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Connected

Grasping the diversity of neuroscience and its community

Internal report of the Master Neuroscience and Cognition

“We are all now connected by the Internet, like neurons in a giant brain.”

- Stephen Hawking

“Only through our connectedness to others can we really know and enhance self. And only through working on the self can we begin to enhance our connectedness to others.”

- Harriet Goldhor Lerner

“The thing you realize when you get into studying neuroscience, even a little bit, is that everything is connected to everything else. So it’s as if the brain is trying to use everything at its disposal - what it is seeing, what it is hearing, what is the temperature, past experience.”

- Paul Allen

Content

Content

#Poll

The long-awaited reveal. The polls distributed throughout the journal are contributions from the students of the Neuroscience and Cognition master programme. We polled a total of 5 questions to our fellow master's students to gather their insights on topics presented throughout the journal. The response from students was amazing and has provided some interesting results! Check them out as you read through the journal.
Page: 42, 45, 57 , 60, 65

Puzzle page

Find the comic from masterstudent Zuzanna Altmann and a crossword puzzle on page 71-72!

Foreword

Dear reader,

Before you lies the first issue of the 15th volume of the Journal of Neuroscience and Cognition.

We are still living in challenging times and the current board faced the challenge of creating this journal in a fully online setting. When the board started in November, they needed to familiarize themselves with the different processes involved in creating a journal. Previous boards have developed very useful guidelines for this, but it was up to this new board to decide how they would deal with starting their new collaboration with each other through Teams and other online channels. I was pleased to see that board meetings start off with the board members asking each other how they are doing, how their internship is going and how their weekend was. I believe such a short round of personal updates each week has facilitated the board in becoming a team and feeling connected to each other.

Perhaps not surprisingly, “Connections” is also the theme of the current issue, and this fits seamlessly with what the board has proven to have a natural talent for, making connections, with each other, but also across and within different fields of study.

I would like to take this opportunity to draw your attention to some highlights in this journal. There is a personal interview with Geert Ramakers, with whom we are all connected to in one way or the other. In addition, you will encounter some interesting interviews that might help you shape a well informed opinion on whether or not to go abroad and to choose a suitable ‘career-path’. And moreover, what other disciplines you can explore while working in the field of neuroscience.

Yours sincerely,

Anouk Keizer

Senior Supervisor Journal of Neuroscience and Cognition 2020-2021

Editorial

Dear reader,

We are all aware of the complexity of our brains – how they function can therefore go beyond the scope of our rationality. This creates a myriad of mysteries to be discovered and unravelled by scientists. What might however be neglected in the first instance, is the diversity of the people studying these mysteries. Besides the fact that these people also possess such complex brains, they are all characterized by their own background, interests and personal history. In light of acknowledging this diversity, and how it benefits the progress within the field of neuroscience, we present to you the first issue of the Journal of Neuroscience and Cognition 2021: “Connected: Grasping the Diversity of Neuroscience and its Community”.

We believe this theme is important since it highlights the fact that neuroscience is not merely an isolated field of research, but instead is connected to, and benefits from, all sorts of varying disciplines and perspectives. Through advancements in technology, the ability to communicate scientific research across the world has become easier. Sharing thoughts, ideas and data across our borders connects the scientific community now more than ever. Although it might feel different because

of the current COVID-19 regulations, this also accounts for the community of the master Neuroscience and Cognition. We would therefore like to introduce our contributors, and how they help in connecting these differing perspectives.

We are thereby excited to announce a newly designed section, in which Dr. Dave van Toor, Lennart van Melis, Lora-Sophie Gerber and Dr. Jasper van Vught explain how neuroscience and their own field of research (i.e. law, toxicology and game research) may mutually benefit each other. Furthermore, we aimed to address our international character, by including personalized interviews with two highly appreciated lecturers: Dr. Ben Harvey and Dr. Mariana Branco, and how they experience cross cultural differences. We extended this idea with personalized stories from both Evan Canny, as current international, and Jet Termorshuizen, an alumna who recently moved to Stockholm. We are also glad to share some career perspectives with you as future alumni, containing stories from Jaenneke Spruit and Dr. Anne-Floor Scholvinck, who are yet connected through their roots in neuroscience.

To highlight the work of both students and researchers and how they help unravel the many mysteries of neuroscience, we start off with some interesting literature reviews from Malouke Visser, Marlyn Bisschop, Aras Maran and Iulia Buzatoiu. Then, we continue with two groundbreaking methodologies, described by Dienke Bos and Naomi Vlegels, and how they map the many connections within our brain. The interview with Dr. Jeroen Dudink thereby shows us the importance of sleep, and how sleep-research benefits from joint-perspectives. Finally, we are truly happy to pay special attention to the face of the Neuroscience and Cognition master's programme, and how he connects the entire community: Dr. Geert Ramakers.

We thereby hope you can appreciate the personalized aspects of this first issue. Besides our own personal recommendations for some relaxation, we aimed to represent you – the reader – with graphs characterizing your opinion. Zuzanna Altmann, chief of the Mind the Brain committee 2021, thereby shares some creativity regarding the preparation of this year's symposium and tops it off with her own designed neuroscience comic!

All in all, we are happy to finally show you the first issue of the Journal of Neuroscience and Cognition 2021. It has been an honour to assemble the comprehensive and interesting set of articles and we hope you are just as amazed as we were when hearing and reading all the stories. We thereby want to thank all the contributors who made this issue possible despite the limitations caused by the current situation.

Enjoy reading, and stay connected!

Yours sincerely,

Nina Dijkstra
Editor in Chief - Journal of Neuroscience and Cognition 2020-2021

'The neurological and behavioural effects of cannabinoids affecting social play during childhood and adolescence and their long-term effects on cognitive development'

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Social play is a fundamental rewarding behaviour in most mammals, including humans. This behaviour is recorded in the developmental ages of these young mammals from the earliest stages of development until the end of adolescence. Social play is important for ensuring a healthy social development, by experimenting with behaviours necessary in adulthood, such as confrontation and resilience. However, social play can be altered by the consumption of recreational drugs, such as opioids, methylphenidate, and THC. Cannabis in particular is one of the most used recreational drugs throughout history and to date. Most adolescents will experience the effects of cannabis at least once before reaching adulthood, and a subsection of these users will likely become a recreational user or will develop an addiction to it. In this review, the importance of social play, the endocannabinoid system, and the research literature available on the effect of cannabinoid consumption on social play behaviour in rats will be analysed. The risk of long-term social development disruption will also be reviewed. Generally, there is an agreement that systemic THC consumption leads to decrease in social play. The research reviewed here shows that cannabinoid intake can alter social play behaviour, via the endocannabinoid system; an important system in modulating the behaviour. Furthermore, as adolescence is a fragile period important for cognitive development, interfering with the endocannabinoid system, and disrupting social play can lead to synaptic and physiological changes and potential disturbances later in life. However, there is still a debate unfolding regarding the long-term effects on cognitive development following THC use in adolescence.

Keywords: *Social play behaviour, Cannabinoids, Recreational drug use, Endocannabinoid system, Reward*

THE IMPORTANCE OF SOCIAL PLAY

Social play is a behaviour displayed in almost all mammals and also some birds, reptiles, and amphibians (Emery & Clayton, 2015). It is a behaviour well-known in humans, through children experiencing the world, playing with toys, and engaging in play with other children. This can be further observed in adolescence through the exploration of emotions and boundaries in relation to peers, as well as the process of self-discovery (Nijhof et al., 2018). Similar behaviours are seen in other mammals, including elephants and rats (Trezza & Vanderschuren, 2008b; Webber & Lee, 2020). Social play behaviour can be described as fun, and at a first glance does not seem to have a defined purpose. To date, its presence in various species leads to the question of its importance, as any behaviour that does not directly aid survival is unlikely to be preserved. However, findings have shown that social play is fundamental for a healthy social, emotional, and cognitive development (Nijhof et al., 2018; Omrani et al., 2020). This is especially seen when looking at children suffering from chronic and mental disorders such as attention-deficit/hyperactivity disorder (ADHD), autism, depression, and anxiety (Nijhof et al., 2018; Vanderschuren et al., 2016). As a result of these disorders, children tend to show decreased or inappropriate social play, leading to a delay in their developmental milestones through childhood and adolescence (Nijhof et al., 2018). This can also be seen in rats; offspring that exhibit decreased social play are prone to show social deficiency later in life; such as rats being more submissive when in confrontation (Trezza et al., 2014). Moreover, social play is also an indicator of the wellbeing of other young mammals, such as elephants (Trezza & Vanderschuren, 2008b; Webber & Lee, 2020). As a result, play therapy has been proposed for alleviating some of the social symptoms of disorders such as ADHD and anxiety (Nijhof et al., 2018; Wilkes-Gillan et al., 2016).

When playing, children display a large repertoire of creative behaviours, related to situations that are beneficial later in life. They show a vast range of creativity through make-belief story plots, at times engaging in mature social scenarios e.g., falling in love, marriage, and fights. During adolescence this behaviour manifests through defining social interactions, where emotions, friendships and boundaries acceptable within the society are learned; this is a vital time for defining an individual's identity (Nijhof et al., 2018). In this way, they develop a large array of social skills that can aid them to be a well-adjusted individual and deal with negative circumstances (Nijhof et al., 2018). Therefore, social play is a way for young humans and mammals in general to explore their

environment, as well as practice social interactions necessary for better adaptability in the future.

Furthermore, social play is an intriguing behaviour as it is intrinsically rewarding. There is a large variety of systems and brain areas involved in reward and motivational processing that are important in social play (Vanderschuren et al., 2016). Animal models can be used to untangle the involvement of these systems (Vanderschuren et al., 2016). Rats are a great experimental model to study social play behaviour, as this behaviour can be easily distinguished via the interactions of pouncing and pinning (Niesink & Van Ree, 1989). Pouncing is described as a behaviour where the rat can touch the nape of the neck of another rat, signalling the start of the playful interaction. The other rat in return can either run away rejecting the play invitation or initiate pinning, which is a typical behaviour where the animal turns on its back, denoting the reciprocation of the play behaviour (Niesink & Van Ree, 1989; Nijhof et al., 2018). These behaviours together with other social play interactions such as wrestling, following, chasing, and social exploration can be scored in experimental setups and give insight into the drive for play (Trezza & Vanderschuren, 2008b). Moreover, this type of scoring can also be combined with pharmacological studies, such as the administration of drugs that alter the reward systems, to pinpoint the brain areas and pathways responsible for the behaviour. However, altering these circuitries using exogenous substances, such as drugs of abuse, during the developmental stages of social play can potentially affect the long-term development of the subject.

Therefore, social play is an important rewarding behaviour that aids healthy development of children and adolescents. Inappropriate social play behaviour can lead to cognitive, social, and emotional dysfunction in adulthood (Omrani et al., 2020). For these reasons, potential factors that can lead to social play misfunctioning should be assessed. This is imperative, as recreational drug use is a substantial part of the society, and their effect on the developing youth should be examined.

CANNABINOIDS AND SOCIAL PLAY

Social play is an intrinsically rewarding behaviour and it was found to be regulated by a variety of systems involved in reward, cognition, and motivation (Vanderschuren et al., 2016). One such system is the endocannabinoid system, which is involved in a large range of physiological and cognitive processes and is regulated by cannabinoids (Mechoulam et al., 2014).

Cannabinoids play a role in regulating a large repertoire of functions including pain, fear, neuroprotection, stress, mood, and anxiety (Mechoulam et al., 2014). Endogenous cannabinoids, such as anandamide and 2AG, are vital for proper functioning and have also been found to play a role in the display of social play (Vanderschuren et al., 2016). Increased levels of anandamide in areas such as the amygdala and the Nucleus Accumbens (NAc) can lead to higher levels of social play; moreover, social play can also lead to increased activity in the endocannabinoid pathway in return (Trezza et al., 2012). Thus, altering the functioning of either social play or the endocannabinoid system can disbalance the system, and potentially lead to dysfunctions.

Furthermore, exogenous cannabinoids, with emphasis on the most commonly used type, tetrahydrocannabinol (THC), can act on the endocannabinoid system and alter social behaviour (Bruijnzeel et al., 2019; Stringfield & Torregrossa, 2020; Trezza et al., 2014). THC is a psychoactive drug that acts on the CB1 receptors of the endocannabinoid system and can potentially disrupt normal social play behaviour (Mechoulam et al., 2014). However, the study into long-term effects of cannabinoid consumption on the neurobiology and social behaviour in adolescents has not been conclusive yet. Nevertheless, given the importance of social play for cognitive development and reaching specific developmental milestones (social and psychosexual) it is debated whether the use of THC at young ages should be allowed.

RELEVANCE

Social play behaviour is needed in the developmental years to gain a repertoire of social, cognitive, and emotional tools aimed at facilitating successful adulthood (Nijhof et al., 2018; Omrani et al., 2020). Alterations to the pathways involved in giving rise to this behaviour could therefore lead to unpleasant consequences later in life; such alterations could arise through substance use.

Recreational drug use has been a part of society for a large part of history due to the psychoactive capacities of these drugs, as well as their hedonic or physiological effects on the well-being experienced by the user. However, adolescence is a fragile period during which the brain is still developing, and the use of substances can interfere with its normal development, potentially leading to changes in both the brain physiology and behaviour (Trezza et al., 2014). Enhanced cannabis use is in part related to genetic factors; however, another factor associated with persistent consumption is through peer interactions. Adolescents and young people (12-26 years of age) that belong to social groups where cannabis is consumed are more likely to become long-term users (Johnson et al., 2019). Thus, via these social interactions with peers, adolescents and young adults are more prone to experiment with cannabis and continue cannabis consumption compared to older individuals.

Cannabis is one of the most common recreational drugs in the youth population due to its euphoric effects (Mechoulam et al., 2014). However, despite being widely used for generations, more data on its long-term effects are only now surfacing. Moreover, the availability of more THC-derived products around the world and the debate of its legalisation might make young individuals more prone to experiencing the drug. A metanalysis performed

in 2019 has found that there was a small increase in use amongst adolescents following legalisation for recreational use (Melchior et al., 2019). Thus, clear research into the possible long-term side effects of cannabis use is needed to ensure that it will not lead to cognitive, emotional, or social deficits later in life.
Here, the effect of exogenous cannabinoids, such as THC, on social play behaviour, as well as the pharmacological activation of the social play brain circuitry as a result of consumption will be discussed. As the consumption of cannabis in humans commonly occurs in adolescence, research using adolescent rats as a translational animal model will be analysed. This will give insight into the possible long-term effects of cannabis intake at young ages, and whether it can be considered safe for cognitive development.

SOCIAL PLAY NEUROBIOLOGY AND BEHAVIOUR

Pharmacological Intervention in Social Play

Three main characteristics of social play were previously studied; the pleasurable, incentive motivational, and learning components, which are mediated by different brain areas and neural mechanisms (Achterberg et al., 2016). Pharmacological studies were designed to assess the pathways and systems that give rise to the motivational and pleasurable properties of the behaviour. This was done through the use of diverse pharmacological agents, such as morphine, methylphenidate, and THC (Schiavi et al., 2019; Trezza & Vanderschuren, 2008a, 2008b; Vanderschuren et al., 2016).
The main pathways identified to play a role in the functioning of social play are the dopaminergic and opioid systems (Achterberg et al., 2019; Achterberg et al., 2016). Their involvement is heavily related to the initiation of pouncing behaviour, denoting a desire for playing (Niesink & Van Ree, 1989). Moreover, the noradrenergic and endocannabinoid systems also play a role in maintaining the behaviour and its complexity (Achterberg et al., 2016a, 2016b). The opioid and endocannabinoid systems are related to the pleasurable effects of social play(Achterberg et al., 2019, 2016b); whereas, the dopaminergic and noradrenergic systems are more associated to the motivational properties of the behaviour (Achterberg et al., 2016a).
The pleasurable effects experienced through social play were linked to the opioid system via a variety of pharmacological studies using opioids. Morphine infusions in the NAc, acting on the mu-opioid receptors showed an increase in social play behaviour, measured as an increase in pinning and longer play times (Vanderschuren et al., 2016). This finding was corroborated with the administration of opioid antagonists, such as naloxone, which led to a decrease in this behaviour (Achterberg et al., 2019). Moreover, it is particularly important that opioid receptor inhibition can modulate the activity of other pathways in social play. For instance, antagonising the mu-opioid receptors can lead to a decrease in the effect of non-opioids such as nicotine and alcohol (Vanderschuren et al., 2016).
The dopaminergic system plays a key role in the motivational properties of social play. However, administration of dopamine receptor agonists has led to mixed results. The non-selective agonists acting on D1 as well as D2 receptors can both decrease and increase social play; whereas agonists selective for either D1 or D2, such as methylphenidate suppress social play (Vanderschuren et al., 2016). However, modulation of dopamine levels via the use of the dopamine reuptake inhibitor GBR-12909 does not have an effect on social play, showing that the effect is not based on the dopamine levels available. (Achterberg et al., 2016a; Vanderschuren et al., 2016). Rather, it has been speculated that dopamine levels must be maintained at a certain level to lead to social play behaviours.
The noradrenergic system was also found to be important in the modulation of social play. Its action is closely related to that of the dopamine system. For instance, treatment with psychostimulants such as cocaine, which elevate noradrenaline levels, have been found to suppress social play via their action on the alpha-2 adrenoreceptor (Achterberg et al., 2016a). This has been corroborated by the use of alpha-2 adrenoreceptor antagonist RX821002, which counteracted the effect of atomoxetine and MPH (Achterberg et al., 2016a; Vanderschuren et al., 2016).
Finally, the endocannabinoid system has been found to both positively and negatively modulate social play behaviour according to the type of stimulation involved (Trezza & Vanderschuren, 2008a). Direct stimulation of cannabinoid receptors leads to a decrease in social play behaviour; but indirect stimulation (e.g. via blocking the FAAH enzyme responsible for degrading the endocannabinoid anandamide) increases social play (Trezza & Vanderschuren, 2008a). Thus, it is believed that the endocannabinoid system plays a role in the modulation of social play as a whole (Achterberg et al., 2016b; Trezza & Vanderschuren, 2008a). The endocannabinoid system and its involvement in social play will be further discussed in sections 3 and 4.1.
It is clear that there is a complex interaction of systems being involved in the production of social play. The involvement and interplay of these systems further support the idea that social play is a complex rewarding behaviour, and interference with its proper functioning may lead to long-term changes in the functioning of the systems, and thus behaviour and cognition.

Neural Correlates of Social Play

The vast amount of pharmacological studies performed which investigated social play also led to pinpointing some of the main brain areas involved in the processing of the behaviour. A surprisingly large number of brain areas work together to give rise to the proper functioning

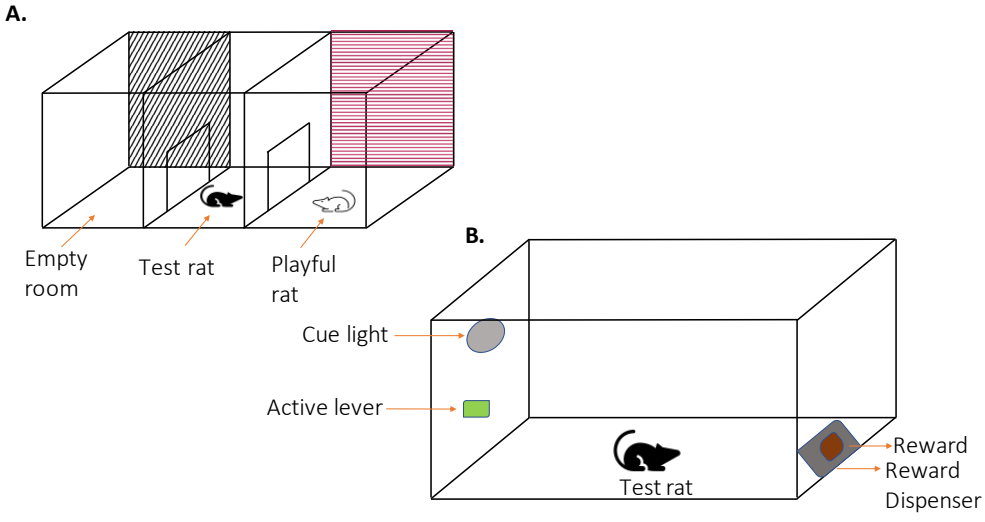

Figure 1. Main areas activated by social play. The figure shows a sagittal view of the rat brain. The main brain areas involved in the social play circuitry are labelled. They are the anterior cingulate cortex (ACC), infralimbic cortex (IL), prefrontal cortex (PFC), Caudate-putamen, Hypothalamus, Nucleus accumbens, Habenula, Amygdala, Thalamus, and the Ventral tegmental area (VTA). The main two areas that elicit a response in the endocannabinoid pathway relating to social play can be seen in red (the nucleus accumbens and the amygdala). The black circles denote larger areas within the brain (Vanderschuren et al., 2016). Sagittal brain picture taken from: https://neuroscience-graphicdesign.com/2017/08/01/post-1-rat-brain-gallery/; and further annotated)

of the behaviour.

Fundamentally, social play is modulated by a variety of structures in the limbic and corticostriatal networks, including the frontal cortex, striatum, amygdala, habenula, thalamus, and hypothalamus (Vanderschuren et al., 2016) (see Figure 1). However, each of these areas is predominantly involved in specific pathways and gives rise to different aspects of social play.

Firstly, the frontal cortex is vital for longer play sessions, as its removal led to shorter playtimes and a decrease in pinning in rats. The frontal cortex is expected to play a role in social play, as it is mostly associated with executive functioning. Particularly important regions for this effect are the anterior cingulate cortex and infralimbic cortex (ACC and IL), as exclusively the infusion of the dopamine reuptake inhibitor, methylphenidate, within these areas suppressed social play (Achterberg et al., 2016a). Secondly, another important area, the striatum, shows a major involvement in social play. Lesions in the striatum led to shorter playtimes and truncated play sequences (Vanderschuren et al., 2016). Moreover, the ventral part of the striatum, the NAc, is a major reward centre. Activation of the mu-opioid receptors here, as well as indirect CB1 activation, can lead to increases in social play (Vanderschuren et al., 2016). The striatum is an important area for reward processes, and thus is involved in the motivational aspects of social play (Vanderschuren et al., 2016). Thirdly, the habenula is an area mostly associated with emotional processing. In terms of social play, it mediates the negative effects of isolation and is involved in responsiveness to play solicitation (Vanderschuren et al., 2016). Fourthly, the amygdala is heavily involved in cannabinoid and noradrenergic modulation of social play. Previous literature thereby showed that differences in the physiological and anatomical development of the amygdala may lead to changes in social play between males and females (Trezza et al., 2012; Vanderschuren et al., 2016). Finally, the thalamus and hypothalamus can also mediate some aspects of social play behaviour. Thalamus dysfunction leads to reduced pouncing, therefore denoting a lack of motivation towards initiating play. The hypothalamus on the other hand, could be associated with sex differences seen in social play behaviour, due to the hormonal differentiation in the perinatal period. (Vanderschuren et al., 2016).

Therefore, it can be concluded that social play is an important and intrinsically rewarding behaviour, as its action is being supported by a large variety of rewarding, motivational, and cognitive centres within the brain. Thus, studies looking at further studying the possible external factors that could have positive and negative short- and long-term effects on this behaviour should be implemented, to ensure its correct functioning.

THE ENDOCANNABINOID SYSTEM AND ITS MECHANISM

The endocannabinoid system is vital in the modulation of a variety of emotional and cognitive processes, and it has also been found to be important in the modulation of social play behaviour (Mechoulam et al., 2014; Trezza et al., 2012; Trezza & Vanderschuren, 2008a). However, before going in depth, it is important to understand the functioning of the system as a whole.

The endocannabinoid system is activated by the binding

of endogenous ligands to the cannabinoid receptors. Such ligands are anandamide, 2AG, 2AG ether, and virodhamine (Pacher et al., 2006). Endocannabinoids are lipid signalling molecules, released following neuronal depolarisation and travelling retrogradely. They are released by the pre-synapse to regulate the release of neurotransmitters and bind to specific GPCR receptors, named CB1 and CB2. CB1 expression is extensive throughout the CNS and its activation is involved in the modulation of neurotransmitter release. On the other hand, CB2 can be found mostly in the brain stem and some microglia and its activity is mostly related to immunological processes (Mechoulam et al., 2014). However, endocannabinoids can also be released post-synaptically, in which case they bind to CB1 and CB2 receptors, leading to various other effects in the body (e.g. mediating synaptic inhibition) (Mechoulam et al., 2014; Gerdeman, 2008). Moreover, endocannabinoids work over a large area of the brain to ensure the proper functioning and appropriate levels of neurotransmitter signalling. These areas vary from the cortex and hippocampus to the reward systems and the cerebellum (Mechoulam et al., 2014). Thus, the system modulates a large number of behaviours, and exogeneous interferences with the system can have detrimental effects on its correct functioning.

The main two endocannabinoids are anandamide and 2AG and they have both been associated with social play behaviour. Increasing amounts of especially anandamide have been associated with an increase in social play (Trezza et al., 2012). The action of anandamide is important for hedonic traits, such as food enjoyment; whereas 2AG is associated with mechanisms involved in pain reduction. (Mechoulam et al., 2014; Pacher et al., 2006). Thus, it is intuitive to suggest that anandamide is more involved in a rewarding activity such as social play. Finally, there are exogenous molecules that can interact with this system. Cannabis is a widely used recreational drug that can hijack this system. It is a drug known due to its capacity to cause a euphoria-like feeling. Cannabis is made up of over 100 cannabinoids, the two main ones being cannabidiol (CBD) and delta-9-tetrahydrocannabinol (Δ9-THC/THC) (Mechoulam et al., 2014). They are activated via binding to the CB1 receptor and lead to general, non-specific effects via entering the neuronal cells through the membrane lipids. (Pacher et al., 2006). THC is the psychoactive compound

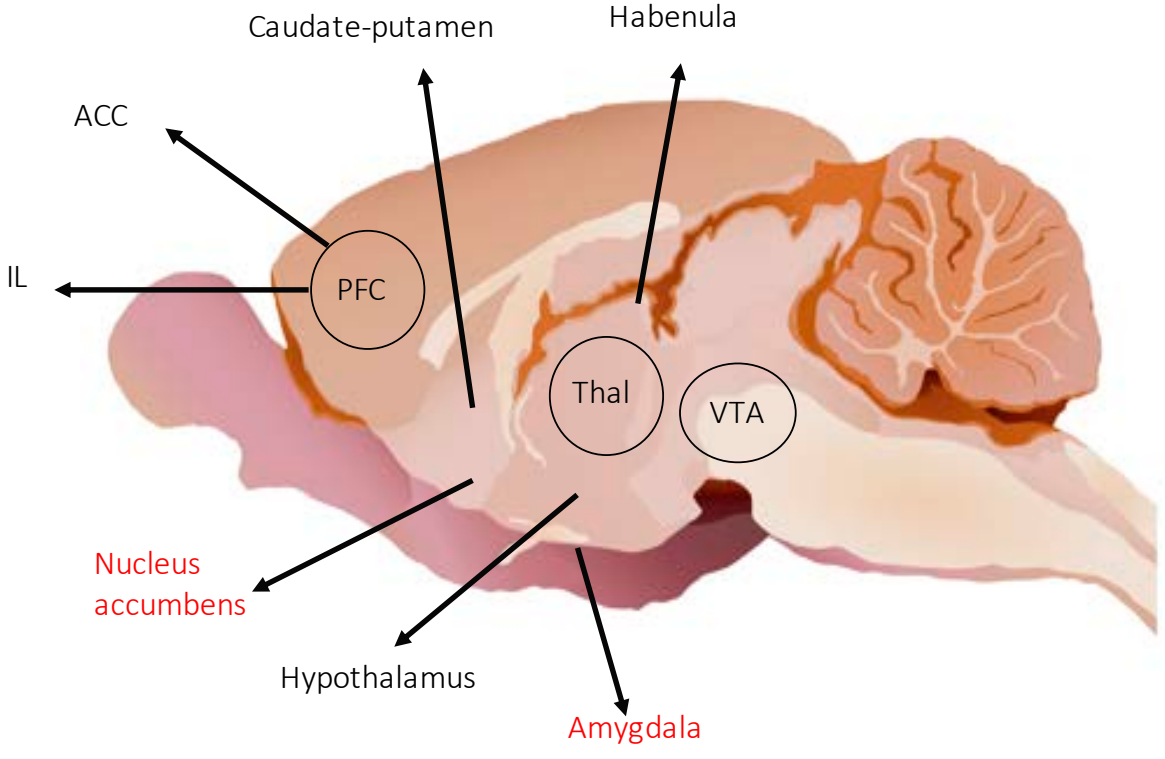

Figure 2. Diagram of the experimental setups used for testing social play behaviour in rats. A. Shows the setup used for place conditioning. There is a three-room setup, where the test rat is placed in the middle room and can choose to go left or right. The left and right rooms have different visual and textile properties, such that they are easily distinguished. Here, one room contains a playful animal and the other is empty. According to their choice, a preference can be inferred B. Shows the setup used for operant conditioning. The test rat is placed in a cage. The animal can press on a lever, which leads to a cue light activation and as a result, a reward is given in the reward dispenser (food pellet). Animals can be trained such that they know that pressing on a lever will lead to the reward; here being a playful animal to interact with. This can be further tweaked, such that the probability of getting the reward is lowered. In this way, we can quantify how willing the animal is to work for the reward. (E. J.M. Achterberg et al., 2019) (own work).

in cannabis, and it has been linked to the feeling of euphoria, but also in rare cases psychotic-like symptoms (Rubino & Parolaro, 2008). CBD on the other hand does not have any psychoactive properties and is believed to have more beneficial anti-psychotic and anti-anxiolytic effects (Rubino & Parolaro, 2008).

Overall, the endocannabinoid system is very versatile and has an important effect on healthy brain functioning, including social play. Interfering with a complex system at young ages, when the brain connectivity is still developing, has the potential to lead to undesirable outcomes. For this reason, the way exogenous cannabinoids affect social play, and the possible long-term effects are further discussed.

THE CANNABINOID SYSTEM AND ITS EFFECT ON SOCIAL PLAY

Rats are a desirable model for testing social play, as their behaviour can be quantified via the pouncing and pinning behaviours (Niesink & Van Ree, 1989). To test this, three main techniques are used, namely social isolation paradigms, place conditioning associated with pleasurable aspects of social play and, operant conditioning associated with the motivational aspects of the behaviour (Achterberg et al., 2019; Trezza & Vanderschuren, 2008a). Firstly, play expression paradigms are based on isolating the animals before social play experimentation to increase, but also equalise the need for social play (ensuring that none of the animals tested had recent social play interactions that could impact their willingness to participate) (Niesink & Van Ree, 1989). Secondly, place conditioning is used to infer a preference. Finally, operant conditioning is a type of conditioning where the animal has to put in the effort to gain access to a reward. It is assumed that the more motivation the animal has, the more effort it will show (see Figure 2).

Generally, the endocannabinoid system activation in relation to social play is versatile and there are a few important factors worth to mention. Systemic administration setups showed that indirect and direct administration of endocannabinoid agonists leads to differential play behaviours (Trezza & Vanderschuren, 2008a). It has also been shown that the endocannabinoid system may modulate play as a whole, rather than the motivational and pleasurable properties alone (Achterberg et al., 2016b). Moreover, some local infusions led to pinpointing the basolateral amygdala as the main site for social play modulation in relation to this system (Trezza et al., 2012).

It has been shown that the effect generated on social play behaviour is dependent on whether the system is directly or indirectly stimulated (Trezza & Vanderschuren, 2008a). One intriguing study looked at the systemic effect of two cannabinoid agents on social play, namely the direct agonist WIN55,212-2 and the indirect agonist URB597 (Trezza & Vanderschuren, 2008b). In this setup, they used a play expression paradigm based on social isolation. Adolescent rats treated with the CB1 agonist WIN55,212-2 showed decreased initiation and responsiveness to social play, when both animals were treated, and also when only one of them was. In the pairs with only one treated animal, the placebo rat would initiate play, but the WIN55,212-2 treated rat would be unresponsive. Interestingly, no effect was seen on the level of social exploration, denoting that this effect is specific to social play (Trezza & Vanderschuren, 2008b). However, for the treatment with the indirect agonist URB597, an increase in social play behaviour can be seen in both pouncing and pinning. Thus, on the one hand, it can be inferred that the direct activation of the CB1 receptors leads to general activation throughout the brain, possibly involving systems that downregulate social play. On the other hand, the action of the agonist URB597 on social play led to the proposition that endocannabinoids are released during play. Therefore, anandamide is released during social play, and its action is prolonged only at the active synapses as a result of URB597 administration, leading to enhanced play (Trezza & Vanderschuren, 2008b). In conclusion, cannabinoids can negatively and positively modulate social play based on whether they directly or indirectly activate the cannabinoid system (Trezza & Vanderschuren, 2008b). These results show again that the endocannabinoid system is extremely versatile, and that its effects are dependent on the way it is stimulated (Trezza & Vanderschuren, 2008a).

To further assess this, the levels of anandamide increase in different brain regions were tested via a similar setup. Infusions in the basolateral amygdala have shown to be sufficient and essential for modulating social play, as agonising the CB1 receptor led to an increase in social play, whereas locally antagonising the CB1 receptors led to a decrease in social play following systemic URB587 agonist administration (Trezza et al., 2012). The NAc was also shown to be involved, as URB597 administration led to an increase in anandamide levels compared to control. However, the local antagonization in the NAc did not lead to a decrease in play. Therefore, the amygdala and NAc are both involved in social play, but the basolateral amygdala appears to be the main site for social play modulation (Trezza et al., 2012).

However, these results only show how rats interact when placed together, but not whether they prefer or are motivated to pursue play. Further studies investigated whether it is the motivational or hedonic characteristics of play that are diminished with cannabinoid administration. It was shown that the endocannabinoid system modulates the expression of social play as a whole, rather than only the pleasurable or motivational aspects of it (Achterberg et al., 2016b). To study this, the motivational and hedonic effects of social play were studied via a combined place and operant conditioning paradigm. The effects of the URB597 indirect agonist compared to the effects of the CB1 antagonist Rimonabant were analysed. Rats were injected intra-peritoneally leading to a systemic effect (Achterberg et al., 2016b). For URB597, there was no

difference seen in the conditioned place preference at doses previously administered, showing no increase in the hedonic effects. A reduction in operant responding was seen, nonetheless. The antagonist Rimonabant decreased operant response. Nevertheless, this decrease has been seen for other rewarding activities including primary rewards such as food. Moreover, side-effects of the drug (e.g., scratching) can lead to interference in social play. This can occur through response competition, as Rimonabant can lead to multiple effects in the organisms, and they can interfere with each other .Therefore, it is perhaps not the motivational aspects that are altered, but the response competition affecting the motivation to play (Achterberg et al., 2016b). Hence, this study shows that the endocannabinoid system may modulate social play behaviour as a whole rather than the motivational or hedonic aspects alone.

The above experiments show that the endocannabinoid system is important for social play behaviour as a whole, as extrinsic agonization and antagonization shows changes in the behaviour. Moreover, as previously indicated, endocannabinoids not only modulate the behaviour, but might be released during play, which could denote a form of feedback. Overall, the direct and indirect agonist use shows that the system is versatile, and that indirect or direct activation can lead to differential behaviours. Therefore, it is possible that, if prolonged, these alterations could modify the behaviour and lead to long-term connectivity changes. Moreover, the direct link to the amygdala in the modulation of social play also poses a risk, as the amygdala is one of the main emotional centres in the brain (Trezza et al., 2012). Thus, the effect of cannabinoid drugs on social play together with the alterations they can cause in the endocannabinoid system could lead to long-term effects on emotional health. Hence, the long-term effects of prolonged cannabinoid use should be further analysed.

LONG-LASTING EFFECTS IN SOCIAL DEVELOPMENT

The studies presented above showed that it is certain that social play can be affected by cannabinoids; however, it is imperative to look into the long-term effects of consumption at young ages.

In the experiment performed by Buijnzeel et al. (2019), adolescent Long-Evans rats were treated with increasing THC amounts and later tested for symptoms similar to those seen in mood and anxiety disorders. Two experimental setups were used. In one cohort, the rats were treated intra-peritoneally twice a day from post-natal day (PND) 35 to 45, with increasing THC concentrations from 2.5mg/kg to 10mg/kg. In another cohort, a smoke setup was used, where cannabis was burned, and smoke was released every few seconds to a concentration of 250mg of total suspended particles per m3. The anxiety and depression-like behaviour of the rats was checked after P70 using a variety of behavioural tests, such as the elevated plus-maze, forced swim, sucrose preference test, and novel object recognition (Bruijnzeel et al., 2019). Following the protocol, the only significant result found was a sex difference between males and females in the elevated plus-maze, where females spent more time on the open arms, denoting that they are more open to exploration, and less anxious overall. However, besides this, no significant effect was seen in relation to depression or anxiety-like symptoms. This is particularly surprising especially for the condition using increasing THC dosage, as the same protocol used previously did show an increase in depression-like symptoms (Rubino et al., 2008). Nonetheless, this may be due to different strains being used in the experimental setups, namely Sprague-Dawley rats and Long-Evans rats; the latter being less sensitive to stress.

However, in another study, long-term behavioural changes were seen for rats voluntarily consuming THC in adolescence, between PND 31 and 52. The animals were implanted with catheters to self-administer THC via a lever press. Here, male rats that self-administered high THC doses showed better working memory compared to females. Furthermore, they observed a decrease in protein expression of CB1 (in the prelimbic cortex, ventral tegmental areas, and the infralimbic cortex) and GABA (in the dorsal horn and the prelimbic cortex), compared to controls (Stringfield & Torregrossa, 2020). The dysfunction in the GABA expression has also been seen before in adolescent rats; however exogenous GABA administration saved the phenotype (Renard et al., 2017).

Further studies into prologed cannabis use have also found differences between female and male rats, with females showing more cognitive deficits in adolescence following consumption; but not in adulthood (Prini et al., 2017). This cognitive decline has been related to epigenetic changes in the prefrontal cortex exclusively in female rats. Moreover, THC administration in rats was also related to defects in object recognition when used by adolescent rats, but not adults. (Quinn et al., 2008). Furthermore, both short and long-term defects were seen for short-term memory in adolescent rats following chronic use (Abush & Akirav, 2012). Similar memory deficits can also be seen in humans. A setup compared 14 to 16-year-old adolescents dependent on cannabis with non-user adolescents. The battery tests showed short-term memory impairments in the dependent adolescents. However, these differences subsided after 4-6 weeks of abstinence, denoting that long-term effects may not occur (Schwartz et al., 1989).

Therefore, there are reported physiological and social changes of cannabis consumption have been reported in both males and females, but in terms of cognition, there may be a difference in long-term effects between males and females.

Moreover, due to the effect of cannabinoids on the release of neurotransmitters, and because brain connectivity is still developing in adolescence, it is

speculated that cannabis use during this time can lead to changes in synaptic plasticity (Rubino & Parolaro, 2008). One study found changes in plasticity and morphology of hippocampal neurons after cannabinoid use in adolescent rats (Rubino et al., 2009).

Generally, the long-term effects of cannabinoid consumption in adolescence are still heavily debated, and a lot of ongoing findings concerning the cognitive, behavioural, and emotional long-term effects are contradictory. There seems to be an effect of the strains and the sex of the animals tested. There is also an effect of the quantities and duration of exposure; however, these factors cannot be related to clear long-term effects. Moreover, this makes the translation to humans even more complex, as humans have more intricate brain circuitry and more heterogeneity in terms of both physiology and environmental exposure.

DISCUSSION

To date, the research performed with the use of rat animal models shows an involvement of cannabinoid consumption in social play, but there is still no consensus on the long-term effects. Many studies, despite using similar protocols, show contradictory results regarding the long-term effects of cannabinoid effects following adolescent cannabis consumption.

The main concept that often resurfaces from these studies is that of sex differences, with females being more affected than males. This may be because cannabis has previously been shown to act as an endocrine disruptor. Cannabis may affect endocrine signalling, with emphasis on estrogen related pathways, which potentially could have long-lasting effects in the future (Bruijnzeel et al., 2019). Moreover, these sex changes have also been related to epigenetic changes, with an emphasis on chromatin modifications, found to occur in the prefrontal cortex (Prini et al., 2017). These alterations in epigenetic modifications could also occur as a result of endocrine disruption. Further studies should be carried out, in order to monitor estrogen and testosterone levels in animals and to pinpoint any unusual fluctuations that may lead to the phenotype following cannabinoid consumption.

Furthermore, there are some translational issues with these studies. It must be mentioned that rats are not humans, and there are differences in anatomy, physiology, and behaviour. Firstly, the age of the animals tested should be taken into account, and it should correlate with human adolescence. In rats, mid-adolescence can be considered to start around PND35, when the animals have reached sexual maturity (Schiavi et al., 2019). This was the case for the aforementioned studies. Secondly, the dosage, frequency, and duration of consumption should be considered. Some of the studies presented above did involve long-term consumption throughout adolescence; however, the THC dosage only correlated to what would be considered mild use in humans (Bruijnzeel et al., 2019). Therefore, further studies should involve higher THC doses, which can be correlated with heavier use in humans.

Moreover, the experimental paradigms presented used a variety of endocannabinoid agonists, one of them being the psychoactive THC in cannabis. However, human adolescents do not use THC alone. They use cannabis, which is composed of 100s of cannabinoids, including THC and CBD (Mechoulam et al., 2014). This could potentially lead to a difference in the expression of social play behaviour. For instance, CBD may reverse some of the damage from THC through anti-psychotic and anti-anxiolytic properties. (Rubino & Parolaro, 2008). For this, a setup where cannabis smoke is inhaled by the animals should be performed, similar to what was done by Stringfield and Torregrossa (2020).

To further pinpoint the problem of translation, an interesting study showed a long-term effect of perinatal THC consumption (Hurd et al., 2019). Such consumption can lead to social deficits in females more than in males in adolescence and later in life. (Hurd et al., 2019). Therefore, if social deficits can be seen after perinatal consumption in model animals that are relatively homogenous, it is even more challenging to predict the consequences in humans. In order to solve the problem of homogeneity, experimental setups should be done comparing several animal strains and pinpointing similar behavioural, social, and cognitive alterations seen in all of them following cannabis consumption. In this way, animals with a slightly altered genetic background and characteristics can be compared to assess whether the changes are seen as a result of consumption or are more strongly related to certain genetic characteristics.

Moreover, systemic cannabinoid administration has been shown to decrease social play. We should consider that social play is necessary for healthy cognitive, emotional, and social development and that social deprivation in rats can be detrimental in the long-term (Omrani et al., 2020). It was shown that such deprivation during childhood and adolescence leads to changes in the formation of cognitive strategies in an operant conditioning setup (Omrani et al., 2020). Furthermore, this has also been correlated to decreased connectivity in their frontal cortex (Omrani et al., 2020). Therefore, social play may be needed for the appropriate development of executive functions (Omrani et al., 2020). Given the decrease in social play seen after cannabinoid administration, it is possible that frequent consumption in adolescence could resemble social deprivation-like symptoms. Further studies should be designed, in which THC is systemically administered by animals over the entire adolescent period, to see if there is any resemblance to the social deprivation results. Various executive functions are to be assessed, together with prefrontal cortex connectivity in rats following consumption in adolescence. This could give further insight into the neurobiological changes seen and could also lead to a better translation of cognitive factors from rodents to humans.

However, the entire interaction between social play,

general social skills, and the endocannabinoid system is more complicated than it seems. For instance, human adolescents with good social skills were shown to be less likely to consume marijuana. Thus, there may be double modulation, where proper social play and interactions decrease the chance of consumption, and consumption leads to decreased social development (Griffith-Lendering et al., 2011). This can be further tested, by ranking animals that are shy and show a disturbance in social interactions prior to administration and assessing whether they are more likely to self-administer the drug. Moreover, the endocannabinoid system is versatile and acts over a large area of the CNS. The differences seen can come as a result of other brain centres or behaviours being affected (e.g., the prefrontal cortex). Further tests could try to only let animals administer THC during play sessions, or infuse THC during play in areas known to modulate social play (e.g. amygdala and NAc) (Trezza et al., 2012). This could however still not ensure that the social play disruption is the cause of future dysfunctions. Nevertheless, it would give insight into the way the main centres involved in social play are affected by prolonged cannabinoid administration.

Finally, most experiments reviewed in this article do not look at THC and social play directly, but rather THC and social interactions generally. Therefore, to test the exact interaction between cannabis, social play, and the long-term effects, a new paradigm should be designed and tested. Cannabis administration should be performed in increasing amounts via a cannabis smoke inhalation procedure (Stringfield & Torregrossa, 2020). Multiple rat model strains (e.g., Sprague-Dawley, Long-Evans, Wistar, etc.). should be tested and compared to see differences observed in all them; in this way starting to solve the problem of genetic and behavioural homogeneity. Furthermore, the administration should take place from mid-adolescence until adulthood (P35- P90). This is done to ensure a better correlation to human cannabis use. Following this, their social, emotional, cognitive, and behavioural wellbeing should be assessed via various tests for wellbeing and memory. Finally, physiological assessments should be done via patch clamping for brain connectivity, by looking at spontaneous discharge (Omrani et al., 2020).

In conclusion, social play is a rewarding behaviour that is correlated with activity in a vast range of brain areas and systems, including the endocannabinoid system. The modulation of play by the endocannabinoid system can be altered via exogenous cannabinoid use which can impact it both negatively and positively, based on whether CB1 activation occurs directly or indirectly. However, there is no consensus on whether using cannabinoids will lead to definite long-term consequences. On the one hand, cannabinoid use is dangerous as we are unsure of its definite long-term effects and their adverse reactions, which could include the development of psychosis, physiological alterations, and cognitive dysfunction (Rubino & Parolaro, 2008). On the other hand, the use of THC has also been correlated with beneficial outcomes in relation to therapy. For instance, treatment of paediatric epilepsy with THC has proven beneficial (Mechoulam et al., 2014). Therefore, despite the findings being inconclusive on the long-term effect of neural changes and changes in social and cognitive development, THC and other cannabinoid compounds should be further used for treatment purposes, but their potential harm should be publicly stated. Moreover, most of the research discussed here was performed in translational animal models; even though the neural circuitry corresponds to that of humans, the effects following consumption may differ. Humans are more complex in their behaviour and the display of social play; therefore, not all aspects of social play will be affected in a similar manner. However, the research findings presented here give an insight into the potential effects of cannabinoid consumption on the social play circuitry. Finally, additional experimental setups should be proposed where the effect of cannabis on social play is directly examined over more extended periods, followed by cognitive, emotional, and behavioural assessments and brain connectivity assays to determine long-term changes.

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CONFLICT OF INTEREST

The author declares no conflict of interest.

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'The role of white matter hyperintensities in vascular cognitive impairment: A literature review'

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White matter hyperintensities (WMH) are visualisations on MRI and CT scans of white matter damage caused by vascular pathology. WMH are found in the brains of elderly, but severity and frequency vary between individuals. The variability is correlated with increased risk of cognitive dysfunction. However, the exact role of WMH in the development of vascular cognitive impairment is yet unclear, which makes it the focus of this review. The main underlying cause of WMH is small vessel disease. Small Vessel Disease results in endothelial dysfunction. Due to endothelial dysfunction, white matter tracts are damaged, which results in decreased neural transmission. This could affect cognitive functioning, depending on the location of the WMH. Furthermore, WMH are not stable lesions, but can progress from periventricular white matter towards subcortical white matter, which most likely increases the effect on cognitive function. Also, the effect on cognitive function is influenced by the number of WMH, since the chances of damaging essential white matter tracts for cognitive functioning increases with the number of WMH. Therefore, the conclusion of this review is that the effect of WMH on the development of vascular cognitive impairment depends on the location, size, and number of WMH.

Keywords: *Vascular Cognitive Impairment, White Matter Hyperintensities, Small Vessel Disease, Vascular Pathology*

INTRODUCTION

White matter hyperintensities (WMH) are frequently found in the brains of elderly and are known to increase with age (Wardlaw et al., 2015). WMH are a form of white matter damage often caused by vascular pathology. These WMH can be observed on Magnetic Resonance Imaging (MRI) and Computed Tomography (CT) scans as hyperintense signals at specific locations in the white matter. For a long time WMH were thought to be unimportant in establishing diseases, since most elderly displayed WMH (Morris et al., 2009). However, brains show high variability in WMH, in frequency and severeness (Iadecola et al., 2019; Wardlaw et al., 2015). A high number and level of severity of WMH is correlated with increased risk of dementia, stroke, and death. Several risk factors for developing WMH have been established, among them aging, hypertension, diabetes mellitus, smoking, hypercholesterolemia and heart failure (Merino, 2019). In addition to that, genetic factors are thought to play a role in the frequency and severeness of WMH (Sachdev et al., 2016). These risk factors mostly relate to vascular pathology or are known to affect the vascular system, which points towards the origin of WMH in vascular diseases (Wardlaw et al., 2015). Furthermore, WMH have been implied to affect cognitive function (Desmond, 2002; Pantoni et al., 2007) and have been suggested to be a cause of vascular cognitive impairment (VCI; Alber et al., 2019; Iadecola et al., 2019).

VCI indicates any kind of problem in cognitive function due to cerebrovascular pathology (Van der Flier et al., 2018). These cognitive problems in VCI can have a wide range of severity, from subjective cognitive decline up to dementia. Patients suffering from VCI especially show impairments in executive function, neurological aspects (e.g. having tremors), information processing speed, and speech (Van der Flier et al., 2018). If individuals display these kind of cognitive problems, and if evidence of vascular pathology is found, patients are diagnosed with VCI (Dichgans et al., 2017). However, vascular pathology is also found in patients with Alzheimer's Disease (AD). Post-mortem brains almost never show solely AD pathology, but often a mix of vascular pathology and AD pathology (Van der Flier et al., 2018). This makes it harder to diagnose a patient with either VCI or AD. It is yet unknown how these two forms of cognitive impairment relate to each other. VCI and AD could develop simultaneously, or VCI could precede AD, since vascular pathology is a risk factor for developing AD. Another possibility is that AD precedes VCI, given that AD pathology develops years before symptomatic onset (Arvanitakis et al., 2016; DeTure et al., 2019).

The vascular pathology involved in VCI can be both macroscopic and microscopic (Gorelick et al., 2011). Especially the microscopic pathology, such as microvascular damage, seems to be important in the development of VCI (Esiri et al., 1997). This microscopic pathology is associated with white matter damage, which can be visible as WMH on MRI and CT scans. Both the macroscopic and microscopic vascular pathology can be caused by Small Vessel Disease (SVD) and by vascular lesions (Neuropathology Group of the MRC CFAS, 2001). The risk factors for developing VCI are highly comparable to the risk factors of WMH, namely age, hypertension (especially in midlife) and diabetes mellitus (Dichgans et al., 2017). In addition, risk factors like obesity, lack of physical activity, smoking and high cholesterol levels have been suggested to contribute to

the development of VCI as well. This suggests that WMH and VCI are related (Dichgans et al., 2017).
Even though WMH are strongly correlated with VCI, the exact role of WMH in the development of VCI is still unclear (Alber et al., 2019; Iadecola et al., 2019). As written before, WMH are frequently found in the brains of elderly. Nevertheless, not all elderly with WMH develop VCI. This aim of this review is therefore to explore the role of WMH of vascular origin in the development of VCI. It is expected that WMH contribute to VCI by disrupting white matter integrity in brain areas associated with cognition.

CHAPTER 1: THE VASCULAR ORIGIN OF WHITE MATTER HYPERINTENSITIES

Genetic factors are presumed to be important in establishing WMH (Sachdev et al., 2016). A twin study by Sachdev et al. (2016), suggested that WMH are highly heritable. This heritability was found to be especially high in the cerebral lobes, both the deep and periventricular areas, and lower in the cerebellum and brain stem. Depending on the cerebral areas in which WMH are found, the heritability is 55-80%. The same study found that the genetic factors contribute to a higher extent to WMH in women than in men, even though men have a higher risk of developing vascular diseases. It is thought that women are more vulnerable to develop WMH due to mother-daughter transmission of genes contributing to WMH. However, the high heritability of WMH decreases with age. Above the age of 75 years, heritability contributes less to the development of WMH (Sachdev et al., 2016). The exact genes responsible for WMH are still unclear. Many different genes have been suggested to play a role in the heritability of WMH (Sachdev et al., 2016). Most of the suggested genes are associated with hypertension and cholesterol regulation, which both are risk factors for WMH. In addition, genes involved in oxidative stress pathways and neural repair systems are suggested to contribute to establishing WMH (Sachdev et al., 2016).
Besides the genes that have been suggested to be a heritable cause of WMH, most WMH are thought to be caused by vascular pathology (Wardlaw et al., 2019). The most important vascular cause of WMH is SVD, which is indicated as an underlying cause of VCI as well. SVD describes a wide range of both genetic and sporadic vascular diseases, among which atherosclerosis, Cerebral Amyloid Angiopathy (CAA), Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL), and inflammatory angiitis (Wardlaw et al., 2019). A common underlying aspect of the different types of SVD is endothelial dysfunction of cerebral microvessels, which can be observed by increased levels of markers of endothelial activation and inflammation (Giwa et al., 2012). This endothelial dysfunction manifests as the breakdown of smooth muscle cells in the tunica media, in a smaller lumen of vessels, and in thickening of vessel walls (Coupland et al., 2018). These changes in microvasculature contribute to chronic hypoxia and hypoperfusion. Both hypoperfusion and chronic hypoxia are believed to be main causes of WMH formation (Van der Flier et al., 2018; Wardlaw et al., 2019). After the development of WMH in SVD patients, lacunes are often seen (Duering et al., 2013). Lacunes are subcortical, fluid-filled cavities of about 3-15 mm in diameter. The fluid in the lacunes is most likely cerebrospinal fluid, based on the MRI signal resembling cerebrospinal fluid in other areas (Ghaznawi et al., 2019). WMH and lacunes are thought to have different causes. Lacunes most likely result from occlusion of a single artery, while WMH seem to originate from chronic hypoperfusion (Duering et al., 2013). However, since WMH and lacunes have been shown to be closely (spatially) connected, they might have overlapping pathology as well.
Chronic hypoxia due to hypoperfusion can result in WMH formation (Van der Flier et al., 2018; Wardlaw et al., 2019). In an earlier study, increased levels of hypoxia markers were found in post-mortem brains in areas containing WMH (Fernando et al., 2006). Therefore, hypoxia was thought to contribute to the formation of WMH. In addition, in a study in individuals with AD and healthy individuals, decreased perfusion and increased

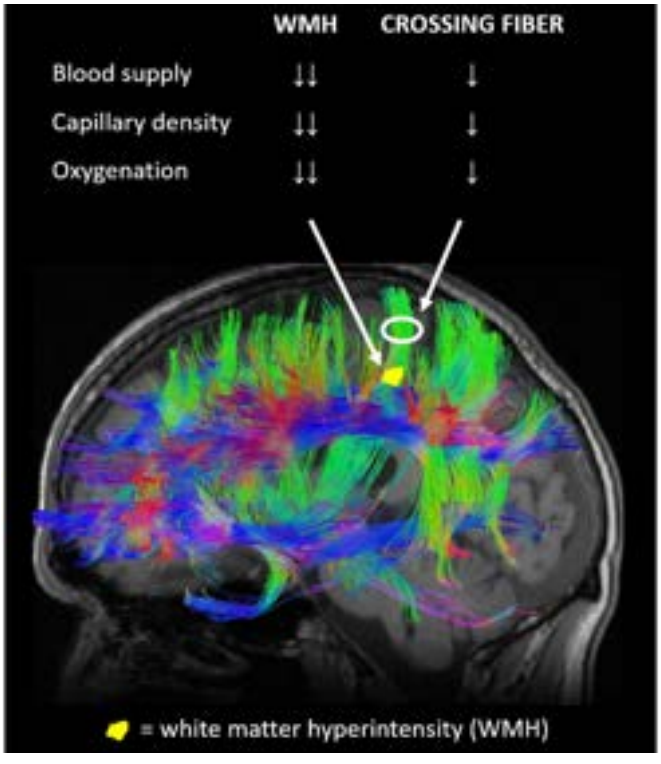

Figure 1. WMH reduces blood supply, capillary density, and oxygenation in the surrounding white matter and in the crossing fibre. The down arrows indicate the reduction of the corresponding aspect in WMH or the crossing fibre. The reduction in the WMH is more than in the crossing fibre (Dalby et al., 2019).

hypoxia markers were also associated with a higher occurrence of WMH and larger WMH (Gurol, 2013). This suggests that the size and number of WMH are partly determined by the perfusion in the brain, indicating that less well perfused areas (e.g., by occlusion) develop WMH more easily. This was examined in a longitudinal study, which showed that areas with decreased perfusion were strongly associated with the formation of WMH after 18 months (Bernbaum et al., 2015). Besides this study by Bernbaum et al. (2015), a recent study assessed the blood flow in WMH themselves and in the white matter fibres they intersect (Dalby et al., 2019). Not only in WMH, but also in the microvasculature of intersected white matter fibres, perfusion was decreased (Figure 1). This decreased perfusion resulted in lower tissue oxygenation. It was even shown that the more and larger lesions were present in the brain, the lower the level of tissue oxygenation was. If tissue oxygenation was too low, it could cause white matter damage. Possibly, hypoperfusion of tissue contributes to WMH formation by inducing deoxyribonucleic acid (DNA) fragmentation in oligodendrocytes,leading to oligodendrocyte apoptosis, as was shown in a study in rats (Tomimoto et al., 2003). Subsequently, oligodendrocyte apoptosis results in white matter damage, because oligodendrocytes are important for the myelination of axons in the central nervous system. Oligodendrocyte loss in WMH has also been found in human brains (Alber et al., 2019). Together, this suggests that especially hypoperfusion due to SVD, resulting in chronic hypoxia, is an underlying cause of WMH formation. Most likely, the white matter damage affects neural function, and it could result in VCI, depending on the size of the damage and the location.

A specific type of SVD is CAA. CAA is characterized by amyloid deposition in the cerebral vascular system. This amyloid deposition causes haemorrhages in the lobes, contributing to VCI (Gouw et al., 2011). The severeness of CAA is correlated with the severeness of WMH (Greenberg et al., 2004). Because CAA has an effect on the vasculature (inducing haemorrhages), more severe amyloid deposition possibly causes more severe WMH due to vascular dysfunction.

Another, genetic form of SVD is CADASIL (Gorelick et al., 2011). Patients with CADASIL show severe WMH on MRI scans and in addition often portray severe VCI. A missense mutation in the NOTCH3 gene of patients with CADASIL causes vascular smooth muscle cell defects, which can cause microvasculature changes (resulting in e.g. hypoperfusion; Coupland et al., 2018; Gorelick et al., 2011). In a study in NOTCH3 knock-out mice, breakdown of the blood-brain barrier was shown (Coupland et al., 2018). This breakdown is a manifestation seen in WMH as well (Simpson et al., 2010). Blood-brain barrier breakdown, like the changes in microvasculature, is believed to be a result of loss of smooth muscle cells from vessel walls (Coupland et al., 2018). This results in disruption of the blood-brain barrier, causing plasma protein leakage into the brain (Simpson et al., 2010). The concentration of plasma proteins leaking into the brain is highly correlated with the severity of WMH. Larger, more severe, WMH are characterized by more leakage than smaller, less severe, WMH. The plasma proteins leaking into the brain activate the brain's immune system, resulting in microglial activation, astrogliosis, and astrocyte apoptosis (Gouw et al., 2011). As a result, microglial phagocytic activity, secretion of neurotoxic molecules, and secretion of proinflammatory molecules is enhanced (Simpson et al., 2007). This increased immune cell activity and secretion could damage the white matter in which the immune cells reside. Furthermore, the astrogliosis and astrocyte apoptosis could cause astrocytic scarring, which indicates severe myelin loss. This scarring is also seen in multiple sclerosis lesions and has shown to be an inhibiting environment for axon regeneration (Simpson et al., 2007). If an axon is unable to regenerate, there is a permanent loss of myelin. Therefore, astrocyte and microglia activation could contribute to WMH formation. To conclude, the number of WMH increases with age and the formation of WMH has several causes. The endothelial dysfunction seen in SVD results in hypoperfusion and blood-brain barrier disruption, which both contribute to WMH formation. As a consequence of blood-brain barrier disruption, glial cells are activated, which also contributes to WMH. Furthermore, even though WMH are found in brains of elderly people in general, there is great variability in size and frequency between people. Severe WMH are correlated with VCI, suggesting that WMH influence cognitive function.

CHAPTER 2: THE EFFECT OF WHITE MATTER HYPERINTENSITIES ON WHITE MATTER AND BRAIN INTEGRITY

WMH are manifestations of white matter damage. This white matter damage can be the result of several of the mechanisms named in previously (e.g., hypoperfusion and blood-brain barrier disruption). Hypoperfusion, which results in chronic hypoxia, can have several causes as well (e.g. CAA, CADASIL, haemorrhages, ischemic stroke). Independent of the cause, hypoxia seems to have a direct effect on the white matter by causing oligodendrocyte apoptosis (Tomimoto et al., 2003). Due to the decreased number of oligodendrocytes, white matter is damaged. In addition, in older brains, the formation of new oligodendrocytes is decreased compared to young brains, which reduces the ability of older brains to remyelinate axons (Fields, 2010). This could contribute to the increase of WMH frequency with age. Because myelin enables fast transmission of neural signals by insulating axons, demyelination results in decreased neural transmission. Fast transmission is essential for proper brain functioning and decreased transmission is associated with impaired brain functioning (Fields, 2010).

Besides hypoxia, white matter damage can manifest due to blood-brain barrier disruption, causing immune cell activation. This could affect brain function as well.

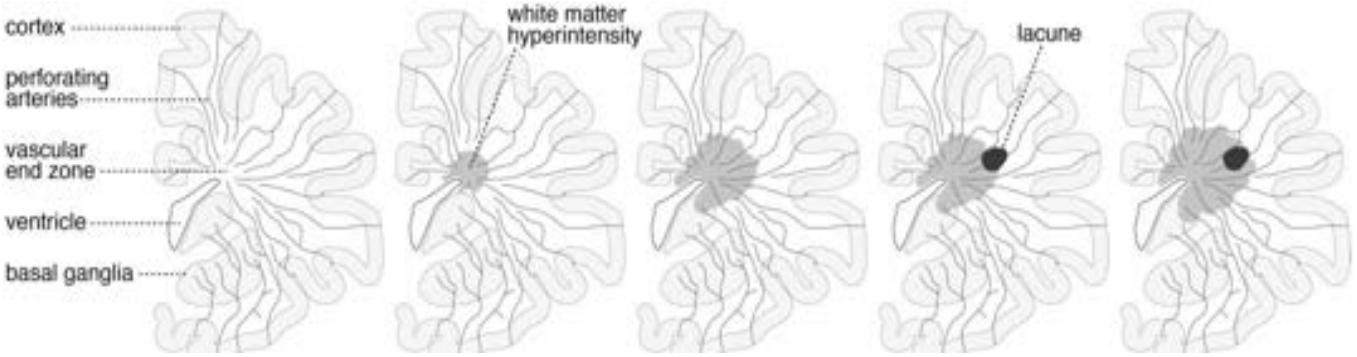

Figure 2. WMH progress towards the subcortical white matter along the perforating vessel. WMH are not stable and can progress through the white matter. If a lacune develops at the edge of WMH, it becomes surrounded by WMH as it progresses (Duering et al., 2013).

As mentioned earlier, glial cell activation and gliosis are present at WMH (Simpson, et al., 2007). However, both glial cell activation and gliosis are not limited to WMH. Changes in microglial activity are also found throughout non-lesioned white matter of brains with WMH. In addition, intact white matter surrounding WMH has also been shown to have a different gene expression from white matter in WMH-absent brains (Simpson et al., 2009). Differentially expressed genes are involved in cell structure, ion transport, proteolysis, and immunity. Especially the genes involved in immunity are of interest, since upregulation of these genes shows that changes in glial cell activation are not limited to WMH. This suggests that altered glial cell activity can spread throughout white matter surrounding WMH. As a result, the white matter damage possibly extends throughout the brain as well (Simpson et al., 2009). This progression of WMH to other brain areas most likely contributes to VCI by disrupting connections between brain areas which are involved in cognitive functioning.

In addition to the speculations of WMH spreading to the surrounding white matter, this extension has been studied as well. WMH are not stable lesions, but have been shown to progress towards the subcortical white matter (Duering et al., 2013). They progress along the vessel perforating WMH, towards this vessel's vascular end zone (Figure 2). The progression of WMH over the white matter has been associated with VCI (Maillard et al., 2012). Therefore, the size, number, and localization of WMH seem to be of importance in the development of VCI. Larger WMH, a higher number of WMH and WMH localization in brain areas important for cognition, most likely negatively affect cognitive function.

Lacunes, which often develop at the edges of WMH, become surrounded by WMH as WMH progress towards the subcortical layer (Figure 2; Duering et al., 2013). About 90% of the lacunes are found in proximity to the edges of WMH. This suggests that the surroundings of WMH are more vulnerable to lesions, most likely due to subtle white matter changes, which enable WMH to progress easily and cause increased white matter damage (Maillard et al., 2011). These white matter changes are possibly reflected in the differential gene expression pattern of white matter surrounding WMH compared to non-lesioned white matter areas. Neural transmission could be decreased in the affected white matter, which could affect cognitive function. However, since these subtle white matter changes in the surroundings of WMH are not visible on structural MRI and CT scans, cognitive impairment could be more severe than these scans suggest.

Besides the effect of WMH on the surrounding white matter, there is also evidence for more extending effects of WMH. WMH affect intersecting white matter tracts as well (Figure 1; Dalby et al., 2019). Since white matter tracts in the cortex can connect one area to another, the effects of the white matter damage can be as extensive as the length of the intersected white matter tract. Depending on the location, WMH disrupt long or short connections (Bolandzadeh et al., 2012). Subcortical WMH have been shown to disrupt short connections, which resulted in for instance motor symptoms (Bolandzadeh et al., 2012). However, periventricular WMH are more likely to intersect long white matter tracts (Kim et al., 2011). Since long white matter tracts connect several brain areas, which can be involved in cognitive functioning, especially periventricular WMH might be associated with VCI.

In addition to WMH being located subcortically or periventricular, the lobes in which WMH are located also seem to matter with respect to the effect of WMH on cognitive function. In patients with CADASIL, more and larger WMH have been found in the anterior temporal and superior frontal lobe compared to sporadic SVD patients (Auer et al., 2001). CADASIL patients almost always develop cognitive deficits and therefore have a higher chance of developing cognitive deficits than patients with sporadic SVD (Peters et al., 2005). Hence, the relative increase in WMH in the anterior temporal and superior frontal lobe possibly contributes to the development of VCI.

Furthermore, patients with CADASIL having extensive WMH show an increase in cerebral volume (Yao et al., 2012). Nevertheless, patients with CADASIL also experience brain atrophy, which is a key MRI marker for

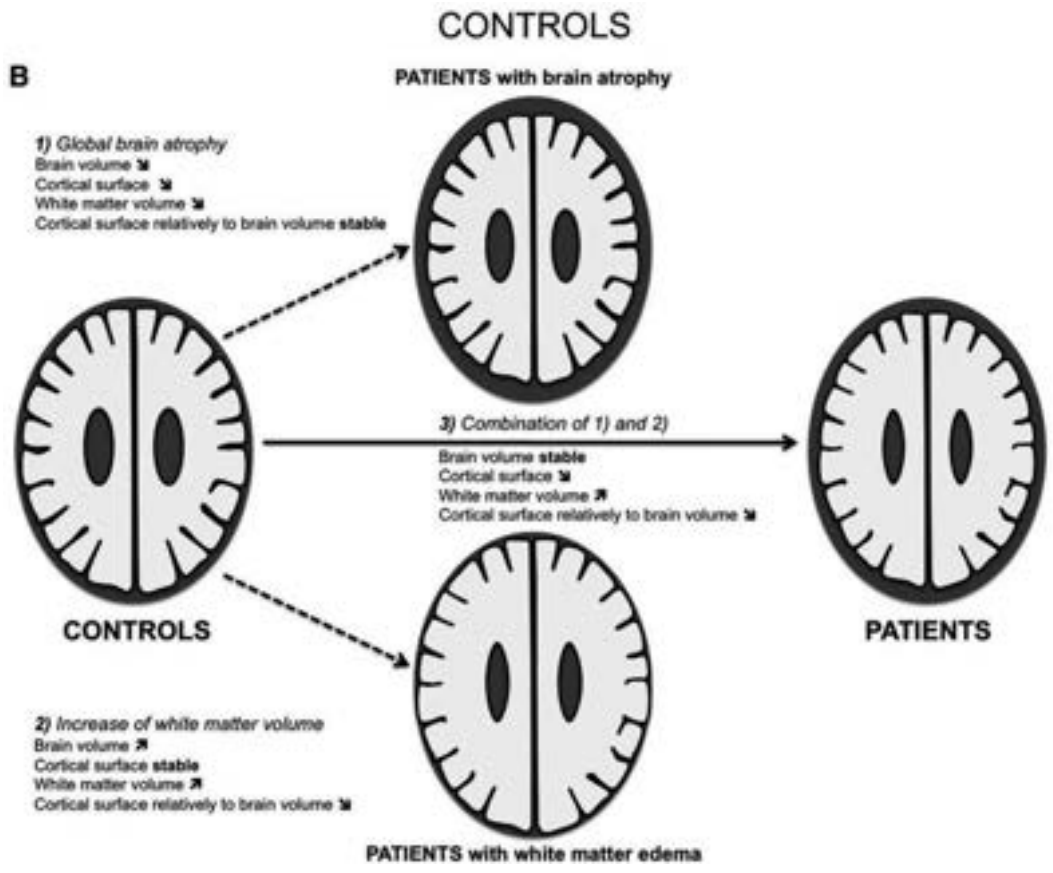

Figure 3. The effects of brain atrophy, white matter oedema and the combination of atrophy and oedema on the brains of patients. Patient 1 shows small vessel disease-related global brain atrophy. Patient 2 shows white matter oedema which leads to an increase in brain volume. Patient 3 shows a combination of both global brain atrophy and white matter oedema. For each patient, changes in brain volume, cortical surface area, white matter volume and cortical surface relative to brain volume are shown, indicated with either an up arrow (indicating an increase) or down arrow (indicating a decrease; De Guio et al., 2015).

SVD (De Guio et al., 2020). This paradoxical finding could be explained by the induction of intramyelinic oedemas by WMH that seem to compensate for the decrease in cerebral volume (Figure 3; De Guio et al., 2015). However, a study in a mouse model for CADASIL showed white matter oedema early in CADASIL. Probably, early in CADASIL WMH and oedemas are less extensive than later in CADASIL. Therefore, oedemas in early-stage CADASIL most likely do not yet cause an increase in cerebral volume. Even though an increase in oedemas and in cerebral volume was found, the influence on cognitive function is not yet known, since early-stage patients without VCI were assessed. While an increase in water content of the brain was found in patients with CADASIL, patients with other types of SVD exhibited a decrease in brain volume, corresponding to brain atrophy associated with SVD. This suggests that WMH in CADASIL patients have another origin and have other effects on the brain than WMH in patients with sporadic SVD (De Guio et al., 2020). At least, brain volume and brain atrophy have been linked to cognitive alterations and VCI. Therefore, brain atrophy resulting from SVD and the increased cerebral volume seen in CADASIL patients most likely influence the development of VCI.

To conclude, the white matter in WMH is damaged, resulting in decreased signal transmission, which might influence cognitive function. In addition, WMH are not sharply delineated lesions, but the white matter damage can spread towards the subcortical white matter. The effect of the spread of WMH on cognitive function depends partly on the location, size, and intersected white matter tracts. Furthermore, brain atrophy in SVD patients is associated with the development of VCI.

DISCUSSION

WMH are representations of white matter damage in the brain, resulting from vascular pathology. WMH are observed in almost every elderly brain. However, not all elderly develop VCI. Therefore, this review focussed on the role of WMH of vascular origin in the development of VCI. Most likely, WMH contribute to VCI by disrupting white matter integrity in brain areas that are associated with cognition.

By assessing the possible origins of WMH, SVD and other vascular pathology were shown to be underlying causes of WMH. Furthermore, reviewing the effects of WMH on brain integrity and white matter revealed that WMH progress throughout the white matter towards the subcortical white matter. Depending on the location, the intersected white matter tracts, and the size of the damage, cognitive functions can be impaired. The severity

of WMH is correlated with the severity of cognitive impairment. The effects of WMH on the development of VCI depend on the size, number, and location of WMH.

As discussed, patients with dementia often display mixed pathology (Van der Flier et al., 2018), which makes it hard to study the effect of only one cause of cognitive impairment (e.g. WMH) on the development of VCI. For example, AD pathology seems to have an effect on vascular pathology, since patients with severe VCI (also called vascular dementia) often exhibit AD pathology (e.g. tau pathology) as well. This indicates that AD could be a cause of VCI besides WMH. Even though WMH are mostly associated with VCI, WMH are also found in AD patients, which suggests that WMH also contribute to AD (Van der Flier et al., 2018). Furthermore, CAA is indicated as a cause for both AD and VCI (Van der Flier et al., 2018). In addition to the link between VCI and AD, VCI is also correlated with alpha-synuclein pathology which is the main cause of Parkinson's Disease (Gómez-Benito et al., 2020; Van der Flier et al., 2018). Taken together, this indicates that VCI is influenced by many factors and is related to other cognitive impairments beyond the scope of this review. WMH size and location make up one side of the story, but also individual differences in terms of cognitive reserve and other cognitive impairments affect the development of VCI (Van der Flier et al., 2018). Because of the many different factors contributing to VCI development, it is hard, if not impossible, to set a threshold for when WMH cause VCI.

Even though some indications of the effects of WMH location on VCI development were discussed in this review, more research is needed to confirm these implications and to further enlighten the association between WMH location and VCI development. However, since the brain areas are interconnected and lesions in one area could have widespread consequences on the functioning of this area and other areas, specifying the contribution of WMH in a certain area to an aspect of VCI is hard to do. Nevertheless, progress could be made by assessing the loss of specific cognitive function in patients with WMH in certain areas. In addition, more research should be performed to study changes in gene expression, since not much is currently known about the effect of WMH on gene expression or possibly the effect of differential gene expression on WMH formation. By conducting further research on the association between WMH and VCI development, treatments could be developed or VCI could be prevented, thereby limiting the effects of VCI on the population.

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CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

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'"It's all my fault": The reciprocal interaction between language and depression'

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Does depression influence language, or does language influence depression? Improving mood and dealing with depression have become a priority for many due to the COVID-19 pandemic. Fortunately, with a greater understanding of depression and neuroscience in general, serotonin is no longer considered the sole modulator of mood, and chemical imbalance is not seen as the only cause of depression anymore. Biological risk factors are not always sufficient nor necessary to explain depression either. Rather, it is psychological adversity early in life, and the interplay with genetic risk factors that contribute to depression. Given the importance of language for the development of a child, the question is raised whether language has an influence on the development of depression as well. In essence, a possible link between depression and language was shown. Firstly, the presented literature indicates that what has been described as depressive schemas are influenced by conceptual knowledge of emotion categories. Given that conceptual knowledge is acquired through and its access influenced by language, there is an interesting direct link between depression and language. Secondly, language-use is influenced by depression, indicated by higher focus on self and negative emotion words. In combination, this could mean that there is a reciprocal interaction between language and depression. The implication is that this could lead to a negative feedback-loop, possibly contributing to the progressiveness of major depressive disorder. Furthermore, potential language-based tools to intervene in the development or the progression of depression are presented.

Keywords: *Depression, Language, Cognitive Behavioural Therapy (CBT), Emotional regulation, Cognitive Act Theory (CAT)*

INTRODUCTION

Depressed mood can occur as a comorbidity of a multitude of mental and physiological illnesses. Major depressive disorder (MDD), an illness with depressed mood as its main symptom, is heterogeneous both in core and in additional symptoms. Apart from depressed mood, the American Psychiatric Association's (2013) Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM-5) requires various additional symptoms to be present for the diagnosis of MDD. However, the additional symptoms can be both cognitive, such as diminished concentration or low energy, affective, such as feelings of worthlessness, and physiological, such as weight loss and change in appetite (American Psychiatric Association, 2013). Considering the wide scope of symptoms, multiple brain areas have been shown to have structural, functional, and molecular alterations in MDD (Maletic et al., 2007). Furthermore, MDD is a recurrent illness, manifesting itself in reoccurring depressive episodes. A neurobiological vulnerability seems to drive this reoccurrence. A family history and early age of onset seem to further increase the likelihood to experience multiple episodes (Maletic et al., 2007; Warden et al., 2007).

As there is no single and universal depression to speak of, it cannot be approached through a "one size fits all" treatment. Despite the relative success of selective serotonin reuptake inhibitors (SSRIs) as a treatment for patients with depression, there are major down-sides to the treatment. Firstly, there is a low difference in effect size between SSRI- and placebo-treatments for depressive disorders (Locher et al., 2017). This suggests that a minority of patients benefits from the SSRI treatment. Secondly, adverse effects, such as insomnia, headaches, fatigue, and gastrointestinal issues, are significantly increased by SSRI intake. The small benefits of SSRIs are therefore outweighed by the adverse effects. Moreover, trials showing a statistically significant effect on depressed mood after SSRI treatment are highly at risk for being biased. Thus, the clinical efficacy of SSRIs seems questionable (Jakobsen et al., 2017). As such, alternatives should be sought out. This is especially critical now, as during the COVID-19 pandemic the prevalence of depressed symptoms has more than tripled in number (Ettman et al., 2020).

One alternative treatment involves cognitive behavioural therapy (CBT). In essence, it is a psychosocial intervention that is used to improve mental health, including the treatment of depression (Beck, 2011). It mainly focuses on changing a person's core beliefs about themselves, about the environment, or about the future. One such method involves the use of language through self-talk, or in conversation with a trained professional. The question is what the role of language actually is. Is it just a means of conveying information from the therapist to the patient? Or is there a deeper mechanism between language and emotion regulation, or even depression? Could language be used in such a way to prevent the onset of depressive episodes, or even protect vulnerable individuals from the development of MDD?

As depression affects not only emotional but also cognitive processing, it is not too unreasonable to

assume that it also affects the use of language. This will be further explored in the following work, which raises an interesting implication for the reciprocity of language and depression: If accepted that language influences and is influenced by depression, that could mean that they interact in a negative feedback-loop, leading to a downward spiral of depression and language, each deteriorating the other. his could be one of the reasons for the progressive nature of MDD. More knowledge on this relationship could shed light on the nature of depression and other emotional dysregulations, such as anxiety disorders, as well. Furthermore, psychotherapeutic interventions for depression could take this suggested interrelatedness into account, to improve their efficacy and improve patient health long-term.

THE BRAIN AND DEPRESSION

Serotonin and depression

For the past 50 years, the serotonin hypothesis of depression had been regarded as the main explanation for depression (Cowen & Browning, 2015). Low levels of the neurotransmitter serotonin were thought to be responsible for the negative mood in depression. This was the conclusion after observations of antidepressant drugs that were later found to potentiate the effect of serotonin (Cowen & Browning, 2015). At the time it was reasonable to assume that the elevation of serotonin levels was causal to the alleviation of negative mood. In other words, the assumption was that depression was negatively correlated with serotonin levels. However, this overly simplistic hypothesis was refined over the years due to its inconsistencies. For example, healthy controls with experimentally lowered serotonin levels had only moderate mood changes, if any. Secondly, as mentioned previously , not all patients with depression benefited from serotonin-level enhancing drugs, such as SSRIs (Albert et al., 2012; Locher et al., 2017). And thirdly, drugs that do not change serotonin levels can still be used as effective mood stabilisers (Albert et al., 2012; Mathew et al., 2008). The chemical imbalance view was a reflection of the Zeitgeist at the time, with single neurotransmitters having single roles, such as serotonin for mood or dopamine for motivation, or single brain areas fulfilling single functions, and functions being fulfilled by single areas. The current neural-network and system-level neuroscience stands in stark contrast to those, now obsolete, ideas (Cowen & Browning, 2015; Maletic et al., 2007). That is not to say that serotonin has no role in depression. However, it plays a bigger role for the recovery of depression than in its causation. Furthermore, dysfunction in serotonin and serotonin precursor regulation might add to a person's vulnerability, but are not the primary cause for depression (Albert et al., 2012; Cowen & Browning, 2015; Ruhé et al., 2007).
Nonetheless, SSRIs have been shown to be effective antidepressant drugs for some patients (Cowen & Browning, 2015). It has been observed that SSRI administration, both in depressed patients and healthy controls, results in a positive shift in appraising emotionally valanced information by the brain (Cowen & Browning, 2015). In other words, emotional information is processed with a more positive shift. This seems to particularly involve the amygdala, along other serotonergic innervation to limbic circuitry. Of note is that this effect occurs before the clinically observed antidepressant effect. It seems that the positively shifted information processing leads to more positively valanced, automatic, emotional responses. The improvement in mood is thus a consequence of the sum of positively biased emotional responses, rather than being influenced itself (Cowen & Browning, 2015). In other words, a person does not suddenly become happy but rather reacts in a more positive way to any events or thoughts they have. This in turn could further contribute to improvement in mood, as at the very least depression as a stressor is removed.

SSRIs go beyond serotonin

Interestingly enough, the effects of SSRIs go beyond increasing serotonin levels. Animal studies have shown that repeated SSRI administration resulted in higher cell proliferation in the hippocampus (HC) and increased expression of neuroplasticity-inducing proteins such as brain derived neurotrophic factor (BDNF) (Cowen & Browning, 2015; Sharp & Cowen, 2011). The HC is understood to play a role in learning and memory (Jarrard, 1993), through the mechanism of long term potentiation (LTP) (Whitlock et al., 2006). Given that BDNF induces LTP in the HC (Ying et al., 2002), it seems that SSRIs play a role in enhancing the ability to learn. It is challenging to link this increased neuroplasticity and learning ability to the antidepressant effects of SSRIs. Cowen and Browning (2015) have attempted to explain the antidepressant effect of SSRIs by induction of re-learning of emotional responses. As noted above, SSRIs have been observed to induce a positive shift to emotional information processing. Coupled with the increase in learning ability, exposure to a variety of experiences, that might have had a negative connotation attached to them, could be long-term reinterpreted in a more positive way. Over time, all previously negative connotations might be replaced by more positive or neutral ones (Cowen & Browning, 2015).

Cortisol and hippocampal atrophy

Interestingly, the effects of SSRIs on the HC are almost the exact opposite effect to what occurs through MDD. Although general atrophy in the central nervous system (CNS) is associated with extended depression, it seems that the HC is particularly vulnerable (Cowen & Browning, 2015; Maletic et al., 2007; Sapolsky, 2001). In some cases, a volume loss of nearly 20% has been reported, even when corrected for alcohol consumption, medication,

and other detrimental factors. The causal relationship between hippocampal volume loss and MMD remains to be elucidated. However, it is assumed that biological changes due to depression lead to the changes in the HC (Sapolsky, 2001). Given that MDD is a stress-related disorder (Maletic et al., 2007), three possible cellular mechanisms have been proposed that could explain how continuous stress causes atrophy in the hippocampus: (I) retraction of dendritic processes in the hippocampal neurons could lead to atrophy as a secondary cause, due to neutrophil volume loss. However, this is reversible with absence of stress, and unlikely to be relevant for MDD. (II) Inhibition of neurogenesis in the adult HC. (III) Neurotoxic effects of continuous stress on neurons of the HC, although this was only reported by some and not all studies (Sapolsky, 2001). According to Sapolsky (2001) a combination of neurogenesis-inhibition and neurotoxicity due to sustained stress could be prominent for hippocampal volume loss in MDD.

Naturally, glucocorticoids, specifically cortisol in humans, are primary suspects in proximal causes for stress-induced hippocampal atrophy (Sapolsky, 2001). Indeed, half of MDD patients have a hypersecretion of cortisol. Furthermore, in Cushing's syndrome, hypersecretion of cortisol due to a tumour leads to volume loss in the HC. However, these findings which link glucocorticoids with HC atrophy are still correlative in nature. Nonetheless, the correlations between stress, cortisol and depression have been found to be significant (Qin et al., 2016). Thus, it is reasonable to assume that stress, which is associated with onset of depressive episodes, also plays a role in the atrophy of the HC seen in MDD patients. This could be one of the factors contributing to the progressiveness of MDD. Moreover, considering the central role of the HC in memory, it could explain some cognitive deficits observed in patients. Similarly, some aging-related cognitive decline has been linked to hippocampal atrophy (Bettio et al., 2017).

In sum, a combination of stress, trauma, and biological vulnerability could lead to elevated cortisol levels, and affective symptoms of depression. Moreover, these could interact with one another, and lead to the hippocampal atrophy, either cortisol levels or affective symptoms being the driving force behind the atrophy. Consequently, this could lead to the cognitive symptoms seen in depression (Czéh et al., 2001; Sapolsky, 2001).

Stress and the onset of depression

Although MDD is a stress related disorder, the momentary stressfulness of life is not the leading predictor of having a depressive episode (Maletic et al., 2007). Instead, it is the number of previous episodes a person has had that best predicts the occurrence of another depressive episode. This progressive nature of MDD is explained by the "Kindling hypothesis" (Maletic et al., 2007). It states that each subsequent depressive episode is triggered more easily than its predecessors. "Kindling" is the process by which either the threshold of stressful event that trigger the depressive episode, are repeatedly lowered, or spontaneous dysregulation is increased. It could be a combination of the two. In line with the observation of family history affecting a patient's number of episodes, is the notion that these patients were "pre-kindled" by their high genetic risk, meaning that the threshold is already lowered compared to patients with a low genetic risk.

Besides genetic risk factors, psychological factors, such as adverse experiences early in life, have been shown to play a role in depression vulnerability (Maletic et al., 2007). This was found to contribute to long-term changes in the brain's biology which correlate with depression. As an example, maternal neglect or deprivation in rat pups led to a hyper-reactivity to stress that changed the behaviour well into adulthood. The interrelationship between genetic- and psycho-social factors was particularly demonstrated in children, as the risk for depression was associated with certain genotypes and a history of maltreatment.

The challenge in treating depression is that SSRIs do not work for a large number of patients, or come with many side-effects (Jakobsen et al., 2017; Locher et al., 2017). Ideally, induction of re-learning of emotional responses that was proposed as the mechanism of SSRIs by Cowen and Browning (2015), could be achieved without the need for SSRIs. The following paragraphs will attempt to explain how language could be fundamental to this mechanism of re-learning emotional responses. Furthermore, possible language-based tools will be explored that could be specifically used to mimic this effect of SSRIs.

DEPRESSION AFFECTS LANGUAGE-USE

It is perhaps not surprising that altered affective and cognitive states, such as in depression, change how a person communicates. This change extends to the way a person uses language as well (Bernard et al., 2015; Rude et al., 2004). It has been found that depression affects pronoun use, with more frequent use of first-person pronouns such as "I" in formerly and currently depressed individuals (Rude et al., 2004). This was found by a study in which college students were asked to write an essay entailing a description of the deepest thoughts and feelings about being in college. Students were assessed on depression score prior to the essay. The written texts were analysed for usage of first-person singular pronouns, first-person plural pronouns, social references, negatively valanced words, and positively valanced words. Interestingly, formerly-depressed participants only showed significantly increased first-person pronoun frequency in the third segment. This suggests that formerly-depressed individuals become progressively concerned with the self, as control over depressive thoughts weaken (Rude et al., 2004). In a similar study by Bernard et al. (2015), students were induced with positive, neutral or negative affect. Linguistic priming was avoided, by showing participants a series of images,

instead of words. The subsequent essays underwent identical analysis. In addition to the findings of Rude et al. (2004), it was found that negative affect was associated with increased use of negatively valanced emotional words.
These findings confirm the notion that language is a reflection of the inner state. In the case of depression, this means that the core mechanisms of increased self-focus and separation from others are reflected in the use of language (Bernard et al., 2015; Rude et al., 2004). Although there are no current studies that causally link depression and language (Bernard et al., 2015), these correlative findings could lead to a better understanding of the two subjects.

COGNITION, AFFECT AND DEPRESSION

Cognitive theory of depression

The findings of increased self-focus and negative emotions are in line with the findings of Beck (1970) and his cognitive theory of depression. It states that depressive schemas lead depressed individuals to a negative perception of self and the world (Beck, 1970; Rude et al., 2004). These depressive schemas are deep level knowledge structures that can give rise to automatic thinking, such as automated depressive and negatively biased thoughts. In this model, the recurring nature of depressed episodes is explained by the latency of those schemas. Stressful events, such as loss of a loved one, can trigger the activation of schemas, leading to the onset of depressed episodes. Considering that subsequent events are more negatively valanced, this can lead to further triggering of schemas. Consequently, this leads to worsening and prolonging of the depressed episodes, which in turn can be perceived as a stressful event by itself and subsequently explains the progressive nature of MDD (Maletic et al., 2017).
It seems that there is a similarity between the Kindling hypothesis and the cognitive model. Kindling describes the progressiveness of MDD through either lowering the threshold of stressful events that trigger the depressive episode, or by an increase in spontaneous dysregulation (Maletic et al., 2007). This threshold of stressful events is very similar to Beck's (1970) description of depressive schemas that trigger depressive episodes. It seems that genetic or other biological vulnerability to depression, by which a person is pre-kindled, have something to do with those depressive schemas as well. Being pre-kindled could either mean that one sets the stress-threshold for depressive schemas lower as it would be otherwise, or it could mean that the amount of stress experienced from events is higher.
Another integrative model of depression is the "Self-regulatory control framework" (Carver & Scheier, 1981) which also considers the role of self-focused attention (Pyszczynski & Greenberg, 1987). The assumption is that depression occurs as a result of loss and failure. The self-regulatory cycle seems to be a normal function that aims to regain what was lost. Depressed individuals are unable to leave this cycle, for any number of psychological or biological reasons. This leads to amplification of negative emotions, constant self-blame, and the interference of productive reasoning of issues at hand, that presumably caused the depressive episode in the first place, as attentional resources are spent to focus on oneself. Again, there is a higher focus on the self, which is reflected in the use of language by depressed individuals.

Emotion regulation through cognitive control

Formerly depressed individuals seem to have learned to cope with their negative emotions by exerting cognitive control over them. This is evident by the increase of negative emotions in formerly depressed students after reduction of their volitional control during tasks with heavy cognitive load (Rude et al., 2004). This suggests that the automaticity of emotional responses is not changed, but rather that the emotions are just being successfully suppressed. In terms of the self-regulatory cycle this could mean that emotion-suppression leads to the inhibition of cycle-entry. This could be achieved for example by reducing the stressfulness of an event, lowering it below the threshold to trigger the self-regulation. However, the threshold itself would then not be altered. If too many stressors occur at once and cognitive control cannot keep up with that load, or if the control is lost otherwise, it could be that the cycle is entered, and the depressed episode is initiated. The impact of cognitive control, influenced by stressor-load and cognitive-load, on depression would be interesting for future research. The ability for cognitive control might be one factor in a person's vulnerability to depression or other mental disorders.

EMOTIONS AND LANGUAGE

Construction of emotions

Language is fundamental to emotional experiences and perceptions, according to the Conceptual Act Theory (CAT) (Lindquist et al., 2015). This psychological constructionist view describes emotions as being emergent entities. Emotions arise as a consequence of basic bodily reactions or stimuli being combined with conceptual knowledge of emotional categories (Lindquist, 2013; Lindquist et al., 2015). Conceptual knowledge is essential to give meaning depending on the context of the situation. In this view, emotions, perceptions, and cognition are not distinct but emerge from the same basic processes. This is in contrast to other older models, that view emotions as separate mental states from cognition and perception. Emotions were regarded as domain-specific, inborn, or inherited. Furthermore, they were thought to have a specific anatomically distinct neural structure associated with each of them. The CAT is in

line with the current neural-network and system-level neuroscience view (Cowen & Browning, 2015; Maletic et al., 2007). According to the CAT model, emotions arise to make sense of bodily senses for any given context, using conceptual knowledge about those emotion categories. For example, the emotion of "fear" is not something that is hardwired from birth, to always react to the same hardwired "fearful" stimuli. The emotion fear emerges, when the conceptual knowledge about fear and external sensations are used together to make sense, to give meaning to the state of the body. For example, a beating heart in a dark alley with loud noises would be aligned with the conceptual knowledge of fear, thus the emotion fear is experienced. In contrast, a beating heart in a restaurant setting with a partner opposite to one would be more in line with love, therefore the emotion love is experienced. In these examples, the same bodily state gives rise to different emotions, based on the context and conceptual knowledge of the context. However, context alone is not sufficient to explain emotions. Rather, conceptual knowledge of the emotion categories links context or external stimuli, and bodily states together.

The implication of this is that a change in conceptual knowledge alters how and what emotions are experienced and how a situation itself is perceived. This is why some people experience different emotions in the same context, depending on the conceptual knowledge the person has. For example, one might feel joyful when hearing laughter after having told a joke, but a feeling of embarrassment to the same laughter when falling over. Another person might feel joyful in both cases, laughing at their own misfortune together with everyone else, ignoring their fall. A third person might feel embarrassment in both cases, for example if they have an anxiety disorder, where they think that people started laughing at them and not with them. Despite the similar contexts, all three persons experience different emotional reactions, and perceive the whole situation differently. What sets them apart is the conceptual knowledge they possess. This was acquired, updated, and otherwise changed throughout their life. Biological factors aside, it is reasonable to assume that the third person has had adverse experiences regarding laughter that led to a sensitivity. In such a case, the conceptual knowledge might include something along the lines of "laughter is not good, try to avoid it". Of course, this is not stored as semantic knowledge, easily accessible to recite. This conceptual knowledge is not stored by the sentence "laughter is not good, try to avoid it".

Language shaping conceptual knowledge acquisition

Where language comes into play, is in its fundamental role in acquiring and shaping conceptual knowledge. For example, children cannot consistently categorize facial expressions of different emotions, such as anger or sadness, until they have acquired the appropriate words, and begin to use them in conversations. Children before the age of 2, where they are considered pre-linguistic, seem to be able to only differentiate facial expressions in their valency, e.g. pleasant or unpleasant (Lindquist et al., 2015). This was shown through experiments where children were given a set of pictures, showing five emotion categories. The children were asked to match an additional picture to those categories, e.g. angry with angry, by placing them in a box. The 2-year-old pre-linguistic children matched all unpleasant faces, including angry, sad, disgusted, and fearful, but left out happy faces. This indicates that they were only able to differentiate between pleasant and unpleasant faces. In contrast 3- to 4-year-olds, that started to gather concepts such as "sadness" and "fear", did not match those faces with "angry" faces. This indicated a more refined knowledge of unpleasant faces. Moreover, 7-year-olds were able to differentiate all faces but disgust, displaying adult level categorization of faces (Lindquist et al., 2015; Widen & Russell, 2008). These findings imply that children improve their ability to perceive, categorize and label facial expressions as they start to acquire emotional words, and start to use them in their daily conversations. Thus, language is fundamental in the acquisition of conceptual knowledge and emotional perception. The influence of language does not end in childhood. Adults continue to update the conceptual knowledge they possess throughout their life. Although, this might not be as strong as in children, as adults already have considerable knowledge on emotional categories.

Moreover, there is evidence that better differentiation of emotional states is linked to improved emotion regulation (Lindquist et al., 2015). Notably, this differentiation ability is found to be worse in patients with MDD. It was shown that depression is associated with difficulty in identifying feelings, specifically in differentiating negative emotional experiences. This is the first indication that depression is influenced by language, albeit indirectly.

Language shaping emotional experience

Language is also fundamental in accessing conceptual knowledge and shaping emotional experiences. For example, impairing a person's access to the meaning of emotion words also impairs their ability to recognize facial expressions (Lindquist et al., 2014; 2015). This was done by "verbal overshadowing", where participants were asked to repeat words during the facial recognition task. Another method for achieving inaccessibility of emotion words is by "semantic satiation". Here, participants repeat an emotion word such as "anger". The effect is that the meaning of that emotion word becomes temporarily inaccessible. The faces are subsequently described as unpleasant, but not as "sad", "afraid", "angry" etc. Furthermore, if someone labels their own unpleasant feeling with emotion words, that emotion is experienced subsequently. Research by Lindquist and Barrett (2008) suggests that priming a person with labels for an emotional category, such as "fear", leads

to behaviour typical for fear after unpleasant music is listened to. In contrast, individuals that were exposed to "anger" category labels, or individuals without any label exposure, were less likely to show fearful behaviour after listening to the same unpleasant music. This indicates that language, through the use of particular emotion words, shapes the subsequent emotion that is felt, even if exposed to the same unpleasant situation. This happens as different conceptual knowledge on emotion categories are accessed after the priming with different emotion words. Interestingly, it was not only the behaviour that changed, but the bodily response as well, such as cardiac responses. For example, individuals engaged in a stressful mental arithmetic task showed physiological responses consistent with an experience of threat, when they labelled their emotions while completing the task. In contrast, individuals that did not label their own emotions showed a physiological profile that was more in line with active coping. The implication is that mere labelling of an unpleasant state, with one emotional word or another, can alter the following emotion that is experienced, and subsequently the whole perception of a state and situation (Lindquist et al., 2015). The suggestion by the CAT is that language is fundamental to accessing emotion concept knowledge, thus shaping emotional experience. Forcing the usage or inhibiting the access of words has direct implications for the emotional experiences that follow.

Neuroscience of language and emotion

There is a growing body of neuroscientific evidence that links language and emotion. Brain regions associated with uncertainty, such as the amygdala, have reduced activity when emotion words are used to label emotional facial expressions (Lindquist et al., 2015). Again, this suggests that emotion words are used to make sense of otherwise unclear facial expressions, that are either pleasant or unpleasant. Furthermore, subsets of brain regions that play a role in emotion experience and perception also play a role in semantic judgements. Thus, the implication is that emotions are not influenced by language after the fact, but rather that language shapes the experience from the get-go (Lindquist et al., 2015). This means that it is possible to shape emotions when they arise depending on the conceptual knowledge a person possesses.

LANGUAGE'S INFLUENCE ON DEPRESSION

Interestingly, there seems to be an overlap between depressive schemas and conceptual knowledge. To recall, depressive schemas are what lead depressed individuals to a negative perception of self and the world. As described by Beck (1970), these schemas are deep level knowledge structures that can give rise to automatic thinking, such as automated depressive, negatively biased thoughts. This sounds a lot like the description of conceptual knowledge of emotion categories, that give rise to emotional reactions by giving meaning to bodily states based on external stimuli (Lindquist et al., 2015). Of course, the exact overlap can be subject to debate, and this work is not meant to, or able to definitively state that there is a 100% overlap. Nonetheless, both concepts are so close in description, that at the very least, conceptual knowledge has an influence on depressive schemas. Regardless of the exact extent to which this overlap is accepted, it would mean that language plays an important role in the development of depressive schemas. This is a more or less a direct link between language influencing the development of depression.

These depressive schemas are essentially what establishes the thresholds for entry into the self-regulatory cycle. During the self-regulatory cycle focus is directed towards the self (Carver & Scheier, 1981; Pyszczynski & Greenberg, 1987). This enhanced self-focus is further reflected in the use of an increased frequency of self-pronouns such as "I" (Bernard et al., 2015; Rude et al., 2004). Considering that language has an influence on conceptual knowledge, this might lead to a self-reinforcing cycle leading to a downward spiral in depression progression in the following way: Depression leads to more thoughts with a focus on the self. Subsequently, language with more self-focus as well as negative valency is used more often, leading to updates of conceptual knowledge that is further depressive. Updated depressive conceptual knowledge, or updated depressive schemas, could lead to an earlier onset of depressive episodes, by lowering the threshold for entering the self-regulatory cycle. Furthermore, conceptual knowledge could be updated such that previously "normal" events are perceived as stressful. Essentially, the conceptual knowledge on when to feel stress is broadened such that previously neutral or positive situations fall into the same category as well. Moreover, experiences already categorized as stressful could be increased in the level of stress that is experienced. Meanwhile, the depression itself, the progression of the depression, and possibly the accumulation of unresolved problems of life, could be further reasons to experience stress. Essentially, the levels of stress are raised during the progression of MDD, while the threshold to enter depression is further lowered. All this could be a result of updating conceptual knowledge on emotion categories to be more depressive, at least in part by language (Lindquist et al., 2015).

The inverse could be an explanation to the link between depression and the HC mentioned earlier. To recall, the HC is constantly being damaged due to stress from cortisol over the course of MDD (Qin et al., 2016; Sapolsky, 2001). As the HC plays a major role in learning, it could be that the ability to relearn or update conceptual knowledge, such to be less depressive for example, is diminishing by each stressful event or depressive episode. Moreover, the inverse of this was suggested to be one of the mechanisms of SSRIs. It was observed that SSRIs lead to an increased hippocampal cell proliferation and increased expression of neuroplasticity proteins, such

as BDNF (Cowen & Browning, 2015; Sharp & Cowen, 2011). Furthermore, SSRIs were observed to exhibit a positive shift in emotional responses. This positive shift in combination with higher hippocampal plasticity could lead to a relearning of emotional responses in the long-term (Cowen & Browning, 2015). Essentially, the conceptual knowledge about emotions can be updated again.

However, language not only plays a role in the acquisition and updating of conceptual knowledge and/or depressive schemas. It also plays a role in the use of conceptual knowledge and thus emotional regulation as well (Lindquist et al., 2015). Therefore, language has potential to be used as a psychotherapeutic tool.

Cognitive Behavioural Therapy and Language

Cognitive behavioural therapy (CBT) is a form of psychotherapy that is used to improve mental health, such as in MDD. The main focus lies in changing unhelpful beliefs and behaviours by improving emotional regulation (Beck, 2011). CBT uses a variety of different techniques, that are each aligned on the individual level, oftentimes developed for and by the patient with help from the therapist. These techniques include self-instruction, biofeedback, development of adaptive coping strategies etc. Language-based CBT techniques, such as self-instructions, could be used to steer conceptual knowledge acquisition away from depression, or in case of already developed depression update it such that the schemas become obsolete, such that the conceptual knowledge is no longer depression vulnerable. Furthermore, strategic language-use could prevent or reduce the access to depressive conceptual knowledge as well. This could serve as a momentary prevention of depressive episodes. For example, self-instructional training is one CBT approach, where self-management is aimed. Statements that are addressed to oneself influence the attentional and appraisal processes. In the case of sports performance, behaviour and performance can be regulated through self-talk (Hatzigeorgiadis et al., 2011). It is feasible that this kind of altered attentional processing could also lead to altered cognitive and affective processing, such that it is useful for depression.

Possible language-based CBT-techniques

As an example of emotional regulation, it might be possible to induce a perspective change through the use of language. Instead of describing a situation as "I don't like this weather" it could be described as "this weather isn't nice" or even better "it is currently raining". The issue is that "I don't like the weather" can quickly lead to a train of thought such as "I always hate the weather in this town, I don't like it here. I don't like the people here, they hate me….". The implication for describing the weather objectively is that there is less focus on the self. Instead, the focus is on the objective statement of the current weather conditions without any connection, thought or valency to oneself. Of course, the usage needs to be trained such that it is easily accessible in a depressive episode. This could be achieved for example, if the perspective change is trained and habituated in the absence of the depressive episode. Audio or written journals could be used for this purpose for example. The habituation ensures the usability, even without cognitive or affective effort. In turn, this perspective-changing language could steer thoughts and feelings away from the negativity and the self, and more towards the problem and solution or just perceive the whole situation through a more objective viewpoint. The mental resources occupied with the self, could be steered deliberately towards the problems at hand. Problem- and solution-oriented language might be able to result in this desired effect. Furthermore, these could in turn counteract the reciprocity of language and depression, where self-focused language is used which could further induce focus on the self.

However, this should not be confused with using overly-positive language, and seeking the positive in everything. Forcing to see things in a positive way would not necessarily shift the focus away from the self; "I like this stormy and windy weather, especially when it affects me outside. I like it when bricks nearly miss my face at 100 km/h", and as it cannot always be applied, such as in truly tragic situations. Furthermore, it is only a shift from negative to positive, which is neither always possible for depressed individuals, nor desirable to every situation. If instead focus is shifted from the self, neither positive nor negative apply anymore.

This would be one of the possible language tools, but many more could be developed for broader or personalized application. Other things to take into account could be how sentences are structured, passive vs active, first vs third person etc., has an influence on the message, the interpretation and thought following the sentence. Thus, if one is trained to speak in a certain way that shifts focus towards or away from something, subsequent sentences and thoughts are shaped to focus on that as well.

THE RECIPROCITY OF LANGUAGE AND DEPRESSION

It could be that the relationship between language and depression is reciprocal, and that it accounts for some of the progressiveness of MDD. As was highlighted before, language is influenced by depression through increasing usage of words with higher self-focus and negative valency on the self. Language is not only a reflection of the inner state, but also influences the inner state. Although language reflects the inner state, it could have an influence on the inner state as well. In terms of emotion regulation, this would mean that a higher frequency of the word "I" leads to increased focus on the self. Every sentence is shaped such that the "I" is involved. If this occurs long enough, it might be that this way of using language becomes a habit. In such a case, those self-focused sentences and words could be used even in the absence of depression. More and more

"depressive" conceptual knowledge is used, by means of accessing it with this kind of "depressive" language. Thus, it could be that just by habit of language-use that depressive states of mind are reached more often and more easily. This in turn could mean that the depressive episodes are triggered more often. Furthermore, the conceptual knowledge on depressive emotional states could be constantly updated, to include more situational and ultimately lower the stress-level needed to induce depressive episodes, or worsen the ability to deal with emotions and stress. Thus, it could be that depression influences language use, which in turn influences depression, which in turn influences language use further and so on. Given the overly abundant use of language throughout the day, this negative feedback-loop is not hard to establish, nor is it easy to avoid. The extent to which this reciprocity indeed occurs, and to what extent it accounts for the progressiveness of MDD would be very interesting to know, as it could lead to a better understanding of depression in general. Factors, such as language, that are not relevant today could be included to improve the models of depression we currently have. Ultimately, this would lead to improved patient care for depression, and other mental health issues.

CONCLUSION

To summarize, there might be a reciprocal link between depression and language, each influencing the other. The serotonin hypothesis of depression is no longer valid, and instead neural-network and system-level neuroscience are more relevant today. This also means that depression does not necessarily have a biology-only cause, but rather needs an element of early psychosocial adversity as well. The presented literature indicates as a whole, that what has been described as depressive schemas are at the very least influenced by conceptual knowledge of emotion categories. Given that conceptual knowledge is acquired through, shaped by, and its access influenced by language, there is an interesting, direct link between depression and language. This means that language could have an influence on the development and the course of depression. Furthermore, depressed individuals seem to show different language-use, with higher focus on self. This implies a possible reciprocity between language and depression, that could lead to a negative feedback-loop, possibly explaining the progressiveness of MDD.

Discussion and Outlook

Whether or not language has a significant effect on "everyday" depression and MDD needs to be further examined. As it was outlined, it could be possible to alter the course of depression using language-based CBT tools or even outright prevent or protect against the development of MDD. However, the actual efficacy has to be studied for its therapeutic use. The applicability might be limited by the patient's status. Severely depressed patients, possibly with suicidal tendencies, might need more drastic intervention. Although this might sound too morbid, using language-based CBT on a suicidal patient might be too slow for their needs. Moreover, a purely biological underlying cause has to be ruled out first. These might include deregulatory neuroendocrine systems that can occur through brain tumours. Here, the priority should be to remove the tumour, for general- and mental-health alike, and then to deal with the depression. However, for moderate severity of depression, and maybe some milder cases of MDD, language-based CBT might be effective. Furthermore, a pre-emptive protective therapy in depression vulnerable individuals might be achieved through systematic language use. This would include (I) learning or updating of conceptual knowledge about emotional reactions, such that the depression is triggered less easily, as well as (II) learning to deal with the depressed mood through strategic use of language as an emotional coping mechanism. Furthermore, the extent to which the progressiveness of MDD is due to the reciprocity of language and depression needs to be examined as well. It might be possible that the altered language in depression could further have an effect on depressions, say through updating conceptual knowledge in a progressively depressive direction.

One thing that has to be clarified, is that by no means is the use of overly positive language suggested. Nor is the use of positive language in relationship to oneself suggested as described in some self-help books. Furthermore, it is not recommended to find the positive in everything. Although this might help some individuals, it could have the exact opposite effect on depressed and depression-vulnerable individuals. Further focus on the self is what is occurring during depression, so if anything, this might just enhance the self-focus. Moreover, it is not always desirable nor possible to find the positive in each situation. Taking away focus from the self and steering it towards something else, preferable towards the problem in an objective solution-oriented manner is preferred.

Given the overabundance of language-use in daily life, the reciprocity of language and depression could have big implications for depression and mental health in general. And although it is just a hypothesis for now, it would be very interesting to further study, and hopefully lead to improved patient care.

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CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

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Review

'Blood-brain barrier dysfunction in sporadic Cerebral Small Vessel Disease'

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Sporadic Cerebral Small Vessel Disease (CSVD) causes widespread microvascular damage and serves as a prominent contributor to the development of Vascular Cognitive Impairment (VCI) in mixed pathology dementia (i.e., the co-occurrence of two or more types of dementia). The precise mechanisms of the relationship between Blood-Brain Barrier (BBB) dysfunction and CSVD are still not completely understood. One suspected underlying mechanism of sporadic CSVD pathogenesis is the dysfunction of the BBB. This review aims to investigate the relationship between BBB dysfunction and sporadic CSVD by creating an outline of what animal models and Magnetic Resonance Imaging (MRI) studies have been able to disclose thus far. Following this, prospects for future research in this field are discussed from a bioengineering perspective. Based on the evidence provided by translational and imaging studies it can be concluded that a correlation between BBB dysfunction and sporadic CSVD is probable. BBB dysfunction in animals is temporarily and spatially linked to the development of CSVD pathology. To investigate whether BBB dysfunction precedes CSVD impairments of cerebral microvasculature, future research should expand toward longitudinal designs and high field strength 7T MRI. Furthermore, Organ-on-a-Chip systems could be an interesting new research area to investigate BBB dysfunction in sporadic CSVD.

Keywords: *Sporadic Cerebral Small Vessel Disease (CSVD), Blood-brain barrier (BBB) dysfunction, Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI), Stroke-prone spontaneously hypertensive rat model (SHRSP), TgNotch3R169C mouse model*

INTRODUCTION

Cerebral Small Vessel Disease (CSVD) serves as a general term, covering a wide range of neuropathological processes that affect small vessels including perforation of cerebral arterioles, venules, and capillaries in the brain (Arba et al., 2017; Charidimou et al., 2016; Wardlaw, 2010; Wong et al., 2019). These neuropathological processes cause widespread microvascular damage and alter microcirculation in the brain (Charidimou et al., 2016; Wardlaw et al., 2019). In many CSVD cases, this microvascular damage and altered microcirculation manifest themselves clinically as ischemic or haemorrhagic strokes (Viswanathan et al., 2010). Roughly one-third of symptomatic strokes are thought to be caused by CSVD (Cannistraro et al., 2019; Charidimou et al., 2016). Typical Magnetic Resonance Imaging (MRI) markers of CSVD include lacunar infarcts, white matter hyperintensities, cerebral microbleeds, enlargements of the perivascular space and parenchymal brain haemorrhages (Charidimou et al., 2016; Schreiber et al., 2013; Wardlaw, 2010; Wardlaw et al., 2017; Wong et al., 2019). For an overview of these MRI markers, see Figure 1.

There is both a sporadic and a genetic form of CSVD. Sporadic (i.e., non-familiar) CSVD results from a complex interplay between vascular risk factors, including age, hypertension, diabetes mellitus, cerebral amyloid angiopathy, arteriosclerosis and hyperlipidaemia (Cannistraro et al., 2019; Charidimou et al., 2016; Kim et al., 2019). The rare genetic (i.e., familiar) form of CSVD is known as Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) and is caused by a mutation of the NOTCH-3 gene (Kim et al., 2019). Both sporadic and genetic forms of CSVD are associated with various behavioural and psychological symptoms such as speech difficulties, parkinsonism, apathy, depression, and anxiety. Due to the progression of associated neuropathological processes, both sporadic CSVD and CADASIL can lead to Vascular Cognitive Impairment (VCI) (Cannistraro et al., 2019; Wardlaw et al., 2019).

VCI is defined as “the entire spectrum of vascular brain pathologies that contribute to any degree of cognitive impairment” (Van der Flier et al., 2018, p. 1) and is mainly characterized by mental slowness and executive dysfunction (Van der Flier et al., 2018). The spectrum of VCI is large in scope and ranges from subjective cognitive decline to dementia. A prominent contributor to the development of VCI in mixed pathology dementia (i.e., the co-occurrence of two or more types of dementia) is CSVD, contributing to 75% of cases (Arba et al., 2017; Cannistraro et al., 2019; Charidimou et al., 2016; Shi et al., 2018; Thrippleton et al., 2019; Van der Flier et al., 2018). To emphasize, it is expected that by 2050, dementia cases will have risen to 115 million people worldwide. If this estimation is correct, approximately 86 million demented people will have CSVD by then (Van der Flier et al., 2018). Additionally, CSVD is prevalent in the general healthy population, where it usually remains asymptomatic and unnoticed (Cannistraro et al., 2019). Hence, it is probable that much CSVD pathology remains unreported.

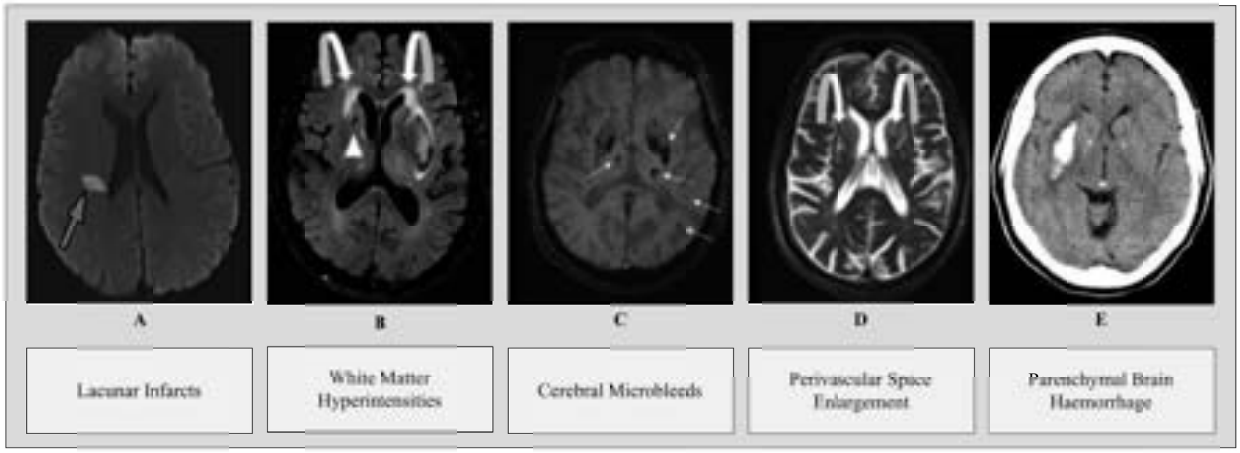

Figure 1. Typical Magnetic Resonance Imaging Markers for Cerebral Small Vessel Disease. Note A) a deep lacunar infarct at the sight of the arrow. B) periventricular white matter hyperintensities at the sight of the curved arrows and a deep lacunar infarct at the sight of the triangle. C) five cerebral microbleeds at the sights of the small arrows. D) an enlargement of perivascular spaces close to the basal ganglia. E) a parenchymal brain haemorrhage. This figure is adapted from Tsai et al., 2018 and Wardlaw et al., 2013.

The current review concentrates primarily on sporadic CSVD, since this is the most common form of CSVD and its vascular risk factors are highly prominent in society (Gorelick et al., 2011; Wardlaw et al., 2019). Due to the complex interplay of vascular risk factors accompanying the development of sporadic CSVD, the disease often occurs in conjunction with other disorders. Therefore, studying the underlying pathological mechanisms of sporadic CSVD in vivo is difficult (Cannistraro et al., 2019; Charidimou et al., 2016; Kim et al., 2019). Furthermore, small cerebral vascular tracts are challenging to image. Not long ago, small cerebral vessels could not be reliably imaged (Wardlaw, 2010). Highly sensitive MRI modalities are needed to capture pathological changes that occur in the brain of a sporadic CSVD patient (Charidimou et al., 2016). In the last couple of years, the availability of ultra-high-field imaging with 7 Tesla MRI scans has progressed sporadic CSVD research, but quantitative data regarding Blood-Brain Barrier (BBB) dysfunction in sporadic CSVD patients remains scarce (Zhang et al., 2017). Evidently, little is known about sporadic CSVD pathogenesis. Therefore, a better understanding of the underlying mechanisms of sporadic CSVD is important and could eventually lead to more suitable therapeutic target interventions. This, in turn, could result in more favourable future outcomes compared to what has been described earlier (Charidimou et al., 2016; Gorelick et al., 2011; Shi et al., 2018; Wardlaw et al., 2013, 2019).

One suspected mechanism underlying sporadic CSVD pathogenesis is the dysfunction of the BBB (Bridges et al., 2014; Hainsworth & Fisher, 2017). An extensive amount of evidence points toward a relationship between a dysfunctional BBB and the development of central nervous system pathologies. Skoog et al. (1998) have already walked the path of BBB research in 1998. They were the first to investigate the relation between Alzheimer's Disease (AD), Vascular Dementia (VaD) and BBB in a large sample of 85-year-olds. Skoog et al. (1998) measured a higher CSF/serum albumin ratio in AD and VaD patients and hypothesized that BBB dysfunction may be a contributing factor in the pathogenesis of these diseases. Recent studies of Wardlaw et al. (2019) and Wong et al. (2019) suggest that BBB dysfunction also plays a substantial role in sporadic CSVD, namely in the development of microvascular damage common to the disease. According to Wardlaw et al. (2019), BBB dysfunction operates as an initiator of CSVD pathogenesis.

This review aims to investigate the relationship between BBB dysfunction and sporadic CSVD by creating an outline of what existing animal models and MRI studies have been able to disclose thus far. Firstly, the healthy function of the BBB is described, after which a brief introduction into measurements of BBB dysfunction is given. Furthermore, important evidence from two animal models is discussed. Following this, an overview of Dynamic Contrast Enhanced (DCE) MRI findings in living patients is presented. Finally, two future suggestions are proposed.

THE PHYSIOLOGICAL FUNCTION OF THE BLOOD BRAIN BARRIER

The BBB is a specialized transport regulation structure along the brain's cerebral microvasculature (Bridges et al., 2014; Freeze et al., 2018). Its main function is to protect and regulate the neuronal environment so that the central nervous system (CNS) can function optimally (Kandel et al., 2013). The BBB contains capillary endothelial cells and complex intercellular tight junctions that together block diffusion through the vessel wall. These tight junctions are the principal component of the BBB's structural anatomy (Kandel et al., 2013). Via the endothelial tight junctions, the BBB prevents blood-borne agents from

leaking into the interstitial fluids of the brain (Bridges et al., 2014; Freeze et al., 2018; Hainsworth & Fisher, 2017). The BBB entails several molecular transport systems. Together, these systems can selectively increase or decrease the permeability of the barrier for certain water-soluble substrates (Kandel et al., 2013).
Covering the endothelial cells are pericyte and astrocyte cells (Kandel et al., 2013). Both pericyte- and astrocyte cells play a role in the regulation of BBB permeability (Herndon et al., 2017). In general, a healthy functional BBB has an extremely low cerebrovascular trans-endothelial permeability rate and a very high resistance towards molecules (2000 Ω/cm2 against 5-10 Ω/cm2 in circumventricular organs) allowing minimal passive diffusion of proteins and other molecules (Bridges et al., 2014; Freeze et al., 2018; Hainsworth & Fisher, 2017). Research shows that BBB permeability increases with age in the healthy as well as in the clinical population (Zhang et al., 2017).

Measuring Blood Brain Barrier dysfunction

Measuring the permeability of the BBB in vivo in humans is mostly done using Dynamic Contrast Enhanced Magnetic Resonance Imaging (DCE-MRI). Using DCE-MRI, the leakage rate of gadolinium-based contrast agent (GBCA) molecules diffusing from capillary blood plasma to the cerebral extravascular extracellular space can be visualized and estimated. This estimation serves as a quantitative measurement of BBB integrity (Thrippleton et al., 2019). Additionally, several alternative imaging-based methods exist for detecting BBB leakage, including Dynamic Susceptibility Contrast (DCS), arterial spin labelling-based methods and positron emission tomography. However, these are shown to be more challenging methods regarding accuracy and reproducibility compared to DCE-MRI (Thrippleton et al., 2019). In research, BBB permeability is often indicated in terms of leakage rate and leakage volume and can be calculated conforming to the Patlak method (Heye et al., 2016). Leakage rate is defined as "the initial concentration increases per time unit (speed) in the tissue relative to the blood concentration" (Shi et al., 2018, p. 427). Leakage volume represents the spatial extent of the BBB leakage (Wong et al., 2019).

ANIMAL MODELS

Several animal models have contributed greatly to CSVD research in the last decades. The biggest advantage of a translational approach is investigating, in detail, the underlying mechanisms of CSVD pathogenesis - such as BBB dysfunction - without confounding factors. One does not have to take ageing or accompanying CNS diseases that occur simultaneously into account. Next, two models that have provided notable information regarding BBB dysfunction in CSVD will be discussed.

The TgNotch3R169C mouse model

The most common genetic form of CSVD is called CADASIL and is seen as a pure form of CSVD due to its monogenic nature. Therefore, CADASIL is often used as a model to investigate sporadic CSVD. An important transgenic CADASIL mouse model is the TgNotch3R169C mouse model. The knowledge about BBB dysfunction that the TgNotch3R169C mouse model has given will be considered first (Di Donato et al., 2017; Ghosh et al., 2015; Shi et al., 2018; Wardlaw et al., 2017). CADASIL is caused by a mutation in the NOTCH-3 gene located on chromosome 19 (19p13.2-p13.1) (Cannistraro et al., 2019; Charidimou et al., 2016; Di Donato et al., 2017; Kim et al., 2019). This gene encodes the Notch-3 transmembrane receptor protein, which is predominantly expressed in vascular smooth muscle cells and cerebral pericytes (Di Donato et al., 2017). Cerebral pericytes are especially interesting here, as they are known to be important for cerebral blood flow regulation (i.e., microvascular perfusion) and maintaining a proper BBB integrity (Kandel et al., 2013). According to Di Donato et al. (2017), the degeneration of these cerebral pericyte cells in humans causes symptoms such as progressive dysfunction of cerebrovascular autoregulation, hypoperfusion and ischemia, often associated with the phenotype of CSVD (Di Donato et al., 2017).
The TgNotch3R169C mouse model is developed by Gosh et al. (2015). In their longitudinal study, they compared CADASIL mutant mice of the TgNotch3R169C type with wild-type controls to study changes in cerebral pericyte cell function at different timepoints (i.e., 2, 7 and 12 months of age). They found several phenomena that can be associated with BBB dysfunction. Firstly, TgNotch3R169C mice developed significantly more aggregations of the Notch3 protein in their cerebral pericyte cell bodies compared to wild-type controls. Secondly, the pericyte coverage of cerebral capillaries significantly decreased with age in the TgNotch3R169C mice. They report that healthy wild-type controls showed no decrease in coverage and their cerebral pericyte cells generally covered most of the cerebral capillary endothelial cells, whereas in TgNotch3R169C mice, cerebral pericyte coverage was already reduced by 30% at 7 months of age. Thirdly, 7-month-old TgNotch3R169C mice show a general progressive reduction in the number (i.e., cell degeneration) of cerebral pericyte cells compared to wild-type controls. Additionally, they found a relationship between this pericyte cell degeneration and BBB dysfunction, which was indicated by a heightened extravasation of albumin and fibrinogen. These proteins are normally not present in neurons and glial cells. An increase in extravasation of albumin and fibrinogen was observed as a result of the general progressive reduction in numbers of cerebral pericyte cells (Ghosh et al., 2015). Gosh et al. (2015) further expanded their study by researching the consequences of cerebral pericyte cell degeneration at a functional level. They compared

the vascular response to inhaling CO2 (i.e., reactive hyperaemia) of TgNotch3R169C mice and wild-type controls. At the age of 12 months, reactive hyperaemia was impaired in TgNotch3R169C mice and their vascular response to inhaling CO2 was no longer optimal (Ghosh et al., 2015).

It appeared that the effect of the Notch-3 protein aggregation on the decrease in cerebral pericyte coverage was more prominent than the actual reduction in numbers of cerebral pericyte cells. According to Gosh et al. (2015) "this may indicate a stronger and early adverse effect of Notch3 aggregation on pericyte processes than on the cell survival itself" (p. 892). In simpler words, this shows that in TgNotch3R169C mice, Notch-3 protein aggregation causes cerebral pericyte cells to firstly undergo damage (i.e., leading to a loss of vessel coverage) and as a consequence to degenerate (i.e., a reduction in cell numbers). This cerebral pericyte cell degeneration will in turn further worsen BBB dysfunction. Another aspect to consider is that the results of Gosh et al. (2015) indicate that BBB dysfunction occurs relatively early in the CSVD process (e.g., at 7 months of age in TgNotch3R169C mice), preceding the phenotypic functional impairments of cerebral vessels surfacing later on in the disease (e.g., impaired reactive hyperaemia at 12 months of age in TgNotchR169C CADASIL mice) (Ghosh et al., 2015).

The Stroke-prone spontaneously hypertensive rat model

As mentioned previously, BBB dysfunction in CADASIL can be investigated relatively straightforward using a transgenic TgNotch3R169C mouse model, as the mutant mouse only addresses the single NOTCH-3 gene mutation found in CADASIL (Ghosh et al., 2015). In contrast, the development of a transgenic mouse model with which one can investigate sporadic CSVD is much more complex. Sporadic CSVD is characterized by a large number of confounding factors of which many are irreproducible in animal models (Cannistraro et al., 2019; Charidimou et al., 2016; Kim et al., 2019). In order to optimally reproduce the complex system of risk factors associated with sporadic CSVD and the disease's diverse nature, a transgenic mouse model must be able to fully address the genetic background of patients suffering from sporadic CSVD. Unfortunately, capturing such a complex system of risk factors in a single transgenic model system is a great scientific challenge that has not been resolved yet (Hainsworth et al., 2012; Wardlaw et al., 2019). Thus far, the transgenic Stroke-prone spontaneously hypertensive rat model (SHRSP) seems to come closest to reproducing damage seen in sporadic CSVD. The SHRSP rat model develops spontaneous haemorrhages similar in nature to damage in sporadic CSVD (Hainsworth et al., 2012; Lee et al., 2007; Schreiber et al., 2013). However, according to Hainsworth et al. (2012) the difference between human and rat regarding microvasculature anatomy is extensive. Hainsworth et al. (2012) therefore, hypothesize that the SHRPS rat model will not be able to fully recapitulate sporadic CSVD.

Despite the limitations of the SHRSP rat model, the explorative translational study of Lee et al. (2007) regarding BBB dysfunction in SHRSP rats is something worth reviewing. The SHRPS rats were on a high-salt / low-protein diet which causes them to have sporadic CSVD-like vascular risk factors such as chronic hypertension and smooth muscle cell disorganisation (Lee et al., 2007). Lee et al. (2007) injected SHRPS rats with a GBCA named gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA), after which BBB permeability was measured. Lee et al. (2007) found an increase in local BBB permeability that, interestingly, predicted the emergence of an intracerebral haemorrhage (ICH) approximately two weeks later. Additionally, the location where a heightened BBB permeability was measured previously, correlated with the area where the SHRSP rats subsequently developed the ICH (Lee et al., 2007).

The SHRSP rat model study of Lee et al. (2007) shows some similarities to the findings from the CADASIL TgNotch3R169C mouse model of Ghosh et al. (2015). Both studies show that detectable BBB leakage temporally precedes the surfacing of CSVD phenotypical functional impairments of cerebral vessels.

DYNAMIC CONTRAST-ENHANCED MAGNETIC RESONANCE IMAGING STUDIES IN PATIENTS

The TgNotch3R169C mouse model and SHRSP rat model study findings seem promising. Both models suggest that BBB dysfunction is spatially linked to the development of CSVD pathology. Nevertheless, owing to the fact that investigating BBB dysfunction in sporadic CSVD using a translational approach is confounded by limitations, most human patient evidence regarding BBB dysfunction in sporadic CSVD is based on imaging studies (Arba et al., 2017; Hainsworth & Fisher, 2017; Freeze et al., 2018; Lee et al., 2007; Li et al., 2018; Schreiber et al., 2013; Wong et al., 2019; Zhang et al., 2017, 2019). In Table 1, an overview of relevant image-based BBB dysfunction studies within the field of sporadic CSVD and their findings is presented.

Evidence for a spatial relation between BBB dysfunction and CSVD pathology is also found during human DCE-MRI studies, as they demonstrate the existence of a correlation between BBB dysfunction and where the CSVD pathology is located in the brain. Studies investigating tissue-specific BBB permeability indicate that BBB permeability is higher in white matter (WM) (i.e., in lacunar strokes, normal-appearing white matter (NAWM) and white matter hyperintensities (WMHs)) compared to grey matter (GM) (i.e., in cortical strokes, cortical grey matter (CGM) and deep grey matter (DGM)) (Wardlaw et al., 2017; Wong et al., 2019). This result is not surprising, considering the fact that micro-vessels are more prominent in WM, and that CSVD is a microvasculature disease (Kandel et al., 2013). Additionally, spatially larger WMHs are associated

Table 1. Overview of Dynamic Contrast Enhanced and Dynamic Susceptibility Contrast Magnetic Resonance Imaging Studies Investigating Blood Brain Barrier Dysfunction in Sporadic Cerebral Small Vessel Diseaseof perivascular spaces close to the basal ganglia. E) a parenchymal brain haemorrhage. This figure is adapted from Tsai et al., 2018 and Wardlaw et al., 2013.

Wardlaw et al. (2017)	Longitudinal cohort DCE	Lacunar stroke (92) and mild cortical ischemic stroke (109)	Gadoterate meglumine 0.1 mmol/kg injection	Significant higher BBB leakage in lacunar stroke compared to cortical stroke. Significant higher BBB leakage in cortical compared to lacunar stroke in NAWM. BBB leakage in NAWM significantly increase linearly when getting closer to WMH edge. Patients with more WMH had the highest BBB leakage in NAWM and WMH.
Zhang et al. (2017)	Cross-sectional DCE	Clinically overt cSVD (80) and age-/sex-matched controls (40)	Gadobutrol 0.1 mmol/kg injection	No significant differences for leakage rate in cSVD compared to controls in all ROIs (NAWM, WMHs, CGM and DGM). Significant higher leakage volume in cSVD patients in WMHs and CGM compared to controls.
Arba et al. (2017)	Cross-sectional DSC	MRI data of acute ischemic stroke before thrombolysis rated on cSVD burden (212)	GBCA injection	BBB leakage within and perilesional of the ischemic area is significantly associated with severity of cSVD burden. BBB leakage within ischemic lesion is dependent on lacunar infarcts.
Zhang et al. (2019)	Cross-sectional cohort DCE	First-ever lacunar stroke or mild VCI due to presumed cSVD (77) and age-/sex-matched controls (39)	Gadobutrol 0.1 mmol/kg injection	Higher leakage volume and lower leakage rate in WMH are significantly associated with larger WMH volume in cSVD patients compared to controls. No significant association was found between higher leakage volume or leakage rate and cognitive performance in cSVD patients. This effect was found in healthy controls.
Li et al. (2018)	Cross-sectional cohort DCE	Participants presented for neurological physical examination (99)	GBCA injection. 0.1 mmol/ kg injection	BBB leakage rate, and leakage AUC for all ROIs (NAWM, WMH, CGM and DGM) are significantly positively correlated with overall cSVD burden.
Wong et al. (2019)	Cross-sectional cohort DCE and DSC	First-ever lacunar stroke or mild VCI due to presumed cSVD (77)	Gadobutrol 0.1 mmol/kg injection	BBB leakage volumes are significantly higher in WMH compared to NAWM and higher in WM compared to GM. BBB leakage rates are significantly higher in WM compared to GM. BBB leakage volume in WMHs significantly increase linearly when getting closer to WMH edge.

Abbreviations. AUC = Area under the curve; BBB = Blood-brain barrier; CSVD = Cerebral Small Vessel Disease; DCE = Dynamic Contrast Enhanced; DGM = Deep grey matter; DSC = Dynamic Susceptibility Contrast; CGM = Cortical grey matter; CSF = Cerebrospinal fluid; GBCA = Gadolinium-based contrast agent; GM = Grey matter; MRI = Magnetic Resonance Imaging; NAWM = Normal-appearing white matter; ROI = Region of interest; WM = White matter; WMH = White matter hyperintensity; VCI = Vascular Cognitive Impairment.

with larger BBB leakage volumes (Zhang et al., 2019). Furthermore, both Wardlaw et al. (2017) and Wong et al. (2019) report a linear increase in BBB permeability in NAWM when getting closer to the edge of a WMH. In line with these results is the study of Wardlaw et al. (2017), who report a higher BBB leakage in NAWM for CSVD patients who had more WMHs.

DISCUSSION AND FUTURE PROSPECTS

A few inconsistencies regarding methodology and findings between the DCE-MRI studies exist. These inconsistencies may have attributed to the differences in participants included in each reviewed study as CSVD is known for its diverse nature (Wardlaw et al., 2019). According to Wardlaw et al. (2019) different subtypes are known to have different pathologies and therefore "different clinical presentations have usually been considered separately in research and the clinic" (Wardlaw et al., 2019, p. 684). Tissue specific BBB permeability might differ for several subtypes of CSVD, as their pathogenic mechanisms are not uniform. Furthermore, BBB impairment is very subtle in CSVD (Thrippleton et al., 2019). Such subtlety can be more accurately measured using higher field strength MRI. As studies pertained to different field strengths (1.5T and 3T), this could account for the variable results. Additionally, little conceptual clarity exists in BBB and CSVD research (e.g., terms such as BBB failure; dysfunction; leakage; permeability or integrity are mixed-together). This further causes a lack of replication and forms a barrier to comparison and interpretation of the data (Thrippleton et al., 2019).

Although the hypothesis of Skoog et al. (1998) has been strengthened, there is still an important challenge regarding imaging studies in general. MRI scans can only measure BBB permeability indirectly and at a single moment in time (Hainsworth & Fisher, 2017; Thrippleton et al., 2019). This is unfortunate, as Cannistraro et al. (2019) suggest that "understanding the sequence of pathogenesis is the key to prevention and treatments" (p. 1148). Fortunately, one can investigate causal relationships via intensive longitudinal monitoring of transgenic animals, such as CADASIL TgNotch3R169C mice and SHRSP rats. Both indicate that detectable BBB dysfunction precedes the surfacing of CSVD phenotypical impairments of cerebral microvasculature (i.e., impaired reactive hyperaemia or the emergence of an ICH) in time (Ghosh et al., 2015; Lee et al., 2007).

It would be useful for the progress of CSVD research if translational methods could be applied to human CSVD patients in vivo. However, this is not possible due to ethical reasons. For instance, one does not simply open a patient's skull to investigate BBB dysfunction directly. Thus, there is an ethical limit regarding investigating BBB dysfunction in CSVD patients that researchers cannot cross (Thrippleton et al., 2019). While translating animal research outcomes into clinical practise remains challenging, new insights into BBB dysfunction in CSVD are still of high relevance (Freeze et al., 2018; Hainsworth et al., 2012; Tsai et al., 2018). It could be fruitful to expand BBB dysfunction research to a new field, such as biomedical engineering (Sances et al., 2018).

As of 2018, human induced pluripotent stem cell (iPSC)-derived cerebral microvascular endothelial cells can be micro engineered in an Organ-on-a-Chip system (Sances et al., 2018). Such chip has the capacity of recreating the brain's dynamic and complex cellular environment (Sances et al., 2018). In the future, it might be possible to investigate the precise mechanisms of the relationships between BBB dysfunction and CSVD using patient-derived iPSC cerebral microvascular endothelial or pericyte cells.

A recommendation that would be easier to achieve in the near future is to encourage researchers investigating CSVD and BBB dysfunction to consider total CSVD burdens, using a longitudinal experimental design and imaging with high field strength 7T MRI. In this way, science might be able to discover whether BBB dysfunction precedes the surfacing of CSVD phenotypical impairments of cerebral microvasculature also in human patients.

CONCLUSION

To conclude, based on translational and imaging studies, a correlation between BBB dysfunction and sporadic CSVD exists. BBB dysfunction in animals and humans is spatially linked to the development of CSVD pathology (Ghosh et al., 2015; Lee et al., 2007; Shi et al., 2018; Wardlaw et al., 2017; Wong et al., 2019; Zhang et al., 2017, 2019). To discover whether BBB dysfunction precedes the surfacing of CSVD phenotypical impairments of cerebral microvasculature also in human patients, future research should expand towards using longitudinal experimental designs and high field strength 7T MRI. Furthermore, Organ-on-a-Chip systems could be an interesting new research area to investigate BBB dysfunction in CSVD (Sances et al., 2018).

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CONFLICTS OF INTEREST

The author declares that there is no conflict of interest.

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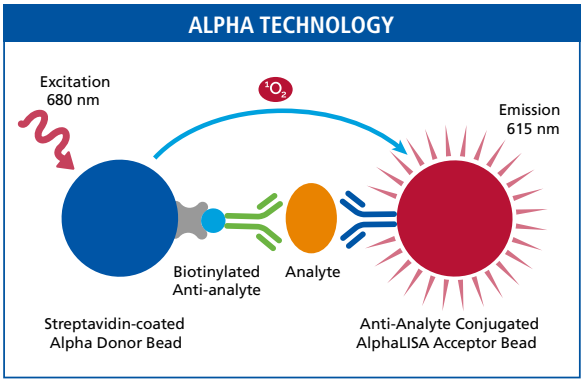

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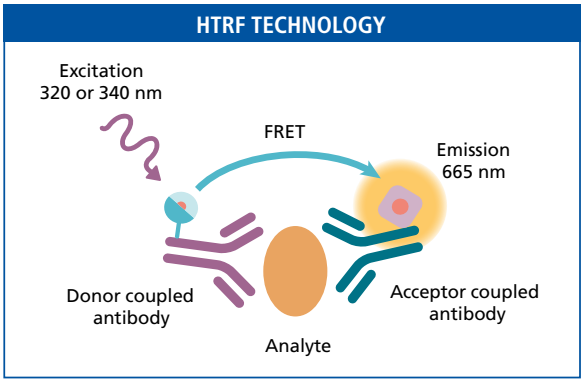

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The perks and perils of being an international academic

Being an international researcher might not always be an easy task. Dr. Mariana Branco and Dr. Ben Harvey, who are both well-known and highly appreciated teachers within the Neuroscience and Cognition master, give their point of view about moving to the Netherlands and establishing an academic career as a foreigner. For the students who always wondered what it takes to make the first move towards starting an international career, both interviewees provide do's and dont's and tips for those who are adventurous.

'Pounds or euros?' - Dr. Ben Harvey

Department of Experimental Psychology, Social and Behavioural Sciences, Utrecht University, Utrecht, the Netherlands

WHO ARE YOU AND WHAT FIELD OF RESEARCH ARE YOU IN?

Hi, my name is Ben Harvey and I am an associate professor in the Department of Experimental Psychology at Utrecht University. My research focuses on 7T MRI, ways of modelling 7T MRI data and neural response selectivity. This technique allows researchers to go beyond the paradigm of MRI which merely shows you which part of the brain is activated when doing a particular task. Instead, you see how each voxel and each neuronal population in the brain responds. How? We look at each voxel and present various different stimulus states. Take for instance images in which something happens in changing visual field positions. You can look at all the responses to all of the visual positions and then you can work out which visual position each voxel is responding to.

HOW DID YOU COME TO WORK IN RESEARCH AT THE UU?

I finished my PhD in the UK in 2009, and it's really common to move somewhere else after you finish a PhD to get experience in something different. So, just as I was finishing my PhD, a researcher moving back from Stanford University, Serge Dumoulin, had just developed the method I described and moved to Utrecht to set up a lab. I saw the position posted online and I was the first person he hired. At the time it was the start of the financial crisis (2008) so it was difficult to find employment, especially in labs in America, which is where I was writing up my PhD thesis at the time. This I think is a very important aspect of working in science, to work abroad and learn what different labs are doing. So, this position came up and it ticked all the boxes. I think that, when choosing where to move, you choose what you want to do; the move should be academically motivated. It wasn't for the country that I moved, but for the scientific approach that I was interested in. But I really liked it here. I got in on the ground floor of this new field of research and now I am quite established in it.

WHAT ARE WORK-RELATED DIFFERENCES IN THE COUNTRIES YOU HAVE LIVED IN?

In the British education system, PhD students are considered students. Therefore, in the UK, as a PhD student you don't pay tax, but the salary is only just about enough to live on. However, in the Netherlands PhD students are really like employees, and given a proper salary. The scientific culture is nice here. In the UK and American academic systems, there is this great hierarchy of institutions. There, if you do a PhD at a non-famous university it can be a dead-end and often doesn't lead to you starting your own lab, which is an important goal of junior academia. In the Netherlands, this is different because the universities are more equal to each other so there is not much difference. Within the student culture, people are therefore more equal, at least in the sense of opportunities but not necessarily in outcomes. Within departments, the PhD student and professor salary are different, yes, but nowhere near as different as they are in the UK and in the US.

WHAT IS THE BIGGEST CULTURAL DIFFERENCE BETWEEN THE UK AND THE NETHERLANDS THAT YOU HAVE EXPERIENCED?

I think it's very common for people who move over here and don't speak Dutch to find it relatively hard to make friends. Even if you do end up learning Dutch, it's not particularly easy to meet people. It is quite a small country, so Dutch people already have plenty of friends nearby and often visit the people they went to school with and grew up with on the weekends. In the UK and US, you stay in the city where your university is, and would not go back home. The lack of, say, a pub culture in the Netherlands makes it harder to meet people as well. Going for a casual drink is a bit different, people like appointments. So socially, people tend to keep to themselves and their existing friends.

WHAT IS THE BEST ADVICE YOU HAVE FOR STUDENTS/ACADEMICS MOVING ABROAD?

"A really nice thing to do is follow a young researcher that you think is really exciting, who is working on the techniques you are interested in, and try to work with them."

'Pindakaas or Pastéis da Nata?' - Dr. Mariana Branco

Department of Neurosurgery and Neurology, UMC Utrecht Brain Center, University Medical Center Utrecht, Utrecht, the Netherlands

COULD YOU GIVE US A SMALL INTRODUCTION ABOUT YOURSELF? WHO ARE YOU, AND WHAT FIELD OF RESEARCH ARE YOU IN?

I'm Portuguese and I've done my Bachelor and Master in Biomedical Engineering in Portugal. In the last year of my master, I wanted to do something different, so I applied for a year at the Delft University of Technology. By then, I had built up an interest in Brain-Computer Interfaces (BCI) and I saw the opportunity to do my thesis on that topic here. I was so impressed by the way people combine work and private life in the Netherlands, that afterwards I decided to look for a job here. I found out about Nick Ramsey's Lab at the UMC Utrecht and contacted them. I was offered a one-year research assistant position, and my research career started there. I was invited to do a PhD after six months, after which I was offered my current post-doc position. I develop BCIs, which is a technology that uses brain signals in order to control a computer or a robotic arm. In the UMC we focus on using BCI for patients that are completely locked-in, meaning they cannot move or communicate. We use their brain signals to control a spelling software, so they are able to communicate.

HOW DID YOU CHOOSE TO WORK AT UU AND HOW YOU GOT HERE

There is always this "chance" in your life, and it was a bit by chance that I came across Utrecht. My husband's sister just started a PhD position at the UMC Utrecht. So I thought "Oh UMC Utrecht, let me have a look", and I found out that there was a BCI lab.

WHAT ARE WORK-RELATED DIFFERENCES BETWEEN YOUR HOME COUNTRY AND THE NETHERLANDS?

Firstly, the work pressure; you feel more pressure in Portugal than in the Netherlands. In my opinion, the work-life balance in Portugal is far from optimal. The way we work in research, especially in universities, is very inefficient; we can get easily distracted with things that are not related to work. Plus, people are very competitive, everyone wants to be the best. There is not much room for collaboration and sharing ideas; you tend to keep everything to yourself. When I came to the Netherlands I was busy, studying full time. My Dutch colleagues looked at me like "Why are you so stressed?", and I was like "Because I want to have a good grade". Then I just realized that people in the Netherlands share everything. They literally showed me all their solutions, and I was mind-blown. For me, that is the biggest clash between mentalities. Also, in Portugal the academic hierarchy is very important. I don't think I have ever called any

professor by their first name, whereas in the Netherlands you can. In the Netherlands we are all equals. The mindset is "you will reach the same place as I am, I can help you getting there". I wish we would share this mentally openly in Portugal too. Portugal has a lot of good scientists, but if you look closely, they work somewhere else around the world. One last thing that surprises me is that Dutchies always complain in order to thrive improvement; everything could be better, could be faster, could be more efficient. From my perspective "If you come from a country like Portugal, this is heaven".

IS THERE SOMETHING THAT YOU APPRECIATE MOST ABOUT PORTUGAL THAT YOU MISS HERE IN THE NETHERLANDS?

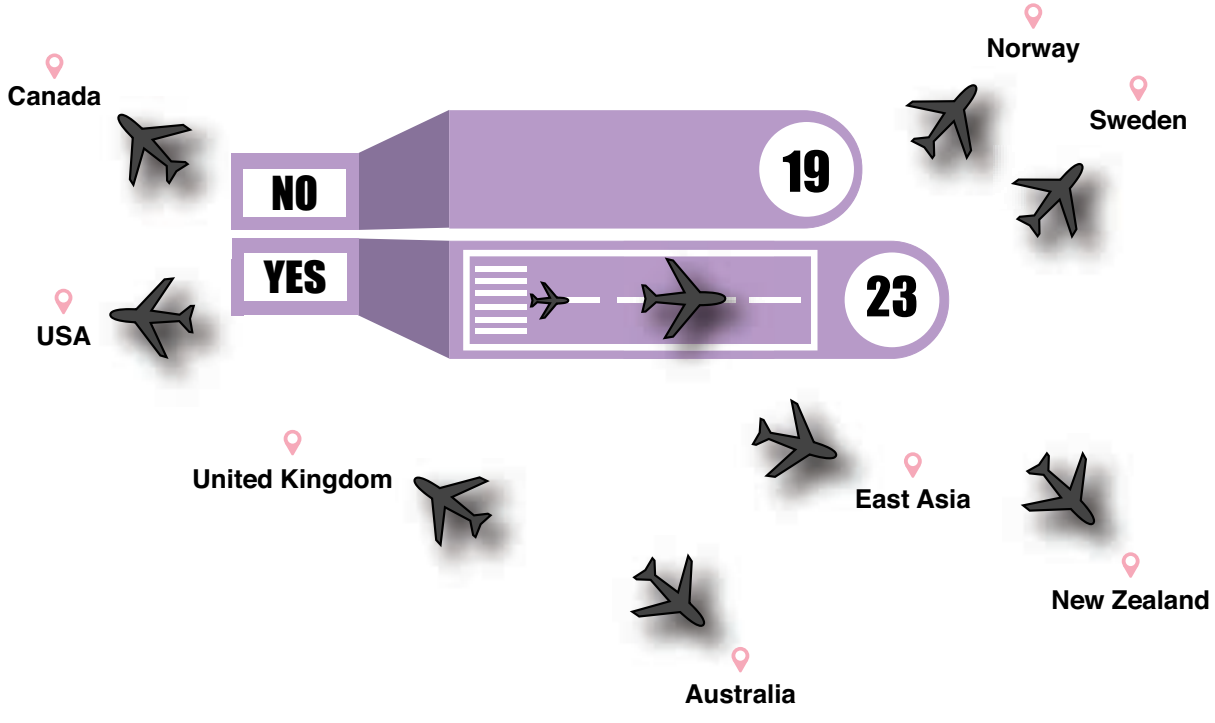
I do miss my hot meal for lunch...but I do try to bring home-made Portuguese soup with me every day.

ANY TIPS FOR STUDENTS WHO WANT TO WORK IN A DIFFERENT COUNTRY?

First, always contact the people that you want to work with. You might not get a reply, but keep on trying. Second thing: write your email, double-check for typos and make it short. Don't give up. Literally, that is the only thing I have learnt that if you really are motivated to do something, you keep on trying. I have students who have been emailing me for internships for more than a year and I know that when I have a position they will be the first to be emailed. Really follow your dreams. Try to find something that you really enjoy, something you could spend hours working on. Another advice: learn the language of the country. It is an effort you should definitely make!

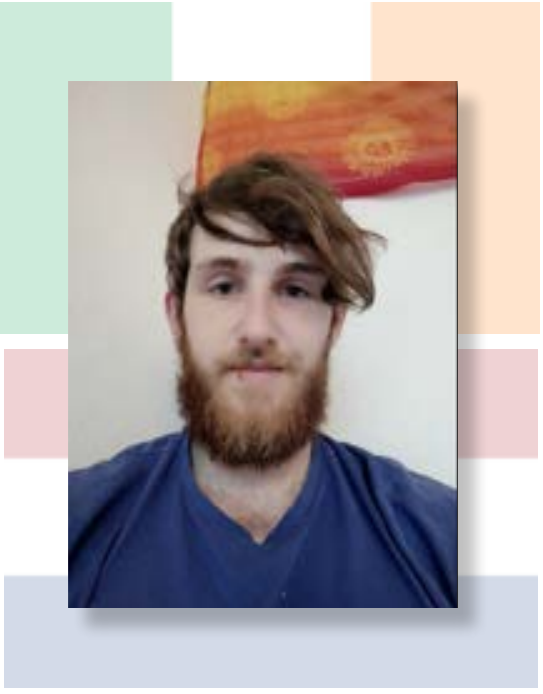
Poll #1

Would you leave for academia and what would your destination be?



To stay or not to stay...

Have you ever toyed with the idea of moving abroad to continue your academic career? Look no further. Jet Termorshuizen and Evan Canny share their experiences on moving abroad to continue their academic careers, giving you the inside loop on what it is like to move abroad and pursue your studies. This piece provides you with a much-needed insight into the advantages and disadvantages of moving abroad and what you can expect if you do decide to move.



Name: Evan Canny
Age: 23
City / country of origin: Ballinasloe, Ireland
City / country of residence: Utrecht, the Netherlands
Current affiliation: Master's student UU

Name: Jet Dieuke Termorshuizen
Age: 27
City / country of origin: Amersfoort, the Netherlands
City / country of residence: Stockholm, Sweden
Current affiliation: PhD student, Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Sweden

COULD YOU GIVE A SMALL INTRODUCTION ABOUT WHO YOU ARE AND WHICH FIELD YOU ARE CURRENTLY WORKING/STUDYING?

My name is Evan Canny, I am originally from Ireland, where I spent 4 years completing my bachelor's degree in Psychology at the University of Limerick (UL). Currently, I am doing my masters in Neuroscience and Cognition, here at Utrecht University. However, after finishing my bachelor's degree I took a gap year to volunteer at the Counsellor Training Institute (CTI) at St Francis Family Helpers Program (SFFHP), Mbarara, Uganda. Here I taught a Cognitive Behavioural Therapy (CBT) course to both undergraduate and postgraduate students, and advised and guided final year students with their thesis. While volunteering I also took some time to travel through East and Central Africa.

Hej! I am Jet, 27 years old, and graduated from the Master of Neuroscience and Cognition in the summer of 2018. In January 2020, I started my PhD at the Center for Eating Disorder Innovation, at the Department of Medical Epidemiology and Biostatistics at the Karolinska Institute in Stockholm, Sweden. My thesis is about studying genetic and environmental factors that influence the course and outcome of eating disorders. Aside from academia I love being outdoors in nature for any kind of activity.

EVAN - FROM IRELAND 

JET - TO SWEDEN 

WHY DID YOU CHOOSE TO STUDY ABROAD, AND HOW DID YOU GET THERE?

I chose to study at UU for a few reasons. First, financial reasons. To do a masters in Ireland, you pay roughly three times what you pay in the Netherlands. Second, I had already spent six months studying at UU for my Erasmus, so I knew how good the school was and what I could gain, academically, out of the experience. And finally, I spent so many years in Ireland doing pretty much the same thing, I just wanted a change of scenery. What better place to move to than one of my favourite cities in Europe?

I've always had the urge to go abroad, or, "somewhere else than where I was". That's why I chose to do my 6-month internship abroad, which I found through my colleagues during my 9-month internship at Utrecht University. I had been in Stockholm once before for a weekend, and thought the city was beautiful — that was the only experience I had of Sweden before I moved there initially for my 6 month internship.

WHAT DO YOU THINK IS THE MAIN DIFFERENCE IN THE WORK/STUDY ENVIRONMENT BETWEEN YOUR HOME COUNTRY AND YOUR RESIDENTIAL COUNTRY?

I think, comparing the Netherlands to Ireland, Dutch students are more enthusiastic about their studies and thus put more effort into it, but I also think they get more from their schools/society to enjoy the student life. As an international student, my perspective could certainly be biased. However, I feel like students have more options to expand themselves here longer into their twenties compared to home, in Ireland, where a lot of pressure is on young people to get a job very quickly when they have finished their bachelor's degree.

First of all, I have to say that my work environment is very international. E.g., my main supervisor is American, while I am in Sweden, so different cultures are blended in my work environment. I would say the Swedish work environment (i.e., taking the whole summer off) is the opposite from the American work environment (i.e., taking nearly no time off during summer), as is evident fromt my American colleagues. The Dutch working culture is, I think, in between those two. The main difference between the Swedish and Dutch working environment is the way of communicating: Dutch are very direct, while Swedes are (generally) not.

WHAT ARE SOME ADVANTAGES AND DISADVANTAGES OF MOVING ABROAD?

Again, saving thousands of euros is a big plus! Attaining education on a topic that was not available in Ireland is another big advantage. Also, getting to live in one of my favourite European cities is a big plus! Regarding the disadvantages of moving abroad: obviously COVID-19 regulations and restrictions make life more difficult. You also face the extra costs of moving again and starting a new life. But overall, I don't perceive many disadvantages of moving abroad to study.

I think those two are related to each other. It is very interesting, energizing and fun to get to know a new culture, its habits, people, and language. On the other hand, it sometimes costs more energy than it gives you. Also, I sometimes miss my friends and family, especially now during the pandemic when it's hard to travel. But in the end, I think it's worth it, mostly because this is only temporary and I have the freedom to go back whenever I want.

EVAN - FROM IRELAND

JET - TO SWEDEN

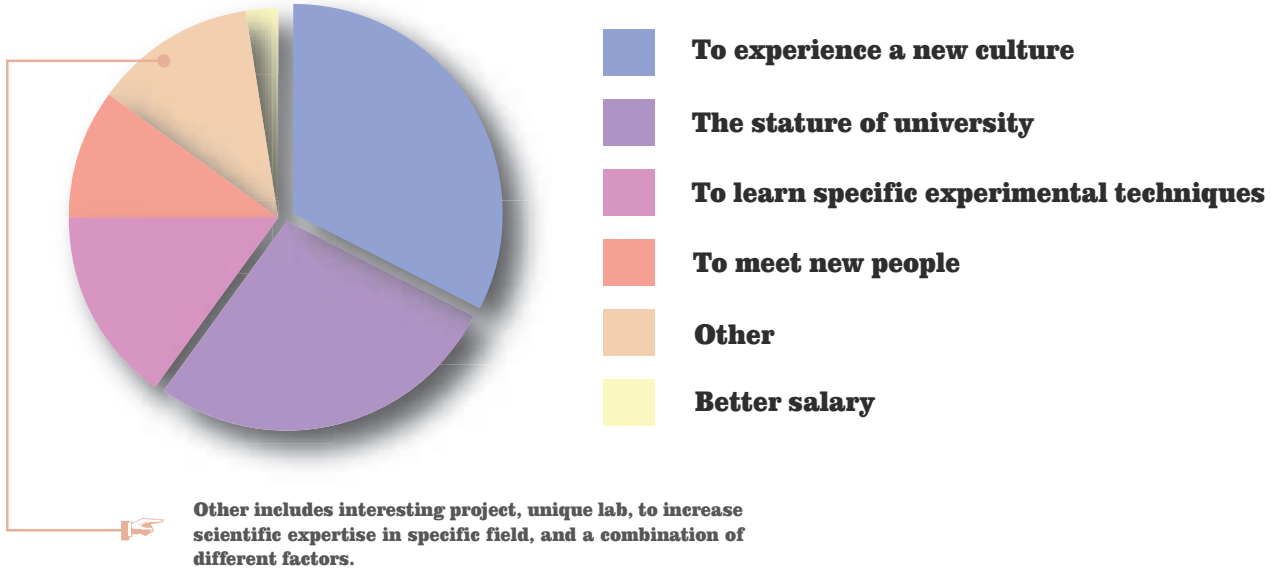
IS THERE AN ASPECT OF YOUR HOME COUNTRY THAT YOU APPRECIATE MOST AND MISS IN THE NEW ENVIRONMENT?

The sense of Irishness and familiarity. I guess the two go hand in hand, but the laid-back nature of Irish people, along with my own familiarity and comfort with my 'home' environment is something I miss. Then again, I have moved a lot recently to achieve my individual goals, so my answer is likely biased by my lack of time spent with my friends and family over the last 12-18 months. However, as much as I love the Dutch culture and people, along with the international culture and people, I do miss the sense of comfort from being in an environment that I'm very familiar with.

To have my friends and family close to me, and to call my mom to meet and eat an "appelbol" in her favorite café in Utrecht, Graaf Floris.

Poll #2

Why would a PhD position abroad allure you?



'The Triple Network model of psychiatry: opportunities and challenges'

Dienke Bos, PhD

Niche Lab/Department of Psychiatry, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands

Dienke Bos is an Assistant Professor at the NICHE Lab/Department of Psychiatry at the University Medical Center in Utrecht. Her research focuses on the influence of individual and environmental factors on the neurobiology of self-regulation, or how youth with and without developmental disorders navigate their daily life. In this piece which focuses on innovative research methodology, Dienke shares her knowledge on the Triple Network model of psychiatry and the opportunities and challenges that have arisen in this field.

How individual differences in human cognition relate to psychiatric symptoms and changes in neurobiology remains much more elusive than we had hoped after more than two decades of neuroimaging research. Yet, neuroimaging has unequivocally taught us that the complex etiology of psychiatric disorders is not found in individual brain areas. Our brain is a complex, highly connected network, and network neuroscience has proven a powerful tool to study changes in the architecture of large-scale functional networks in relation to psychiatry.

The Triple Network model suggests that dynamic cross-network interactions between the Central Executive Network (CEN), the Salience Network (SN) and Default Mode Network (DMN), three large-scale functional networks that show great inter-individual variability (e.g. Gordon et al., 2017a; Kong et al., 2019), underlie individual differences in cognitive functioning and as such, also give rise to the large spectrum of different or dysregulated behavior that is currently classified in DSM-V (Menon, 2011). The CEN is involved in maintaining information in working memory and decision making in goal-directed behaviors (Power et al., 2011; Yeo et al., 2011), i.e. acting upon our outside world. The DMN represents our internal world, it is involved in self-referential thought and autobiographical memory and typically suppressed during goal-directed behavior (Spreng and Grady, 2010). By mapping both internal and external salient events, the SN modulates activity of the DMN and CEN, connecting our inside and outside worlds and allowing us to plan and adapt behavior flexibly in the face of ever changing daily circumstances (Dosenbach et al., 2006; Seeley et al., 2007; Uddin, 2015).

Changes in functional connectivity between the CEN, DMN and SN have been observed across the psychiatric spectrum (e.g. Menon, 2018; Sha et al., 2019; Supekar et al., 2019). Yet importantly, there are no homogeneous biological, or even behavioral, subgroups associated with DSM-V diagnostic categories. The 'traditional' case-control method has in fact hindered progress in psychiatry research (Satterthwaite et al., 2020). As a result, advances have been made in precision mapping of individual-level functional networks (e.g. D'Esposito, 2019; Gordon et al., 2017b; Gratton et al., 2020; Satterthwaite et al., 2018). However, there is one practical obstacle: the high-resolution, extended scanning sessions that are needed for precision functional mapping are not yet clinically feasible (D'Esposito, 2019; Gratton et al., 2020). Furthermore, there remains the conceptual challenge that symptom-related variability in the flexible adaptation of network interactions (Elliott et al., 2018; Jiang et al., 2015) may not be the same during rest in an MRI-scanner versus daily life. Naturalistic paradigms such as 'movie' MRI may provide a solution (e.g. Eickhoff et al., 2020; Vanderwal et al., 2019), although it has also been suggested that functional brain networks are relatively stable and that day-to-day variation or task-state only modestly contributes to individual variation (Gratton et al., 2018).

All in all, the Triple Network model provides an interesting conceptual framework to study individual differences in cognition in relation to psychiatric symptoms. The challenge now is to take it from bench to bedside.

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'Diffusion Tensor Imaging to study the white matter integrity of the brain'

Naomi Vlegels, Msc

Department of Neurology and Neurosurgery, UMC Utrecht Brain Center, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands

Forms of dementia, like Alzheimer disease, are commonly studied with the use of neuroimaging within the neuroscientific community. In this piece, the PhD candidate Naomi Vlegels explores and explains how Diffusion Tensor Imaging (DTI) can be revolutionary in studying dementia and provides evidence on how the technique helps us to create a better understanding regarding the involvement of white matter.

In this piece, I would like to briefly introduce the advanced MRI technique: diffusion tensor imaging (DTI) and how it is used in dementia research. With DTI we can study alterations to the microstructure of the white matter. These alterations are frequently observed in the most common forms of dementia and show a strong association with cognitive performance in these patients (Caballero et al., 2018; Mito et al., 2018).

White matter alterations can be measured in vivo with DTI, an MRI technique that measures the diffusion of water molecules along different directions in the brain. In CSF, water molecules can diffuse freely and unrestricted. Water diffusion along all directions will be equal and we can visualize this by a sphere (Figure 1A). In the white matter, water diffusion is restricted by axons and will follow the main direction of the axon bundle, which can be visualized by an ellipsoid (Figure 1B-C). By quantifying the extent of water diffusion (mean diffusivity) and the directionality of water diffusion (fractional anisotropy) in the white matter we can indirectly measure the integrity of the white matter (Assaf et al., 2019). In patients with dementia, we often observe an increase of mean diffusivity and a decrease of fractional anisotropy, which is hypothesized to reflect a loss of integrity of the white matter (Figure 1C) (Caballero et al., 2018). In addition, DTI can be used to reconstruct the white matter connections by determining the preferred direction of water diffusion in each voxel and then piece the direction of each voxel together (Figure 2). With this, we can perform tract-based and network analysis, and observe how different tracts or how the structural brain network is affected

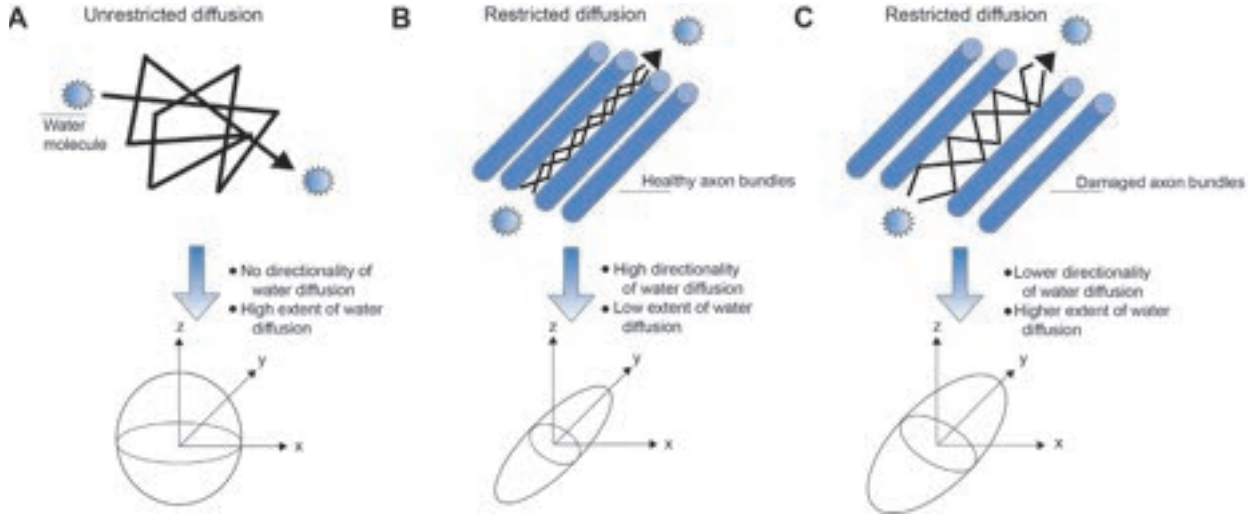

Figure 1. Visualizing (A) unrestricted diffusion in CSF and (B) restricted diffusion in healthy and (C) damaged axon bundles.

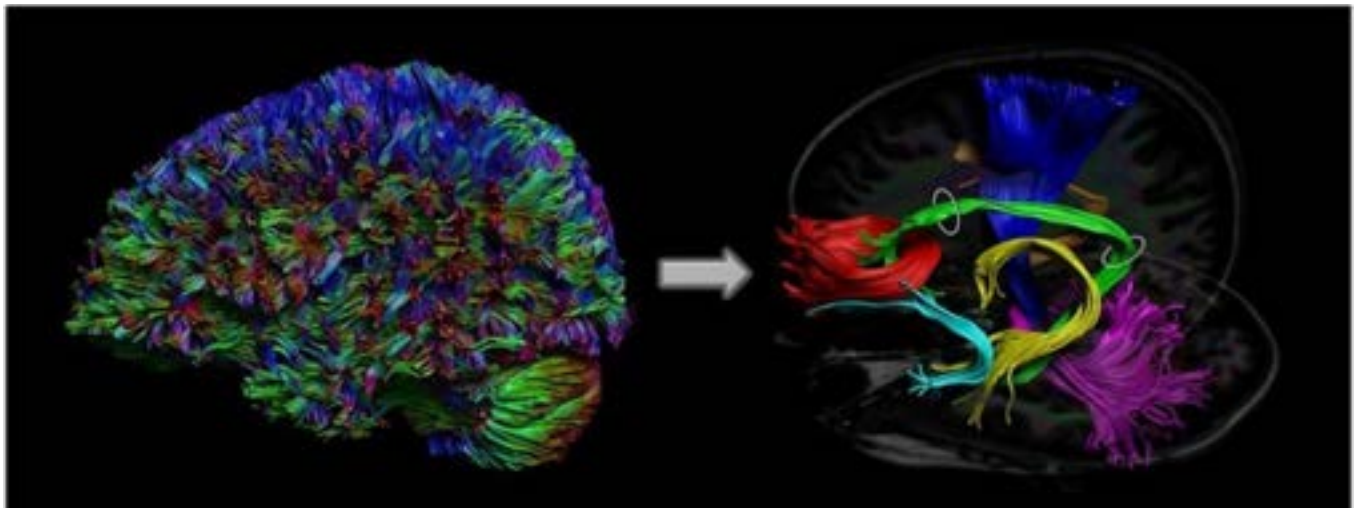

Figure 2. The left image shows an example of tractography in which all white matter connections of the brain have been reconstructed. The right image shows major white matter tracts that have been virtually dissected from the whole brain tractography. (Figure from Jeurissen et al. (2019).)

by the disease. In case of disease, the structural brain network can become less efficient and this lower efficiency is associated with cognitive impairment (Heinen et al., 2018).
One big advantage of DTI is that it allows us to quantify tissue damage that is not (yet) visible on a conventional MRI scan, thereby giving us insight into otherwise invisible damage. While DTI is sensitive to relatively early tissue damage and strongly associated with cognition, a limitation to the technique is that the measured white matter alterations are not specific and thus do not inform us about the underlying type of dementia (e.g. Alzheimer's dementia, vascular dementia) (Assaf et al., 2019).

I envision that in the next five years, the way diffusion MRI scans are acquired (e.g. acquisition protocols) and modelling techniques will be further improved. With these improvements, we will hopefully be better at disentangling which underlying type of dementia is present, getting a higher specificity for different diseases. Furthermore, the research field is working hard on developing treatments for dementia. In order to test the efficacy of these treatments, we need clinical trials with solid outcome markers. Because DTI has a strong relationship with cognitive problems in patients, I think DTI could be an important outcome marker to test the efficacy of the treatment for the patient and I am curious to see how this method will develop.

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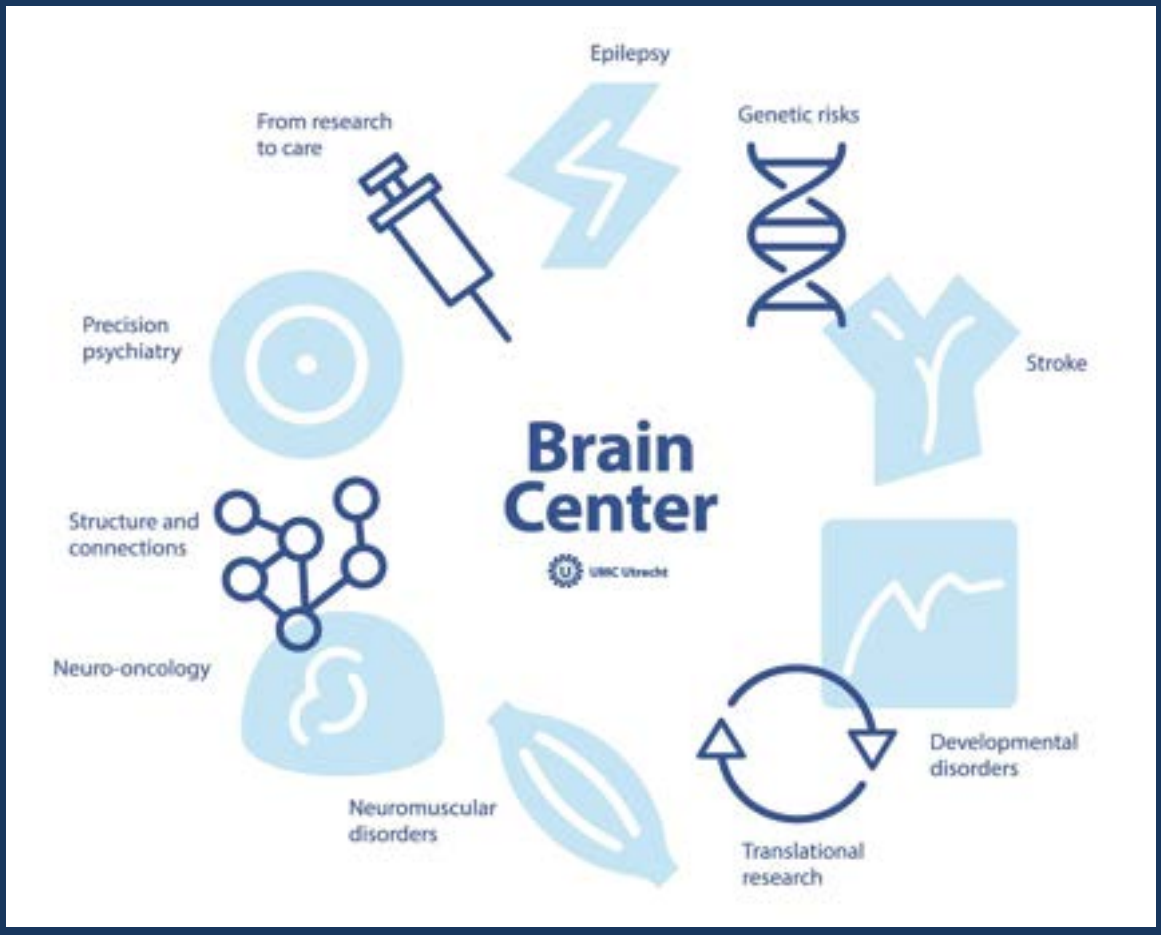

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The interdisciplinary nature of sleep research: insights from a neonatal pediatrician

Dr. Jeroen Dudink

Department of Neonatology, University Medical Center Utrecht Brain Center, Utrecht University, Utrecht, The Netherlands

Before you lies a fascinating research interview with Dr. Jeroen Dudink, a neonatal paediatrician who shares his experience and insights into neonatal sleep research. The article highlights the importance and benefits of interdisciplinary research and its impact on the advancement of sleep research. Jeroen also shares his experience and journey in becoming a clinician and provides readers and students with valuable advice when pursuing a career in academics.

EXPLAIN WHO YOU ARE AND THE FIELD OF RESEARCH YOU ARE IN?

My name is Jeroen Dudink, I am a pediatrician and neonatologist in the Wilhelmina Children's Hospital and associate professor neonatal neurology, doing clinical and research work.

EXPLAIN THE MOTIVATION FOR YOUR FIELD OF RESEARCH AND WHY IT INTERESTS YOU?

I did my PhD on diffusion-weighted imaging (DWI) of the neonatal brain. As a neonatologist the majority of the children I treat are born preterm (born before 37 weeks of gestation). Preterm infants have a higher risk of abnormal brain development leading to social and economic consequences e.g., their place in society and their ability to participate in society in the most optimal way is compromised. This can have a big impact on the children and their families. Besides an expensive neonatal intensive care stay, treating children born preterm can be costly due to the need for physiotherapy, special education and developmental psychologists. As a clinician, I wanted to know more about the basics of neuroscience in order to understand more about brain development and decided to do a Masters in Neuroscience, studying in between my oncalls, weekends and holidays. It taught me a lot about brain activity and the influences on brain growth. I studied the developing cerebellum and got infected with the 'cerebellar bug', as I was intrigued that injuries to this small brain could have such big consequences on the big brain. Eventually, someone told me it would be interesting to see how sleep influences cerebellar growth, as the most important brain activity in a young child is sleep. The endogenous neural activity babies generate while asleep seems to impact and shape early brain development. Therefore, my ultimate goal is to study the influence of sleep on cortico-cerebellar connectivity.

WHAT WAS YOUR MOTIVATION FOR CHOOSING YOUR PHD AND THIS PATH?

Sometimes it is the walk of life, but I have always been interested in pediatrics, and its many different aspects. I soon realized that neonatal intensive care is where everything is combined. It was also a combination of my parents; my father is a developmental psychologist and my mother is a biologist with an interest in the brain. My family is full of people working on the brain and development. As a clinician it can be very frustrating to have to wait so long to see some of the consequences of early life events e.g., how are you performing at school? Therefore, a big motivation to do the PhD was to try and find future biomarkers to be able to assess new treatments.

> Science is always about ups and downs and never from A to B. You think you go from A to B but you end up at C.

HOW DO YOU PERSUADE UNIVERSITIES TO GIVE YOU GRANTS FOR YOUR RESEARCH?

That is a challenge because neither sleep, neonatology or the cerebellum are on the top of the list for funding so it has some disadvantages. It should be the goal of researchers to gain momentum and do outreach as well, and it is important to do both. I have invested a lot of time in outreach. Usually, you do this after you find out a discovery, but we as a team wanted to put sleep on the agenda before that by giving talks with groups of sleep enthusiasts. More and more research has shown that sleep is so important for many therapies to work and for the treatment of mental disorders. To use the analogy, you do not know if it was the chicken or egg that came first but you can be certain that disorders get worse if you are sleep deprived. You sleep 1/3 of your life and babies that are born preterm sleep around 16- 18 hours. Also, all animals sleep, even fruit flies. So, if sleep was a mistake then it was the biggest mistake evolution made.

WHAT ARE THE METHODS YOU ARE USING IN ORDER TO STUDY SLEEP?

A combination between observational and machine learning on vital sign parameters. We also include MRI volumetrics and diffusion tensor imaging to look at white matter microstructure. We are planning to observe fMRI network analysis of sleep and EEG as well. Another new technique we are using and developing is Doppler ultrasound. This arose as the downside of MRI is that it is costly to get a baby to the MRI scanner. I once mentioned to an acoustic engineer that it would be great if you could have a continuous ultrasound of the brain and to have at least a minute where you have a full 3D swab of the whole brain. I also asked if it could come with a wireless probe that you can place on the baby's head, which can be sent to a computer and get an update on cerebral perfusion and elastography. Therefore, you can look at the stiffness of the brain and its microcirculation. This allows you to study circulation both in sleep and the awake state and is very related to brain injury.

HOW HARD DO YOU FIND IT TO BECOME AN EXPERT IN A NEW TECHNIQUE?

Now everything is online so it makes it much easier to gather information on a new technique. But to become an expert in it requires a lot of effort to really grasp it. Doing a PhD, where you can have a few years dedicated to a certain technique or disease is really necessary because then you can start asking the questions that are unanswered. In the beginning, you just read what everyone else is saying about a certain topic but now you know all the pitfalls of it yourself. I think it's really nice that the N&C do the 9-month internships because you get a feel of the topic and techniques. You have to suffer a little bit. I think that is a challenge for a lot of people. Almost all students go through a hard phase where you are used to getting the data and working on it and having a solution in a week, now it takes months and you can encounter a variety of problems. Going through the whole process is really good for students as you have to learn to do things again and question whether you really understood it, or if your experiments failed. Science is always about ups and downs and never from A to B. You think you go from A to B but you end up at C.

Dare to ask 'why?!'

ARE THERE ANY DISADVANTAGES YOU WISH YOU COULD GET RID OF USING THE TECHNIQUES YOU DO NOW?

What we are working on now and have a problem with is long term EEG monitoring. Placing electrodes on babies with vulnerable skin for a long time is not possible. What you would really want are electrodes that are wireless and that have no gel. We are currently trying to develop these right now. You can therefore look at EEG recordings for days on end.
For MRI the difficulty is getting it to the clinics. It is very difficult to get advanced studies to clinicians. For example, there are thousands of DTI studies but there is very little DTI used in clinics. There is so much work out there and It would be nice to see this effort enter into the clinics.

WHAT ARE THE MOST PROMISING METHODS IN RESPECT TO WHAT YOU USE AND WHAT OTHER DISCIPLINES DO YOU GET INSPIRATION FROM?

For me some really good advice is to collaborate with other research disciplines. As a clinician I collaborate with neuroscientists because then you understand what is going on at a deeper level. There is already so much experience in basic neuroscience and a lot of clinicians forget this and do an intervention study without talking to basic neuroscientists. It is so important to know the basics behind it. Collaboration with engineers is also very important. They have such a nice solution-based way of thinking. For example, manipulation of data, especially engineers into machine learning. A biomedical engineer can also come up with so many solutions and ways of processing and it is worth a lot. Collaboration with the technology industry. Many have a great mindset. You still find top professors there. If you are really open about what you are doing and transparent then it can be very

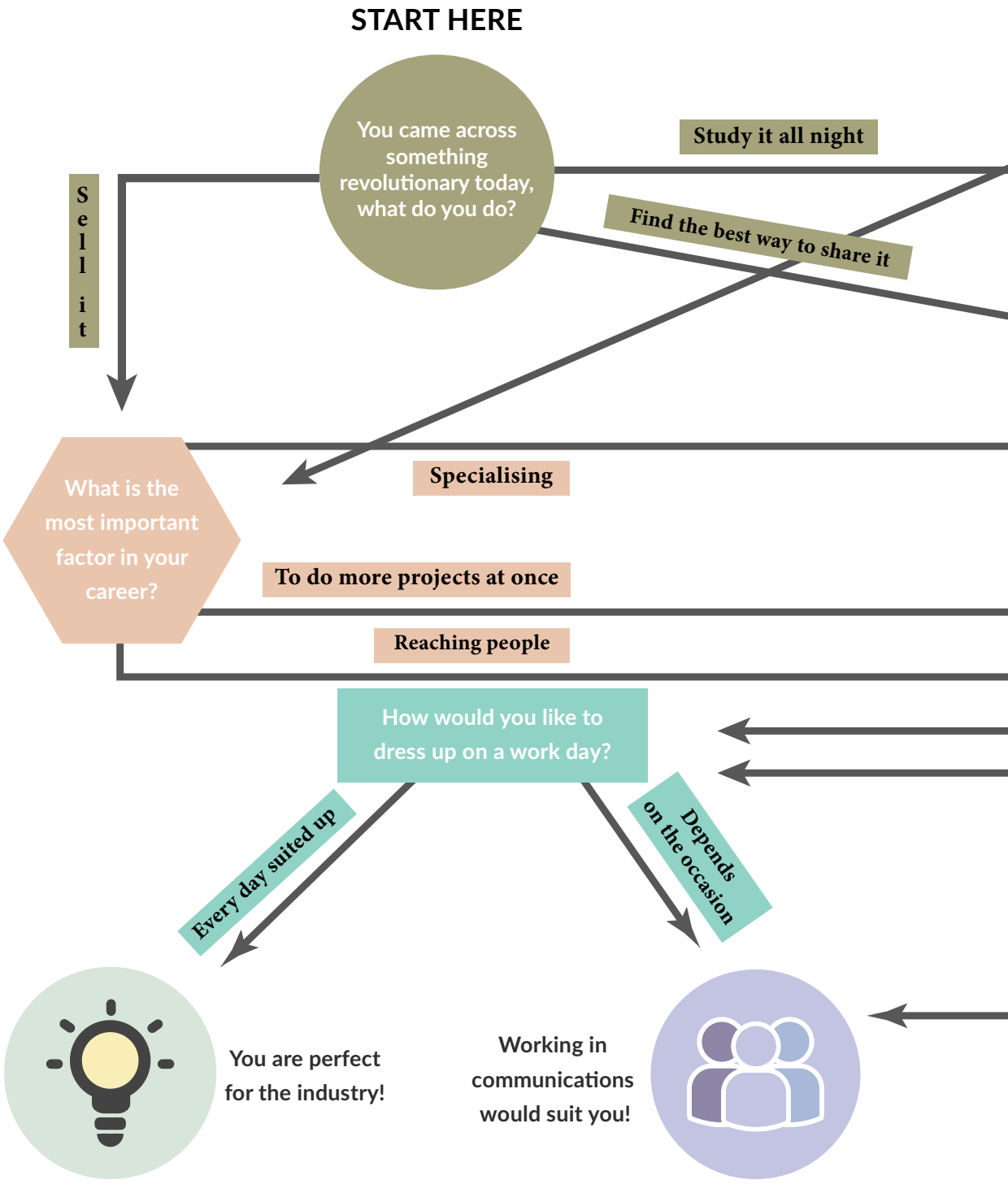
fruitful as well. Main takeaway: be open and transparent and then they can be very good partners.

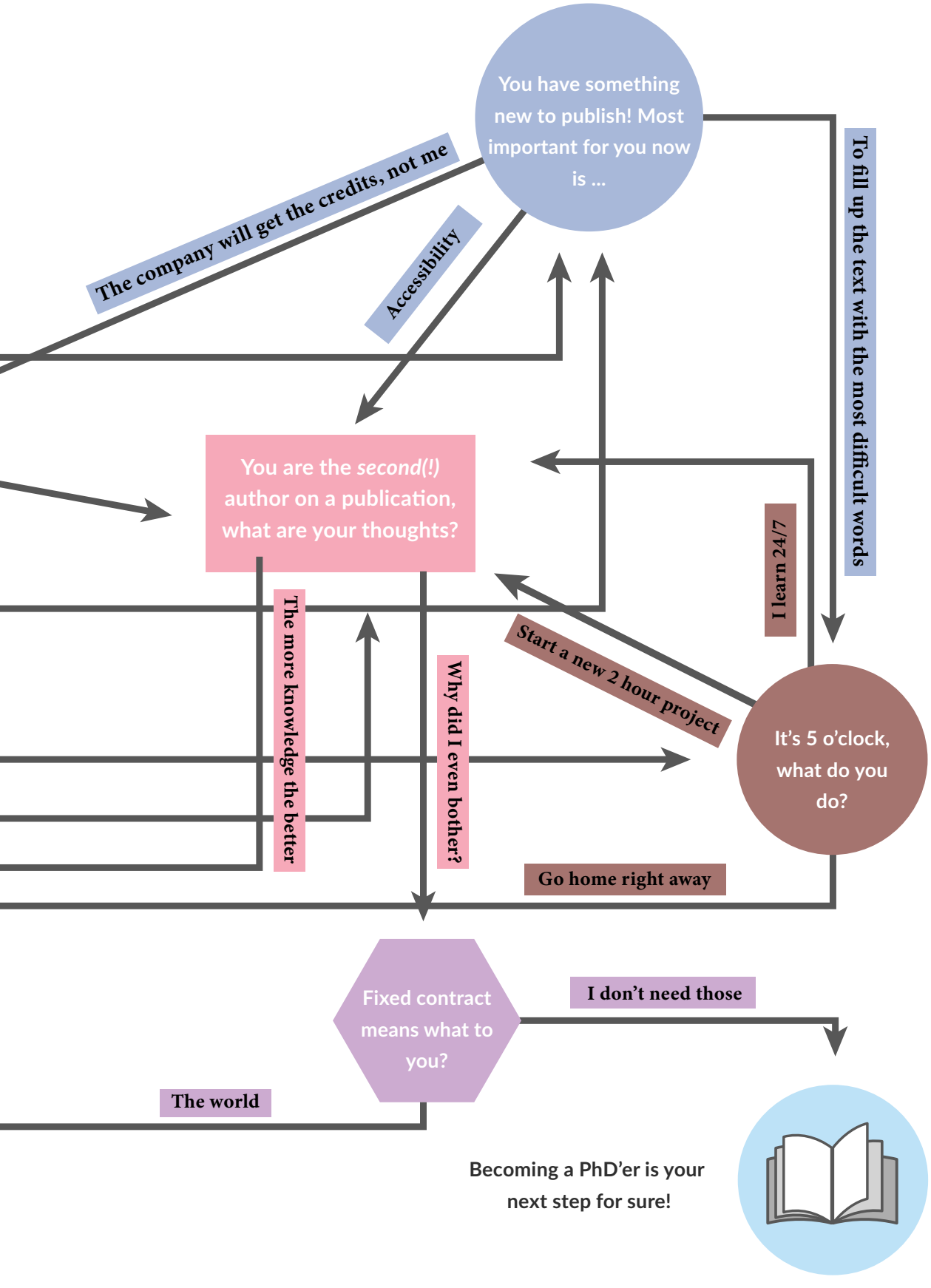
DO YOU HAVE ANY ADVICE TO PASS ONTO THE STUDENTS?

Sounds corny but be inquisitive, because that is what makes you a great researcher. A lot of people don't ask the question "but why?". A lot of people don't ask this question and it is such an easy question to ask. Just ask why and you are on your way to a thesis. Question every sentence you read. The nicest things I discovered have come from me 'accidentally' asking why. I remember looking at Purkinje cells under a microscope and someone in the lab said "I see them injured here but not there" so I asked why? You may think it is common knowledge and therefore we tried to look for the evidence in papers. We kept looking and could only find a few studies on this topic, which led to a whole study we are doing now on the selective vulnerability of Purkinje cells depending on their location. Dare to ask 'why'?!

What is your job 'supposed' to be?

Find out who you resemble career-wise and you see which path you should follow the coming years. Beware, this flow-chart is based on student stereotypes of the different jobs: in academia, in a company or in communications. You can find the real stories on the categories company and communications on the next pages. Have fun finding your dream job!

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It's 5 o'clock, what do you do?
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Becoming a PhD'er is your next step for sure!

Debunking stereotypes: three N&C alumni on their career choices

Choosing the next step after the N&C master can be challenging for many students. While some are convinced that they want to do a PhD, others might not be so sure. However, alternative career options can be hard to think about, because our master programme prepares you for a career in academia. Moreover, many careers are surrounded by (often negative) stereotypes, which makes the choice even harder. Therefore, we talked to three N&C alumni about their career choices and related stereotypes. Continue reading to find out which stereotypes can be debunked!

'Communication within science' Dr. Anne-Floor Scholvinck

"Going off the beaten track is not a failure, it is looking for what you truly like."

As an alumna of our master's programme, Dr. Anne-Floor Scholvinck has a career path that some may call unconventional: she would not consider herself a neuroscientist anymore. Rather, Anne-Floor is an expert on the relationship between medical science and society. She currently works at two institutes: the Rathenau Instituut and UNESCO. She is generally based at the Rathenau, a research institute that informs the Dutch government and parliament on the impact of science, technology, and innovation on our lives, in order for them to take policy action. Here, Anne-Floor studies public engagement in scientific research and public trust in science.

For the past half a year, Anne-Floor has been seconded to UNESCO in Paris, the UN organisation for science, culture and education. Among the wider public, UNESCO is mostly known for its World Heritage list, but it is in fact a political body that also assists countries to invest in, and develop policies regarding, science, technology and innovation (STI). At UNESCO, Anne-Floor is writing a global Recommendation on ***OPEN SCIENCE***. She tells us how Open Science is currently a big deal in the scientific world in Europe and Latin America, whilst UNESCO aims to make it a truly global movement. In contrast to her work as a researcher at Rathenau, at UNESCO she is negotiating and providing STI-policy advice at a global scale.

Open Science is commonly perceived as an initiative to make scientific research more available to the public, yet she explains it is ***NOT ONLY*** about ***AVAILABILITY*** but ***ALSO*** very much about ***ACCESSIBILITY***: the public needs to be able to grasp the information conveyed in research articles. Furthermore, being a researcher in the true spirit of Open Science, you would not only want to reach more people, but you also want ***MORE PEOPLE TO REACH YOU***.

As an Open Science expert and researcher, Anne-Floor has a broad range of interests: compared to researchers in the natural sciences, she explores a wider range of topics in her work, rather than becoming increasingly more specialised in one specific topic. Yet how did she get to these positions, after graduating from the Neuroscience and Cognition programme in 2013? Anne-Floor ***DEVIATED FROM HER NEUROSCIENCE PATH*** in her PhD, which was on public engagement in the medical domain. Her doctoral supervisor accepted her into the PhD programme because she had seen Anne-Floor's enthusiasm on patient involvement during her short stay at the Hersenstichting. As Anne-Floor describes, her path was "windy, but it's always windy for everyone".

Despite her deviation from Neuroscience, she is happy with her master's degree, because it helped her end up where she is now. If she were to do it again, she might have switched halfway to a master's degree that suited her better. She explains that, at the time, it felt like this would be failing, which she obviously didn't want to do. 'But then what is failing if you just say "okay, it doesn't suit me, I'm looking for something else"? That can also be an option, but it just didn't occur to me'. Even though Anne-Floor acknowledges it is 'kind of odd' to do a PhD in a field you don't have a master's degree in, to her it was paramount to do what sparked her interest: "to me, that is way more important than following the path that other people expect from you".

‘Industry: consultancy’ Jeanneke Spruit, MSc

“You never know if you can do it until you try.”

Only an alumna for a small two years, Jeanneke works as a junior consultant at the company Iperion Life Sciences Consultancy. Rather than having her mind set on a job in consultancy, Jeanneke was not so sure where she would be going right after she graduated from the N&C master’s programme: ‘I think many people will recognise that at the end of their masters, they know some things that they don’t want to do, but have no clue what they actually want to do: I was one of those people’.

While looking for work after graduation, she kept her LinkedIn profile up to date, via which she was approached by a recruiter of Iperion and invited for an interview. At first, she was unsure whether she would be fit for a consultancy job. She doubted whether she had the right skills, and believed that consultants were workaholics ‘who never slept’. For this reason, she started working at Iperion in data entry rather than consultancy, a position she soon outgrew. After some encouragement from her boss and some colleagues’ assurance that consultants have a ***HEALTHY WORK-LIFE BALANCE,*** Jeanneke started as a junior consultant, advising pharmaceutical companies about their data management.

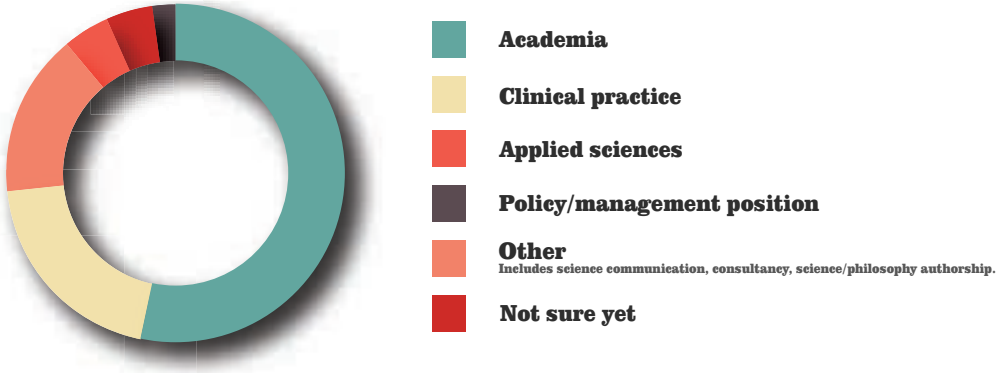
What she enjoys most about her work is that she can rapidly ***SWITCH PROJECTS***, going from one client to another. Yet Jeanneke also explains that consultants are often perceived as ***EXPENSIVE*** and ***USELESS***. She believes this stereotype is fed by the fact that consultants often only speak to their direct contact at the company, usually a manager, but not with all the people affected by the consultancy advice. For this reason, not all employees may understand the need for a change in their way of working. Furthermore, even though she usually works from ***9 TO 5***, consultancy work sometimes does require you to be ***FLEXIBLE***. For instance, when you have a client in a different time zone or have a big deadline coming up, you always need to adapt to your clients.

Consultancy is also not the kind of business job in which one generally settles down in the same position until retirement: it is quite the opposite. Typically, consultants are ***AMBITIOUS***. As Jeanneke puts it: “you need to want to grow”. Even though the N&C master does not prepare you for a job as a consultant, it challenges you to try new things, show perseverance, and deliver an end product when completing your internships. “Funnily enough, that is very similar to what a consultant does”, and Jeanneke’s small company even has five consultants with a neuroscience background.

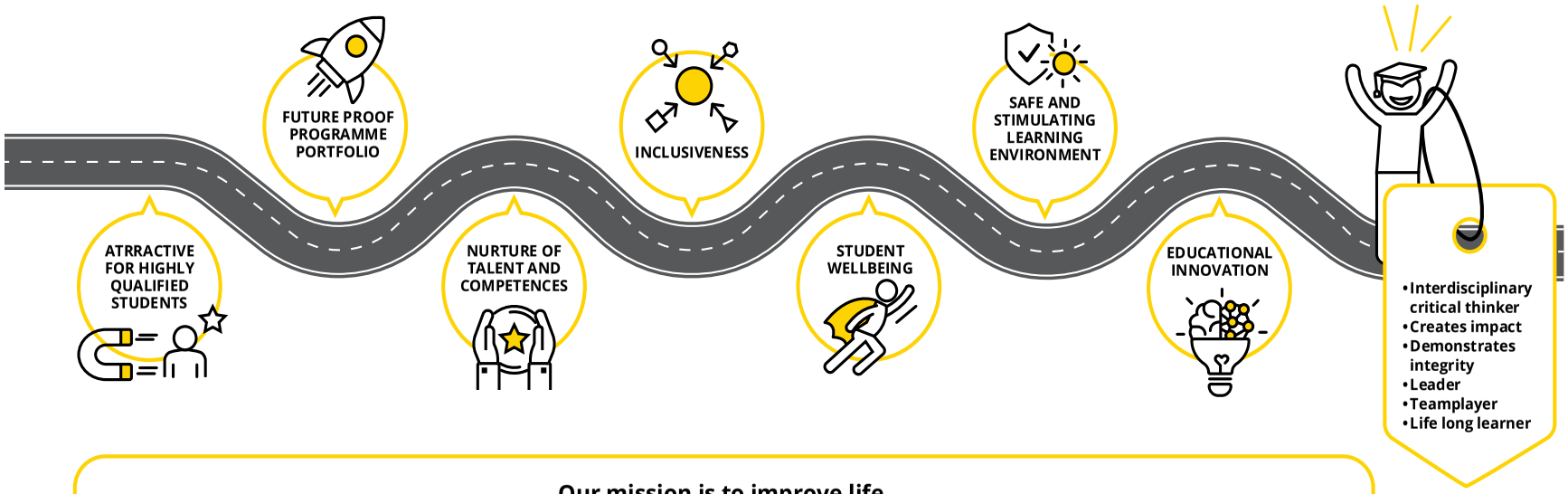
Scientists often possess an insatiable ***CURIOSITY,*** which is useful in consultancy. A common scientific trait that is not very helpful in consultancy is ***PERFECTIONISM***. Consultancy projects usually only last two months, so perfectionists can have a hard time getting them done. Sometimes, regardless of whether you want to get a project to a full 100%, 80% can be sufficient for the client. As Jeanneke explains: “It is important that you deliver high-quality work, as it is in any job, but it is also important that your client perceives the work as good work”. Nonetheless, she is convinced that expertise in a field of work is something you can develop, also in consultancy. Most importantly, as a consultant, she says: “you should like talking to people, and you should be curious”.

Poll #3

What is your current career of choice?



Graduate School of Life Sciences



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‘Get to know your coordinator’

Dr. Geert Ramakers

Department of Translational Neuroscience, UMC Utrecht Brain center, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands

Geert Ramakers is an Associate Professor Neurophysiology at the department of Translational Neuroscience at the University Medical Center in Utrecht. His research focuses on cellular and synaptic plasticity of the hippocampus and the midbrain dopamine system. In addition to his research, Geert is also involved in multiple educational activities. He is program coordinator of the master Neuroscience and Cognition, the neurotrack within the bachelor Biomedical Sciences, and the PhD program Clinical and Experimental Neuroscience at Utrecht University. Because of his great involvement within our masters programme, we are excited to shine a spotlight on his work and personal life, which hopefully makes you feel more connected to our program coordinator.

WHAT INSPIRED YOU TO PURSUE A CAREER IN NEUROSCIENCE?

Geert started off his career in Nijmegen where he studied Biology. During his bachelor, he was taught by two inspiring Belgian professors who gave lectures on development and adaptation of invertebrates. It were these lectures that sparked his enthusiasm for how organisms develop and how they adapt to their environment. Following his interests, he chose to pursue a biomedical-oriented track. Over the course of his studies, Geert did several internships which gradually introduced him to the field of neuroscience. His internships were comprised of a broad range of topics including the role of the pituitary gland in fish, the murine hippocampus and the establishment of a rodent model for epilepsy. During these internships, his interest in neuroscience was born. After his studies Geert obtained his PhD in Utrecht, where he researched biochemical processes involved in synaptic plasticity of the hippocampus in rats. He became fascinated by the electrical transmission between neurons, which fueled his interest for the brain even further.

After finishing his PhD, he continued his career in research doing a postdoc in Oslo, Norway. He describes his experience abroad as brilliant, and it has brought him a lot: ‘I was able to bring my family (wife and daughter) with me which was an amazing experience for all of us. Norway is a beautiful country with stunning nature and the people are very nice’. Funded by his own grant money, he was in charge of his own research project and he could fully focus on his research which he really enjoyed. His supervisor was an internationally renowned scientist who allowed him to meet many interesting people and to start building his network: ‘During the 2 years of my postdoc I met a lot of other scientists with whom I still collaborate today’. To top off his incredible experience abroad, he was then offered a permanent position at what now is the Translational Neuroscience department at Utrecht University.

DID YOU EVER THINK ABOUT A CAREER OUTSIDE ACADEMIA?

During his career, Geert also looked for jobs outside of academia. In fact, he was almost hired by a company to develop biochemical techniques: ‘I really did what I liked the most at the moment. I made choices one step at a time and then I went for it. If something came up that I really enjoyed I would go in that direction. That is how I ended up where I currently am’.

WHAT INSPIRED YOU TO BECOME A COORDINATOR OF THE MASTER’S PROGRAM?

Becoming a coordinator of a master’s program was not something Geert envisioned for himself. He

initially planned to continue his research on synaptic communication between neurons. However, during his research he supervised master and PhD students and he became involved in more educational activities: 'I noticed that I liked to talk about my research, and I started off giving lectures to bachelor students. From there it all developed gradually'. He went from being a co-organizer of a course, to the coordinator of a track within the bachelor Biomedical Sciences, to where he is now: coordinator of the N&C master's program and the PhD program Clinical and Experimental Neuroscience. When asked about what he likes the most about his job, his answer is clear: 'I think the development of students from young scientists into adult scientists is the most beautiful thing to see. I like to see everyone develop their own skills and capacities, and that they end up doing what they love and where they are happy.'

HOW DID YOU EXPERIENCE YOUR TIME AS A STUDENT?

Geert's experience as a student was the best time of his life: 'There were no worries, no limits, I could do whatever I wanted'. He thinks the period between the ages of 18 and 30 is the best period of your life: 'You are young, you have lots of energy, you can really focus on those things that you like'. An advice that he would give to current master students would be to enjoy yourself and to do what you like. He recognizes that this is easier said than done, as we live in a society that is very result oriented: 'Try to find a balance between what you like to do and what you need to have to be able to continue your career'

WHAT DO YOU LIKE TO DO IN YOUR FREE TIME?

Going for a run is one of Geert's major hobbies: 'I love to go running on a daily basis, especially now that I am sitting behind my computer almost the whole day'. Another hobby of his, and possibly a less expected one, is going to rock concerts. 'One of my favorite bands is Rush, a Canadian rock band that visited the Netherlands every two years and I would always go to their concerts. I also went to concerts of U2, The Rolling Stones, Metallica and many more! I must say I am not the one who joins these mosh pit things, I am always a little bit more in the back. When my daughters come along to these concerts they always laugh at me, because I am always standing in the back, very relaxed. I also really enjoy going to smaller venues like Tivoli de Helling and just see what bands are playing'. Geert also loves reading: 'I like to read but I can only do so when I am relaxed, for instance on a holiday or when I have time off. I really like Scandinavian novels'.

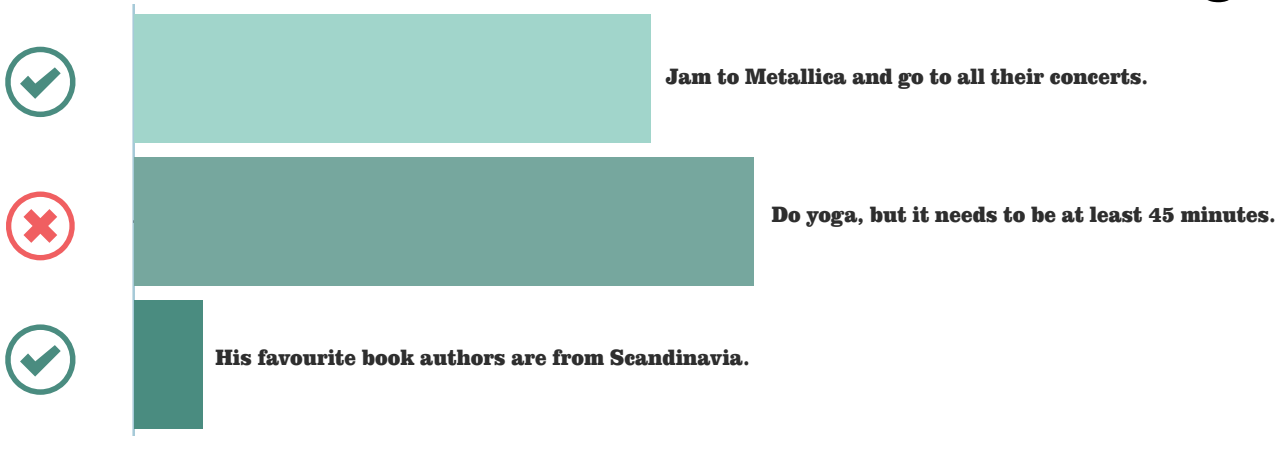
> I like to see students develop their own skills and capacities, and that they end up doing what they love and where they are happy.

CORONA TIMES ARE HARD, WHAT WOULD YOU SUGGEST STUDENTS DO TO CLEAR THEIR MIND AND FIND INSPIRATION AGAIN?

'What works for me is to go out and exercise, it always empties my mind and it makes me feel refreshed. It enables me to focus again. It does not have to be running, you could also go for a walk or make a jigsaw puzzle, just to do something else for a while to refresh a bit'.

Poll #4

Which statement about Geert was wrong?



Finding the crossroad between neuroscience and other fields of research

The interdisciplinarity of neuroscience has gained more and more attention throughout the past years. Some topics have already gained their acknowledgement, like neuropsychology and social neuroscience. However, when thinking out of the box you soon come across other, perhaps less well-known, disciplines which behold a promising and exciting angle of approach for neuroscientific research. In this section, three experts will share recent advancements in their field of research and how neuroscience and their field will mutually benefit each other. And who knows...you might find inspiration for your own research career!

'NeuroLaw and judicial decision-making – a legal scholar's call to neuroscientists to delve into judicial decision-making'

Dave A.G. van Toor

PhD LLM LLB BSc, Assistant Professor of Criminal (Procedural) Law, Utrecht University, Willem Pompe Institute for Criminal Law and Criminology, Montaigne Centre for Rule of Law and Administration of Justice

The scientific field that combines neuroscience and law – the field is often referred to as NeuroLaw (Jones et al., 2013; Kolber 2014) – is hot, as can be seen in the graphic illustration of the MacArthur Foundation (Figure 1): Research Network Law and Neuroscience, to illustrate the increase in NeuroLaw publication over the last years. Over years, the most common topic of NeuroLaw scholars was the influence of the neuroscientific insights of free will, especially a deterministic perspective of free will, on imposing responsibility on offenders (Catley, 2016). The field proved to be more than a one-trick pony: NeuroLaw is a rapidly developing field in which the impact of neuroscience on law is investigated, on all the phases of the criminal procedure. Several handbooks have now been published, both at conceptual (Pardo & Patterson, 2013) and descriptive (Jones, Schall & Shen, 2014) levels, and three doctoral theses have been published in the Netherlands.

In two of those theses, the researchers investigated the prisoner's brain. Cornet obtained her doctorate on a (neuroscientific) dissertation on 'whether certain neurobiological factors can contribute to the prediction of the treatment outcome of detainees' with the inspiring title 'Brains Behind Bars' (2016). Meijers completed his dissertation 'Do not restrain the prisoner's brain' (2018) aiming 'to expand fundamental knowledge on the neuropsychological functioning of prisoners, and to study the influence of the prison environment on executive functions and self-control'. In addition and in contrast, Van Toor obtained a doctorate on a legal dissertation, entitled 'A guilty memory?' (2017), answering the question of whether the suspect can be forced by the Justice Department to undergo neuroscientific investigative methods to gather evidence of crime(s) (i.e., if a suspect's brain can "invoke" the right to silence).

In the aforementioned handbooks and dissertations, one topic, which is of paramount importance, is largely overlooked: that of judicial decision-making (which is dominated by legal psychologists). The law of evidence and judicial decision-making is bound upon the idea that judges are (completely) rational decision-makers. In the years following the seminal work of Tversky and Kahneman (1981) on bounded rationality, we have seen an upsurge in studies exposing heuristic and biased thinking in judicial decision-making. Knowledge about the fact that judicial judgment is not and cannot be fully rational, and that heuristics and biases influence judicial decision-making, can slowly but surely be counted as general knowledge of lawyers (Keulen & Knigge, 2016; 492). Yet the influence of legal psychological experiments in day-by-day court decisions is limited, if not altogether absent (Sagana & Van Toor, 2020). So, it is time for neuroscientists to join legal psychologists and legal scholars to delve into the research on judicial decision-making with the aim to reduce the influences of heuristics and biases.

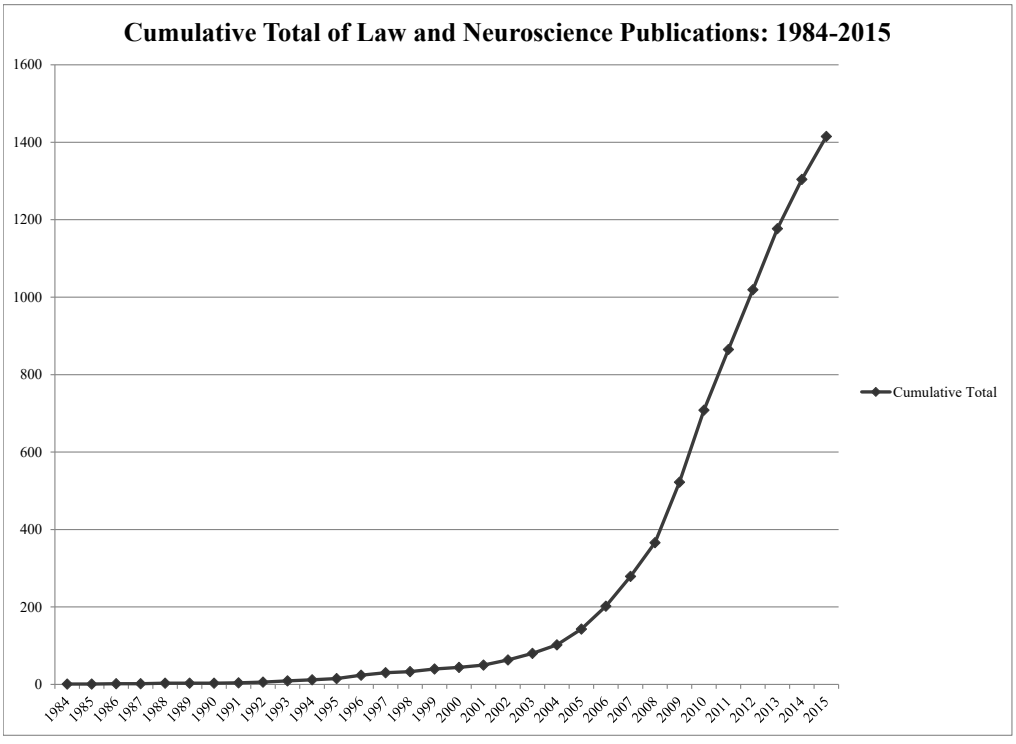


Figure 1. The increase in NeuroLaw publication over the last years.

Almost all legal cases end somehow with a decision by a judge, a court or a jury, and the importance of multidisciplinary research on judicial decision-making cannot be stressed-out enough. The risk of miscarriages of justices can only be reduced through cooperation with other scientific fields. However, that is easier said than done: while everyday judgment is usually free of form, national criminal procedural law forces the court to observe certain formal rules before, during and after the trial. Therefore, judicial decision-making is an interplay between human judgment (and all heuristics and biases that may apply) and strict procedural frameworks. It is this interaction between procedural law and human judgment that is characteristic of judicial decision-making. To unlock the potential of experimental research on judicial decision-making, researchers should incorporate procedural laws in their experimental set-up, as to promote the translatability of the experiment to real-life settings.

Please feel free to contact the author at d.a.g.vantoor@uu.nl when you're interested in discussing your NeuroLaw idea(s).

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'In Vitro Neurotoxicology Research at Utrecht University'

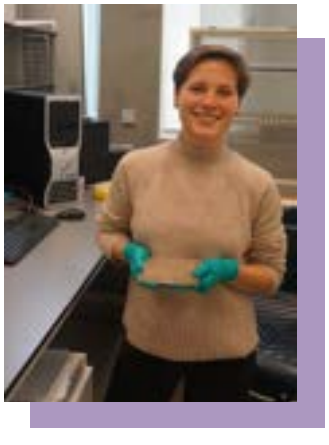
Lennart van Melis & Lora-Sophie Gerber, PhD candidates

Neurotoxicology Research Group, Toxicology Division, Institute for Risk Assessment Sciences (IRAS), Faculty of Veterinary Medicine, Utrecht University, Utrecht, the Netherlands

Neurotoxicity refers to "any form of substance-induced structural alterations or dysfunction of the nervous system". This broad definition already implies that it is possible to study neurotoxicity in many different ways, including (neuro)epidemiology, neurology, neuropathology, neurobehavior, neurophysiology, and neurochemistry. As can be derived from the name, the field of neurotoxicology is situated at the crossroads of neuroscience and toxicology. The Neurotoxicology Research Group at the Institute for Risk Assessment Sciences (IRAS; Utrecht University) investigates the neurotoxic potency of environmental chemicals and toxins on the nervous system in vitro. To do so, primary rat cortical cells and human induced pluripotent stem cell (iPSC) derived neuronal cells, that develop spontaneous neuronal activity, are used to screen for exposure-induced changes in neuronal activity and network synchronicity. In these studies, the cells are cultured on special microelectrode array (MEA) plates, allowing extracellular recordings of neuronal (network) activity. The exposures that are of particular concern can undergo further in-depth investigation using real-time, single-cell calcium imaging and electrophysiological approaches to measure the effects on exocytosis, ion channels and neurotransmitter receptors.

In the neurotoxicology research group, Lennart works on the European H2020 ENDpoiNTs project, which focuses on the neurodevelopmental effects of endocrine-disrupting compounds (EDCs). Worldwide, serious concern has arisen about the levels of EDCs people are exposed to during their lifetime via food, water, and air. Although there is much evidence that EDCs can adversely affect the endocrine system, little is known about how EDCs affect neurodevelopment. To address this knowledge gap, Lennart investigates the species- and sex-specific effects on neuronal function after both acute and developmental exposure to various EDCs. In his experiments, sex-separated primary rat cortical neuronal cultures and human iPSC-derived neuronal cultures are exposed to different concentrations of selected endocrine model compounds and endocrine-disrupting chemicals. During these exposures, both acute neurotoxic effects and neurodevelopmental effects are investigated using multi-well MEA recordings to characterize the impact of the compounds on neuronal function, network formation and maturation. In parallel, the effects of these different exposures on gene and protein expression are measured. Based on these results, in vitro testing and screening tools are being developed and validated so they can be applied to identify endocrine-disrupting chemicals that have the potential to induce developmental neurotoxicity.

Lora-Sophie works on the European H2020 TUBE project and studies the direct and indirect effects of traffic-related ultrafine particles (UFPs), specifically deriving from combustion engines, on brain health. Due to their extremely small size (< 100 nm in diameter), UFPs can translocate through epithelial barriers and finally reach the brain. Therefore, exposure to such small particles does not only constitute a risk to the lungs but also to extrapulmonary target organs such as the brain. While it is evident that traffic-derived air pollution is a significant contributor to neurological diseases, the relative impact of UFPs in the pollutant mixture remains unclear. A major aim of Lora-Sophie's project is to identify potentially neurotoxic UFPs and to understand the underlying mechanisms leading to their neurotoxicity. Furthermore, she is interested in the indirect effects of UFPs on the brain, the impact of cytotoxic and inflammatory effects at the port of entry (lung) on neuronal development, function, and degeneration. To tackle these research questions, it is important to thoroughly understand the brain's physiological and biological processes.



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‘Cognitivist approaches in videogame studies‘

Jasper van der Vught

Dr. Jasper van Vught, Assistant Professor, Department of Media and Culture Studies, Utrecht University, Utrecht, the Netherlands

Cognitive science is a highly multidisciplinary field of research. The word cognitive often functions as a prefix that is capable of turning almost any discipline into a new subdiscipline with an added focus on the mind (e.g., film studies (Bordwell, 1989) or game studies (Perron & Schröter, 2016)). While Gregersen (2014, p. 419) is right about the risk of these multiple disciplines functioning in relative isolation of one another, this multidisciplinarity also offers wonderful opportunities for cognitive science students to traverse a highly versatile landscape in search of more holistic contributions. Here, aiming to spark the reader’s interest in the cognitive approaches taken in videogame and media studies, I will briefly outline some examples of their use and usefulness in my field below.

At the most general level there is research that approaches the player-game interaction loop in terms of cognitive operations. Here the player forms expectations and tests hypotheses against a game system which in turn confirms or denies these expectations. Gregersen (2014), following Sternberg (2003), subdivides this interaction loop into three “universal cognitive dynamics”: suspense, surprise and curiosity. Focusing on the first can for instance help to see a difference between watching a film and playing a game.

Suspense occurs in between two prospect emotions, fear and curiosity, and is coupled with a state of uncertainty (Ortony et al., 1988). In films, as Hitchcock “the master of suspense” has shown, suspense is often triggered by giving an epistemic superiority over a character (Smith, 2000). When a liked character, oblivious to the danger s/he’s in, moves ever closer to her/his doom, we’re left in a helpless state of suspense, where fear is increased, and uncertainty remains. For games, this works differently. Rather than helplessly experiencing suspense for a character, we can control the character, moving it away from the danger, emphatically experiencing suspense with it. Furthermore, uncertainty is not just dependent on the feedback from the game/film system but also on our own coping skills, turning suspense for the character into suspense about our own play performance (van Vught & Schott, 2012).

This last point also means that emotions like suspense can have different focal points in games than in films. Suppose we follow Frijda’s (1986) functional theory of emotions, where emotions always include a dimension of cognitive appraisal and goal-related actions, then emotions in games will differ from those in films because our cognitive appraisal concerns goal-related actions that are executed (rather than only perceived).

Here, Perron (2005) and Frome (2006), following Tan’s (1996) work in film theory, argue that the gameplay experience can include three different categories of emotions. R-emotions are experienced in relationship to the represented world and the characters in it; A-emotions concern the aesthetic qualities of the game as a manufactured artefact; and G-emotions concern the player’s attention to planning and executing actions to achieve the game’s goals. As Frome puts it, these G-emotions are “emotions of competition, emotions generated due to winning, losing, accomplishment, and frustration” (2006, p. 19).

Recognizing how our cognitive appraisal may shift to different aspects of the game, thereby resulting in different emotions, helps us understand how we may experience games and be affected by them. For example, if violent actions occur during a difficult, fast-paced sequence, the experienced emotions may not concern the violent content but instead the preparation and execution of game tasks (van Vught, 2016). This would, in turn, require a significant rethinking of effect-studies into violent game content.

The research described here only scratches the surface of approaches identified as cognitivist in game studies. Nevertheless, I hope this brief outline has managed to show some contributions of cognitive sciences in game studies, perhaps even inspiring some of this journal’s readers to embark on their own videogame studies. I, for one, welcome your contribution wholeheartedly!

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Poll #5

In what other discipline could neuroscience be an asset?

Sponsor

Sponsor of the Journal of Neuroscience and Cognition:

Another year of the Mind the Brain Symposium!

The Mind the Brain symposium is an annual neuroscience event organised by first-year master's students from the Neuroscience and Cognition (N&C) programme. Although participation in the symposium is compulsory for all N&C students, we hope it provides them with a great experience! The students have an opportunity to present their research in the form of a poster or presentation, listen to inspiring keynote speakers, and follow illuminating workshops.

Mind the Brain symposium 2021

The academic year of 2020/2021 brought us the 17th edition of the Mind the Brain, meaning that the first edition was organised in 2005! Every edition of the symposium has a theme from within the field of neuroscience, which sets the tone for the whole event. The most recent themes include: Critical Periods, Criminal Minds, Advances in Neurotherapy, Stressed Brain, and Eat your Brain Out.

2018

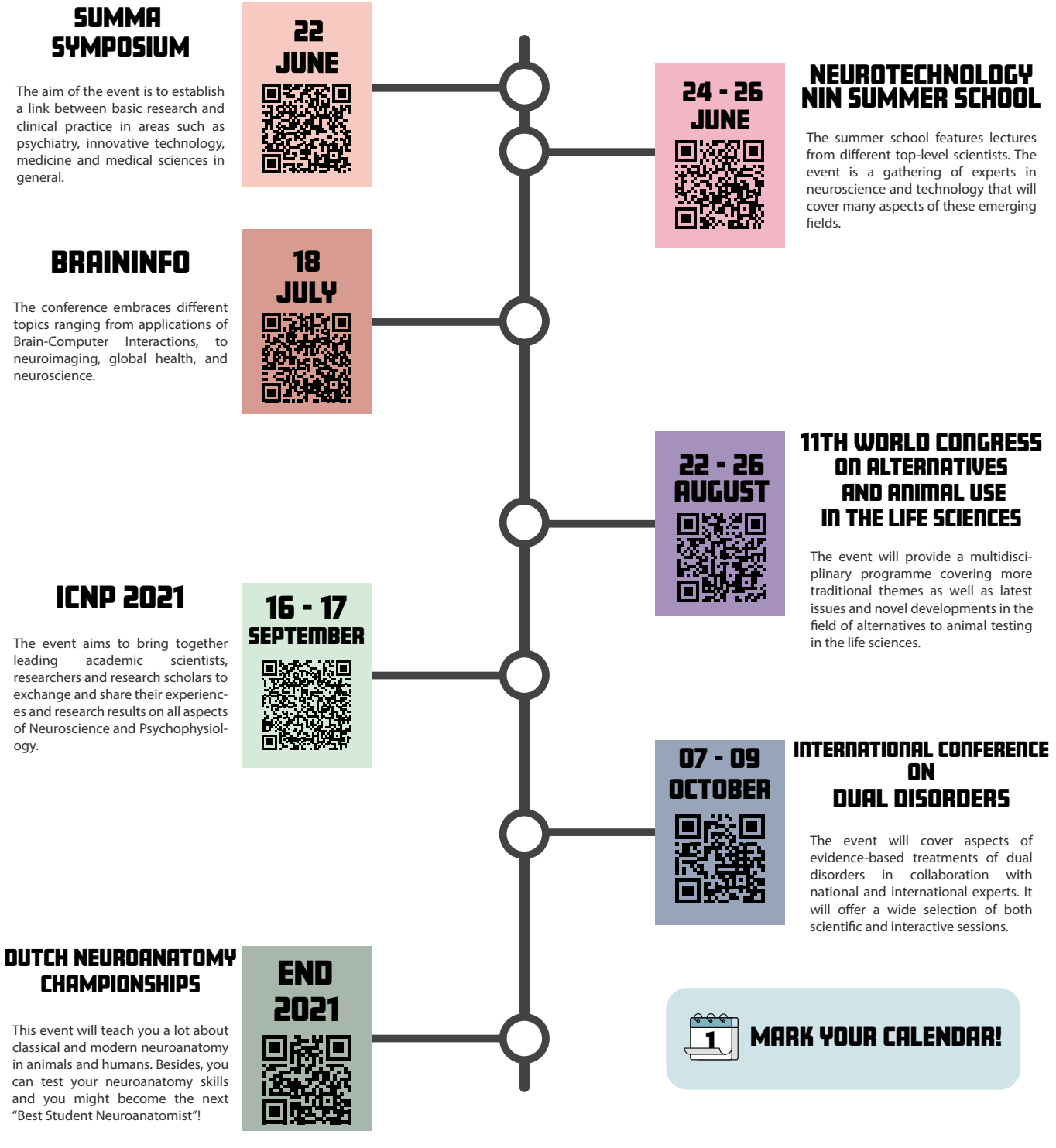
2019

2020

This year's theme, Brain on Lockdown, probably did not surprise anyone. Although it may have seemed like an obvious choice, it was also necessary. The COVID-19 outbreak has very apparent consequences on our daily lives. However, physicians and research groups around the world share alarming findings: the virus disrupts not only the social and economic state of affairs but also brain functioning. The Brain on Lockdown zooms in (pun intended) on cognitive and cellular consequences of SARS-CoV2 as well as personal development strategies we all need in these challenging times. Our intention was to address less popular topics in the COVID-19 discussion. Experts of the field covered issues such as the influence of loneliness on mental health and the risk of ischemic stroke in patients. We hope that this year's symposium provided you with some illuminating insights. See you during the poster sessions!

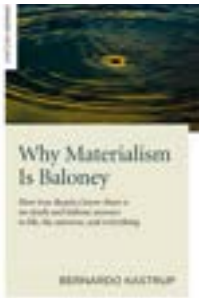
UPCOMING EVENTS IN 2021

TIMELINE



Reconnecting to yourself: time for relaxation

Throughout the journal we hope you came across topics that inspired you or sparked your interest! We like to continue this by introducing you to some of our personal recommendations which inspire us in our daily lives. We made a selection of diverse options which can hopefully entertain you in your spare time: from interesting books, to inspiring podcasts and relaxing yoga exercises. As important as your (academic) career might be, you might enjoy it even more when you find a healthy balance between work and time-off!



Are you in for a truly mind-bending book? And are you fascinated by consciousness? Then "Why Materialism is Baloney" by Bernardo Kastrup is the right choice for you. The hard problem of consciousness refers to the issue of how consciousness arises from physical matter. This problem exists in the first place, because we assume that the brain generates consciousness. Kastrup offers an interesting alternative which does not answer the hard problem of consciousness, but rather does away with it completely. Kastrup's view on consciousness is based on a mix of philosophy and neuroscience. This book may seem intimidating at first, but Kastrup offers many examples to explain his points. A fascinating read!

- VERA AALBERS

Brené's Brown TED Talk, even though first released ten years ago, could not be more up to date. While explaining how meaningful connections are and how the brain needs them, Brené highlights the importance of showing others your vulnerability. While living in the corona pandemic's eye, the topic could not fit better what many are struggling with: making new connections and respecting each other and themselves. For me, her talk is necessary for all to open their eyes to the fact that we shouldn't be ashamed of having a hard time but in fact, be aware of how beneficial it is to open up.
(Youtube: TED - Ted Talk - The power of vulnerability | Brené Brown)

- CATARINA SIMÕES PADILLA

The book 'Human kind: A Hopeful History' (Dutch: De meeste mensen deugen) is a must read for everyone. It has challenged me to see humanity from a different perspective and changed the way I think about history. This book combines insights from psychology, economics and history, and I had never read anything like it before. I highly recommend it to everyone!

- LOTTE VAN HOUT

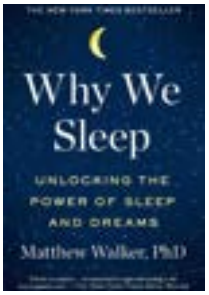
Daniel Dennets "The Self as a Centre of Narrative Gravity". For all the Neurophilosophers out there, this is a thought provoking and stimulating article that asks the question, what is the self? In Dennett's article he likens the self to the analogy of "centres of gravity". We know they exist; they are nicely defined theories but have no physical properties in the world, they are abstract objects. Just like the self, it is a narration of our experience and existence. It has no physical properties in the world but it is known to exist. It is a fascinating read that can be understood with various analogies that appear throughout the article. This gives a great perspective on the nature of the self and makes the theory easy to follow. If you are interested in consciousness and thought provoking philosophical arguments this article is for you. It will open your eyes to a new way of thinking.

- HAYDN MERLE

Recommondations

There are times when we are too busy to find some moments for ourselves. Especially now that we spend the majority of the day in front of our computers. I try to find at least 20 minutes a day for a physical activity, as it really helps me to clear my mind and stretch my body. I usually find a workout video on youtube and do a training by myself or with friends (facetime). The recommended workout video includes yoga and breathing practice to “Up Your Connect”. It is perfect for relaxing your body and mind after a stressful day and to reconnect with yourself.

- SARA RAPUC



If sleeping is not the most relaxing thing you could be doing, then what is? For some it may be easy, for some it is hours of trying every night. You must have heard many tips to sleep better by now, such as: ‘do not put your phone under your pillow’ and ‘try to make the room as dark as possible’. Did you also know a cold room (17-20 degrees celsius) is best to fall asleep in? Do you want to learn more about why we sleep and what happens when we do or don’t? Start reading before bedtime and try: ‘Why we sleep’ (Dutch: ‘Slaap’) by Matthew Walker! Both educational and nice to read!

- CHANEL SAM

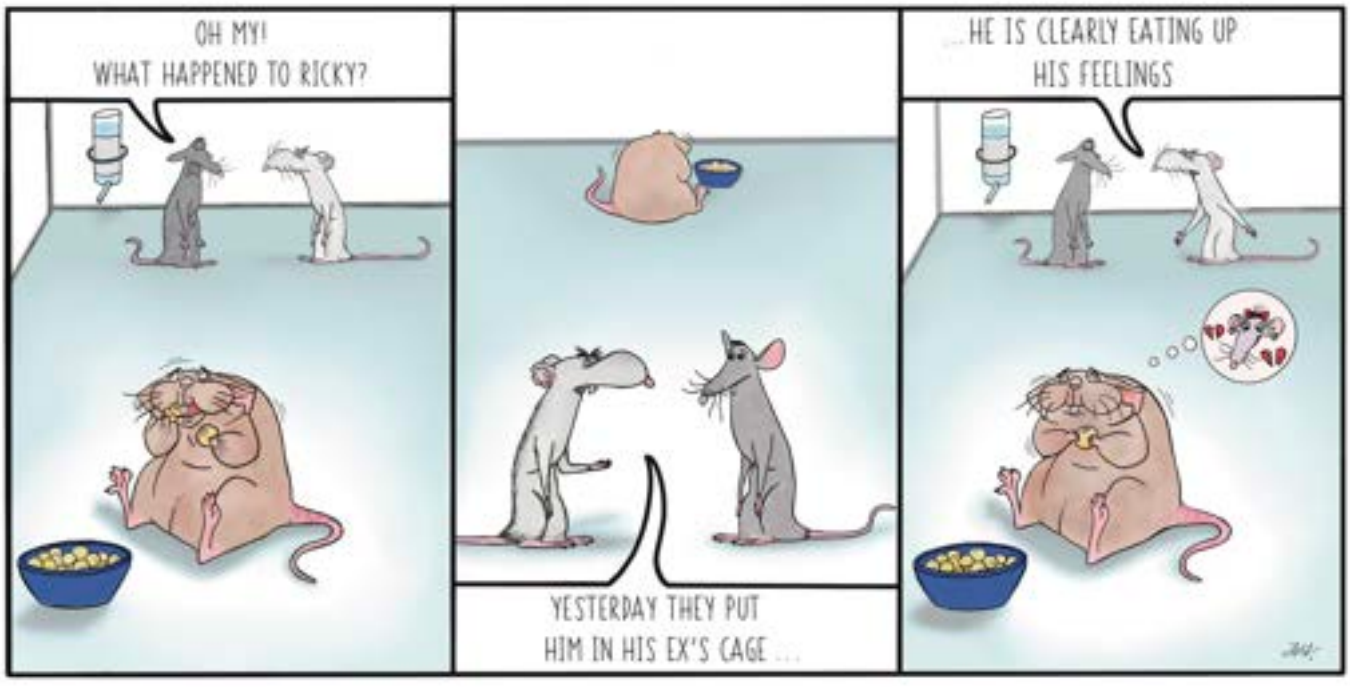
One of my favourite things to start the day with, is to listen to a podcast. The podcast ‘Sean Carroll’s Mindscape’ to me is a perfect intersection of science, philosophy, and good chat. Sean Carroll has fascinating conversations with scientists from various disciplines. A good share of the episodes have a topic in Neuroscience, often with a philosophical or moral perspective. The level of difficulty of the discussions is not too high, but the topics are refreshing, often going beyond the things we learn about the brain in lecture halls. Plus, this means you get some free knowledge on interesting themes in many other sciences, like Maths, History, and Physics!

- JANA HERMANS

Book “Waarom wij vreemdgaan en parachute springen” by Luc Swinnen. Unfortunately the book is not available in English, but I would still like to give this recommendation for the Dutchies among us and perhaps for those who want to learn Dutch! One reason why I study neuroscience is because I keep astonishing myself about the weird ‘irrational’ choices people can make: and that is exactly what this book is about! It is a really easy-written book in which the author explains, from a neuroscientific and evolutionary standpoint, why we for example have romantic affairs at the office or why we jump out of planes ‘for fun’.

- NINA DIJKSTRA

Tickle your brain



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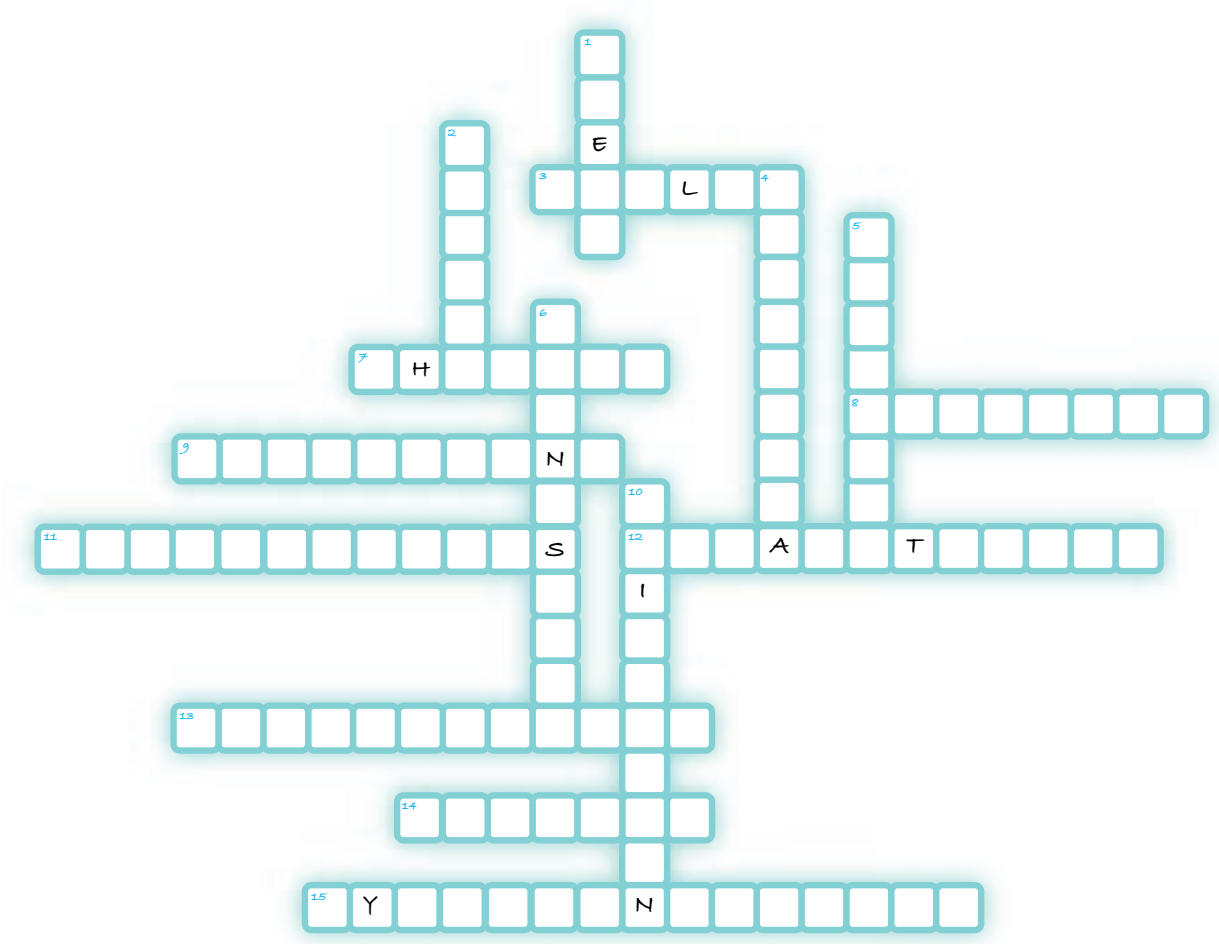

DOWN:

1. The founder of psychoanalysis

2. A neuron that fires both when someone acts and observes the same action performed by another subject

4. Star shaped cells that play a number of active roles in the brain

5. The relay center of sensory signals

6. Patients can visually respond to stimuli but cannot consciously see it

10. A drug acting upon a serotonin receptor that is showing promise in the treatment of depression and addiction

ACROSS:

3. Individual instances of subjective, conscious experience. The term used to describe the feeling of "what it is like"

7. The hunger hormone

8. Commonly assumed threat detector of the brain

9. Something people seek and a hormone

11. A process by which new neurons are formed in the brain

12. Perceptual phenomenon in which senses merge together leading to an experience of cross modal sensory perception

13. A technique that manipulates light to control neuronal activation

14. A substance or treatment that is designed to have no therapeutic value

15. A condition that results in the complete loss of the cerebral hemispheres leaving only cerebral spinal fluid and subcortical structures

1. Freud 6. Blindsight 11. Neurogenesis
2. Mirror 7. Ghrelin 12. Synaesthesia
3. Qualia 8. Amygdala 13. Optogenetics
4. Astroglia 9. Adrenaline 14. Placebo
5. Thalamus 10. Psilocybin 15. Hydranencephaly

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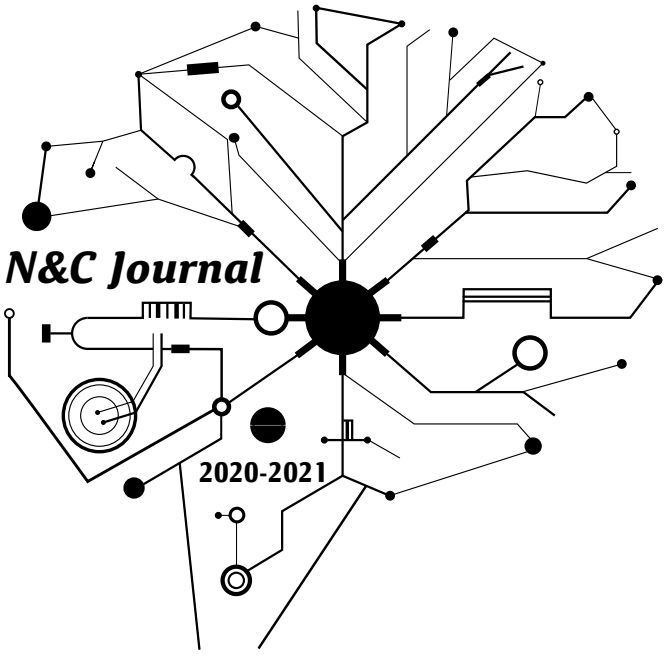

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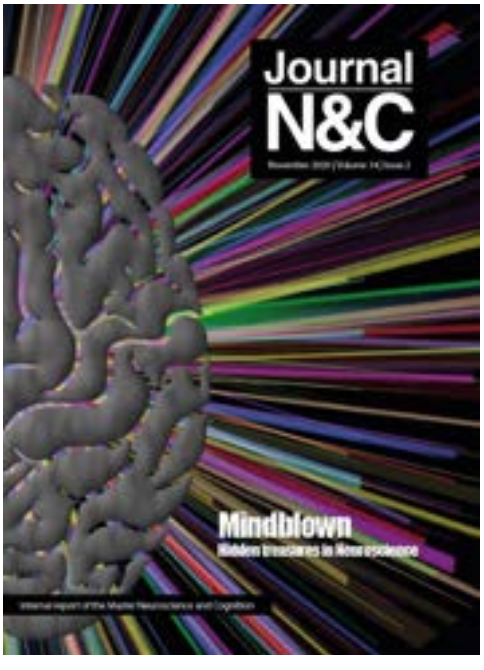

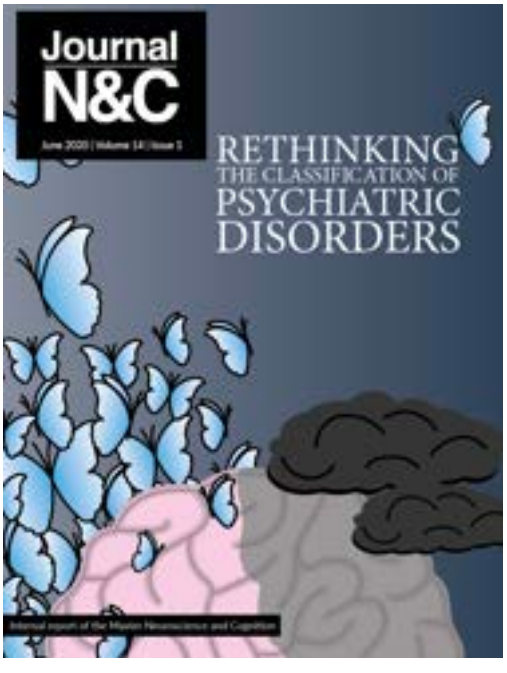

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