast immer zu Ende. (45)	○	○	○	○	○
Stichprobenartige Antwortkontrolle: Bitte wählen Sie "trifft eher nicht zu" (46)	○	○	○	○	○
Es gibt so viele kleine Dinge zu erledigen, dass ich manchmal einfach alle ignoriere. (47)	○	○	○	○	○
Ich lasse mich schnell von nebensächlichen Gedanken ablenken. (48)	○	○	○	○	○
Es fällt mir schwer, an langfristigen Projekten zu arbeiten, weil mir dabei so viele andere Dinge durch den Kopf gehen. (49)	○	○	○	○	○
Bei den Hausaufgaben tendiere ich zu Tagträumereien. (50)	○	○	○	○	○
Meine Gedanken schweifen ab, wenn ich an etwas Mühsamem oder Schwierigem arbeite. (51)	○	○	○	○	○
Selbst wenn ich gerade eigentlich andere Dinge im Kopf habe, fällt es mir leicht, mich auf meine Arbeit zu fokussieren. (52)	○	○	○	○	○
Es fällt mir schwer, meine Intentionen in die Tat umzusetzen, weil ich durch andere Gedanken im Kopf abgelenkt werde. (53)	○	○	○	○	○
Wenn ich an etwas Bestimmtem arbeite, schweife ich oft in andere Gedankengänge ab. (54)	○	○	○	○	○
Es fällt mir schwer, mit dem Kopf bei der Sache zu bleiben. (55)	○	○	○	○	○
Meine Gedanken kommen mir so geballt und schnell in den Kopf, dass ich Probleme damit habe, mich auf eine einzelne Sache zu fokussieren. (56)	○	○	○	○	○

Forsan et haec olim meminisse iuvabit.

Perhaps even these things will be good to remember one day.