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The future of Neuroscience

Science fiction or fact?

Internal report of the Master Neuroscience and Cognition

“The brain is the organ of destiny. It holds within its humming mechanism secrets that will determine the future of the human race.”

- Wilder Penfield

“The brain is conceded to be the master organ of the body, the regulator of life, the source of human progress.”

- Frederick Tilney

“Neuroscience over the next 50 years is going to introduce things that are mind-blowing.”

- David Eagleman

ALS is characterized by motor neuron degeneration. This degeneration is due to protein accumulation in motor neurons, which can be caused by superoxide dismutase 1 (SOD1), among others. SOD1 mutations lead to the misfolding of SOD1, which results in a loss-of-function of SOD1 as transcription factor for DNA repair genes. Together with a disrupted removal of oxygen radicals and toxic gain-of-function of Bcl-2, SOD1 mutations lead to neuron apoptosis. Prion-like transmission of misfolded SOD1 can explain the spread of ALS pathology from site of onset to other sites. However, wildtype SOD1 can exhibit neuroprotective effects against ALS disease progression.

Brain computer interfaces (BCIs) transform brain activity into artificial binary output. To direct brain computer interface research and provide insights in the marketability of the technology, it is essential to consider the opinions of disabled potential users, non-disabled public, researchers in the field and caregivers. As such, this paper explores the public opinion on brain computer interfaces technology by answering the following research questions: (1) Do the various stakeholders have a difference in opinion regarding invasive and non-invasive BCIs? and (2) What feature of BCI technology is deemed the most important according to the several stakeholders?

Amyotrophic lateral sclerosis is a neurodegenerative disease with progressive muscle weakness leading to death by respiratory failure. Unsuccessful bench-to-bedside translation calls for a critical look at current model systems. In this review, the validity and (potential) value of mouse models, simple animal models and induced pluripotent stem cell (iPSC)-derived models are discussed. The main findings are: (1) Knock-in technology may improve the chance of successful translation. (2) Advancements in 3D cell cultures allow for complex modelling of sporadic ALS. (3) Age induction, vascularization, microfluidics, and complex co-culture techniques could allow ALS-on-a-chip technology to evolve into a highly valuable tool with unprecedented validity.

The functioning of the brain is a combination of heavy local redundancy as well as intricate, complex mechanisms on a small scale. This leads to difficulty in assessing the optimal spatiotemporal scale on which to describe brain functioning, including consciousness. This review article explores what this means for one of the most influential modern theories of consciousness: Global Workspace Theory.

Content

#Poll

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: 17, 37, 56, 74, 80

References (cover page)

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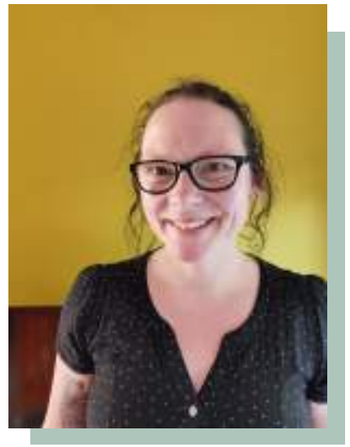
Foreword

Dear reader,



Before you lies the 2nd issue of the 15th volume of the Journal of Neuroscience and Cognition. The theme of this issue is "The Future of Neuroscience: Science Fiction or Fact?", and in line with this theme the Editorial Board of the Journal has brought together state of the art research and opinions from different disciplines.

This issue of the Journal of Neuroscience and Cognition focuses on where we stand and especially on what lies ahead of us. I would like to take a moment here to also reflect on what lies behind us. By considering scientific practices that were state of the art in the past we might appreciate more what (technological) advances have brought us. The advances in experimental paradigms are quite obvious, we can probably all think of examples or studies that we worked on that would never have been possible before we had computers with high processing speed, fantastic graphic cards, and, before the internet existed. We might tend to forget, or not even hear about, the more practical aspects of academic work that have changed massively over the past decades. I remember that during my time as a (PhD) student, senior staff would talk about publishing their articles when they were PhD students themselves. They shared stories about putting a physical copy of your manuscript in an envelope, putting stamps on it, and literally mailing it to a journal, instead of submitting it through an online submission system. Stories of repeatedly checking your (physical!) mailbox, hoping to find the reviewer reports in there, instead of being able to interact online with your reviewers from across the globe. Each year the Board of the Journal of Neuroscience and Cognition is able to construct two issues of a professionally printed journal. It is not only the scientific work that the journal reports on, but even the existence of the journal itself that is only possible by advances in science and academia.

The student articles in this issue touch on various recent developments in the field of neuroscience, ranging from brain computer interfaces to global workspace theory of consciousness and ALS research. Besides, senior researchers discuss both recent advancements and promising future aspects of Neuroscience through articles and personal interviews. This theoretical and methodological expertise of senior staff is important for groundbreaking advances in Neuroscience. If you ever end up in a conversation with a senior staff member, you might be eager to hear all about their new and innovative ideas. But why not ask them where they have been, what they have seen, how they conducted research ten, twenty, maybe thirty years ago? This will provide you with a historical perspective and might lead to a fun and engaging conversation. The historical perspective can also become very relevant when "old-fashioned" treatment methods, such as electroconvulsive shock therapy (ECT) regain interest. Although ECT was once considered inhumane, recent technological and theoretical advances have resulted in putting ECT back on the map as an effective treatment method, as further discussed by Jesca de Jager. Finally, there is touched upon changes in scientific practice, such as open science and science communication. Here you can for example find a piece by Prof. Dr. Stefan van der Stigchel on the (mis)interpretation of science in the media.

This issue of the Journal of Neuroscience and Cognition made me very enthusiastic about the future of Neuroscience, but at the same time also appreciate the past. As such the board of the journal has succeeded in putting together a very inspiring issue once again, and I hope you will feel the same.

Anouk Keizer,

Senior Supervisor Journal of Neuroscience and Cognition 2020-2021

Dear reader,

"The future lies ahead of you" is what we have heard from childhood onwards. Whether it is about choosing a holiday destination or your master program, the future is mainly framed as promising and exciting. This is continued during our master program, in which we get to develop our understanding of new techniques and uncover certain neuronal mechanisms. Brains in a dish, brain-computer interfaces and personalized medicine are examples that, at first glance, may seem to come straight from a science fiction movie. Therefore, as a board we are excited about creating an issue characterized by these opportunities brought about by the field of neuroscience and are happy to present to you the second issue of the Journal of Neuroscience & Cognition – *The Future of Neuroscience: Science Fiction or Fact?*.

For this edition we developed a new division of sections and articles from our previous issues, which aims to mirror all the various subfields of neuroscience that have experienced a fast proliferation in techniques and theories over the past years. Besides, every section will highlight some promising prospects and how they are likely to advance scientific research and clinical practice. We thereby hope that our collected articles and interviews inspire you to pursue a future in which you believe, may this be as a neuroscientist or science fiction director: the future has shown us that sometimes even the impossible is possible! For starters, I would like to give you a small sneak-peek into the content we have enjoyed collecting over the past months.

We start on the molecular scale. Niek Renckens starts off by providing us a thorough review about Cu/Zn superoxide dismutase 1 (SOD1)-associated amyotrophic lateral sclerosis. This section, which aims to highlight recently discovered neuro-molecular interactions of clinical relevance, is continued with an article written by Werner Dykstra: Who introduces you to the recent history of cerebral organoids and how they help him unravel neuron-glia interactions in Alexander Disease. This is followed up by two articles that provide us further insight into using a non-conventional psychopharmacological treatment for psychopathology: Prof. Dr. Leon Kenemans tells you more about psychedelics and their interaction on the serotonin receptor, and Ineke de Vries, Nadia Leen and Caroline Kwee will unravel the promising role of cannabinoids in treating clinical anxiety disorders.

Since the future stands central in the current issue, we can not omit the contributions of artificial intelligence (AI) within neuroscience. Dr. Chris Janssen wrote an approachable introduction on AI, followed by an article written by Dr. Sjoerd Stuit, which applies this knowledge in the study of face perception. Dorinde Korteling has thereby contributed with a review that bridges the AI section with the following section about futuristic treatment options, with her review on BCI technology and its potential stakeholders. The following section will continue with a review written by Marthe Kaal about the validity and potential of ALS modelling. This is followed up with articles written by Jesca de Jager, Livia Dominicus and the team of Dr. Tanja Nijboer, who discuss how revolutionizing technologies aid in clinical prognosis, treatment and rehabilitation. Moreover, we hope you will appreciate the collaborative article written by the Department of Neonatology, Brain Center, Digital Health and FB Medical Technology and Clinical Physics of the UMCU on automated real-time sleep-state prediction algorithms in preterm infants.

We continue with a section in which four researchers tell you about their research and how it changed the way we conventionally approached specific questions within the field of (neuro)science. Dr. Dennis Schutter and Dr. Jacco Zwanenburg tell us more about (neural) structures influencing human behaviour and health, which has not gotten much attention in the past years. Prof. Dr. Maarten Kole and Dr. Vanessa Donega further unravel the complexity of neuronal cells and what is yet to be known of them. Martijn Klop thereby offers an in-depth review of Baars' global workspace theory of consciousness, a phenomenon that has eluded and provoked the minds of many philosophers and scientists over the past ages and is an important issue to think about in our future.

What science might look like in the future, and how this can impact the scientific community and society, is further highlighted in the last section: Science in the future and society. We thereby gave the word to one of our program coordinators, Prof. Dr. Stefan van der Stigchel, who gives us advice on communicating your scientific findings by sharing his personal story. This is followed by an interview with Dr. Anna-Lena Lamprecht about open science,

accompanied by personal advice on how we as young academia can promote this.

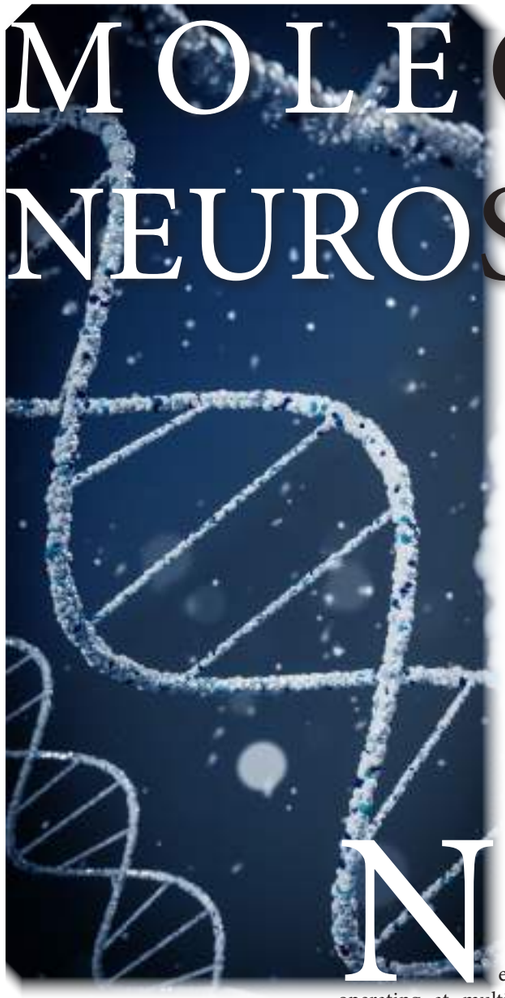
Although this issue aims to address the promising future of neuroscience, it should be acknowledged that one should have an understanding of one's past before gazing into the future. The Chair of the Mind the Brain Committee, Zuzanna Altmann, thereby looks back at the Mind the Brain Symposium of 2021 and provides some advice on how to create an informative and enjoyable event. Besides, since it is the last issue that we, as the editorial board of 2020-2021 have created, it is also time for us to look back at the past year. Despite the challenges of creating two issues during a pandemic, I think it is safe to say that we can be proud of our teamwork and what it has achieved. Weekly meetings, interviews, and (a lot!) of reviewing are all part of the process that has made us learn a lot and has brought us closer together. We thereby want to thank every contributor and reviewer who has helped us create the second issue, with particular importance to our supervisor Dr. Anouk Keizer who has supported us with her enthusiasm and helpful advice!

We hope you enjoy reading this issue and that you find some inspiration for choosing your future!

Yours sincerely,

Nina Dijkstra,

Chief of the Editorial Board 2020-2021



‘The smallest things can have the biggest effect’

Neuroscience is an inherently interdisciplinary field, operating at multiple levels and each influencing each other. Minuet changes in our molecular structure can have huge consequences on our psychological output. The section before you highlights the work conducted at the molecular level. We start with a fascinating student article written by Niek Renckens discussing the role of SOD1 expression in amyotrophic lateral sclerosis. This is followed by an in-depth interview at Utrecht’s Military Hospital, discussing the importance of the endocannabinoid system and the potential therapeutic benefits of using cannabinoids in the treatment of a host of psychiatric disorders. Next, Prof. Dr. Leon Kenemans provides captivating insights into the ever growing and popular role of psychedelics for the treatment of psychiatric disorders. Leon analyses recent work, breaking down the effectiveness of psychedelic compounds and addresses the future of psychedelics. Finally, Werner Dykstra enlightens us on the fascinating methodological technique that are Organoids, growing and modelling brain and neuronal tissue to understand the molecular mechanisms influencing disease.

‘Cu/Zn superoxide dismutase 1 (SOD1)-associated amyotrophic lateral sclerosis’

A report reviewing the different roles of SOD1 during ALS and an assessment of the part these roles play in the pathology of the disease.

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ALS is a devastating disease, for which neither a cause nor a cure is known. What we do know, is that ALS is characterized by motor neuron degeneration. This degeneration is due to protein accumulation in motor neurons, commonly either TAR DNA-binding protein 43 (TDP-43), RNA-binding protein Fused in Sarcoma (FUS) and/or Superoxide dismutase 1 (SOD1) form the so-called Lewy body-like inclusions. This prompted an analysis of the homeostatic and disease-associated functions of SOD1, which hopefully will help clarify a complex interplay of mechanisms and prompt novel research questions from fellow researchers.

Mutations in SOD1 can explain 20% of familial ALS development. These mutations lead to the misfolding of SOD1, which results in a loss-of-function of SOD1 as transcription factor for DNA repair genes. Together with a disrupted removal of oxygen radicals and toxic gain-of-function of Bcl-2, SOD1 mutations lead to neuron apoptosis. Prion-like transmission of misfolded SOD1 is likely to explain the spread of ALS pathology from site of onset to the rest of the body. However, wildtype SOD1 can exhibit neuroprotective effects against ALS disease progression.

Keywords: *ALS, SOD1, protein folding, neurotoxicity*

INTRODUCTION

RELEVANCE (ALS PREVALENCE)

Amyotrophic lateral sclerosis (ALS) is a disease that is becoming increasingly prominent nowadays, both in terms of number of ALS patients and the societal awareness of the disease. The increase in the number of patients is due to the increasing average lifespan in most countries combined with the fact that the mean and median age at onset of ALS is between 51 and 66 years of age. The incidence of ALS is reported as between 2.1 and 3.8 per 100,000 person-years in Europe, while in Asia it has an incidence of only 1 per 100,000 person-years (Benjaminsen et al., 2018; Zhou et al., 2018). This difference is thought to be due to the higher prevalence of ALS-linked mutations in certain genes in European individuals, which leads to a higher frequency of familial ALS (fALS). Familial ALS is ALS with a clear hereditary component, which is more frequently present in Europe as compared to South Korea (Kwon et al., 2012).
Determining what symptoms/clinical outcomes are the result of ALS is very complicated, because in most cases the cause of the disease is not known. Only in some cases, mainly the familial ones, mutations that are strongly correlated with disease progression are present. It is known that the disease causes the death of both the corticospinal (upper) and spinal (lower) motor neurons, which results in general weakness, difficulty speaking and physical pain common in most patients. There is no known curative therapy or medicine for the disease yet, which means that the motor neuron degeneration caused by ALS is lethal to all patients (Arrighi et al., 2010).
However, the life expectancy of an ALS patient varies wildly with age at disease onset. Patients who experience their first symptoms before age 40 typically live longer than 10 years with the disease, while patients who have symptom onset after their 80th birthday have a median survival time of lower than 2 years. Age at symptom onset is not the only variable that predicts life expectancy. Clinical factors, such as site of onset and diagnostic delay, are also prognostic factors in ALS (Chiò et al., 2014).
SOD1 is an antioxidant enzyme which was the first genetic marker for ALS found. When SOD1 is mutated, it aggregates intracellularly thereby inhibiting protein degradation which is closely correlated to cellular toxicity (McAlary et al., 2016). While this research clearly shows that SOD1 can be at least partially responsible for the neurodegeneration which is a characteristic of ALS, a recent study from Parnsarasa et al. (2018) shows that higher SOD1 re-localization to the nucleus correlates with slower disease progression, which suggests a potential protective role of SOD1 in the nucleus or at least a decreased role in ALS pathology.

The presence of certain mutations in SOD1 significantly correlates with specifically SOD1-associated ALS prognosis. Some of these mutations are associated with fast neurodegeneration, whereas others are indicative of a slower neurodegeneration. Patients with fast disease progression mutations, like SOD1 A4V, have a mean survival time of as little as 12 months. On the other hand, patients with slow disease progression mutations in SOD1 (G37R, G41D, and G93C) have a median survival time of more than 80 months post diagnosis (Cudkowicz et al., 1997).

RESEARCH QUESTION

Based on this newly discovered protective role of SOD1 in ALS, the following research question was proposed: "Does SOD1 activity influence ALS disease progression in a net beneficial or detrimental way from the perspective of the patient based on its roles?" This research question immediately caused some related questions to appear, namely: "How does each of these roles influence disease progression? For the average ALS patient, what role(s) does SOD1 have at the highest frequency?" At the end of this report, I hope to give a more established overview of the roles of SOD1 in ALS and provide advice for potential therapeutic targets and new avenues to explore for other researchers interested in ALS.

SEARCH STRATEGY & LITERATURE OVERVIEW

For the report, Google Scholar will be the primary search engine used to find research articles and review articles about specific subjects pertaining to the subject of the report. The search terms used will be centred around familial ALS and the protein SOD1. The recency of chosen articles and the reliability of the journals where the articles were published will be taken into account when selecting, comparing, and contrasting the information from these articles. The source articles for this review will be referenced in APA[J1] style.

CLASSIFICATION OF ALS

ALS is a very complicated motor neuron disease. There are not many similarities between any two ALS patients. The only aspect that is consistent in all ALS patients is the degeneration of the upper and lower motor neurons of skeletal muscles. The first symptoms experienced by ALS patients are muscle twitching, stiffness of the muscles and weakness due to muscle atrophy. The atrophy is caused by the skeletal muscles not being used as frequently anymore due to a lack of synaptic input as a result of denervation. Also, as many as half of all ALS patients will develop cognitive (and resultant behavioural) deficits during disease progression. In 13% of patients, this cognitive deficit progresses to frontotemporal dementia (Phukan et al., 2012).

The first important distinction to be made is which motor neurons are the first to degenerate. Two thirds of patients have symptoms starting with muscle stiffness in the limbs, with the lower motor neurons connected to the spinal cord being the first to degenerate. This presentation of symptoms is characteristic for spinal-onset ALS. However, the remaining one third of the patients have facial muscle stiffness as their first symptoms due to upper motor neuron degeneration. This stiffness shows itself as difficulties in swallowing (dysphagia) and talking (dysarthria). This presentation is called bulbar-onset ALS. In both types of ALS, the upper and lower motor neurons will experience degeneration, the onset is based on which group of motor neurons is the first to degenerate (Brown & Al-Chalabi, 2017).

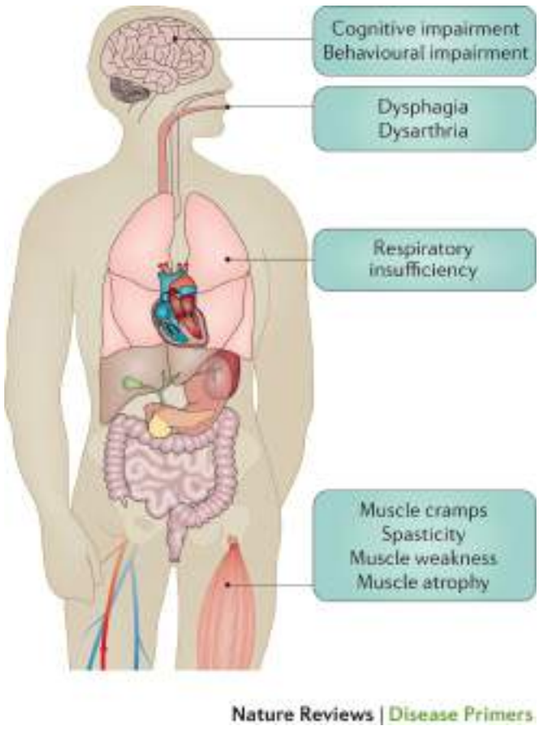

Figure 1. Schematic representation of symptoms potentially present in ALS. The muscle cramps, spasticity, and weakness due to atrophy are present in all ALS cases, both spinal- and bulbar-onset. The dysphagia and dysarthria are characteristic for bulbar-onset ALS. The cognitive and behavioural impairment is a complication present in up to 50% of ALS patients (Hardiman et al., 2017).

The second important distinction to make is whether a patient has sporadic or familial ALS. Approximately 90 percent of patients are diagnosed with sporadic ALS and the remaining 10 percent of patients are diagnosed with familial ALS. Sporadic ALS is defined as ALS which occurs without a family history of the disease. A family history of ALS can be found in familial ALS, as it is inherited like a dominant trait would be. The genetic basis of this inheritance is unclear, although many different mutations in SOD1 have been documented in fALS patients (Bakavayev et al., 2019). For example, an investigation of the spectrum of and variability in mutations in Chinese patients with familial ALS showed that 52.9% of these patients had a known or novel mutation in SOD1 (Liu et al., 2019). However, this high frequency of mutation was in a small, Asian population of patients. In comparison, an Italian study showed SOD1 mutations present in 12-23% of fALS cases (Battistini et al., 2005). This shows that the frequency of mutations is highly variable between populations. There are at least 30 genes which significantly increase the chance for ALS development, but having one gene variant associated with ALS risk is not likely to cause the disease. Another study has provided evidence that both oligogenic inheritance, where a phenotype is determined by multiple genes and genetic pleiotropy, where a gene has multiple different manifestations as its phenotype, might play a significant role in ALS inheritance. Evidence of these factors have been found in patients with sporadic ALS, indicating that perhaps the dichotomization of ALS into familial and sporadic is due to incomplete knowledge of these factors in its inheritance (Renton et al., 2014).

It is certain that there are 4 genes, C9ORF72, TARDBP, SOD1 and FUS, which on their own can explain approximately 70% of familial cases of ALS (Chiò et al., 2014). To understand why the development of familial ALS and mutations in SOD1 are so closely correlated, we will first have to learn about the functions of SOD1 in healthy individuals and the dysfunction in ALS.

Due to the oligogenic inheritance, where multiple genes interact to manifest a phenotype, present in ALS, it is important to discuss not just the gene of interest for the research question, SOD1, but also the other 3 genes, C9ORF72, TARDBP and FUS, which together explain the majority of fALS cases.

C9ORF72, TARDBP AND FUS

C9ORF72 is a protein with 2 different isoforms, namely, isoform A (481 amino acids in length) and isoform B (222 amino acids in length). There is a GGGGCC repeat in the DNA sequence, which is present 20-30 times on average, but this repeat can occur hundreds of times in people with the repeat expansion in C9ORF72. This repeat expansion decreases the amount of mRNA and protein for C9ORF72, especially C9ORF72 isoform B is significantly reduced in expression (Gendron & Petrucelli, 2018). The expansion makes C9ORF72 the most common genetic cause of familial ALS and frontotemporal dementia (FTD) (van Blitterswijk et al., 2015).

TARDBP is the gene encoding for TAR DNA-binding protein 43 (TDP-43) (Kabashi et al., 2008). TDP-43, as the name implies, is a protein which can bind to DNA and RNA. Furthermore, the protein is normally localized in the nucleus of the neuron. This binding activity and localization is essential, as it has proven cellular functions, such as mRNA stabilization, processing, transport, and translation by ribosomes (Cohen et al., 2011). The pathogenic mutations in TARDBP causes the redistribution of TDP-43 into the cytoplasm instead of to the nucleus, which in turn leads to the formation of the inclusion bodies in the cytoplasm. There are two pathogenic mechanisms by which TDP-43 causes its proteinopathy, namely, toxicity of the ubiquitinated TDP-43 inclusions to the neuron or loss of TDP-43 function in the nucleus (Gao et al., 2018).

FUS is an RNA-binding protein encoded by the FUS gene. FUS is very comparable to TDP-43, as it is also a protein which is normally involved in RNA metabolism. Like with TDP-43, FUS with mutations is mislocalized to the cytoplasm instead of the nucleus, where it forms ubiquitinated, cytoplasmic inclusions. The mislocalization of mutated FUS protein into the cytoplasm are directly toxic to the neuron, which is shown through amelioration by addition of autophagy stimulating drugs, which indirectly remove the inclusions in the cytoplasm (Marrone et al., 2019).

SOD1

Cu/Zn superoxide dismutase-1 (SOD1) was the first protein found to be associated with the development of ALS and mutations in its gene SOD1 can explain approximately 20% of familial ALS cases, as shown previously in the chapter 'Classification of ALS'. Mutations, such as single-nucleotide polymorphisms, in SOD1 can also be prognostically relevant for survival after disease onset and symptom severity (Battistini et al., 2005). For example, A4V-SOD1 presence is prognostically very unfavourable, as it causes a rapidly progressing form of ALS with lower motor neuron disease with a mean survival time of less than 12 months (Saeed et al., 2009). Wildtype SOD1 forms a homodimer from two 32 kDa subunits, which each have a Cu/Zn site. The copper and zinc ions in these sites can catalyse the reaction of an oxygen radical (superoxide) and water to hydrogen peroxide and molecular oxygen. Neutralization of radicals produced in the mitochondria is important, as radicals are toxic to the neuron through oxidative stress. SOD1 is therefore present mostly in the intermembrane space of the mitochondria as well as in the cytoplasm. SOD1 is localized to the nucleus if high amounts of hydrogen peroxide are present in the neuron. SOD1 has an additional function in the neuron, where it is a transcription factor for genes implicated in oxidative resistance and DNA repair (Tsang et al., 2014). SOD1

is also suggested to regulate apoptosis in healthy cells through its interaction with the apoptosis regulator BCL-2 in the membrane of the mitochondria (Lei et al., 2006).

PATHOPHYSIOLOGY OF SOD1-ASSOCIATED FAMILIAL ALS

The complete cause of ALS is still not fully understood, this is especially true for sporadic ALS. The cause of familial ALS is partly due to oligogenic inheritance of certain mutations in ALS-linked genes, as discussed above in the chapter 'Classification of ALS'. There is a complex interplay of several molecular and neuropathological mechanisms found in animal models of ALS which might explain part of the neurodegeneration found in ALS patients. However, the fact that ALS is heterogeneous in humans means that the major mechanisms leading to the motor neuron degradation differ between individual patients (Phukan et al., 2012).

In cases of fALS where a mutation of SOD1 is present, ubiquitinated, phosphorylated and misfolded SOD1-positive Lewy Body-like inclusions can be found in the motor neurons. These inclusions cannot be caused by either TDP-43 or FUS, as the inclusions do not contain either of those proteins (Saberi et al., 2015). SOD1-associated ALS can have one of two causative agents, either SOD1 with a mutation, called mutant Tau, or wildtype SOD1, which has misfolded due to oxidative/environmental stress or the presence of catalytic copper ions (Bakavayev et al., 2019). The misfolded wildtype or mutant SOD1 that forms the inclusions in the cytoplasm is likely to be neurotoxic through a gain-of-function for SOD1. This is likely due to missense mutations leading to a loss-of-function for SOD1 dismutase activity in the nucleus, after which it is transported into the cytoplasm. In mice, SOD1 mutations have been shown to cause neurodegeneration through several different pathways, starting with protein accumulation, leading to mitochondrial dysfunction, oxidative stress, and inflammation, before ending with the death of the neuron. These pathogenic mechanisms are not only present in ALS with SOD1 mutations, but also in ALS without a specific genetic cause (Guareschi et al., 2012). The possible mechanisms which might cause the neurodegeneration were studied and discovered in mutated SOD1 animal models of fALS, therefore, some mechanisms might be unique to a non-human species and not a cause of neuronal loss in humans. The pathogenic mechanisms found showed a complex interplay of pathways which interact concurrently and lead to apoptosis of the neuron in question. This complex interplay is also called pathophysiology, in this case the pathophysiology of SOD1-associated fALS (Hardiman et al., 2017).

When a mutation is present in several ALS-linked genes in an individual, such as SOD1, FUS, C9ORF72 and/or TDP-43, which is then combined with age and or environmental factors, SOD1-associated ALS pathology can start within a neuron. This pathology is likely catalysed by the mislocalization of the mutated protein from the nucleus to the cytoplasm (TDP-43/FUS) and aggregation of the misfolded protein (SOD1). The removal of TDP-43 and FUS then causes changes in (m)RNA metabolism in the nucleus. Furthermore, C9ORF72 loss of function due to repeat expansion will cause a deficit in autophagy, which would normally clean up the inclusions. Mutant SOD1 or altered WT-SOD1 forms a toxic complex with Bcl-2. Bcl-2 which undergoes conformational changes, leading to the exposure of a toxic domain. This domain causes damage to the membranes of the mitochondria, leading to cytochrome C release (Pedrini et al., 2010). The continuous presence of these inclusions in the neuron together leads to mitochondrial dysfunction, which in turn leads to the production of radicals, which cause oxidative stress. This stress overwhelms the neuron and apoptosis is initiated, as shown in figure 2. This motor neuron loss is shown to propagate outwards from the site of onset, which is likely due to cell-to-cell spread of ALS. This spread of disease is likely due to prion-like transmission of misfolded SOD1 protein complexes, which will cause wildtype SOD1 in the other neuron to misfold too and thereby seeds the aggregation of proteins in other neurons nearby (Lee & Kim, 2015).

SOD1 has also been shown to be either directly or indirectly involved in the death of wildtype motor neurons in vitro through ALS oligodendrocyte pathology. First, SOD1 was present in ALS patient oligodendrocytes derived from induced human neural progenitor cells (iNPCs). After knocking down SOD1 in these iNPCs, before their differentiation into oligodendrocytes, a heightened survival rate for the motor neurons from 35-40% to 70-80% of cells was found. The fact that this knockdown only changes the survival rate if it is performed before differentiation suggests that the presence of SOD1 aggregates in the oligodendrocytes is implicated in the pathogenic mechanism leading to motor neuron loss (Ferraiuolo et al., 2016).

SOD1 is also implicated in the development of sporadic ALS, as modified WT-SOD1 was found in a sample from the spinal cord of sALS patients in 2007. It was then proven that wildtype SOD1 can become over-oxidated through post-translational modification. This alteration of SOD1 causes the protein to gain toxic properties analogue to the presence of an ALS-linked mutation in SOD1 through the formation of the SOD1-Bcl2 complex (Guareschi et al., 2012).

All in all, there is a lot of evidence for the fact that SOD1, if altered from its normal form, is very much implicated in the development of ALS. The protein also clearly has neurotoxic roles which are at the least partly responsible for the neurodegeneration characteristic of ALS. However, there is also evidence to support the claim that SOD1 can confer a protective effect, which slows down ALS disease progression.

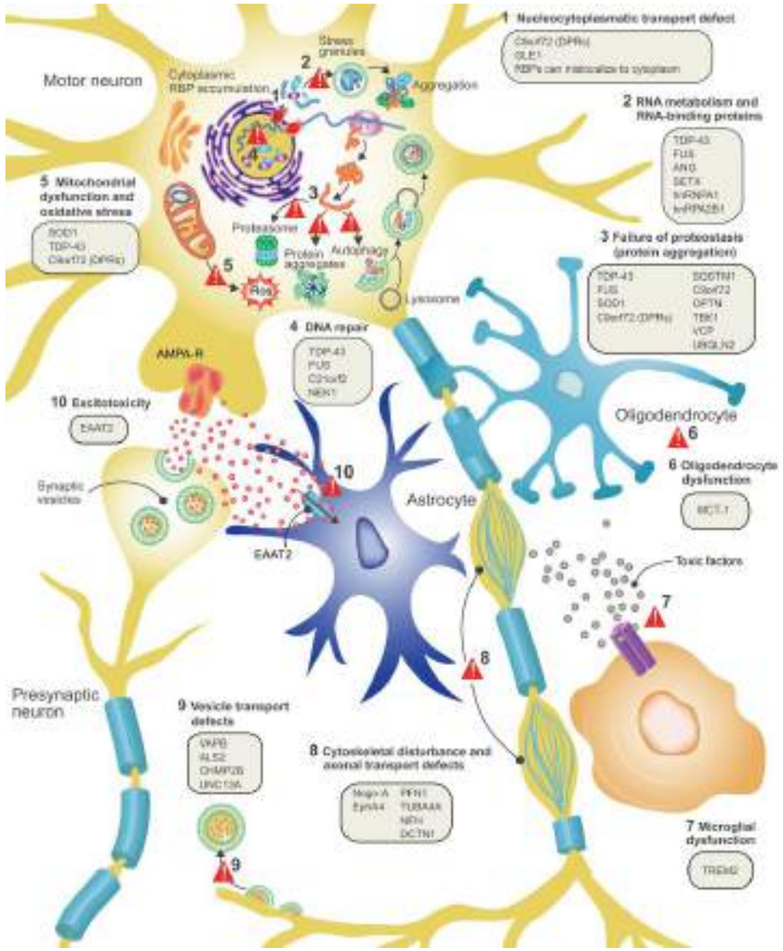

Figure 2. Schematic overview of the different pathogenic mechanisms involved in neurodegeneration in ALS, with genes correlated with certain mechanisms shown. Adapted from: (Van Damme et al., 2017).

SOD1 AS A PROTECTIVE AGENT AGAINST ALS

Patients with sALS who have higher amounts of soluble SOD1 in the nucleus of their motor neurons have a longer disease duration compared to patients who do not have the high nuclear SOD1 concentration (Cerada et al., 2013) This suggests a protective role for SOD1 in the nucleus against ALS disease progression, which we can explain with SOD1's function as transcription factor for DNA repair and oxidative resistance genes. As expected, the presence of SOD1 in the nucleus is correlated with a decrease in DNA lesions. The depletion of SOD1 leads to increased sister chromatid exchange (SCE) frequency and a full knockdown of SOD1 was lethal to chicken DT40 cells (Inoue et al., 2010). The presence of SOD1 in the nucleus is also inversely correlated to the number of aggregates in the cytoplasm (Pansarasa et al., 2018). This presents us with two possible roles for SOD1 after translation, either misfolding and aggregation of SOD1 in the cytoplasm or SOD1 responding to oxidative stress, in the form of hydrogen peroxide, and re-localizing to the nucleus to function as a transcription factor to indirectly decrease oxidative stress and DNA damage, as shown in figure 3.

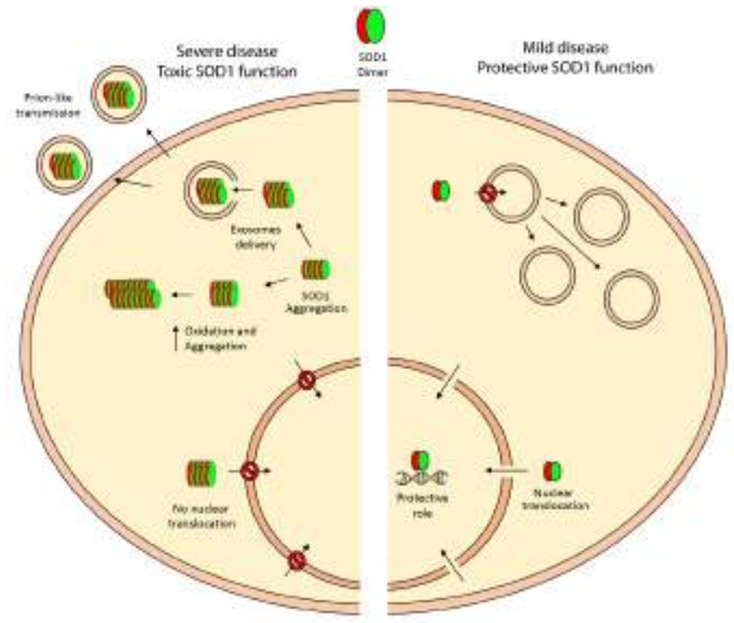

Figure 3. Schematic model of severe ALS with misfolded SOD1 as seed for cell-to-cell spread of ALS pathology on the left and mild disease where SOD1 is not misfolded but localised to the nucleus by signalling from reactive oxygen species (ROS) where SOD1 functions as transcription factor for DNA damage and oxidative resistance genes. Adapted from: (Pansarasa et al., 2018).

This relocalization of SOD1 to the nucleus is likely established through the following mechanism of action: The reactive oxygen species (ROS) in the cytoplasm, either superoxide or hydrogen peroxide, causes SOD1 to become susceptible to phosphorylation. This phosphorylation is then performed by Chk2 on threonine residues of SOD1, phospo-SOD1 is more likely to pass through a nuclear pore into the nucleus itself (Pansarasa et al., 2018).

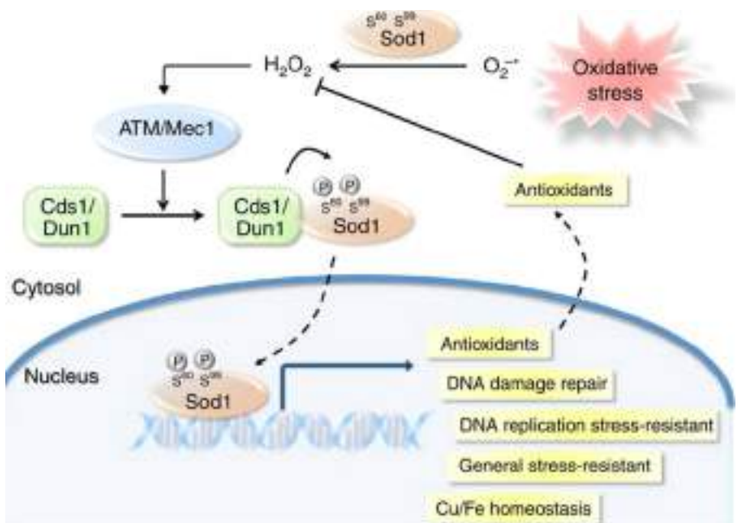

Figure 4. Schematic representation of proposed sequence of events leading to wtSOD1 relocalization to the nucleus, where Dun1 is a yeast homolog for Chk2 and the genes transcribed by SOD1 transcription factor function. (Tsang et al., 2014).

G37R-SOD1 EXPRESSION IN MOUSE SCHWANN CELLS

After the observation that ALS symptoms, such as motor neuron degeneration, happened to transgenic mice with mutant SOD1 with and without its dismutase activity still intact, researchers theorized that the misfolding of SOD1 and its subsequent novel toxicity is at the core of ALS development (McAlary et al., 2016). Using cell-type specific Cre-recombinase with LoxP sites on both sides of the SOD1 gene, SOD1 excision from certain cell types was established. This showed that mutant SOD1 reduction leads to delayed disease initiation if done in motor neurons and slower disease progression if done in astrocytes or microglia. Using the Cre-Lox system, G37R-SOD1 was then excised from the Schwann cells in these mice. Interestingly, the mice where the excision took place had significantly lowered overall survival to the ones where G37R-SOD1 was still present, despite onset of disease and early disease progression being very similar. This suggests that the dismutase activity of SOD1 is neuroprotective when present in the Schwann cells, this is consistent with previous findings that correlate inactive dismutase activity in SOD1 mutants with a lower disease duration and survival past onset of disease (Lobsiger et al., 2009).

CONCLUSION

SOD1 is very neurotoxic when mutated or misfolded due to other protein aggregates. Mutations which abolish the natural dismutase activity of SOD1 are correlated with faster disease progression and lower survival after onset of disease when compared to SOD1 with mutations which keep dismutase activity intact. This is due to the fact that a lack of dismutase activity means the cells cannot compensate for oxidative stress. The neurotoxicity of misfolded SOD1 seems to be due to mitochondrial disruption through interaction with Bcl-2 in the mitochondria, leading to cytochrome C release and eventually apoptosis. Furthermore, prion-like transmission of misfolded SOD1 from neuron to neuron was shown, leading to spread of the neurodegeneration. Also, loss of nuclear import of misfolded SOD1 seems to lead to reduced capacity of the neuron to compensate for ROS and DNA damage incurred.

It seems that SOD1 that stays soluble instead of aggregating can respond to markers of oxidative stress, and even induce heightened transcription of genes encoding proteins which are responsible for DNA repair and oxidative resistance. Neurons from patients where SOD1 aggregated less show that SOD1 then can perform its function by localizing to the nucleus. These patients also have longer disease progression than patients who have little SOD1 in their neuronal nuclei.

Also, the presence of G37R-SOD1, a mutation which keeps the dismutase activity of the protein intact, specifically in the Schwann cells is strongly correlated with a significantly slower disease progression in mice. This slower disease progression is due to the intact dismutase activity in the Schwann cells in these mice. However, this is only a delaying effect, as the motor neuron's axonal degeneration will still take place despite the presence of G37R-SOD1.

SOD1 is responsible for many pathogenic mechanisms which cause ALS pathology, but if SOD1 is present in its correct conformation and without mutations that inhibit its dismutase activity, it suggests protection for the neurons of those ALS patients through its roles as both a transcription factor and a protein which confers oxidative resistance. Sadly, it seems that the benefit of soluble SOD1 in the nucleus does not outweigh the harm caused by misfolded SOD1 in ALS, as the misfolded SOD1 is present in far larger quantities than the soluble SOD1 in the nucleus in most ALS patients. To conclude, SOD1 activity influences the ALS disease progression of the average fALS patient in a net detrimental way based on its roles, as most of it will be misfolded and/or overoxidized and by extension neurotoxic in nature.

DISCUSSION

Based on the conclusion, SOD1 can be a potential therapeutic target if a way can be found to keep SOD1 soluble and correctly post translationally modified in the neurons of ALS patients. Also, the experiment with G37R-SOD1 in the Schwann cells (Lobsiger et al., 2009) shows that the dismutase activity of SOD1 can ameliorate disease progression if present in certain cell types. This could be done by replacing the SOD1 gene in patients with SOD1-associated ALS, using a viral vector with a wildtype SOD1 gene. This would be a curative and preventative therapy, as it could prevent ALS development from initiating due to misfolded SOD1. This therapy would need to be given years before the first onset of ALS symptoms to actually effectively prevent neurodegeneration. When symptoms are present, SOD1 will be present in its misfolded form, and we know that misfolded SOD1 can misfold wildtype SOD1 in a prion-like manner. Repairing the SOD1 gene would therefore not reduce the neurodegeneration, which is the goal of the therapy.

It is important to keep in mind that most of the findings that correlate SOD1 with specific deficits in neuronal functioning were found in mouse models of the disease, which means they might not translate well to the human brain. To be sure of these functions ascribed to SOD1, they should be replicated in brain organoids made from induced pluripotent stem cells with organoid-grown microglia present.

ACKNOWLEDGEMENTS

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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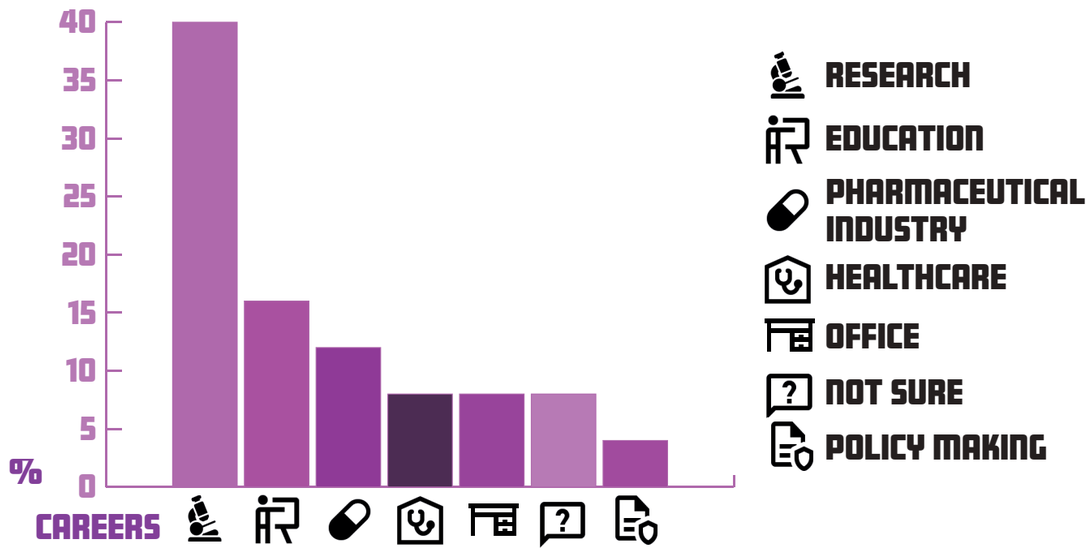
POLL #1

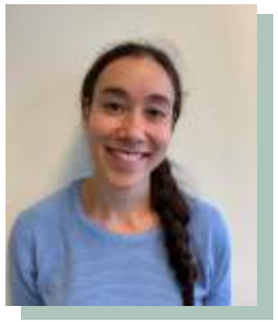
Where do you see yourself in 10 years?



‘The therapeutic potential of cannabinoids in psychiatric disorders’

This piece is an interview with Nadia Leen (PhD candidate at The Brain Research and Innovation Center Utrecht Military Hospital) and Caroline Kwee (PhD candidate at Utrecht University and psychologist at Altrecht Academic Anxiety Center, discussing their research with Cannabidiol (CBD) as a potential avenue for the treatment of psychiatric disorders.

Nadia Leen, *PhD Candidate*



Caroline Kwee, *PhD Candidate*

COULD YOU GIVE A BRIEF INTRODUCTION AS TO WHO YOU ARE?

I work at the military hospital with a background in Neuroscience and Cognition having done the Neuroscience and Cognition master’s programme at Utrecht University. For my research I work mainly with patients with PTSD or anxiety disorders.

I am working on a part time PhD trajectory while also working part time as a psychologist. My focus is on work with anxiety disorders, including post-traumatic stress disorder (PTSD) and obsessive-compulsive disorder (OCD).

CAN YOU OUTLINE THE CURRENT RESEARCH YOU ARE CONDUCTING?

In my research we have a different approach to research the effects of CBD; we give 200 mg of CBD for longer periods, over 2 weeks, 3 times a day without any therapy. I focus on anxiety symptoms, and to add to this we have a fear conditioning task to see how CBD influences memory processes as well as the effects it has on sleep and stress regulation. We measure sleep via a sleep watch which the patients keep on them. To further assess anxiety symptoms we use questionnaires, after which we use fear conditioning tasks to see if the CBD improves the acquisition of the extinction memory or more on the consolidation of the extinction memory. During this research, half of the patients will get the CBD before the extinction part of the task and the other half after the extinction part of the task to measure the effects on extinction consolidation. The stress task consists of alternating trials of immersing your hand into ice-cold water and engaging in a mental arithmetic task. We will be measuring heart rate and cortisol levels since CBD has been shown to improve the regulation of stress. We are conducting these trials before patients undergo therapy.

A large project in my PhD is a clinical trial using Cannabidiol (CBD) as augmentation of exposure therapy, in patients with panic disorder and agoraphobia or social anxiety. The current gold-standard psychological treatment option for these anxiety disorders is exposure-based cognitive behavioural therapy (CBT). We use a lot of exposure in vivo, meaning that you are there, physically, in real life. For example, we may ask patients to get themselves into a prototypic social situation that provokes anxiety. In general, patients have assumptions about the consequences of facing these situations. By first-hand experience patients can learn about the validity of these assumptions, so fear extinction can take place. This therapy is generally effective in reducing pathological anxiety, but not for everyone. We investigated whether CBD augmented exposure-based CBT would lead to stronger, faster, or more enduring improvement in treatment resistant patients (compared to placebo augmented treatment).

WHAT PROCESSES DOES CBD INFLUENCE IN THE BRAIN AND WHY IS THIS IMPORTANT FOR THE TREATMENT OF CERTAIN PSYCHIATRIC DISORDERS?

The endocannabinoid system (ECS) consists of the cannabinoid receptor type 1 (CB1) and 2 (CB2). The two major endogenous endocannabinoids which can activate these receptors are anandamide (AEA) and 2-arachidonoylglycerol (2-AG). AEA and 2-AG are synthesised ‘on demand’ and one of their primary roles is to suppress neurotransmitter release into the synapse. An exogenous compound that can reliably facilitate the ECS comes from the cannabis plant, cannabidiol (CBD). CBD has a diverse pharmacological profile and is safe without major side effects. A major mechanism through which CBD is thought to facilitate the functioning of the ECS is by inhibiting the degradation of AEA.

Nadia Leen, *PhD Candidate*

In the research I am currently conducting we are looking at different memory processes in the brain where CBD can have an influence, therefore we use a fear conditioning and extinction paradigm. For this reason, we give CBD either before the acquisition of the extinction memory or after this, so that we can see if it affects the formation of the extinction memory or on the consolidation of the extinction memory. This is an important question since studies in healthy people demonstrated an effect on the consolidation of the extinction memory. However, patient studies only focused on giving CBD before the acquisition of the extinction memory.

‘A snapshot of Nadia Leen conducting a fear conditioning task in the Lab’

Caroline Kwee, *PhD Candidate*

We know from preclinical studies that endocannabinoid signalling at the CB1 receptor is involved in fear extinction. The latter is of high clinical relevance since fear extinction is considered the prime working mechanism of exposure-based therapy. Data from rodent studies suggest (although not unequivocally) that CBD, a modulator of the CB1 receptor, enhances fear extinction. We hypothesised in our study that CBD would enhance fear extinction in patients and improve treatment outcome. However, our results showed that clinical improvement did not differ between the CBD and the placebo condition.

More information regarding the projects can be found below

WHERE DO YOU SEE THE FUTURE OF CBD RESEARCH? DO YOU THINK IT HAS THE POTENTIAL TO REPLACE CURRENT TREATMENT OPTIONS?

I think it is always good to have an alternative treatment option. Nowadays when people have a certain psychiatric disorder, it is common to start out with SSRIs and other common treatments. What would be good for the future is to focus on personalized treatment, as people differ so they need different kinds of treatment. The focus could then be on the development of the disorders and what kind of mechanisms underlie these specific disorders, so that we can help patients more precisely and choose a fitting treatment option. I see CBD being a good treatment option for some people, as a more personalised medicine.

I would not directly think of CBD as a replacement of current treatment options. Many patients do benefit from established psychological and pharmacological treatments. However, these are no one size fits all solutions. What may work for one person may not be effective for the other. In addition, some patients are bothered by specific side effects and decide not to continue with a prescribed agent. Therefore, alternatives are needed.

Nadia Leen, *PhD Candidate*

We are also currently working on a project called "PREDICT". For this project, we focus on investigating the individual differences in anxiety and PTSD patients on how they learn and unlearn fear. We wanted to investigate whether maladaptive fear learning patterns can predict treatment success in this group of patients. An example is if we find that in a group of patients, some show a poor extinction mechanism, this may be a group that responds better to CBD treatments. Therefore, CBD treatment doesn't have to be for everyone, but can be a good option for certain types of people, contributing to a patient's overall wellbeing. I also hope that more people will stimulate this research on CBD and for psychedelics, given the stigmas surrounding them due to their recreational use. We have our own endocannabinoid system in our brain that can be explored. Ultimately the stigma will fade, and promising research can come through and help patients that need the help.

Caroline Kwee, *PhD Candidate*

With respect to CBD research, I believe the field may benefit from cross-fertilisation among animal and human research. There is a wealth of preclinical research into CBD, and more broadly, the endocannabinoid system. Anxiolytic effects have been demonstrated in several animal models. Whether and how this work translates to applications in clinical populations is not so clear-cut.

Brain Research and Innovation Centre

A perspective piece from a current Neuroscience and Cognition master's student, Ineke de Vries, outlining her experience in her current internship at the Brain Research and Innovation Center.

INTRODUCE YOURSELF, YOUR PAST STUDIES AND WHY YOU CHOSE TO DO AN INTERNSHIP AT THE MILITARY HOSPITAL?

My name is Ineke De Vries and I studied my bachelors in psychology. I am currently doing two masters, whereby I study Clinical Psychology and the Neuroscience and Cognition programmes. My internship is based at the Brain Research and Innovation Center which is a part of the Military Mental Healthcare of the Netherlands Ministry of Defence. This is a research-based internship as a part of my Neuroscience and Cognition masters. I chose to do this internship as the military mental health care is a different population than anywhere else due to their life circumstances. I also wanted to stay away from working at the cellular level and working with animals, as I prefer working with people.

YOU STATE YOU WANT TO WORK MORE CLINICALLY; DO YOU KNOW WHY THIS IS?

I can see a more direct view of how you can help people, although I understand how important animal and cellular research is. Furthermore, the main reason why I started studying psychology is because I think it is important to help people who need it. This is also how I knew I wanted to work at the military hospital, and to have a real and positive impact on the mental health of people who are willing to risk their lives for the safety of others.

WHAT IS THE DAY IN THE LIFE OF A MASTERS STUDENT UNDERTAKING YOUR SPECIFIC INTERNSHIP?

I do a lot of different things day to day. Currently, I am working with PhD candidates on a systematic literature review of the influence of Cannabidiol (CBD) on anxiety. I also helped my supervisor set up the "BOOSTCAMP" CBD study. For this I helped with a lot of the operating procedures for experiments, for example working with a medical ethical committee and writing up questionnaires that would assess psychological measures of patients. I am also

working on a study called the "PREDICT" study. The aim of this study is to investigate if fear learning trajectories in anxiety patients, determined before start of cognitive behavioural therapy (CBT), are able to predict reduction in anxiety symptoms. For this study I have also had a lot of interactions with patients. For example, I go to the Military Mental Health Care in Amsterdam and Zwolle to visit patients undergoing the experiments. The internship is also fun because I see my supervisor every day and get along with her very well. My supervisor is a PhD student who has a lot of time to supervise me, which is great. Next to this, I felt part of the team since the day I started my internship.

WHAT ARE YOUR FUTURE PLANS FOR YOUR RESEARCH?

In my opinion, the perfect combination would be if I could do research for two or three days a week and become a clinical psychologist for the other two or three days. I am going to start my internship at Altrecht (a mental health organization) where I will be working with patients diagnosed with personality disorders. This is a patient population known to have a lot of comorbidities such as anxiety problems. There is a possibility that I go on to do a PhD, but I really need to find out what specific area I would go into.

HAVE YOU GOT ANY ADVICE FOR FUTURE AND CURRENT RESEARCH STUDENTS?

You should do something you really like and work on a topic you are enthusiastic about. Also, look for a place where you can see yourself working - that is very important. I also think that the connection with your supervisor is important and to discuss your mutual expectations. So, if you like a subject area and you feel like you like the supervisor from interacting with them throughout the course, then go for it.

Sponsor of the Journal of Neuroscience and Cognition:

‘Psychedelics and psychopathology’

Prof. Dr. J. Leon Kenemans

Experimental Psychology, Helmholtz Institute, Utrecht University, The Netherlands

Prof. Dr. Leon Kenemans (Head of Department, Experimental Psychology) analyses the use of psychedelic compounds in the treatment of psychiatric disorders, outlining their safety, efficacy and potential future as therapeutic medicines.

It is sometimes asserted that recent clinical trials have shown promising results in the treatment of psychiatric disorders. But how promising are these results? The answer to this question depends on the definition of a promising result. For some researchers, a desired therapeutic effect in an open-label study may be promising. In such a setup there is no (placebo-) control group, so any therapeutic effect may be due to other factors such as placebo. The promise then is that the effect will also surface in a subsequent randomized placebo-control trial (RCT), with a sufficiently large sample size (which could be considered as a phase-2 trial). For others, only a desired therapeutic effect found in exactly such a phase-2 trial would count as promising. In that case, the real proof of the pudding must come from subsequent phase-3 trials: multi-site combined phase-2 trials, compounding samples from different subpopulations (for a given diagnosis), to find out about replicability and generalizability across these different subpopulations, which may differ in clinical background and ethnicity, social-economic status and so on, but also etiologically.

Here are some specific examples. The application of MDMA in the treatment of anxiety disorders, especially PTSD, is at a phase-2-phase-3 transition stage. A number of successful phase-2 trials (summarized in Mithoefer et al., 2019) have been reported, conducted by mainly the same research group, and invariably using MDMA as an adjuvant for a rather specific form of psychotherapy. Recently, a first phase-3 study has been reported, with positive effects observed from 15 sites in patients from three countries (USA 77; Canada 9; Israel 5) (Mitchell et al., 2021). On the other hand, the application of psilocybin for depression and/or anxiety is probably more in an open-label-phase-2 transition, as RCTs have so far been published only for subgroups of cancer patients (Goldberg et al., 2020). A third more or less celebrated application, ketamine for depression, has also seen a number of successful phase-2 trials (e.g., Canuso et al., 2019; Daly et al., 2019; Reinstatler & Youssef, 2015). By now, two full-blown phase-3 studies have been published, one finding a significant improvement as a result of ketamine plus a more standard antidepressant over placebo plus this same standard antidepressant (Popova et al., 2019), whereas another one found no significant effect (Fedgchin et al., 2019). Two other phase-3 studies have so far been published only as conference proceedings, which have usually not been subjected to rigorous peer-review procedures (Daly et al., 2019; Ochs-Ross et al., 2019).

So, when will psychedelics become a viable option for treating mental disorders? Somewhat oddly, ketamine has been approved in 2019 by the FDA as well as the EMA for treatment-resistant depression as a supplement to a regular antidepressant (Breeksema et al., 2020). Most researchers, clinicians, and policy makers would state that only after sufficient phase-3 evidence, a substance can be registered for clinical application. One may question whether all current standard medications have met this criterion, but that is certainly no reason to relax it with regard to new alternatives such as psychedelics. As explained above, phase-3 trials have all kinds of added value relative to phase-2 trials. To highlight one specifically: It has repeatedly been shown, especially during the last decade or so, that there is great interindividual variation in treatment response within a population with any certain diagnosis. Furthermore, this variability may manifest easily in inconsistencies between isolated phase-2 trials, hence the need for phase-3 trials. The awareness about interindividual variability is increasingly accompanied by the advocated need for precision or personalized psychiatry (Wu et al., 2020).

If psychedelics become a viable option, can they replace existing therapies such as SSRIs? All the above is part of the answer to this question, but there is more to it. Some further promising results suggest that psychedelics may at least supplement traditional interventions such as SSRIs, for at least two reasons. The first is that they may have immediate, acute positive effects. For example, open-label or phase-2 trials have reportedly revealed symptom-reducing effects within hours or at most a day after administration. This may potentially fill an important gap, as most traditional pharmaceutical interventions take one to several weeks of administration for a noticeable clinical effect. Note also that ketamine has

been FDA/EMA approved as a supplement to regular treatment, that is, to fill the gap. Secondly, it may be that these immediate short-term effects are complemented by desired longer-term effects, over the course of weeks, months, perhaps as much as years, even after only a limited amount of initial administration. If this bears out in studies with corresponding periods of observation, then psychedelics could not only supplement traditional pharmaceuticals but also replace them. However, as of yet, the true nature of such longer-term effects is mainly unexplored territory.

Another question is whether psychedelics are useful at all without (assisting) psychotherapy. For ketamine the answer seems to be yes, although perhaps not so much without assisting regular pharmacotherapy. Other psychedelics (including MDMA, psilocybin, but also cannabinoids) have been evaluated mainly, but not always, in combination with various kinds of psychotherapy. It is conceivable that especially psilocybin may also induce desired effects by itself, as the subjective effect of the drug may include a psychedelic experience that is instrumental in improving psychopathology by itself (probably much more than in the case of MDMA or ketamine); however, of two RCTs in cancer patients, one examined psilocybin in combination with psychotherapy (Ross et al., 2016), whereas the other did not (Griffiths et al., 2016). An alternative perspective is that psychedelics, or other non-traditional substances, are especially effective in enhancing learning processes that in turn facilitate the termination of pathological conditions. One example is D-cycloserine (DCS) and its application as adjuvant to exposure therapy in a variety of anxiety disorders, which produced beneficial effects in quite a number of initial studies (see Kenemans, 2020, p. 122). That is, DCS at least reduced the number of exposure-therapy sessions needed to achieve the desired clinical effect. Importantly, this apparent learning-promoting effect of DCS could be explained (or perhaps even predicted) from its known properties as an allosteric NMDA-agonist, the NMDA receptor being one of the most prominent receptors known to be involved in learning and memory. This is another aspect to consider: insight into the biochemical functional mechanism underlying the possible beneficial effect of a new substance not only facilitates its acceptance as a viable treatment option by the scientific community, but also offers possibilities to improve its efficacy, e.g. by identifying specific subpopulations of responders versus non-responders. A similar detailed neurobiological analysis has surged with respect to ketamine and the NMDA receptor (H. Wu et al., 2021).

So what does the future hold for psychedelic medicine and what needs to be done? The turn MDMA research has taken is probably the way to go, and will ultimately reveal how substantial the psychiatric application of ketamine, psilocybin, MDMA itself, and other psychedelic substances can be. But even for MDMA itself, a number of issues have to be resolved. These include whether the effects will stand in combination with other forms of psychotherapy and in the hands of other research groups, but also in (head to head) comparisons with other established therapies, in terms of both efficacy and cost-effectiveness.

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‘Cerebral organoids to model human brain development and neurological disorders’

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Grow your own brain, did you say? Werner Dykstra (PhD candidate at University Medical Center Utrecht Brain Center) provides a brief history of how pluripotent stem cells are used to produce 3D brain structures called Organoids and further discusses how they influence his work on Alexander Disease.

In 2008, Shinji Yamanaka and his group made an astonishing discovery. If you would take skin cells and put some factors (thereafter catchingly referred to as Yamanaka factors) on them, they would miraculously transform into stem-like cells (Takahashi et al., 2007; Takahashi & Yamanaka, 2006). This was a massive breakthrough, because stem cells have the potential to virtually become any other cell type, allowing us to bypass the barrier of actually having to take cells from people’s organs for research. This is especially challenging when it comes to the brain and the very procedure of doing so could actually inflict more damage to the person’s brain than the benefits of research would reap. Dr. Yamanaka would call these cells “induced pluripotent stem cells”, or iPSCs for short. “Induced”, because they were not always like that and he induced them to be that way (with his factors). “Pluripotent”, because they have the potential to acquire multiple faiths, meaning they can become any kind of other cell. And finally, “stem cells”, because they have stem cell-like properties, which again mostly refers to the fact that they can become any kind of other cell. Another brilliant aspect of these iPSCs is that they have the same genetic make-up as the skin cells from which they were derived, including some (possibly) disease causing mutations. As if this discovery were not brilliant enough, Madeline Lancaster, in the lab of Jürgen Knoblich, building on the work of Yoshiki Sasai who pioneered the very first 3D brain-like structures, published the first article on brain, or cerebral, organoids (Lancaster et al., 2013). They discovered that when you grow these iPSCs in 3D, that is, you cluster them in the center of a cell-culture plate and do not allow them to attach to the plate, these balls of iPSCs called embryoid bodies (probably called embryoid, because they are reminiscent of the very early stages of development when humans are nothing but a ball of pluripotent cells, and probably called bodies, because that’s what they are) could then be allowed to acquire features of early human brain development, simply by removing the factors that keep the cells of the embryoid bodies in the stem cell like state (Figure 1).

What was most remarkable about this transition from pluripotency to actual brain development was that the embryoid bodies independently knew how to form certain brain structures.

Apparently, the information on how to build a brain, which is arguably the most complex object that nature has developed, actually exists somewhere in those cells. Scientists quickly discovered that certain gene expression patterns were activated, which were quite similar to those patterns expressed during actual human brain development (Renner et al., 2017). As if this were not enough, other scientists quickly jumped on the bandwagon and applied it to their own research. They even improved the model and started to combine it with other established techniques such as single-cell RNA sequencing (Bhaduri et al., 2020; Birey et al., 2017; Di Lullo & Kriegstein, 2017; Pollen et al., 2019; Sloan et al., 2017; Velasco et al., 2019). The most important thing to know about it is that it allows scientists to get an idea of what individual cells in a lump of cells are doing. Quite astonishing when you think of the fact that tissues contain millions of cells. Anyway, the development of these organoid models has rapidly progressed in recent years and it has allowed us to gain great insight into human brain development and neurological disorders. Not just neurological, no, no: Organoid models of numerous, if not all, organs exist. In fact, the very first organoid model was not a brain organoid, but a gut organoid (Sato et al., 2009) (discovered by this Clever(s) man). Regardless of the kind of organoid, or even organoid models in general, I think it can be said that medical science is on an exponential growth curve with new techniques being discovered almost daily. And with that I would like to end this introduction and dive a little deeper in my own PhD project about Alexander Disease.

Alexander Disease (AxD) is a fatal leukodystrophy caused by de novo mutations in GFAP encoding for glial fibrillary acidic protein (GFAP)(Brenner et al., 2001). This mutated GFAP gets cleaved by caspases (Battaglia et al., 2019) and

subsequently accumulates into cytoplasmic, astrocytic aggregates together with small heat shock proteins, other intermediate filaments such as vimentin, and proteasome related proteins (Hagemann et al., 2006; Tian et al., 2010). It is assumed that these hallmark aggregates called Rosenthal Fibers (RFs; named after the German neuropathologist Werner Rosenthal) wreak havoc on homeostatic cellular functions, leading to astrocytic dysfunction(Quinlan et al., 2007; Tian et al., 2010; Wang et al., 2015; Wang et al., 2018). This initiates a cascade of degenerative events, whereby myelin, the fatty nerve conductor, gets destroyed (van der Knaap et al., 2001). How exactly mutant GFAP leads to a leukodystrophy is still unclear. Recent research has shown that post-translational modifications are involved in the caspase-dependent cleavage of GFAP that favors subsequent aggregation (Battaglia et al., 2019). Moreover, AxD iPSC-derived astrocytes co-cultured with oligodendrocyte precursor cells (OPCs) limit OPC growth and myelination by secreting a molecule called CHI3L1 (Li et al., 2018). Inhibiting the receptor of this molecule on OPCs rescued the defects. This provides insight into how myelination defects occur in AxD patients. A less well studied mechanism in the context of AxD is neurogenesis and gliogenesis. Neurogenesis and gliogenesis, the processes of generating new neurons and glia respectively, starts with neuroepithelial cells undergoing an epithelial-to-mesenchymal transition (EMT) into radial glial cells (RGCs)(Hansen et al., 2010). These RGCs gain polarity and migratory properties and, as their name suggests, migrate radially thereby providing a scaffold for neurons to migrate. Moreover, these RGCs are the precursors to neurons or to intermediate progenitor cells (IPCs) that divide a couple of more times before acquiring their final neuronal (or glial) fate. The reason that these processes are relevant to AxD, is the fact that GFAP is expressed in RGCs during human corticogenesis (Middeldorp et al., 2010). Being an intermediate filament, GFAP forms part of the cytoskeleton in the RGC scaffolds. As such, it can be imagined that mutant GFAP distorts this RGC scaffold. Moreover, GFAP is involved in mitosis and mutant GFAP could thus distort this process. Mouse models cannot fully recapitulate human neurogenesis, because mice do not have an outer subventricular zone (OSVZ) where outer radial glial cells (oRGCs) reside (Ostrem et al., 2017; Pollen et al., 2015). These oRGCs, expressing GFAP, are enriched in primates and especially in humans. Due to the lack of human fetal tissue availability, studying human neurogenesis has been quite challenging. iPSC-derived cerebral organoids provide a unique opportunity to study human neurogenesis in vitro (Lancaster et al., 2013). Here at the UMC Utrecht at the Department of Translational Neuroscience, we have acquired multiple iPSC lines (+ isogenic controls) of AxD patients that I use to generate cerebral organoids. These organoids will develop neurons, astrocytes and microglia, which allows us to study neuron-glia interactions at later stages of development, as well as neurogenesis all throughout their development (Ormel et al., 2018). Results are promising and we aim to contribute our findings to the scientific community in the coming year.

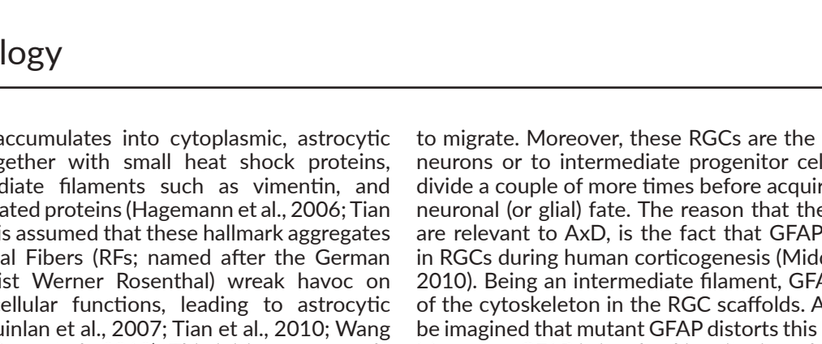

Figure 1. Cerebral organoid protocol (Ormel et al., 2018). Human iPSCs are grown up until 70-80% confluency, are dissociated and allowed to aggregate into embryoid bodies in ultra-low attachment wells. After removal of FGF from the culture media, the embryoid bodies will exit pluripotency and start to differentiate into the ectodermal lineage and establish neuroectodermal tissue, which is favored by the neural induction medium. When these neuroectodermal tissues are put in a droplet of Matrigel extracellular matrix, they rapidly differentiate and expand. The cerebral organoid differentiation medium further supports neurogenesis. Vitamin A is typically excluded at first to minimize patterning and allowing cerebral organoids to rely on their self-organizing principle. Because Vitamin A is also important for neurogenesis, it is added after four days to the culture medium. From this point onwards, the cerebral organoids are cultured on an orbital shaker. This shaking motion enhances nutrient uptake into the inside of the cerebral organoids, thereby decreasing the level of necrosis at the center of the organoid where nutrient uptake is difficult due to the lack of vasculature.

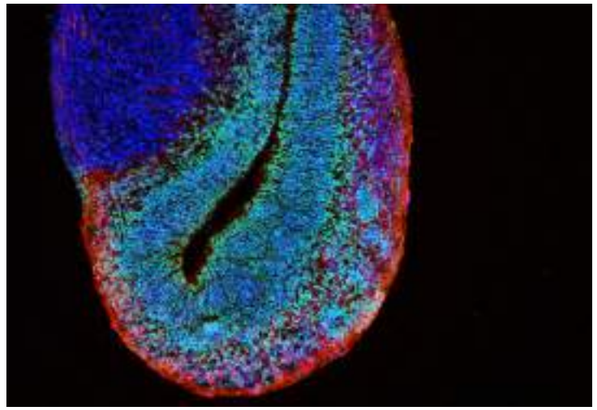

Figure 2. iPSC-derived cerebral organoid at 45 days old. Nuclei are stained in blue by Hoechst, radial glia are stained in green by anti-SOX2 and neuronal filaments are stained in red by anti-TUJ1.

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ARTIFICIAL INTELLIGENCE

‘Will technology control us in the future?’

The following section aims to give a brief insight on what and how Artificial Intelligence (AI) can help neuroscience and how they are related to each other. Often people think of AI as only robots, but little do they know how many creative solutions AI can provide to different topics. By asking two experts on the topic, we hope to enlighten you with some new ideas and perhaps, a change of career.

‘What does the public want from brain computer interfaces?’

A systematic review comparing the opinion of non-disabled individuals, disabled individuals, researchers and caregivers

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Brain computer interfaces transform brain activity into artificial binary output. To direct brain computer interface research and provide insights in the marketability of the technology, it is essential to consider the opinions of disabled potential users, non-disabled public, researchers in the field and caregivers. As such, this paper aims to capture the public opinion on brain computer interfaces technology by answering the following research questions: (1) Do the various stakeholders have a difference in opinion regarding invasive and non-invasive BCIs? and (2) What feature of BCI technology is deemed the most important according to the several stakeholders? This review revealed that all stakeholders unanimously prefer non-invasive brain computer interfaces. Furthermore, the group of disabled potential users is most open towards the technology and deems communication and wheelchair control the most important features. From the perspective of marketability, it is advisable to focus on further developing non-invasive technology with the disabled public as the intended target audience.

Keywords: *BCI, Brain Computer Interfaces, public opinion, marketability*

INTRODUCTION

Over the last decade research on brain computer interfaces (BCIs) has seen fast development (Kögel et al., 2019). BCIs, which are devices that measure brain activity and transform these signals to artificial output, allow for the generation of computer-mediated outputs while bypassing the need for movement (Kögel et al., 2019; Sample et al., 2020). Two types of BCI techniques can be distinguished: invasive and non-invasive (Lahr et al., 2015). Invasive BCIs involve intracranial implantation of electrodes and have a favourable signal-to-noise ratio, however, there are risks regarding the implantation of the device. Non-invasive BCIs, which capture signals via skin electrodes or extracorporeal sensors, often involve long setup time and training.

Researchers have been able to use BCI to enable individuals to move paralysed limbs and spell out words without making use of limbs, as well as other applications that are based on passive monitoring of the user’s brain activity (Sample et al., 2020). The technique has long been described as a means of enabling people to operate computers without any physical movement. This would highly benefit people suffering from, for example, amyotrophic lateral sclerosis (ALS), severe paralysis or the locked-in syndrome (LIS; Funk et al., 2016; Huggins et al., 2011). Thus, most early BCI research was aimed towards enabling communication or motion control for people suffering from affections that would make these actions impossible otherwise. However, over time additional applications for BCIs have been recognised (Vansteensel et al., 2017).

More recently, BCI research has looked into the possible applications of BCIs for healthy individuals, aimed at enhancing the daily life of a non-disabled person (Vansteensel et al., 2017). This would for example be achieved by using BCIs to increase an individual’s attention span or even increase the number of limbs a human normally has by adding a third, robotic arm.

As the possibilities of the BCI technology sound so futuristic that they would not be misplaced in a science fiction novel, it makes sense that the research on BCIs has been extensively covered by the media. Indeed, the media often reports on recent BCI research, however this is often done inaccurately (Nijboer et al., 2013). The media has frequently and inaccurately reported that BCIs are able to uncover what you are dreaming and read your mind (Alleyne, 2010; Beal, 2016; Ghosh, 2010). In contrast to these media reports, most BCI researchers noted that the current devices were merely able to receive a binary signal and are thus not equipped to perform something as complicated as reading minds and dreams (Nijboer et al., 2013).

Although incorrect, the extensive media coverage has sparked a hot debate amongst ethics researchers regarding the ethical implications regarding BCI usage (Sample et al., 2020). Most of the concerns of these researchers regard the safety of BCI users, potential infringement of their privacy and autonomy and potential distortion of the sense of self (Klein et al., 2015; Kögel et al., 2019). Additionally, many ethicists expect an increase in inequality and note that offering BCIs to aid people with their disability implicitly creates an image of the ‘perfect human being’. This way, BCIs could exacerbate

the stigmatisation of disabled people (Sample et al., 2020). It is for these reasons, among others, that ethicists argue that not enough attention has been paid to the potential ethical problems that could emerge from BCI usage (Cabrera et al., 2018; Sample et al., 2020).

As is evident from the aforementioned literature, BCIs have the possibility of enhancing people's abilities, but they will only be of practical benefit if they are incorporated in such a way that they are useful to the individual. Therefore, it is essential for researchers in the field of BCIs, healthcare institutions, as well as venture capitalists, to know what features are useful to the intended target audience in order to create a highly desired product. This notion is reflected by the universal design principles as postulated by the Center for Universal Design, which advocates for active user involvement in the design process, as this would make the product more desired amongst the target audience (Preiser & Smith, 2001). Furthermore, lack of user involvement during the design process is a significant factor as to why patients decided to abandon assistive technologies (Phillips & Zhao, 1993). This goes hand in hand with the notion that the decision to abandon a technology is highly impacted by the value the technology has for the user (Sugawara et al., 2018). Products that are important for everyday life have a lower chance of being abandoned. It is thus essential to gather insights into the desires and concerns of potential target audiences when developing a product, as this will ensure a lower abandonment rate, and thus an improved product marketability.

In order to more deeply investigate the marketability of BCI technology, a comprehensive perspective of the opinions of the general public is needed (Anderson, 2009; Kögel et al., 2019; Sample et al., 2020). In order to achieve this, it is essential to compare and contrast the opinions of various stakeholders. As such, this paper aims to capture the public opinion on BCI technology by comparing four different groups of stakeholders, namely disabled individuals, non-disabled individuals, BCI researchers and caregivers, on the basis of the following research questions: (1) Do the various stakeholders have a difference in opinion regarding invasive and non-invasive BCIs? and (2) What feature of BCI technology is deemed the most important according to the several stakeholders?

METHODS

This paper will be conducted as a structured literature review in which empirical data regarding the public opinion on BCIs will be gathered and examined. The opinion of potential BCI users as well as non-disabled people and other stakeholders, namely BCI researchers and caregivers, will be considered. The group of potential BCI users will be represented by individuals suffering from lack of motor control, often taking shape as a paralysis, as this is currently most prominently covered in BCI research. As the research on BCIs has seen such fast development, the focus will mostly lie on papers published from 2010 onwards. Multiple search bars and databases were used in order to find relevant articles. These search bars and databases include, but are not limited to, Pubmed, Embase and Google Scholar. To find directed results, specific keywords were used. These keywords included the following: BCI, brain machine interface, user opinion, caregivers and public opinion.

OPINION OF DISABLED PUBLIC: BCIS AS AN ASSISTIVE TECHNOLOGY

The majority of studies investigating the opinion of disabled individuals regarding BCIs have focussed on assessing the interest that this group has in using BCI as assistive technology (Kögel et al., 2019). Additionally, studies frequently focus on the expectations that this group has about using BCIs as assistive technology. Research on this topic frequently included solely participants that experience a lack of motion control due to underlying afflictions, for example ALS and spinal cord injury (SCI), as most BCI research is targeted towards these conditions (Geronimo et al., 2014). Overall, research into the opinion of patients with a paralysis has revealed a high interest in BCIs (Kögel et al., 2019; Lahr et al., 2015).

For example, Huggins et al. (2011) surveyed 61 people with ALS to investigate their attitude towards BCI usage. They found that 91.8% of participants were interested in BCI use as well as participation in BCI research. When it came to BCI functionality, participants emphasised the importance of accuracy of execution as well as standby reliability, meaning that accidental exits from standby-mode should not occur more than once every 2-4 hours. These findings were mirrored by Geronimo et al. (2014), who surveyed patients with ALS about BCIs used for assistive communication methods. In addition to accuracy and standby reliability, Huggins et al. (2011) found that patients prioritised a timely reaction from the BCI when in use. When participants were allowed to pick the potential BCI functions that they desired most, computer, phone, TV and wheelchair control came out as most desired (Geronimo et al., 2014). These findings were mirrored by Kögel et al. (2019), who stated that incorporating TV and phone control would generate more desired BCI designs. Rated as functions of least interest were robotic arm use and temperature regulation (Geronimo et al., 2014).

In addition to the aforementioned points addressed by potential BCI users, Kögel et al. (2019) note that there was an emphasis on the importance of user-friendliness and home-based use. A follow-up study of Huggins et al. (2015) also stressed the importance of simplicity of BCI use. They aimed to identify the priorities of BCI-users by analysing a sample of 40 participants with SCI. Of the participants that experienced low functional independence, according to the Functional Independence Measure, 96% showed interest in using a BCI. For these

people, communication in case of an emergency was a priority function of a BCI. Supporting recent findings of Kögel et al. (2019) and Anderson (2009) found computer and wheelchair control ranked second and fourth in the list of appealing features of a BCI. However, they also found that the ability to control a robotic arm was placed third, which contrasts findings by Geronimo et al. (2014).

Various studies noted that invasive and non-invasive BCIs are looked upon differently (Huggins et al., 2011; Huggins et al., 2015; Kageyama et al., 2014; Lahr et al., 2015). Unanimously, non-invasive techniques were preferred over invasive techniques. Even though invasive BCIs were considered less favourable, Huggins et al. (2011) found that 71% of their participants would be willing to undergo surgery to obtain a BCI and 41% of participants would accept a short hospital stay after surgery. Lahr et al. (2015) investigated the appeal of invasive BCIs by surveying 131 patients with a paralysis on their stance regarding invasive and non-invasive BCIs. The participants experienced paralysis due to different underlying factors, including stroke (50.4%), ALS (28.2%) and SCI (7.6%). Nearly half of the participants (48%) were open to the idea of invasive BCIs if this could seriously improve their mobility and level of communication (Figure 1a). Especially the participating group of ALS patients were open to the concept of invasive BCIs (Figure 1b). 7% of participants would not consider using invasive BCI at all. This difference in stance towards an invasive BCI might be the case as ALS will progress in severity over time, whereas the other diagnoses are not inherently progressive in nature.

18 out of 131 participants expressed that they had worries concerning BCIs (Lahr et al., 2015). Out of this particular group, 17 participants (94.4%) expressed that they were worried about the surgical intervention needed to obtain an invasive BCI. Furthermore, participants were uncertain about the current performance of BCIs. As stated by one of the participants, they worried that the current technology was 'not yet enough elaborated to be ready for everyday use'. This concern was also observed in two studies by Huggins and colleagues (2011, 2015). Both studies concluded that potential BCI users have positive feelings towards the idea of using BCI as an assistive technology, but highlight that current BCIs do not meet the desired performance yet.

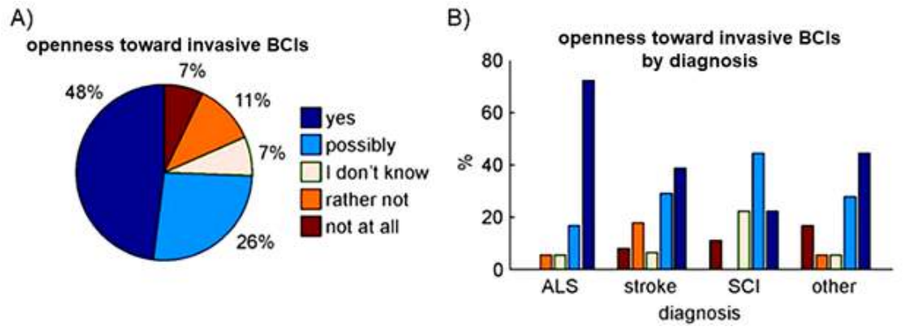

Figure 1: A) openness toward invasive BCIs of people experiencing a disability. B) openness toward invasive BCIs by diagnosis. Adapted from Lahr et al., 2015.

OPINIONS OF NON-DISABLED PUBLIC: BCIS FOR ENHANCEMENT

As research in the field of BCIs progresses, there has been more attention for the possible applications of BCIs for non-disabled individuals (Vansteensel et al., 2017). For these people, BCIs would be used with the aim of enhancing the daily-life of a healthy person. The Pew Research Center looked into the opinion of American citizens concerning the possibility of using BCI-like technologies without having a specific medical need for these devices (Funk et al., 2016). Participants were asked to imagine a hypothetical scenario in which computer chips could be surgically implanted into the brain to increase cognitive abilities, such as concentration and information processing. Overall, it was found that Americans are much more likely to be worried about the implantation of brain chips for improved cognitive abilities than enthusiastic about this possibility (Figure 2). A minority of respondents would want an implanted device for improved concentration and information processing for themselves. Interestingly, about one-third Americans (32%) showed to be more accepting towards temporary implanted devices, which can be seen as a proxy for non-invasive BCIs. Furthermore, Americans expect that the availability of BCIs for healthy people would bring about

more negative societal changes than positive. Most notably, 74% respondents were concerned that these implanted devices would become available before their functionality and implications are fully understood. This has also been found by Carmichael and Carmichael in 2014 when interviewing healthy participants about their views on several BCI use for enhancement. Funk et al. (2016) found that a similar number of participants were concerned that inequality would increase, as BCI would only be available for the wealthy, and that people with an implanted BCI would feel superior to those without.

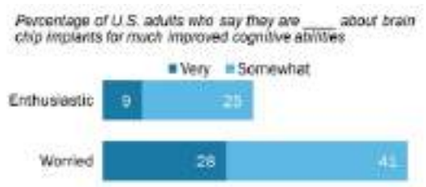

Figure 2: Percentage of U.S. adults who say they are worried/enthusiastic about brain chip implants for much improved cognitive abilities. Adapted from Funk et al., 2016.

Americans showed to be more closely divided on the question whether brain implants for enhancing the cognitive abilities of healthy individuals would be crossing a line, as is evident from Figure 3. This figure also shows that participants with high religious commitment were far more likely to state that a BCI-like device is meddling with nature than participants with low religious commitment are. In line with this, religious Americans were less inclined to want a brain implant to improve brain function compared to atheists and agnostics (Funk, 2016). Sample et al. (2020) found similar results, when surveying citizens of Germany, Canada, and Spain on their view towards BCIs. This indicates that religion could play an important role in the marketing of BCIs for non-disabled individuals, as a different marketing strategy might be required for secular and nonsecular areas.

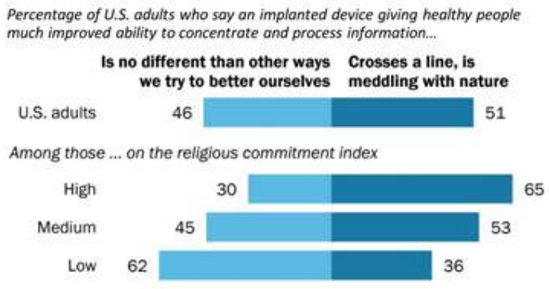

Figure 3: Percentage of U.S. adults who say an implanted device giving healthy people much improved ability to concentrate and process information is no different than other ways we try to better ourselves, is crossing a line, or is meddling with nature. Percentage of people among those which are high/medium/low on the religious commitment index. Adapted from Funk et al., 2016.

Taken together, Sample et al. (2020) concluded that respondents were enthusiastic as well as worried about the concept of BCI technology, highly dependent on the domain of application. The possibility of BCI usage in context of the police, military and security worried the respondents, as well as BCI use in marketing and commerce. In contrast, respondents expressed enthusiasm towards BCI use in education and learning. Participants were especially enthusiastic about the possibility of incorporating BCIs in healthcare and as an assistive technology.

Limited studies have allowed healthy participants to experience a BCI before forming an opinion on the technology. In the few studies where this did occur, healthy participants enjoyed using the BCI. When functioning as a control group in evaluating the performance of BCIs to aid people with cerebral palsy in their interaction with computers, Heidrich et al. (2015) noted that healthy individuals highly enjoyed using a BCI. Mulvenna et al. (2012) found similar results, when evaluating the quality of BCI performance. These results correspond to those of Funk et al. (2016), who found that people who had prior knowledge on the topic of BCIs were more positive towards its use.

OPINIONS OF EXTERNAL STAKEHOLDERS: BCI RESEARCHER AND CAREGIVERS

The opinion of stakeholders besides the disabled and non-disabled public, here named external stakeholders, regarding BCI technology is often merely marginally addressed (Kögel et al., 2019). Additionally, external stakeholders are often grouped together with BCI users, thus obscuring potential differences in their opinion. Studies that do address external stakeholders separately often concern two groups: BCI researchers and caregivers. Studies investigating the opinions of researchers often focus on the marketability of BCI technology, as it is usually assumed that BCI researchers, aiming to develop BCIs, feel that the technology can improve the quality of the life of people with a disability (Kögel et al., 2019; Nijboer et al., 2013). For example, Vansteensel and colleagues (2017) surveyed BCI researchers from all continents on their ideas about the future prospects of BCIs. One-third of the 298 respondents argued that BCIs that could replace the natural output of the central nervous system would be completely feasible within 5-10 years. Other functions that were deemed feasible include improving rehabilitation, home automation and restoring lost communication abilities. When Nijboer et al. (2013) assessed the expectations of BCI researchers of marketability of BCIs back, all 145 respondents noted that BCIs as an assistive technology would be on the market within the next five years. Nearly half (44.8%) of the respondents argued that BCIs for healthy people would be on the market within that time-frame as well. BCI researchers note that user-friendliness, wearability and durability are factors that need to be optimised to maximize the marketability of BCIs, but mention that BCIs will only become satisfactory regarding these factors in the far future (Vansteensel et al., 2017).

It was also found that over 80% of respondents believed that BCI used as assistive technology could aid families of disabled individuals (Nijboer et al., 2013). Family members themselves seem to believe this as well (Diep & Wolbring, 2015). Nine mothers, functioning as the main caregivers of non or barely communicative children, saw BCIs as a potential aid in their daily life, as it could help them in interpreting their children's needs and held the potential of expanding their child's social network. However, all but one mother did not feel that the benefit of a possible larger social circle outweighs the costs of an invasive BCI. This was mostly because they did not think the procedure of implanting an invasive BCI was safe enough, although some participants would not consider an invasive BCI for their child regardless of hypothetically improved safety measures. These participants argued the brain was too delicate an organ, stating that 'the brain is so sensitive […] if you hurt any cell it's not coming again' (Diep & Wolbring, 2015).

When asked about the most relevant advancements in BCI technology, some mothers expressed that technological development should ensure that BCIs are affordable to anyone in need of such a device (Diep & Wolbring, 2015). Various studies show that the features of assistive BCI technology deemed important by caregivers, including mothers, often mirror the needs of the people they are caring for (Gernomino et al., 2014; Kögel et al., 2019), indicating that caregivers have a reasonable idea of what their patients want and need.

DISCUSSION

This paper aimed to provide a comprehensive perspective on the opinions of the public with respect to BCI technology, which could be used to direct BCI research in a manner that is meaningful to the intended target audience. In order to do this, this paper aims to answer the following two questions: (1) Do the various stakeholders have a difference in opinion regarding invasive and non-invasive BCIs? and (2) What feature of BCI technology is deemed the most important according to the several stakeholders? From the aforementioned literature it is clear that not all stakeholders have the same desires and concerns when it comes to BCI technology, and thus they should be treated as if this were the case.

For people suffering from a disability in the form of a paralysis, non-invasive BCI technology is preferred over invasive BCI technology. This is the case because participants feel that the cost of surgery does not outweigh the benefit of enhanced performance as provided by current BCIs. General performance is a common concern with emerging technologies, which often stems from the phenomenon that emerging technologies are often oversold, sometimes with a cure narrative (Newell & Goggin, 2005; Yumakulov et al., 2012). However, out of all

stakeholder groups represented in this paper, the disabled public proved most open towards the idea of invasive BCIs. This is mostly due to the prospect of improvements in communication skills and mobility. There was a striking difference in openness towards invasive BCIs between ALS patients and patients with other underlying causes of paralysis, with ALS patients being significantly more open towards the technology. This could possibly be due to the progressive nature of ALS, indicating that future prospects of the patient involved can significantly shape their opinion on BCI technology.

The non-disabled public is more worried about BCI technology in general. They worry that the technology would become available before the functionality and implications is fully understood and that widespread BCI usage could exacerbate inequality, as only wealthy individuals could obtain it. This way, BCI technology might increase the quality of life of an individual, but not of the public as a whole. However, this group of stakeholders did reveal to be overall enthusiastic about the possible applications of BCI in healthcare and assistive technology. The non-disabled public felt that implanted devices resembling BCIs were more acceptable if they were temporary, thus indicating that they would prefer non-invasive BCIs technology over invasive.

Caregivers, especially familial caregivers, strongly prefer non-invasive BCIs over invasive ones, as they do not deem invasive BCIs as safe enough. For some, invasive BCIs would only be an option if the safety of the technology would be ensured, but some participants noted that the brain was too sensitive to be exposed to invasive technologies at all. Various studies show that the features of assistive BCI technology deemed important by caregivers often mirror the needs of the people they are caring for (Gernomino et al., 2014; Kögel et al., 2019), indicating that caregivers have a reasonable idea of what their patients want and need. These features focussed mostly on communication skills and movement.

Most BCI researchers believe that it is feasible for BCIs to improve (lost) communication skills and as such, former BCI research has largely targeted this feature (Vansteensel et al., 2017). However, to increase research speed and safety, ethical guidelines are needed. This has also been highly requested by BCI researchers (Nijboer et al., 2013).

LIMITATIONS

This paper suffers from a couple of limitations, the main one concerning the fact that an exhaustive representation of the general public was not provided. This paper has represented the general public as four stakeholder groups, namely disabled individuals suffering from a paralysis, non-disabled individuals, BCI researchers and caregivers. This was done as these groups have been covered most often in former research. However, this disregards other potential stakeholders, including insurance companies, BCI production companies and possibly governmental entities. Additionally, there are many disabilities that have not been covered in this paper, even though they could potentially be aided with a BCI. As research on different groups of disability is sparse, the decision was made to focus on paralysis in order to obtain a more complete view for this specific situation. However, it should be taken into consideration that investigation of groups of individuals with disabilities besides paralysis might have rendered different results, as they are experiencing different symptoms and thus have different needs. In order to create an optimised BCI product for them, further research should elaborate on the desires of this group. This paper points out the heterogeneity of desires and concerns of stakeholders, again highlighting the importance of directing BCI research in a manner that is meaningful to the intended target audience.

Furthermore, most former research into the opinion of people on BCI technology has been centred in North-America and Europe, with only Vansteensel et al. (2017) incorporating a substantial number of participants from Asia in their study. In order for BCI technology to be marketable on a global level, it is advisable to investigate the opinion of people from outside of North-America and Europe in more depth.

CONCLUSION

As the literature has shown that all stakeholders have different needs and concerns, BCI research should be directed towards meeting these needs and concerns in a manner that is meaningful to the targeted stakeholder group. The most promising field with regard to the marketability of BCI is the disabled public, in this paper represented by people suffering from underlying mechanisms resulting in paralysis. This group is the most open to the concept of BCIs compared to the other represented stakeholders. When aiming to optimise the experience of BCI use for this group, it can be derived from aforementioned literature that focus should lie on computer, TV, phone, and wheelchair use. It is thus advisable to direct research towards these features as this will create a highly desired product.

From the perspective of marketability, research should focus on non-invasive BCI technologies. Although the possibilities are not as limitless and performance might be suboptimal compared to invasive BCI technology (Lahr et al., 2015), more people would be willing to try out the technology if it is temporary and non-invasive, and thus less risky. This could in turn improve the overall opinion of individuals on BCI technology, possibly improving their opinion on invasive BCIs as well. This has been noted before, as participants with prior knowledge on the topic of BCIs or experience with a BCI were more positive towards its use (Funk et al., 2016; Heidrich et al., 2015). This indicates that raising awareness on the possibilities of BCI usage, as well as allowing people to experience the technology themselves, might improve the opinion of the general public on the technology.

Raising awareness on the possibilities of BCIs can be achieved by correctly marketing the right target audience, as this will increase the number of people with experience with BCIs, thus normalising BCI technology.

CONFLICT OF INTEREST

The author has no conflict of interest to declare.

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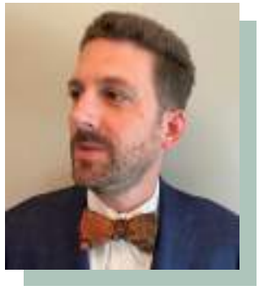
‘Artificial Intelligence: an exciting area for neuroscience’



Dr. Christian P. Janssen

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Artificial Intelligence is an extensive term; thus, understanding what is possible within its scope is fundamental. In this piece, Dr. Chris Janssen introduces us to two branches of Artificial Intelligence and neuroscience. By navigating between human-AI interaction and computer stimulation, he presents more options for young scientists to invest in their careers.

Artificial intelligence (AI) is in the news almost every day. Topics range from self-driving cars, personal health, and “deep fake” videos. Cognitive (neuro-) science has always played an important role in the development of AI, and has an even larger role to play in the future.

The 2-month “Dartmouth workshop”, sometimes considered as the birthplace of AI, proposed that: “The study is to proceed on the basis of the conjecture that every aspect of learning or any other feature of intelligence can in principle be so precisely described that a machine can be made to simulate it” (McCarthy et al., 1955). That is, the goal was to understand how intelligence (or more broadly: cognition) arises in the brain and affects behaviour, and the method was computer simulation. Notable cognitive scientists (e.g., Allen Newell and Nobel prize winner Herbert Simon) were involved from the start. Neuroscientific topics that are sometimes thought of as only recent AI initiatives were already discussed in 1955, for example: neural nets, abstraction, and creativity.

Today, there are at least two exciting paths for AI and neuroscience. The first path is continuing to increase our understanding of human behaviour and thought using computer simulation. What constitutes a model or simulation can vary tremendously between fields (Janssen et al., 2021). For instance, recent work in Utrecht focuses on modelling decision making (van Maanen et al., 2021), responses to emotional faces (Stuit et al., 2021), timing (Harvey et al., 2020), dual-tasking (Janssen et al., 2019c; Schmidt et al., 2020), and distraction (Brumby et al., 2019; Brumby et al., 2018). Models can be used to further test the implications of existing cognitive neuroscience theories (“top-down”), or to identify so-far unknown patterns from highly dimensional data (“bottom-up” machine learning).

The second exciting path is to study human-AI interaction. AI technologies are applied in more and more domains, ranging from robotic vacuums and intelligent thermostats, to robotic social companions and semi-automated vehicles. They are also used by a wider variety of people: not just experts, but also people that do not read the manual before using a device (such as their phone). There is a need to understand how humans respond to and interact with AI (see review in Janssen et al., 2019b). Neuroscience can contribute to this understanding by developing detailed, predictive theories of human behaviour and thought, and by testing those theories in applied settings. These efforts can refine theory and inform system design. Recently, researches in Utrecht have started to investigate brain processes during alerts in automated vehicles (van der Heiden et al., 2020; van der Heiden et al., 2018; van der Heiden et al., 2021), human-robot interaction (Henschel et al., 2020, 2020), theories of distraction (Janssen et al., 2019d), and potential confusion between user beliefs and AI system modes (Janssen et al., 2019a).

Many of these initiatives are incorporated in the teaching at Utrecht University (e.g., Janssen et al., 2020) and shape further research. For example, this research is integrated in the human-centred AI focus area, particularly within the focus group on Social and Cognitive Modelling that I lead (Utrecht University, 2021). I hope you can take part in this exciting area of research!

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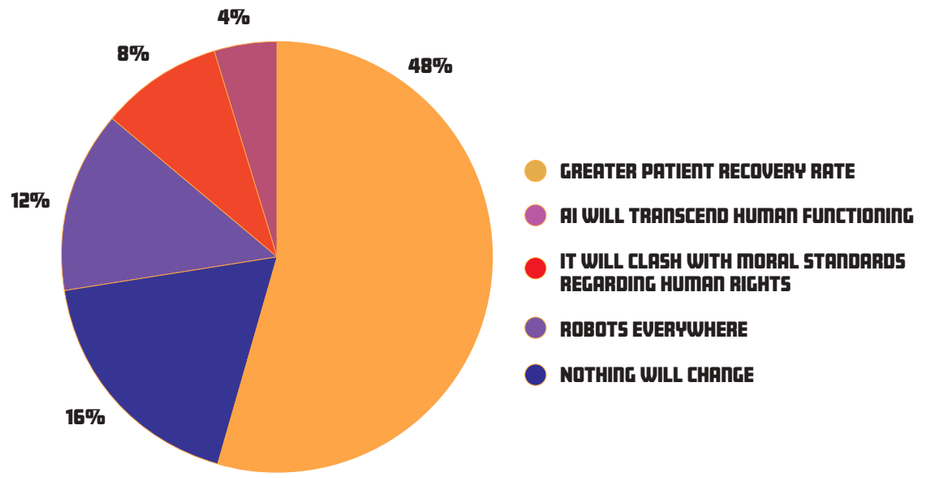
POLL #2

What do you think the world will look like when Artificial Intelligence is more accessible?



‘Keep it natural’

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In this piece, Dr. Sjoerd Stuit dives into machine learning and feature selection while explaining the importance of both. Further, he shows how much natural stimuli may contribute to neuroscience and how many new outcomes we can get

Many types of experiments compare behavioural or neurophysiological responses between conditions based on different categories of visual stimuli. With all else being equal, the categorical difference between conditions is then considered the potential driver of the responses. However, since any difference between the stimuli for the different conditions is a valid candidate to explain a resulting effect, knowledge about the objective differences between conditions is crucial for the interpretation of the responses. With, for example, two conditions consisting of differently oriented lines, interpretation is not that difficult since these conditions will only differ along one dimension: orientation. However, natural images will differ in many dimensions, such as their local and global contrast, local and global orientations, luminance, colours, et cetera. Therefore, one might want to manipulate the stimuli to equate them as much as possible, removing all possible confounding variables. However, this may not be the best solution. First off, it is an almost impossible task. For example, if all visual aspects of an angry face image were to be equated with those of a happy face image, the two images would be the same. Second, and more relevant, the stimuli will then deviate from how they occur naturally, creating a gap between the intent behind the experiment, and its execution.

However, by using machine learning and feature selection in novel ways, the multi- dimensional variances in the stimuli become an advantage. Machine learning classification aims to create a model that can accurately classify the category based on given characteristics. Feature selection takes this a step further from the characteristics given, it finds those that are most useful for classification. Usually, this is used to maximize classification performance, but it also leads to new, better, questions than ‘is there a difference between conditions?’. Instead, the researcher can ask ‘what aspects of the stimuli predict the responses?’ as well as ‘what aspects of the stimuli predict the category of the stimulus?’. If the effect found is truly based on the chosen conditions, the answers to the former and the later should align. If not, the key players for a new hypothesis, the aspects of the stimuli that predict the responses, are already known and ready for interpretation. In conclusion, the time has come to embrace the complex multi-dimensionality of natural stimuli instead of avoiding it and find out what aspects specifically relate to the responses.

FUTURISTIC TREATMENT OPTIONS

‘A glimpse of what the future may hold for the development of new treatments for diseases of the brain’

A fascinating and promising area of research is that of treatment of the various disorders of the brain. Treatment of neurological and neuropsychiatric conditions has seen many advancements in the past couple of decades. This section will give you a little insight into what more might be to come in the future. We are excited to share with you some of the most recent research on the treatment and rehabilitation of various brain disorders conducted here in Utrecht by three research groups, research conducted by one of our alumni, and a review by one of your fellow students. We hope they spark your interest and make you curious for more!

‘The future of ALS modelling: an overview of validity and potential’

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Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease with progressive muscle weakness eventually leading to death by respiratory failure often within five years from disease onset. The lifetime risk of developing ALS is estimated to be 1:400. There is no cure, and besides one mildly therapeutic drug (Riluzole) there are currently no treatments. The unsuccessful translation from the lab to the clinic calls for a critical look at the model systems we have used, are using, and are developing. In this review, the face and construct validity of mouse models, simple animal models and induced pluripotent stem cell (iPSC)-derived models are discussed. In addition, necessary improvements and future potential are addressed. The main findings are: (1) Knock-in technology and increased implementation of simple animal models and iPSC-derived models can drastically reduce the number of rodent studies needed and improve the chance of successful translation. (2) The advancements in patient-derived 3D cell cultures and microfluidics open up the avenue for complex modelling of sporadic ALS rather than mere post-mortem studies and simple cell cultures. (3) Development and integration of age induction, vascularization and microfluidics, and more complex co-culture techniques could allow ALS-on-a-chip technology to evolve into a highly valuable tool with unprecedented validity.

Keywords: *Amyotrophic lateral sclerosis, induced pluripotent stem cells, simple animal models, knock-in, translation*

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder affecting upper motor neurons (UMNs) and lower motor neurons (LMNs) (Morrice et al., 2018; Van Damme et al., 2017; van Es et al., 2017). It presents itself as progressive muscle weakness, typically accompanied by muscle atrophy, spasticity, hyperreflexia, and fasciculations (individual motor unit twitches caused by sporadic discharges of motor neurons) (Morrice et al., 2018; Van Damme et al., 2017). Over time, this progression leads to paralysis and patients generally survive for about 3-5 years from the onset of disease before passing away from respiratory failure (Morrice et al., 2018; van Es et al., 2017). Approximately half of the patients also develop impairments in cognitive functioning (e.g. language, fluency, social cognition and executive function), or changes in behaviour (e.g. apathy, loss of sympathy). About 1 in 10 affected individuals acquire associated frontotemporal dementia (FTD) (Van Damme et al., 2017; van Es et al., 2017).

The prevalence of ALS has been estimated for populations of European descent to be around 3 in 100,000. The lifetime risk of developing ALS is approximately 1:400 for women and 1:350 for men (Van Damme et al., 2017; van Es et al., 2017). ALS is typically classified as either familial ALS (fALS)(in which a hereditary genetic component is found) in 10% of affected individuals or sporadic ALS (sALS) in 90% of affected individuals. In these sporadic cases, environmental factors might play a large role. For the familial cases, around 30 different genes have been found as the hereditary component (Morrice et al., 2018; Van Damme et al., 2017; van Es et al., 2017). This genetic heterogeneity, in combination with the variety of clinical subphenotypes, has led to a redefinition of ALS. Rather than a single disease, ALS is now starting to be recognized as a syndrome with several underlying pathophysiological mechanisms (van Es et al., 2017).

Despite this diversity, some cellular hallmarks for ALS pathology have been established. These include the occurrence of astrogliosis, microgliosis, defective axonal transport, defective RNA-binding proteins, axonal retraction, and the loss of UMN and LMN cell bodies (Morrice et al., 2018; Van Damme et al., 2017). In addition, in approximately 95% of ALS patients, the surviving neurons contain ubiquitin-positive inclusions that contain the RNA-binding protein TDP-43. TDP-43 pathology is, therefore, also a major hallmark of ALS (Van Damme et al., 2017; van Es et al., 2017).

The translation from ALS model systems to clinical interventions has been highly unsuccessful so far, yielding Riluzole as the only widely approved and obtainable drug to treat ALS. Despite Riluzole’s mild therapeutic effects, multidisciplinary care and symptom management remain the standard care for ALS patients (Morrice et al., 2018; Van Damme et al., 2017; van Es et al., 2017). The inability to translate from model systems to the clinic demands a critical look at the model systems we have used, are using, and are developing.

Genetic mouse models are the most frequently used ALS model systems. They have provided us with meaningful insights into the disease mechanism. However, the translational value is being questioned as a result of the lack of successful translations to the clinic (Morrice et al., 2018; Van Damme et al., 2017). An alternative species that is emerging as a useful model for neurodegenerative diseases, including ALS, is the zebrafish (Morrice et al., 2018; Sher, 2017; Van Damme et al., 2017). In addition,

the rise of human patient-derived stem cell models could transform translational ALS research. They are highly promising because of the preservation of genetics and epigenetics from the patient. However, they are still in a developmental phase, and the translational value is yet to be determined (Morrice et al., 2018; Van Damme et al., 2017; van Es et al., 2017).
In this paper, the current knowledge on the validity (face and construct) and value of model systems already being used and model systems currently being developed will be reviewed. In particular, animal models will be compared to patient-derived stem cell models. What characteristics should the ideal ALS model system possess? What is the cause of the translational gap of current animal models? What insights could human stem cell models provide us with, and are there any major pitfalls we are ignoring in our enthusiasm to revolutionize?

Search method. *The contents of this paper were put together by use of recent review articles in combination with the 'most recent' search function on PubMed for any additional developments. All journal articles used for this review were acquired from PubMed. The articles are dated from 2009-2020.*

PART 1: THE FACE AND CONSTRUCT OF ALS

In order to systematically assess the value of different model systems, two validity criteria will be applied. The two validity criteria used in this paper are face validity and construct validity. Face validity refers to the extent to which the phenotype of the disease model corresponds with that observed in humans. We can assess face validity by comparing pathological features or hallmarks between model systems and human disease. Construct validity refers to the extent to which the disease-inducing mechanism in the model system reflects our current knowledge of the aetiology of the disease in humans. A third validity criterion, predictive validity, is also relevant. It refers to the degree to which a model is able to predict human mechanisms (of either pathophysiology or response to therapeutic agents). This is, however, not an applicable criterion to many models currently used, since they have only recently been developed and have not yielded clinical trials yet (Morrice et al., 2018). To assess the face and construct validity in each model, it is necessary to have an overview of the 'face' and 'construct' of human ALS. Of course other benefits and limitations such as cost, availability, and characterization of the model systems also play an important role in research. These features will also be discussed.

The 'face' – phenotype

ALS presents itself most primarily as degeneration of motor neurons. Specifically, it concerns LMNs in the spinal cord's anterior horn, LMNs in motor nuclei of the brainstem and UMNs in the motor cortex (Saberi et al., 2015; Van Damme et al., 2017). Besides this degeneration, reactive astrogliosis and microgliosis are well-established hallmarks of ALS. Astrocytes and microglia both accumulate at the sites of degeneration. The immunoreactivity and expression of inflammatory markers are increased in astrocytes. Microglia secrete proinflammatory cytokines, reactive oxygen species, chemokines and neurotrophic factors (Morrice et al., 2018; Saberi et al., 2015). The fourth hallmark of ALS is the ubiquitin-positive aggregates in the cytosol, which were discovered to have TAR DNA-binding protein 43 (TDP-43) as their main component. Under healthy circumstances, the ubiquitination of a protein would lead to its degradation. In sALS, as well as fALS, there is loss of functional TDP-43, and pathologic aggregate formation in the cytoplasm. However, TDP-43 inclusions have also been found in other disorders, such as Alzheimer's disease, and in a portion of people 65 years or older. Thus TDP-43 inclusions are not entirely exclusive to ALS pathology (Saberi et al., 2015). Furthermore, mitochondrial dysfunction, excitotoxicity (dendrite degeneration and cell death triggered by glutamate receptor activation), protein mislocalization, impaired protein degradation, and axonal degeneration and transport defects have been named ALS hallmarks (Alrafiah, 2018; Morrice et al., 2018; Van Damme et al., 2017; van Es et al., 2017).

The 'construct' – aetiology

The disease mechanisms of this phenotype are only partly understood. Many studies point out similarities in the genetic framework between sALS and fALS. Previous literature suggests that multiple pathways need to be affected for the development of ALS. A multi-step model of disease has been proposed and is compliant with many ALS features, e.g. the late onset, the phenotypic variability, and more (van Es et al., 2017). In 60-80% of fALS cases, the presumably pathogenic mutation can be identified. sALS twin studies suggest 61% genetic contribution, with a remaining environmental component of 39%.
From fALS cases, many associated genetic mutations have been found, of which the four most common mutations will be discussed here. A hexanucleotide (GGGGCC) repeat expansion in open reading frame 72 of chromosome 9 (C9orf72) is the most common mutation associated with ALS: it is present in 40% of fALS cases and 7% of sALS cases (Alrafiah, 2018; van Es et al., 2017). The second gene, implemented in 20% of fALS cases, is Cu/Zn superoxide dismutase 1 (SOD1). Over 180 different mutations have been found in this gene, often causing pathology without loss of enzymatic functioning (Alrafiah, 2018; van Es et al., 2017). The third affected gene, implicated in around 5% of patients, is the RNA-binding protein fused in sarcoma (FUS). Lastly, mutations in the TARDBP gene, coding for TDP-43, are only found in 3% of sALS and fALS. However, TDP-43 pathology is found in approximately 95% of ALS patients and is therefore a significant hallmark (Alrafiah, 2018; Van Damme et al., 2017).
Environmental risk factors have been difficult to establish. High incidence rates in specific populations have brought forward cyanobacterial neurotoxins and physical exercise or athletic disposition as risk factors (van Es et al., 2017). Smoking is the only definitively proved risk factor (van Es et al., 2017). Occupational exposure to solvents, pesticides and organic toxins, and exposure to electromagnetic fields and metals were also found as risk factors in a population-based case-control study (Filippini et al., 2020). However, the number of exposed subjects was low, and some bias may be present in this study (Filippini et al., 2020).

PART 2: ANIMAL MODELS OF ALS

MOUSE MODELS

c9orf72

Mouse models are the most frequently used models for ALS, despite only being able to represent fALS. A wide variety of mouse models have been established based on our current understanding of familial ALS genetics. In such genetic model systems, the distinction between loss of function (LOF) and toxic gain of function (GOF) is an important one (Alrafiah, 2018). For instance, a knockout model will not accurately mimic the disease if the mechanism is based on GOF. For c9orf72- and SOD1-related ALS the general consensus is that GOF is the primary mechanism of disease (Alrafiah, 2018). In the FVB-C9orf72-BAC model originally described by Liu et al. (2016), mice contain a BAC construct with the full-length c9orf72 gene with approximately 500 GGGGCC repeats and substantial flanking sequences. These flanking sequences were included to more accurately recapitulate the sense and antisense transcription in humans. Contrary to previous models, great face validity was observed; cortical, hippocampal and spinal cord degeneration of neurons, neuromuscular junction (NMJ) denervation, microgliosis, astrogliosis, RNA foci, dipeptide-repeat proteins (DPR)(typical of c9orf72-related ALS) and behaviour measures. TDP-43 inclusions were found in end-stage animals (Liu et al., 2016; Nguyen et al., 2020). However, the disease penetrance is incomplete and there are some (yet) unexplained sex differences in fully penetrant mice (Liu et al., 2016; Morrice et al., 2018). The described phenotype has been replicated by multiple other labs and has been reasonably well characterized (Nguyen et al., 2020). Interestingly, the degeneration of neurons and the aggregation of DPR were found to be proportionate to the length of the repeat expansion (Alrafiah, 2018; Liu et al., 2016).

SOD1

To model SOD1-related ALS, mice expressing a number of copies of the human SOD1 gene with the G93A mutation are most frequently used (Alrafiah, 2018). This model with 25 copies is the only model so far to yield a drug that was shown to be (mildly) effective in clinical trials (Riluzole). It displays very strong face validity. Besides lacking UMN degeneration, it shows the majority of known ALS pathological features, including loss of motor neurons, micro- and astrogliosis, proteinopathy, excitotoxicity, axonal transport deficits, and mitochondrial dysfunction (Alrafiah, 2018; Morrice et al., 2018). However, this model is based on overexpression of the mutant protein, and overexpression of human wildtype SOD1 also induced damage: specifically axonopathy (Morrice et al., 2018). As of yet, no studies were found describing a mSOD1 knock-in mouse model to overcome the overexpression issue. Also, there were significant strain-dependent effects on the disease progression and life expectancy in these mice, although these are starting to get more characterized (Nardo et al., 2016). In addition, copy number can spontaneously decrease in these models, which affects the disease manifestation (Morrice et al., 2018).

FUS

Both TDP-related and FUS-related ALS are known to consist of both LOF and GOF mechanisms. TDP-43 and FUS are both RNA-binding proteins that play an important part in RNA metabolism. They are predominantly localized in the nucleus, however mutations of these proteins often lead to mislocalization of these proteins to the cytosol. This results in a loss of function in the nucleus of these cells and a toxic gain of function in the cytosol because of the abundance of these proteins outside of the nucleus (Humphrey et al., 2020; Morrice et al., 2018; Van Damme et al., 2017). This dual LOF/GOF theory is currently the most supported idea.
For TDP-related and FUS-related ALS, many mouse models, including those based on overexpression, have been developed and used (as reviewed by Alrafiah (2018)). These models have given us important insights into the physiological functions of these proteins (Humphrey et al., 2020), however also have shown us that neurons are highly sensitive to the dose of FUS protein (Devoy et al., 2017) and that both TDP-43 and FUS are very tightly regulated (Humphrey et al., 2020). Therefore, overexpression-based models are likely not an accurate representation of ALS disease mechanisms, and there is a need for alternative models. Devoy et al. (2017) describe a knock-in mouse model that recapitulates the ALS phenotype while maintaining physiological levels of FUS. They observed late-onset progressive motor neuron loss, increased denervation of NMJs, mitochondrial deficits, proteinopathy and a motor behaviour deficit. This model is yet to be further characterized (e.g. features of gliosis, possible strain-dependent effects, etc.). Interestingly, the extent of protein mislocalization correlated with the

disease severity.

TDP-43

When looking at many of the mouse models of TDP-related ALS, a trade-off between construct and face validity was observed. Models of mild overexpression (better construct validity) showed only partial face validity; for instance lacking TDP-43 cytosolic aggregation. Full overexpression is less likely to recapitulate the disease mechanism in humans, although some of these models did show better replication of pathological features, including TDP-43 aggregation (Alrafiah, 2018; Morrice et al., 2018). Having said that, also for TDP-related ALS, knock-in models are being developed. Not many of these studies were found but Ebstein et al. (2019) were able to show slight but significant motor neuron degeneration in a knock-in model of a TARDBP mutation. They observed specific denervation of muscles particularly affected in ALS in an asymmetric manner. The neurodegenerative effect was not visible until the mice were 2,5 years of age. This suggests a strong potential for this method to model early disease development mechanisms, but not the late disease progression. Notably, this model is yet to be properly characterized and proven effective.

Overall, the mouse as a model system for ALS has its strengths: mice and humans are both mammals, and therefore have a high degree of homology in their genetics. They provide the means for intricate mechanistic studies and results are undoubtedly relevant to human physiology (Van Damme et al., 2017). Unfortunately, these models have yet to yield an effective therapy, questioning their predictive value. In addition, they have a low throughput and are more expensive than for instance simple animal models. Also, the strain-dependent effects and sex differences are yet to be clarified and characterized. Lastly, the ethics around animal wellbeing are encouraging to narrow down the use of (complex) animal models in research.

SIMPLE ANIMAL MODELS

Simple animal models, e.g. the worm (Caenorhabditis elegans), the fly (Drosophila melanogaster), and in particular the zebrafish (Danio rerio) are increasingly being used in (ALS) research. Because of their compact size, short life span and straightforward growth conditions, they can be used at a very low cost (Patten et al., 2016). In addition, contrary to e.g. rodent models, simple animals allow for extensive compound screens and unbiased genetic screens (Patten et al., 2016; Van Damme et al., 2017). They are the only animals fit for whole animal phenotypic compound screening, which can even be done with multiple species in the same study (Patten et al., 2016).

Because of our rather incomplete current knowledge of ALS aetiology, mechanism-based therapeutics have not yet been identified. Instead, large-scale compound screens in simple animals could aid in finding therapeutic targets, which can then be validated in complex animal models. Several potentially therapeutic small molecules have already been identified using this method. Screens like this could also be used to work back from the results and discover the underlying mechanisms (Patten et al., 2016; Van Damme et al., 2017).

Due to the simplicity of these animals, they have been very well characterized over the last years. The genomes of all three simple animals mentioned above have been fully sequenced. In C. elegans, of which the nervous system is composed of 302 neurons, the synaptic interconnections have even been characterized (Patten et al., 2016; Van Damme et al., 2017). In addition, because of the transparency of zebrafish embryos and C. elegans, live imaging (e.g. by labelling certain proteins with GFP) can be done in vivo. Furthermore, simple animals allow for highly efficient transgenic expression. Moreover, a large array of genetic tools is available for use in these models. These include zinc-finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs), and Clustered Regularly Interspaced Short Palindromic Repeats with associated Cas 9 protein (CRISPR/Cas9) (Patten et al., 2016).

Existing simple animal model systems recapitulate several aspects of the neurodegenerative phenotype of ALS; In a SOD1-related C. elegans model, late-onset motor deficits, axon guidance failure and SOD1 aggregates were observed. In flies (D. melanogaster) with a c9orf72 repeat expansion transgene, effects on locomotion, a decrease in neuromuscular synaptic boutons and nuclear retention of hexanucleotide RNA was found. Lastly, in a zebrafish model of SOD1-related ALS, researchers found an age-dependent decline of swim endurance, muscle atrophy, loss of NMJs, paralysis and in some cases shortened lifespan (Patten et al., 2016).

An important limitation of simple animal models lies in the lack of complexity and therefore the inability to fully recapitulate human disease mechanisms. In any case, results or possible therapeutic targets have to be translated to a mammalian model first, in order to be approved and move towards a possible clinical trial (Patten et al., 2016). It is, however, important to note that many of the genes affected in neurodegenerative disorders have been largely evolutionarily conserved from zebrafish to humans (Morrice et al., 2018), so they ought to have substantial translational value. Lastly, the majority of these models are still dependent on overexpression (Patten et al., 2016), although the knock-in technique using CRISPR/Cas9 will likely offer a solution to this issue in these models as well.

PART 3: HUMAN-DERIVED CELL MODELS

2D CELL MODELS

Two-dimensional human-derived cell models have been used in research extensively. Cells are being cultured on a rigid surface, coated in substrates that recapitulate the composition of the extracellular matrix (ECM). This environment allows the cells to adhere to each other, to differentiate, to attach to the surface, and substrates can even regulate synaptogenesis, synaptic activity, migration and neurite outgrowth. It is an easy, cheap, reproducible, animal model-free method to study disease progression at a cellular level in vitro (Centeno, Cimarosti, & Bithell, 2018). Because the material is human, the genetics of the disease are preserved, and there is no overexpression issue like the one in rodents and simple animals. Several methods of co-culture can reveal insights on interactions between cell types (Centeno et al., 2018; Pasteuning-Vuhman et al., 2020). Nevertheless, 2D cellular models do not completely recapitulate the tissue organization and complexity because a) cellular interaction is limited to side-by-side contact and b) there is little diffusion of nutrients, oxygen, and waste products (Centeno et al., 2018).

For a long time, this type of modelling was not feasible for ALS, since the only patient-derived tissues that were available, were post-mortem materials. When the Yamanaka reprogramming factors (OCT3/4, SOX2, C-MYC, KLF4) were discovered to turn fibroblasts into induced pluripotent stem cells (iPSCs), this changed. iPSCs are now widely studied and using our knowledge of in vivo developmental programmes, it is possible to re-differentiate the iPSCs (e.g. derived from ALS patients) into specific types of neurons (e.g. motor neurons) and glia. A great benefit of iPSCs is that they can self-renew endlessly, and they are therefore an unlimited source of cells (Centeno et al., 2018).

An alternative way to obtain patient-derived motor neurons is through direct lineage reprogramming. This method skips the stem cell stage, and directly changes for instance a fibroblast into a motor neuron. This has been successfully done using ALS patient fibroblasts (Centeno et al., 2018; Zhao et al., 2020). The transcriptome and DNA methylome of the directly reprogrammed motor neurons and primary motor neurons were much alike. Notably, directly reprogrammed motor neurons maintain their (epi)genetic as well as age-related information of disease, contrary to iPSC-derived motor neurons, that lose ageing hallmarks and possibly epigenetic information when being transformed into stem cells (Zhao et al., 2020). A great limitation of direct reprogramming is the limited amount of cells yielded from the obtained fibroblasts (Ziff & Patani, 2019).

Since age is the main risk factor of ALS (Ziff & Patani, 2019), the loss of ageing information when producing iPSCs is a major loss. Models consisting of iPSCs (which are in a maturational stage equivalent to a fetus) generally take a long time before mature cell types or phenotypes are obtained. Techniques of faster maturation are under development, but in order to model an age-dependent disease mechanism, further ageing of these cells might be necessary (Centeno et al., 2018). Efforts have been made to induce ageing in cell cultures. Methods that are being explored include: a) inhibition of telomerase (Zhao et al., 2020; Ziff & Patani, 2019), b) exposure to toxins, such as reactive oxygen species, to simulate stress-induced cellular changes (Centeno et al., 2018), and c) overexpression of progerin. Progerin is a protein that is implicated in premature aging syndromes (Centeno et al., 2018; Ziff & Patani, 2019). Its overexpression has already successfully induced late-onset disease phenotypes in an iPSC-derived cellular model of Parkinson's disease, however is yet to be applied in an ALS-related study (Centeno et al., 2018).

In addition to the loss of ageing hallmarks, the short longevity of iPSC-derived motor neurons also limits the timeframe during which disease can be studied. Improving the longevity would improve the recapitulation of the ALS timeline (Zhao et al., 2020). In addition, cell lines need to be better characterized (Centeno et al., 2018). Furthermore, when using patient-derived cell lines the differences between cell lines could be attributed to the genetic background instead of the disease. In fALS cases this can be solved by using isogenic control lines, in which the patient-derived cells are compared to mutation-corrected cells. In the case of sALS, there is a need for large cohorts to make up for the genetic differences (Zhao et al., 2020). However, it is important to note that patient-derived iPSC models can already be made useful on an individual level. These models provide a possibility for personalized- or precision medicine. In the future, precision medicine using patient-derived iPSC models may predict how a patient will respond to certain medications.

3D CELL MODELS

3D Human-derived cellular models have recently emerged as a more state-of-the-art alternative to 2D models. The higher degree of complexity and the three-dimensional spatial organization are a more accurate representation of in vivo conditions. One of the reasons for this is that cell to cell connections and interactions can happen in all directions. In addition, interactions with the ECM, cell differentiation and electrophysiological network characteristics were found to be more accurately represented in 3D models (Centeno et al., 2018).

Generally, 3D cultures are either scaffold-free or scaffold-based. Scaffold-free cell models are based on the self-assembly of iPSCs into spherical shapes, or spheroids, without adding any biomaterials. When using this technique, the ECM is made by the cells themselves, meaning that they can replicate the in vivo development of the cellular niche. Scaffold-based cell models are acquired by dispersing cells throughout three-dimensional matrices. These matrices provide the physical and/or chemical signals that stimulate cell-matrix interaction, proliferation, differentiation and survival. Many aspects of the matrices can be controlled, including the nutrient/oxygen permeability and electrical conductivity. This controllable environment increases the reproducibility of

the model (Centeno et al., 2018).
A combination of scaffold-free and scaffold-based techniques has resulted in 3D organoid technology. Organoid technology makes use of the self-organization and tissue structure generation of scaffold-free techniques, while implementing the beneficial use of matrices for provision of structure and external cues from the scaffold-based technique. Neural organoids from patient-derived stem cells can already be kept alive for up to 10 months in bioreactors. They can mimic aspects of mammalian neurodevelopment and complex CNS organization. Differentiation of independent domains within brain regions, aspects of human cortical development and typical radial glial cell morphology and behaviour have been observed in neural organoids. These advantages set organoids apart from simpler protocols e.g. neural rosettes (2D) and neurospheres (3D) (Centeno et al., 2018).
However, 3D models come with some limitations as well. Firstly, they are expensive compared to 2D models. They can require advanced highly specified techniques and equipment. Also, because of the novelty of the technology, protocols have not yet been standardized, and characterization has a long way to go. Despite the control on the composition of the matrix, the heterogeneity and complexity of the models could have negative consequences for the reproducibility. Furthermore, 3D models and their complex morphology can be harder to visualize or perform microscopy on than 2D models (Centeno et al., 2018). However, protocols for making organoids transparent combined with the use of light sheet microscopy could overcome this issue.
Another key issue when culturing organoids, is the difficulty in distributing nutrients and oxygen throughout larger cultures. The lack of vascularization can result in necrotic cores. Innovations to improve this are either based on promoting vascularization or implementing microfluidic systems (Centeno et al., 2018). Cakir et al. (2019) developed cortical organoids from embryonic stem cells (ESCs) including stem cells that were engineered to express ETS variant 2, an important transcription factor in vascular endothelial cell development. They found that these cells formed a vascular-like network that enhanced the functional maturation of the organoids. Pham et al. (2018) did a comparable study using iPSC-derived organoids and endothelial cells with promising results. An example of a microfluidic system for perfusion is described in Rambani et al. (2009).
Contrary to using microfluidics merely as a solution to a problem, microfluidics also can be -and have been- used for innovative design of new advanced in vitro model systems: organ-on-a-chip systems (Centeno et al., 2018; Pasteuning-Vuhman et al., 2020). Microfluidic chips allow for several cell types to be cultured in separate yet connected compartments. In the case of ALS, neurons (2D) or neural organoids (3D) can be cultured close to muscle cells or bundles, allowing them to form NMJs. There are even promising findings that the blood-brain barrier can be modelled using a 2D microfluidic chip (Pasteuning-Vuhman et al., 2020) (Figure 1). An example of a microfluidic chip system (Osaki et al., 2018) will be discussed more elaborately below.

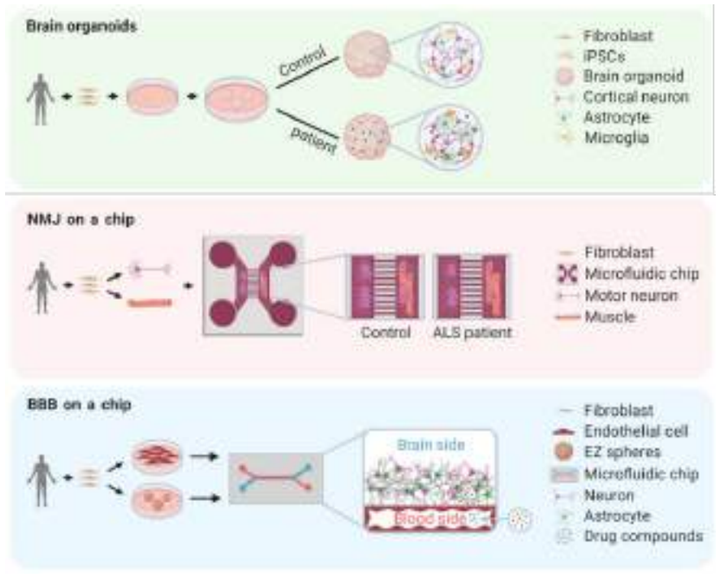

Figure 1. iPSC-derived cellular model systems for amyotrophic lateral sclerosis. Brain organoids: From self-assembly of stem cells cerebral, cortical or motor neuron spheroids can be made. NMJ on a chip: motor neurons and muscle fibers are cultured in a compart-mentalized way, allowing for the formation of NMJs. BBB on a chip: neurons (and e.g. astrocytes/ microglia) and vascular endothelial cells are cultured in a compart-mentalized manner, allowing researchers to study a blood-brain barrier. The innovative study design by Osaki et al. 2018, integrates all three techniques in an ALS-related study.
Figure edited from Pasteuning-Vuhman et al. 2020

CELL MODELS USED IN ALS

Regarding ALS specifically, a good amount of 2D cellular models have been developed and used for unravelling disease mechanisms and searching for new therapeutic targets. Motor neurons have been successfully derived both from patient-derived iPSCs through re-differentiation and from patient fibroblasts through direct reprogramming (Centeno et al., 2018; Zhao et al., 2020). The 2D models were able to recapitulate disease processes and phenotypical properties in vitro, which include neurite degeneration, increased cell death, degeneration of astrocytes in co-culture, TDP-43 proteinopathy, hexanucleotide repeat toxicity and dysregulation of synaptic activity (Centeno et al., 2018).
Application of 3D cell model technology to ALS research was not found in many studies so far. One example is a study by Osaki et al. (Chang et al., 2020; Osaki et al., 2018). It concerns a 3D organoid microfluidic chip model consisting of 3D skeletal muscle bundles derived from iPSCs combined with iPSC-derived motor neuron spheroids which were made to be light-sensitive (inducible by channelrhodopsin-2 activation). The iPSCs were induced from sALS patient fibroblasts. The two structures were cultured in separate compartments that were connected via a microfluidic system. Neurites grew out from the motor neuron spheroid to form NMJs onto the muscle fibres. Muscle contraction could then be induced and measured after activating the motor neurons with light. Indeed, the patient-derived motor units generated fewer muscle contractions. Also, motor neuron degeneration and apoptosis were accelerated in the ALS motor units compared to controls (Osaki et al., 2018).
In this same study (Osaki et al., 2018), the effect of a possible treatment was already assessed. Treatment with either rapamycin (an enhancer of autophagy) or both rapamycin and bosutinib was able to recover the muscle contractions in the patient-derived motor units. An increase in autophagy and degradation of TDP-43 was observed in the motor neurons. The promising effects of rapamycin and bosutinib had already been observed in other models, thus the replication of these effects shows the potential of this 3D patient-derived cell model for the future research of ALS (Chang et al., 2020; Osaki et al., 2018). In addition, Osaki et al. added a tight monolayer of induced endothelial cells to the model, to represent the blood-brain barrier and study its influence on the drug administration. Using this model, they were able to assess the interaction between the two drugs and the influence of this interaction on the permeability of the endothelial monolayer (Osaki et al., 2018).
A variant of the model by Osaki et al. with some small improvements was developed by Yoshioka et al. (Yoshioka et al., 2020). Their stronger contractility makes it easier to measure changes in e.g. a compound screening. Also, they were able to shorten the construction time from a month to a mere 20 days (Yoshioka et al., 2020).

PART 4: DISCUSSION

In this review, a brief overview of the status quo of ALS model systems is provided. We are far from fully understanding ALS, let alone finding a cure. Below, we will discuss what improvements are expected and needed to increase the predictive value of our current model systems. Also, we will consider the role of specific model systems in the future of ALS research.
Regarding mouse models of ALS, one of the most prominent issues is the construct validity of overexpression-based models. Now that CRISPR/Cas9 has opened the avenue of knock-in models, the use of overexpression-based models should be minimalized. New knock-in models will have to be developed, and importantly, characterized. Notably, these knock-in models display more mild symptoms, like in the study by Ebstein et al. (2019). This offers a great potential to study early disease mechanisms. However, it might not be able to recapitulate late disease progression. A second difficulty of many mouse models is variation between strains, sexes, and copy number. Since human ALS is also highly variable, these variations could be used to our advantage, provided that they are properly characterized, and protocols are standardized.
Simple animal models are generally already well characterized. Here, the overexpression issue can also be resolved using CRISPR/Cas9 technology. The largest improvement in the use of these model systems could lie in the automation and computerization of the compound screens, making them easier, more cost-effective and even more high throughput. The expanding role of simple animal studies in the future will be discussed further below.
3D human-derived cellular models and microfluidic ALS-on-a-chip systems are novel technologies and still highly under development. Evidently, these systems still need to be characterized, and standardized protocols are an important aim. Depending on the technical advances and successes, these models have the potential for unprecedented construct and face validity. One hurdle on the way there is the lack of vascularization, for which solutions based on endothelial cells or microfluidic perfusion have been proposed and found to have benefits in some studies (Cakir et al., 2019; Pham et al., 2018; Rambani et al., 2009). A factor that currently faults the construct validity is the loss of ageing hallmarks when using iPSCs. An important question to be asked in a future study is how age induction can be applied in 3D models. Progerin expression in iPSCs before self-assembly induces the ageing effect before maturation, which is not an accurate representation of the in vivo conditions. Instead, manually inducible progerin expression in iPSCs, activated after motor neuron spheroids are formed could be an interesting subject of future study.
Furthermore, many different variants of ALS-on-a-chip can be designed with increasing complexity. A next step of the model developed by Osaki et al. (2018) could,

for instance, be integrating astrocytes or microglia in the motor neuron spheroids. Also, cortical or cerebral organoids could be used in such a system to mimic the UMN environment. At the Pasterkamp Lab in Utrecht, Netherlands, cerebral organoids were formed in which microglia innately developed (Ormel et al., 2018). This is a promising tool for studying ALS-UMN behaviour, also with respect to frontotemporal dementia.

One of the main setbacks in ALS research is the inability of rodent models to yield therapeutics that are effectively translated to humans. Thus, there is a need for more reliable predictions. One way to achieve this might be through the usage of several model systems; not only within a species, but also cross-species. A cross-model approach in which mechanisms or therapeutics are first explored in simple animals and subsequently tested in complex animals and human iPSC-derived models has been proposed by van Damme et al. (2017). Doing a simple animal screen before application in rodent models, would hopefully decrease the number of unsuccessful rodent studies. In addition, testing hypotheses in iPSC-derived models could help reduce the number of these unsuccessful studies, as well as improve the translation from rodent to human, reducing the total rodents needed and reducing unsuccessful clinical trials as well. Ethics are an important reason to decrease the use of complex animals in research. By using simple animal models and iPSC-derived models as described above, the efficiency of research would likely ameliorate and rodents' lives would be spared. It is even thinkable that -provided technological advancements keep forging ahead- iPSC-derived models might one day be accurate and complex enough to facilitate translation from simple animal model systems to human application and the necessity of rodent models will diminish.

Since our knowledge of the precise mechanisms of ALS is so limited, mechanism-specific therapeutics are a tough challenge. Large-scale high throughput compound screens using approved drugs offer a shortcut towards possibly effective drugs. However, as was mentioned before briefly, simple animal compound screens are not only useful for the direct assessment of possible therapeutic agents. Information about the compounds that are found to be effective to any extent can be used to decipher new possible underlying mechanisms. Therefore, simple animal studies can even facilitate the path towards mechanism-specific therapeutics. Despite their low complexity, their worth should not be underestimated.

The substantial heterogeneity of ALS forms a great challenge for translational neuroscience. Notably, the rodent and simple animal models discussed in this review were all based on the genetic mutations associated with fALS. This does not represent all cases of fALS. Moreover, this does not represent any variant of sALS, which comprises 90% of all ALS cases. Post-mortem material and iPSC-derived model systems are the only ways to model sALS. Since post-mortem materials are difficult to obtain and only show the latest stage of disease progression, the evolution that is currently happening regarding iPSC-derived models is a huge step ahead for sALS research. Although big cohorts will be necessary to compensate for the large interpatient genetic variability, patient-derived 3D motor units and cerebral organoids will revolutionize research on the sporadic type of ALS. It is also important to note the worth of patient-derived iPSC models for the future of precision medicine. In addition, both iPSC-derived model systems and simple animal models could be used to study environmental factors. For instance, large-scale toxicity screens could elucidate much about the way that the environment influences the development of ALS.

In summary, the lack of successful translations from the lab to the clinic calls for a re-evaluation of classical model systems of ALS. Knock-in technology and increased implementation of simple animal models and iPSC-derived models can drastically reduce the number of rodent studies needed and improve bench-to-bedside translation. Further development and integration of age induction, vascularization and microfluidics, and co-culture techniques will allow ALS-on-a-chip technology to evolve into a valuable tool with unprecedented validity. Lastly, the rise of iPSC-derived models has opened a whole new avenue for the study of sALS disease mechanisms and therapeutic targets, environmental factor studies, and precision medicine. These advancements give hope that, despite the paucity of successes in the past, the future has many new discoveries to offer.

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CONFLICT OF INTEREST

The author has no conflict of interest to declare.

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‘Cognitive assessment in daily situations: potential niche of mixed reality’

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Cognitive rehabilitation starts, preferably, as early as possible following brain injury. Neuropsychological assessment (NPA) is the first component of cognitive rehabilitation, serving to estimate a patient’s cognitive strengths and weaknesses under optimal circumstances. NPA is administered in a low-stimulus, quiet room by the neuropsychologist, therefore not reflecting the dynamics of daily life with time pressures and distractions (Anderson & Catroppa, 2007; Javouhey et al., 2006; Verheul et al., in press). Additionally, individuals with milder consequences of brain damage often perform within normal range on NPA, despite experiencing cognitive complaints in daily life (Bielak et al., 2017; Chaytor & Schmitter-Edgecombe, 2003). To better explain or predict cognitive impairment following brain injury, there is urgent need for more sophisticated tests which measure subtle cognitive impairment and the complexities and dynamics of daily life (Parsey & Schmitter-Edgecombe, 2013; Spreij et al., 2020). In turn, this will provide enhanced cognitive rehabilitation.

The field of both psychology and rehabilitation will benefit from more dynamic ways of assessing cognitive functions. Virtual Reality (VR) is a computer-generated, 3D environment that allows the development of ecologically valid environments eliciting more natural behavior and cognition, without losing control over stimulus presentation (e.g., auditory and/or visual distractors) (Spreij et al., 2020; Verheul et al., 2016), and is promising in neuropsychological assessment and training (Spreij et al., 2020; Verheul Gosselt et al., in press). Due to continuous data acquisition, VR captures detailed performance measures (e.g., time and a specific number of distractors; Spreij et al., in revision). In contrast to conventional outcome measures (e.g., reaction time, total accuracy, total time), novel outcome measures provide greater insight into subtle cognitive impairment or underlying processes, such as fluctuating attention or cognitive effort, which may negatively influence performance (Milberg et al., 1986). Spreij et al. (2020) investigated a simulated driving method in patients with visuospatial neglect and found that the driving simulation proved to be more sensitive than conventional NPA. This was a first step in using non-immersive VR in a rehabilitation setting.

We are currently collaborating with De Hoogstraat Rehabilitation in a Knowledge Broker project to improve the treatment of visuospatial neglect. Knowledge Brokers are occupational and/or physical therapists who integrate clinical guidelines and current state-of-art research to improve healthcare. We will use innovative technologies, Augmented Reality (AR) and VR, in conjunction with a Serious Game. One of the VR-Serious games is HEMIRehAPP, developed by Hanne Huygelier, post-doc at KU-Leuven and Utrecht University. HEMIRehAPP is designed for patients

with visuospatial neglect to improve visual scanning. In addition to real-time feedback, an advantage of a Serious Game is that training can be tailored to a patient’s individual level of functioning using dynamic difficulty progression. Therefore, the patient is continuously challenged and motivated (Huygelier et al., 2020). Another technique is the Augmented Game Museum, developed by Judy Bakker, jr. researcher and occupational therapist at Omring. AR is a combination of a real-life environment that is infused with digital elements. Here, patients can move around in their living room and have to search for digital paintings. This AR-game is promising for use in rehabilitation with the focus on the independence of patients with visuospatial neglect (Bakker et al., 2020).

To conclude, mixed reality is predominantly used in research, however, demonstrates promise in supplementing conventional cognitive rehabilitation. Several types of software and hardware are employed to pinpoint feasibility, user experience, potential added value compared to conventional NPA, but also work on novel outcome measures to assess ‘new’ cognitive skills during more dynamic situations and further cognitive models.

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‘Neuroplastic effect of electroconvulsive therapy’

Next-generation of fast-acting antidepressants

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INTRODUCTION

Depression is a severe and disabling disorder affecting patients and their social network tremendously (de Graaf et al., 2012; Whiteford et al., 2013). Although various pharmacological and psychological treatment options exist, 50-60% of patients do not achieve an adequate response (Fava, 2003). Fast-acting antidepressants serve as a potent alternative for these individuals. Electroconvulsive therapy (ECT) is one of the most effective options and is used in various psychiatric and neurological disorders (van den Broek et al., 2010). During ECT, a convulsion, resembling an epileptic seizure, is induced by a current passing through the brain. Unfortunately, ECT is a stigmatized treatment and is known to frequently induce cognitive side effects (Nuninga et al., 2018; Payne & Prudic, 2009). Therefore, gaining new insights into ECT’s mode of action is a target of research to eventually promote clinical use. It has already been observed that ECT causes a volume increase of the brain (Ousdal et al., 2019) and specifically of the hippocampus (Oltedal et al., 2018). The next question is: what is the underlying biological mechanism of ECT’s antidepressant effects?

ECT’S MODE OF ACTION

Preclinical studies have shown that increased hippocampal volume following ECT may be caused by stimulated neurogenesis (Jonckheere et al., 2018; Malberg et al., 2000; Perera et al., 2007; Rotheneichner et al., 2014). This theory is further supported by observations of specific volume increase in the dentate gyrus (DG), a substructure of the hippocampus (Joshi et al., 2016; Nuninga et al., 2020a; Takamiya et al., 2018). Since functional neurogenesis occurs in the DG, this finding implicates that ECT may stimulate neurogenesis. Several studies have revealed that specifically DG volume positively correlated with clinical outcome (Cao et al., 2018; Nuninga et al., 2020a; Takamiya et al., 2019). In contrast, when looking at total hippocampal volume there are conflicting findings (Oltedal et al., 2018; Wilkinson et al., 2017). In addition, preclinical studies have also shown that ECS stimulates spine maturation, spine density and synapse number (Chen et al., 2009; Jonckheere et al., 2018; Zhao et al., 2012). Taken together, both neurogenesis and synaptic plasticity seem to be affected by ECT, resulting in enlargement of the hippocampus.

KETAMINE AS FAST-ACTING ANTIDEPRESSANT

In the last decades, the anesthetic drug ketamine has been discovered as a promising antidepressant (Aan Het Rot et al., 2012; Kishimoto et al., 2016; Schoevers et al., 2016). Ketamine is a high-affinity N-methyl-D-aspartate (NMDA) receptor antagonist, primarily targeting the excitatory neurotransmitter glutamate. A single dose of ketamine elicits a rapid and sustained decrease in depressive symptoms and even reduces suicidal ruminations (Berman et al., 2000; Dadiomov & Lee, 2019; Zarate Jr et al., 2006), generally with mild and limited side effects (Short et al., 2018). Ketamine has been associated with neuroplastic effects in the hippocampus, like stimulating synaptogenesis (Ardalan et al., 2017). Accordingly, ketamine and ECT could have a shared biological mechanism underlying their therapeutic effects.

CONCLUSION

ECT is a highly potent, fast-acting antidepressant but cognitive side effects occur frequently. State-of-the-art research points towards hippocampal neurogenesis and synaptic plasticity as ECT’s underlying mechanism. Reducing its side effects and developing predictor models of its treatment response will transform this therapy into precision psychiatry. In addition, ketamine may act on the same functional processes as ECT, indicating a possible shared biological mechanism. Future research could concentrate on the neural substrate of both therapies to develop new treatment options with the same antidepressant effects but without the undesirable side effects.

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'An automated real-time sleep-state prediction algorithm in preterm infants: the Sleep Well Baby Project'

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Anne Bik, Chanel Sam, and Eline de Groot are N&C students and a N&C alumna working at the research lab of Dr. Jeroen Dudink. Here, they helped with the development of a machine learning algorithm for prediction of sleep states in preterm infants. In their piece, they will give insight into this revolutionising technique and touch on some of the implications it could have for treatment at the neonatal intensive care unit.

BACKGROUND / RELEVANCE

Sleep is paramount in infants born preterm. It has proven to be a neuroprotective factor and a facilitator of healthy brain development (Ednick et al., 2009; Knoop et al., 2020). At the neonatal intensive care unit (NICU) however, infants are often exposed to environmental conditions that radically alter sleep-wake states, such as light, invasive procedures, noise, and caregiving activities (van den Hoogen et al., 2009). To improve sleep in preterm infants, it is important to adapt an elective treatment (e.g., nursing activities) to the sleep-wake rhythm of the infant. However, assessing sleep and wake states by real-time behavioural observations can be time-consuming, labour-intensive, and requires specialized training. Our aim was to develop a non-invasive automated method to classify neonatal sleep-wake states in real-time in infants born preterm. Therefore, we designed a novel and robust automated sleep-wake state prediction algorithm based on vital signs, called Sleep Well Baby (SWB).

TECHNIQUE

A traditional supervised machine-learning workflow was used. Labels consisted of three-hour behavioural observations in (n = 26) very preterm infants (born ≥ 28 weeks and < 34 weeks of gestation), during which sleep-wake states were annotated by trained researchers in one-minute epochs. Vital physiological parameters (heart rate, respiratory rate and oxygen saturation) were used as input for a random forest classifier in order to classify the sleep-wake states as active sleep, quiet sleep and wake. Model accuracy was estimated at 88,3% [87,3-89,4%] using stratified grouped cross-validation during the training procedure, which performance was validated in an independent cohort of 9 patients, where an accuracy of 87,0% [85,2-88,8%] was found. The area under the receiver operating characteristic curve (AUC ROC) value of wake vs the other sleep states was 80,2% [77,3-83,1%] and 76,8% [73,1-80,4%], for the training phase and validation cohort, respectively.

WHY IS IT REVOLUTIONIZING?

For the first time, a real-time sleep state classifier for preterm infants is developed with the aim to steer elective intensive care treatment. Comparing human interrater agreement and algorithm performance shows that the model approaches the performance of human observers. The real-time automated classifications by the algorithm, combined with the instruction of a neonatologist, can be used by the NICU nurses to time the moments of elective care and

reduce disturbance of the baby during active and quiet sleep.

WHY DO WE NEED THIS NEW TECHNIQUE?

Preterm infants can spend up to 90% of the time asleep during the period that is associated with rapid brain development. Especially active sleep, complying 40-60% of the total time preterm infants spend sleeping, seems to contribute to brain maturation (Curzi-Dascalova et al., 1988; Knoop et al., 2020; Peirano et al., 2003; Roffwarg et al., 1966). More specifically, active sleep is thought to steer synchronization between developing sensorimotor areas and for functional connectivity between these areas such as the cerebellar-cortical network (Blumberg et al., 2020). While active sleep is proposed to provide essential input for the development of brain circuitry, quiet sleep seems to play an essential role in consolidating these processes and preserving neural plasticity (Graven et al., 2008). It should be a primary focus of NICUs to facilitate brain development, and thus promote active sleep in infants born preterm. As active sleep is characterized by motor activity and rapid eye movements, it takes some training to recognize this behaviour as being different from wakeful behaviour. Sleep-wake state prediction by SWB may help nurses with classifying sleep states and steering elective treatment (i.e., not disrupting active sleep) accordingly.

FUTURE OF TREATMENT IN NICU

Scientific insights gained by the SWB project will directly radically change current NICU care as it will allow personalized treatment strategies, while simultaneously creating by-proxy biomarkers for future outcome and define stratification tools for future neuroprotection studies which will all lead to an improved outcome of the next generation of preterm infants.

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POLL #3

What would you like to see different in academia if you could pick one thing?

GREATER INTERDISCIPLINARITY MORE OPEN SCIENCE

LESS COMPETITION

IMPROVED COMMUNICATION TO THE MEDIA LESS PRESSURE

BETTER PAY AND HOURS MORE JOB SECURITY

RECENT NEUROSCIENTIFIC ADVANCEMENTS

This section will highlight several topics that did not receive much acknowledgement within neuroscience until recently. However, the 'future' (i.e. the time that we live in right now) has proven that these areas of research are, in fact, essential and promising! Therefore, we are honoured to introduce you to four researchers who will shortly explain to you what they research and what has inspired them to choose their field of research. They will thereby explain how they obtained a fellowship and how they experienced this process. We hope these stories inspire you in realizing your own (academical) future!

'On the implications and concretization of Baars' global workspace theory of consciousness'

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Cognitive and computational neuroscience converged on key aspects in their models of consciousness. Fuelled by the upsurge of network models and imaging techniques with high spatiotemporal resolution, computational models describing the functioning of the mind have started testing cognitive concepts like the Global Workspace and Dynamic Core hypothesis. However, the field of neuroscience is broad and computational models need to be up to date with advances in neuro- and electrophysiology as well as neuronal connectivity and architecture. Simultaneously, assumptions and simplifications of spatial and temporal dynamics necessarily made in computational models need to be based on our current understanding of the structure and functioning of the brain on the smallest relevant scales. In this review paper, I discuss key findings from the field of neuroscience and their implications for models of consciousness, in the light of the global workspace architecture as proposed by Baars.

Keywords: *Global Workspace Theory, Modelling, Working Memory, Small World Network, Criticality*

1. INTRODUCTION

Imagine you are living on a desolate island with minimal technology. One day, you find a container filled with fully operational Macintoshes and some generators. After a day or two, you have figured out how to turn on the machine. A couple of months of struggling later, you and your fellow islanders have figured out how to operate the computer. A decade later, the first islanders succeed in making applications of their own, using the already installed program called "Lisp". This marks the mastery of the computer - at the user-interface level, that is. Sometime after, one of the islanders utters the radical idea to take one of the Macintoshes apart. What you find there seems to be radically different from the user-interface that you and your peers have grown familiar with. "Surely," you say, "this can't be all there's to it! These are just some green sheets filled with small metal bits that are quite randomly organized."

This anecdote is a metaphor for the scientific study of consciousness, albeit a functionalistic one. In the modern functionalistic view, the brain is a very complex computer and the mind is the software that runs on it. This view circumvents difficult problems about the `nature' of consciousness, as we are all very familiar with the way two radically distinct features of a computer, the software and the hardware, are related to each other. However, many difficult questions remain, similar to those of the low-tech islanders who have to reverse-engineer the Macintosh.

After behaviourism and its anti-mentalism stance largely fell out of fashion around the 1970s, consciousness has regained interest as a scientific concept (Miller, 2003). In this same period, microcomputers and PCs became mass products for the first time, leading to a rise in popularity of the computer metaphor of the brain (Watrin, 2012). Combined, this led to a wealth of hypotheses on the workings and functions of conscious experience. The main motor of this `renaissance', as argued by Baars (1988), has been contrastive analysis, in which conscious (reportable) experience is experimentally compared to analogous unconscious (unreportable) experience.

Baars is well known for his global workspace theory (GWT) of consciousness. This theory combines many contemporary cognitive hypotheses about conscious experiences and tries to account for the wealth of evidence collected by cognitive psychologists such as William James. The development of GWT came at about the same time as the explosion in brain imaging techniques with high temporal or spatial resolution, which have since been used to test GWT (Baars & Franklin, 2007; Lundervold, 2010; Dehaene et al., 1998). The theory states that consciousness is a workspace in which a coalition of separate specialized and in themselves unconscious processors can cooperate to deal with (novel) perceptual input (internal or external) requiring an interdisciplinary and integrative approach (Baars, 1988). This theory aims to explain what makes unconscious brain activity different from its conscious counterpart and makes testable predictions on the capabilities and limitations of both.

Although there is gaining scientific consensus on the functional description of consciousness, it is still quite elusive what neural mechanisms exactly perform these functions. As of yet, GWT does not bridge that gap. Current efforts to reconcile the cognitive models of consciousness with contemporary brain and network science are diffuse. The most concrete model is Stanislas Dehaene's extension of GWT, Global Neuronal Workspace Theory (GNWT) (see Dehaene (2014) and more recently, Mashour et al. (2020)). The difficulty this model faces, just as any effort to make a network

model of the brain will do, is to find the right level of description. That is, it must be low enough (close to single neuron/synapse level) to give rise to bottom-up processes and the emergence of complex behaviour while simultaneously being high enough to function as a useful model. Namely, the virtue of a model is that it can leave a lot of details out: modelling every single cell and synapse in the brain is inconceivable. GNWT tries to model part of the brain on the level of neural masses (considering average activity) while incorporating some detail on the level of single neurons. It is, however, not yet clear if cross- or subcolumnar neural circuits or other functional domains should be incorporated for better results.

On top of this problem of spatial resolution, there is a problem of temporal resolution. The brain displays activity and plasticity on timescales ranging from tens of milliseconds (e.g., metabolic changes) to years or decades (e.g., long term episodic memory). A neuroscientific model of cognition needs to account for both the seeming stability and the lability (for example, in exogenous attentional shifts) of our conscious access. Just as with spatial resolution, temporal resolution is limited. A model that produces expectations of activity of (parts of) the brain cannot incorporate all changes of connectivity and synaptic strength down to the millisecond.

There are a couple of requirements for a model to simplify the system to be modelled. These requirements coincide largely with why it is necessary to simplify in the first place. Local redundancy calls for modelling simplifications if the system is in some way symmetrical, if meso- or macroscopic properties such as density suffice, if parts of the system respond in a predictable/idiosyncratic way, if the outcome of a model is only a global property (such as the centre of mass of an object) or if the scale of the system is way larger than its constituents (clouds made out of water molecules).

Going back to the metaphor of the mysterious Macintosh, we have to find and understand the organic equivalent of the segregate transistors of a computer and the logic gates, the smallest functional components of any PC. Also, we would have to figure out the equivalent of ASCII and Unicode, the universal languages spoken by any computer and its parts. However, as our brains are a design of nature and have a staggering regenerative capacity as well as an intractable list of parts (mainly complexly folded protein), we should not expect to find such orderly parts and languages as transistors and Unicode.

1.1 OUTLOOK

The goal of this review paper is to discuss different levels of description, differing in spatio-temporal detail, that models of consciousness can and should wish to attain.

The next chapter includes an up-to-date overview of the (dynamic) global workspace theory and global neuronal workspace theory. This will include a discussion of the theatre metaphor and the concept of ignition as initially discussed by Baars et al. (1988) and the current description of the GNWT. Chapter three discusses the potential candidates for the role of the basic functional unit of the parallel-interactive human cortex.

Chapter four is a discussion on the temporal resolution of conscious experience. Imaging techniques with high temporal resolution like EEG and ECoG as well as invasive paradigms used to study synaptic plasticity can now be used to test the temporal dynamics of conscious experience. A model of consciousness will have to give clear answers to some questions about the experience of time and on what time scale objects of conscious experiences are represented.

In chapter five, I discuss some critique on the global workspace theory and the cognitive approach as a whole. I will also discuss why these modelling attempts are promising in the first place, as many have questioned whether any scientific advancement regarding the problems of consciousness is possible in the first place.

1.2 TERMINOLOGY

As this domain of cognitive science is riddled with ambiguities and controversies, it is important to be precise in the use of terms and concepts. I will follow Baars and Dehaene in their `restriction' to the effort of explaining access consciousness (what consciousness does), leaving aside phenomenal consciousness (what it is like). The former is easier to examine experimentally, whereas the latter is notoriously elusive, predominantly because of the controversial use of the word qualia, the `purely qualitative and ineffable' aspect of consciousness (Chalmers, 2007). There is no consensus on the existence, status and role of qualia and the phenomenal/access dichotomy is in itself disputed (Dennett, 1993). This is why I mainly consider `access consciousness' which I will simply call `consciousness'.

Baars (1988) further uses the following distinction: conscious access (confusingly, a subset of access consciousness) is concerned with abstractions such as beliefs and knowledge. Conscious experience is concerned with perception, episodic memory and the thereto ascribed qualities by the senses. This also includes mental images, which can be of any modality. The main goal in theory building is to make increasingly more precise and testable predictions. This is a reasonable place to start. It is hard to assess the metaphysical status of conscious experience when its functional roles and parts have not been established yet.

2. CONSCIOUSNESS AS A GLOBAL WORKSPACE

In A cognitive theory of consciousness, Baars (1988) put forth the first elaborate theory on the global workspace (GW) architecture of consciousness. He placed the local-global interactions in the brain at the centre of conscious cognition and argues that the brain consists of many specialized "local processors". Yet, for many problems faced by a complex organism, an interdisciplinary approach is needed. For example, memory and hearing need to be integrated before a certain ambiguous visual stimulus is understood. Therefore, as Baars put it, there is a natural need for "global" broadcasting of information.

The basic feature of GWT is that it describes consciousness and working memory as a limited capacity, serial workspace that forms a platform for a coalition of specialized and unconscious processors to broadcast information to all other processors in an iterative (feedback-fuelled) way. Baars (1988) has pointed out that such an architecture can be found in many natural as well as man-made phenomena, leading to a wealth of possibilities for metaphors. Two of these capture the essence of the theory: the theatre metaphor and the boardroom metaphor.

The theatre metaphor compares consciousness with a stage (workspace) on which actors (specialized processors) can step into the spotlight of attention to perform (conscious experiences). The audience (the whole brain) that watches (processes) the stage is in the dark (unconscious). Behind the scenes, many other unconscious processes determine what comes on stage, where the spotlight should go and how the play is presented.

The boardroom metaphor compares the global workspace to a meeting hall with many specialists that can communicate to each other centrally via a blackboard. Only one coherent message of limited capacity can be broadcasted at a time and a message has to gain a critical popularity over other alternatives to get to the blackboard. During and after broadcasting, the message can be adopted, framed, resonated with and adapted to by the individual specialists (Baars, 2020).

These are just metaphors, but they do express two of the core features of GWT: The theatre metaphor emphasizes that conscious processes are shaped and orchestrated by unconscious processors (the actors before they come up and the playwright behind the scenes) and received by the also unconscious audience to respond and adapt to. The boardroom metaphor emphasizes the bottom-up nature of this process, with the experts competing for the global stage, the bottleneck of conscious processes.

Baars (1998, 2013) has summarized the essence of these metaphors in a non-exhaustive list of five necessary features for a conscious system:

1. A local-global architecture performing serial-parallel interactive processing.
2. An informative novel stream of signals that microprocessors can adapt and habituate to.
3. A single consistent stream of information at a time.
4. A minimal sensory involvement.
5. Access to an implicit self-system, composed of frames (coalitions of specialized processors that process specific information in an idiosyncratic manner).

Dehaene and Changeux (2011) have supplied the functional account of GW with a neuronal basis, resulting in the global neuronal workspace theory (GNWT). They and others have come up with extended evidence that the thalamocortical system is just the parallel-interactive system that can facilitate a global workspace (Baars, 2013; Dehaene & Marti, 2014; Groenewegen, 1991; Steriade, 2006). GNWT represents the GW as a clustered, modular neuronal network that allows for `any-to-many' signalling. The main difference between conscious and unconscious brain activity is that conscious activity passes a certain threshold after which it `ignites' and is sent out to many receivers, mediated by the global workspace (See Figure 1).

The status of the global workspace theory should not be conflated with the current status of the global neuronal workspace theory. The latter is of course much more recent and because of that also more controversial. The concept of a global workspace is expressed in many subsequent theories of consciousness, not only in GNWT but also Integrated World Modeling Theory or the Dynamic Core Hypothesis. GWT is built on a large and diverse set of evidence including data from psychophysics, psychology and linguistics, and has been tested rigorously in contrastive analysis studies. The advanced neuroimaging, on which GNWT is built and tested, is much more recent, and hence the theory is still less developed and widespread. An example in which the difference between GWT and GNWT comes to light is the topic of conceptual awareness.

Baars (1988) proposed that every conscious experience might need or happens to have some minimal sensory quality. We often use prototypes, such as the American flag, to think about an underlying concept, such as "democracy". Baars argues that there is a real distinction between conscious experience and conscious access to beliefs and concepts, but that the two might not really feel different because of this minimal interaction with sensory parts of the cortex. This is endorsed by research, contrary to Dehaene's and Changeux' hypothesis that we can be aware of a pure concept (Carruthers, 2015; Kemmerer, 2015). In the following chapter I will thus presume and analyse GWT as proposed by Baars, although I will use many ideas from GNWT as it is the most direct and developed neurophysiological extension of GWT.

If GWT is correct as a competence model of how the brain functions, its predictions about the architectures should align with a corresponding neuronal performance model of how the brain performs this function. As alluded to earlier, this raises two central questions:

(1) What are the individual actors or experts in the boardroom and how individual are they?

(2) What language do they speak, how do they understand each other and what is the unit of communication corresponding to words and gestures communicated by the actors and experts in the metaphors?

These questions will be central in the following chapter. It is important to mention that what is discussed here is

not the full extent of GWT. Baars(2020) has also included the difference between sleep, wake and comatose states, as well as an interpretation of internal goals as stacked coalitions ("frames") of microprocessors and the implicit self as a dominant goal frame. A discussion on these aspects is outside the scope of this paper.

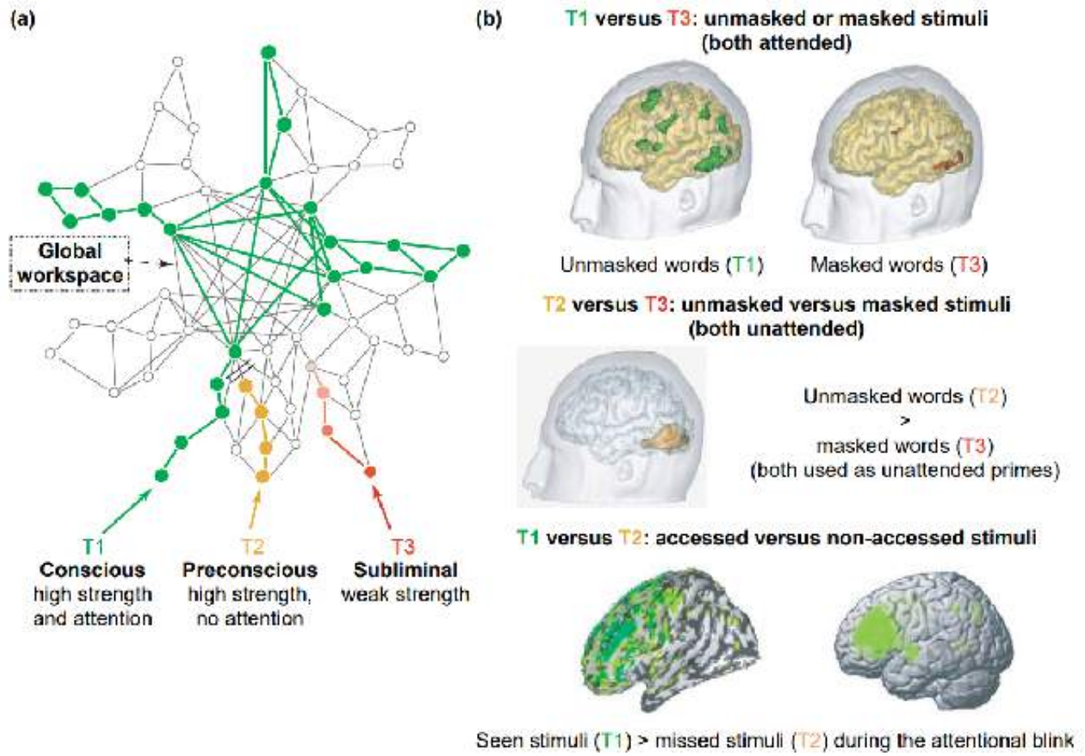

Figure 1. In Global Neuronal Workspace Theory (GNW), the global workspace is represented as a central hub in a clustered, modular graph (a). The difference between masked and unmasked stimuli is visualised, as measured using paradigms such as attentional blink and backwards masking on neutral words. According to GNWT, the difference between conscious experience and subliminal brain activity is that only the former is broadcasted brain-wide through the global workspace, which shows a clear difference in localization between masked and unmasked stimuli (b). Figure reprinted from Dehaene, S., Changeux, J.-P., Naccache, L., Sackur, J.,& Sergent, C. (2006). Conscious, preconscious, and subliminal processing: A testable taxonomy. Trends in cognitive sciences,10(5), 204–211.

3. THALAMOCORTICAL SYSTEM AS MODULAR, PARALLEL INTERACTIVE MACHINE

Baars (2020) took over the view from GNWT that the only system in the brain that has the massively parallel interactive architecture that can give rise to a global workspace is the thalamocortical system. In what he calls "dynamic Global Workspace Theory" (dGWT), he gives an account of the dynamics of the global workspace that combines his initial hypotheses on the working of GWT with Dynamic Core Hypothesis (Edelman & Tononi, 2000) and GNWT.

dGWT takes the thalamus and cortex (including paleocortex and neocortex) as one single functional system. The thalamus has been shown to not only serve as a relay station, but also to have a broadcasting function as it projects bidirectionally to all parts of the cortex, allowing for widespread cortico-cortico communication (Deschenes et al., 1998). Any specialized part of the cortex can send information to the thalamus, which in turn broadcasts it to a large part of the cortex ("any-to-many broadcasting"). If this broadcasting is stable over a long enough period of time, it is consciously accessed. Empirical data suggests an approximate 100-200 ms cycle time (Baars, 2013; Freeman, 2003; Wu et al., 2009). Through contrastive analysis and EEG, it has been shown that indeed, the main difference between a consciously attended stimulus and an unconscious one is global broadcasting (Nakatani, 2005; Sergent, 2005). However, this is not sufficient to show that the cortex works exactly as predicted by Baars. In order to accord with GWT, a significant level of functional segregation and specialization should be observed. In particular, dGWT predicts the global workspace to be an anatomically distributed, functional hub (Baars, 2020). In order to come to a concrete model, much more detail should be provided on how the cortex can be subdivided and what neurons do and do not constitute this functional hub, even when distributed.

Functional mapping and subdivision of the brain has been a central challenge in neuroscience. The main trend of decades of research seems to be that although the cortex can be roughly divided into specialized, tightly interconnected regions, this division is blurry, variable between subjects and highly plastic within subjects. This seems to put a limit on how strongly specialized the cortical sub-processors can be. There have been many attempts to define the elementary functional unit of the cortex, though. These roughly fall apart in four categories: mesoscopic domains such as macro and hypercolumns (1), connectivity hubs in the small world network of the cortex (2), more dynamic territories such as resonance units (3), the microscopic areas where the bulk of processing takes place being the synapse, astrocytic gap junctions, the axon and its onset (4).

3.1 The cortex as sheet of vertical columns

With the discovery of the columnar organization of the cortex by Mountcastle roughly 65 years ago (Mountcastle, 1955), huge simplification of the description of cortical structure seemed possible. It was shown that radially grouped neurons respond to visual input in roughly the same, selective way. However, as argued by Horton and Adams (2005), the clear anatomical structure of the cortex does not seem to correspond with a clearly functional one. Although neurons that fire while observing lines of slightly varying orientation are close to each other and the whole 180◦ orientation map is well confined, this confinement does not strictly coincide with the columnar organization in the visual cortex. The visual cortex, although most widely studied because it is easy to manipulate in a reproducible way in experiment, might not be representative. Visual perception is so complex that the unconscious processing of visual information needs to occur seamlessly on a larger scale than that of cortical columns. Rather than columns, larger areas such as the primary visual cortex (V1) feature more prominently in modern functional descriptions of vision, though the information itself might be encoded on the lower level, closer to the cortical columns (Cichy et al., 2015).

As Horton and Adams (2005) argue, the idea that cortical columns are the crucial units of organization is falsified by evidence from comparative neuroscience. Throughout the mammalian kingdom, some pairs of closely related species can have very different degrees of columnar organization in the visual cortex but show little to no difference in perception. Even within some Mustelidae species, there is a large variety in the degree of columnar organization that cannot be predicted from phenotype or behaviour. Understanding cortical columns has definitely helped research on the functional organization of the brain. However, they are no convincing candidates for the basic units of organization of a global workspace and it remains unclear whether they are more than a common neurodevelopmental by-product (Da Costa et al., 2010; Haueis, 2016).

3.2 The cortex as a directional weighted graph

Recently, a lot of attention has gone to the effort of mapping the (human) connectome. Much like mapping the location and variety of all human genes (the Genome Project) has helped a lot in the progress of genetics as a field, the Human Connectome Project or similar efforts ought to do the same for neuroscience. A variety of methods are deployed to map the roughly 50 billion axonal tracts in the cortex or the millions of bundles. A popular, non-invasive technique is diffusion tensor imaging, in which the shape and size of fluid tracts in the white matter is measured. Complementary, anterograde tracing methods can be used to do more fine-grained tracing of weaker connections and in areas where axonal tracts cross each other. The combination and improvement of these and other imaging techniques has led to a wealth of data on the connectivity of the brain (Van Essen et al., 2013)

The fruits of a detailed connectome are not yet fully clear. Knowing exactly how the roughly 50 billion axons in the cortex are wired up does not directly tell us how it functions or why it is wired up this way, let alone which aspects are important for cognition and behaviour. This data can, however, help demarcate areas that function as one unit upon further functional imaging.

One growing scientific discipline in particular serves as a candidate for untangling the connectome: network science. Data from the connectome can be used to produce graph models of the brain, a method commonly used in GNW theory. A graph consists of nodes, the units of a graph, connected to one another through edges. The edges of a graph have two properties: directionality and weight. Graphs come in many shapes and sizes, from random graphs to organized lattices.

An interesting result from neural network science is that the cortex is at least to some degree wired up like a small world network (Bassett, 2017; Yu et al., 2008). This type of graph is characterized by collections of tightly clustered

nodes that are wired up through weak connections to other collections of tightly clustered nodes over a long distance. This result matches up nicely with the global workspace view of the cortex, which predicts a specialized, interacting network of unconscious processors. Furthermore, the neuroscientific measure of small worldness and modularity grants us with a mathematical, objective yet gradual way of deciding which neurons form a group or a unit.
Small world networks have three relevant properties (Wang, 2003):
1. Robustness: The small world architecture is a very robust configuration, meaning that it is able to resist the deletion of many edges without disconnecting parts of the graph or changing other global properties.
2. Information propagation: Because of short mean path lengths between nodes, information can spread efficiently, an important requirement for a global workspace. It also supports the brain's ability to integrate new information effectively in longer term, memorized information.
3. Wave synchronization: Oscillatory behaviour spreads efficiently through dynamic small world graphs and can also be quickly overridden by a new dominant oscillatory pattern.
One problem for the network description of the brain is that it is dependent on both the resolution of the data and the definition of the basic units. However, the concept of scale independence and self-similarity discussed in the next chapter could provide a general solution. Furthermore, the concept of modularity and the importance of weak, long distance connections seems to be of significance to achieve developments in neuroscience. There seems to be a correspondence between the global workspace neurons in GNWT and the long distance, weak ties in network science.

3.3 The cortex as dynamic architecture of resonance units

The bidirectional cortico-cortico and cortico-thalamic connections mentioned in the previous section are not only functionally important for feedback and recursion of information; they also give rise to the large variety and complexity of activity patterns observed in the cortex. The thalamocortical system displays many types of complex wave patterns such as bursting, resonance, phase-locking and cross frequency correlations (Timofeev et al.,2005; Kandel and Buzsáki, 1997). Brainwaves can be divided according to their frequency into alpha, beta, gamma, delta and theta waves. In imaging techniques with a high temporal resolution, such as EEG, MEG and electrocorticography (ECoG), the activity of a certain area of the waking brain is measured in the power of beta and gamma waves. Especially interesting is the interaction between waves of different frequencies in both strength and phase (synchrony). By analysing the oscillatory behaviour of different parts of the cortex, it is possible to identify parts of the cortex that fire synchronously. This is another way of defining which neurons form a unit (Grossberg, 2013).
Using the dynamic-systems approach to demarcate elementary units and measuring global activity in the cortex has the benefit that it is directly connected to the active cortex, which is not the case for the static picture of the connectome. For example, the difference between brain activity during a waking, deep sleep or REM sleep state shed light on the different operating modes of groups of neurons (Massimini, 2005; Steriade, 2006). However, correlation between phases of two neurons or neural circuits does not necessarily imply correspondence of function. Llinás (2003) proposed that the thalamocortical loop, made up of bidirectional projections between cortex and thalamus, is the basic neuronal, functional unit of organization in the cortex. This view is tempting as electrophysiologists try to find elegant ways to describe complex wiring circuits containing multiple neurons. However, this description makes it difficult to explain the fact that one collection of neurons can fulfil multiple functions and their functioning can be highly plastic (Katz, 2001).
Much is still to be known about the complex and long-range oscillatory behaviour in the brain, and the combination of network science and electrophysiology could come a long way in understanding the significance of phase-locking and correlation of waves for important aspects of conscious experience such as temporal binding, wakefulness and coherence.

3.4 The cortex as a network of neurons

So far I have shown methods through which the brain can be divided into functional subunits. They are all imperfect, however. Representing a neuron as a node in a network or an integrated part of a circuit or column does not do justice to its complexity and autonomy.
There are good reasons not to abandon the neuron doctrine, which places the individual neuron at the centre of the architecture of the brain. It is important to realize how complex and varying these cells are, owing to the billions of years of evolution during which there were only single cells. The postsynaptic density alone consists of more than a thousand different types of proteins. Most importantly, a neuron still resembles its single cellular ancestor in many ways, having many aspects of a living organism. As argued by Deacon (2011), this is essential in understanding the brain and its workings such as its plasticity and connectivity.
A neuroscientific model of the global workspace will likely have to incorporate a mixture of the ways to subdivide the brain described above. In summary, a GW description of the cortex could use the notion of a small world network while doing justice to the complexity of individual cells and synapses and simultaneously taking into account the columnar organization of the cortex, in which neurons with similar functions are often spatially close. This view could be used to describe the oscillatory behaviour and

phase interaction between weakly connected regions.

4. THE TEMPORAL DYNAMICS OF CONSCIOUSNESS

Understanding on what time scale brain activity should be analysed and modelled is closely related to the question of what "trade language" is spoken in the brain. As a metaphor, imagine you are an alien anthropologist studying human linguistic communication. You have no background knowledge and all you manage to obtain is years and years of high-quality audio recordings. Making sense of all the complex wave patterns observed in the data requires you to find the smallest timescale on which information is encoded. In this case, you would not come much further than generalities about loudness of voices and some heuristics about intonation unless you understood the basics of phonemes, the units of linguistic communication that last between 100 and 500ms. In our case, we would have to find the neuronal analogy to phonetics to really make sense of the observed complex wave-phenomena found in EEG and ECoG recordings.
Many believe breakthroughs in understanding how the brain encodes and communicates information are imminent or at least realisable and much progress has indeed been made (Churchland, 2012; Rols and Treves, 2011). Hope for a full account seems justified for the brain activity that represents information, although much of our brain activity is homeostatic (internal balancing) or allostatic (balancing specifically in relation to dynamic environments) and is better compared to human humming, or screaming, in our analogy.
This being said, there are still many observations from psychophysics as well as neuroscience and even complex systems studies that are closely related to the question of the temporal dynamics and resolution of the brain. I will discuss these in the following paragraphs.

4.1 Consciousness and Simultaneity

Large physical systems can be described momentarily. That is, a description can be given that sufficiently captures the state of the system at exactly time t. This counts for the solar system, the atmosphere or a moving bridge. Time is not a real issue when modelling these systems. When modelling, time often has to be discretized merely for limiting computational capacity because exact solutions are not possible. The higher the computational power, the smaller this discretization can be. How does this work in a model of the mind?
Writing down the state of the brain and solving differential equations to predict its evolution is computationally impossible. But would it make sense in the first place? It is sensible to regard consciousness as a process, one of integrating information (Massimini & Tononi, 2018). It is not really possible to capture a process in a time frame. Just as with a computer performing arithmetic for a piece of software, there is a clear beginning and an end, but what is in between? Surely, a description can be given of the state of all the transistors of the calculator at a time t, but at that exact moment, does the calculation exist?
When trying to model or simulate (parts of) conscious experience, several questions have to be accounted for around time. For example, is there a minimal time a global message has to last to become conscious? When, if at all, are conscious experiences simultaneous? When can they no longer be distinguished from simultaneous? On what timescale does the global workspace evolve? Several lines of research suggest that conscious events must last for a minimum of about 100 ms (Michel and Koenig, 2018). For example, this is the time window in which stimuli can be effectively masked. The information of the masked stimuli is still locally processed to some extent but does not reach consciousness (Baars and Franklin, 2013; Ortinski and Meador, 2004).
Closely related, Dennett (1993) describes that on a time scale of tenths of seconds, it is not really possible to say that a conscious event was simultaneous to a certain stimulus. Psychophysical evidence shows that we cannot observe a difference between two rapidly blinking and one rapidly moving square (Muckli et al., 2002). Dennett used this example as an argument for his multiple drafts model of consciousness, or pandemonium. Dennett's model is more horizontal where GWT accounts for both bottom-up and top-down hierarchical organization. Still, his arguments are in line with the GW account that also does not assume specific conscious events to take place at a specific time, like in a movie-theatre.
All the above can be seen as support for a cognitive GW approach. The minimal duration of conscious processes lines up well with the concept of ignition in GNWT. Figure 1 shows that conscious content first needs to gain some critical support, before it is broadcasted globally. However, the ambiguity of simultaneity is also troubling for the outlook of a computational GW model of consciousness. As it is not possible to pinpoint certain conscious events down to an exact point in time on the higher level and it is still unknown how exactly the brain represents, encodes and processes information on the lower level, computational models of consciousness remain heuristic and inexact. There are reasons to be optimistic that the problem of neural encoding of information might be resolved to some extent as more and more is becoming clear about the complex dynamics of the synapse.

4.2 Complex dynamics and synaptic plasticity

Local activity in the brain can vary in many ways. Individual neurons can fire at rates from 0.1 Hz to 100 Hz, approximately. Their rates of activity can themselves also vary on an independent timescale, for example while synchronizing with other brain regions or while resonating with a projected cortical area. The specific behaviour of a neural circuit can also change over time, in either short term, long term or homeostatic plasticity. These types of

plasticity, governed by both neuron and glial cells, alter the way synapses respond to the presynaptic potential (Magee & Grienberger, 2020). This is ultimately where the processing of information takes place. However, the processing of a single neuron is much more complex than a simple logic gate (Goldental et al., 2014).
In the previous chapter, we have already discussed the concept of functional resonance units in the thalamocortical system. Llinas (2003) proposed the ability to specifically tune the firing rate among themselves and others gave thalamocortical loops an important function in temporal binding. The problem of temporal binding needs to be solved in a dynamic global workspace model too. Dehaene (2011) proposed that as we are conscious of only one thing at a time, there must be strong inhibition to all other information. Event related potentials (ERP), the underlying signal that can be obtained by averaging the EEG signal of multiple electrodes over multiple cycles of the same task, show that the activity of large amounts of neurons is correlated during a task. Resonance and phase locking underlie these large-scale correlations and form the basis on which a neuronal GW model should build its temporal dynamics. (Cohen et al., 2008).

4.3 Cortical Criticality

The field of complex systems dynamics is driven by a search for universal properties and characteristics displayed by a wide variety of systems. As it is concerned with complex systems, gross simplifications or symmetries have to be found in order to model these systems and reduce them to some overseeable collection of basic rules. Secondly, finding universal behaviour opens the possibility of employing advanced methods from one field on a problem from another, seemingly unrelated one. One such universality of particular interest here is the concept of criticality.
Criticality is a phenomenon where the stable or meta-stable state of the system lies exactly between a disordered and an ordered one. During criticality, spatial and temporal fluctuations tend to be scale-free. This means that the characteristics of the fluctuations, such as bursts of brain activity, look the same on a wide range of scales. These fluctuations follow a power law distribution. So, if we plot the temporal or spatial size of all fluctuations against their occurrence rate on double-log paper, we get a negative sloped straight line (Cocchi et al., 2017).
Both EEG/ECoG and fMRI studies have shown signs of temporally and spatially critical brain activity, respectively, especially during restful states. In fact, many systems in nature display criticality by default, and it has some advantages that make it plausible that natural selection has driven complex central nervous systems to behave this way. Firstly, information storage and dynamic range (the amount of states that could be represented with the same parameters) are maximized. Most relevant to GWT, however, correlation persists throughout all length scales in the brain during a critical period. This makes it a useful property for global access and temporal binding, two main functions of the GW hypothesized by Baars (1988).
Although Baars endorses the prospects of criticality in modelling the global workspace (Baars, 2020), the concept seems to be slightly at odds with models within GNWT (Dehaene, 2014). In these models, there are global workspace neurons that perform the integration and broadcasting of local input, although this set varies per task. From the viewpoint of criticality, there are no such governing units. Global coherence happens merely as a product of local interactions, fluctuations and external parameters. A central broadcasting centre through which information is relayed is simply absent. Which view of the global workspace will come out on top, or whether none or both of these viewpoints holds the truth, will depend on the future success of the corresponding models.

5. THE GLOBAL WORKSPACE AND ITS LIMITATIONS

5.1 Cortex-centrism

A common criticism is that current cognitive models like GWT focus too much on the cortex (Merker, 2007). From an embodiment perspective, one might criticize these theories for reducing consciousness to the brain alone, leaving out its relation to the body and the body's relation to the environment. Or, if consciousness is indeed a property of the brain alone, a theory of consciousness should include other parts of the brain than the cortex. I will discuss both these criticisms shortly.
Whether the global workspace resides only in parts of the cortex, the whole cortex or throughout the brain is still an unanswered question. Although the functional description is arguably more important, some (time-dependent) localization seems to be necessary in a full neuroscientific account of the global workspace. From the perspective of evolutionary development, it can be argued that the beneficial integrative features of a local-global architecture are expected to predate the cortex. In fact, a recent fMRI study by Deco et al. (2021) suggests a GW role for the precuneus and cingulate gyrus (cortical) as well as subcortical areas like the amygdala, hippocampus and nucleus accumbens. This conclusion was drawn after analysis of fMRI data of large groups of subjects performing a wide variety of tasks (see Figure 2). The subcortical areas composing this `functional rich club', especially the basolateral amygdala, are heavily connected with the cortex, so these results do not contradict that the bulk of the conscious processing of the global workspace takes place in the cortex. Although some stronger claims by GNW seemed to predict that GW neurons were only cortical, the results of the fMRI study seem to align with broader functional predictions (Dehaene et al., 1998). The GW serves an integrative and broadcasting function for past, present and evaluative

input, which requires a collaboration of the whole brain. Any theory that puts cortical columns or thalamocortical loops at the centre of a neuroscientific theory of the global workspace should therefore also look for analogies found in the subcortical areas. Most importantly, the basic framework of Baars' Global Workspace is agnostic about the contents of consciousness and the location of the functional hub in the brain. It also accounts for both bottom-up as well as top-down control over the global workspace. Therefore, it is not at odds with affective models of consciousness that put more subcortically, bottom-up, affective content of consciousness at the centre.

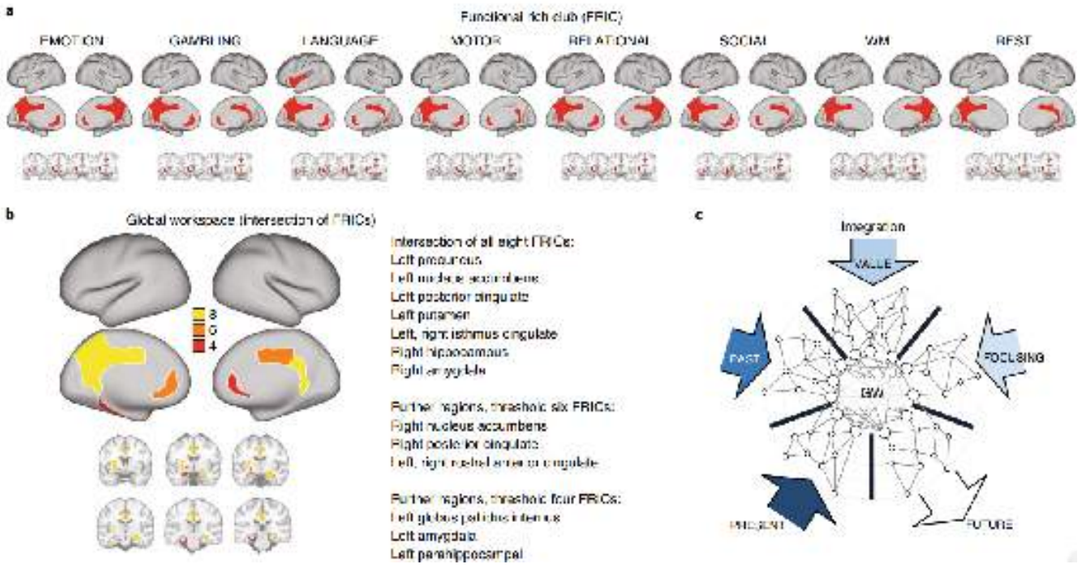

Figure 2. The "Functional Rich Club". This collection of brain areas performs an integrative function over large areas of the brain. By measuring connectivity and bidirectional information flow using their newly defined normalized directed transfer entropy in a variety of tasks (a), they were able to identify the most important areas of intersection between different fMRI measurements (b). According to the authors, their findings lined up well with the GNW description of Dehaene's and Changeux' description of the Global Neuronal Workspace (c). Figure reprinted from Deco, G., Vidaurre, D., & Kringelbach, M. L. (2021). Revisiting the global workspace orchestrating the hierarchical organization of the human brain. Nature Human Behaviour, 1–15.)

5.2 The unfinished theatre?

Although I have been largely unconcerned with questions of phenomenology and ontology in this paper, it is worth elaborating why cognitive and functional network models are so useful. Some people have objected that these models leave out the most important part: the raw sensations, or "qualia" (Deacon, 2011). I want to argue that this criticism is misleading. Dennett (1993) has already gone through great lengths to argue why qualia, as existing separate from the act of perception, cannot serve any function. A reproduction and discussion of these arguments would be superfluous here. I agree with Dennett's view on the uselessness of the common notion of non-physical, ineffable, private qualia as a scientific concept. A true naturalistic and non-dual understanding of experience does not leave room for qualitative experience on top of (self-) perception and thought. Additionally, many claims about the ineffable and non-physical properties of qualia are inconsistent (Dennett, 1988; Kirk, 2008). The point I want to make here is slightly different, however, and underlines why functional models are so useful.
It is all in the question asked. The problem starts when asking what the "fundamental nature" of consciousness is. People often find the complete absence of a plausible and satisfying answer to this question to be informative and give it names such as "the hard problem" (Chalmers, 2007). In fact, this absence is not informative about consciousness at all. One can ask about the fundamental nature of anything and, prying for long enough, notice that there is really nothing substantial to find.

Allow me to explain. One might ask: “What is the fundamental nature of water?”. A slightly naïve, phenomenological answer might be: it is part wetness, part fluidity, part transparency. However, some chemical background teaches us that these properties are illusions, phenomena emerging from a more fundamental layer: that of molecules and their chemical properties. These chemical properties, we might come to discover, are still not quite fundamental. The polarity of water molecules, which we could come to experience directly if we are equipped with a statically charged balloon and a running tap, are mere emergent phenomena from their atomic composition. Ultimately, we are left with subatomic particles such as electrons, far away from our illusory level of wetness. What is left? An electron, we will find, has no notable size, a relativistic mass and not even a well determined state. The only thing that is left, is a coherent enough to be characteristic set of answers to questions (of spin direction, absolute spin, charge, etc.) that can be asked to the electron.
So, when asking about the fundamental nature of a glass of water, we are left somewhat empty handed. This does not, normally, lead someone to conclude that there must be more to water than mere subatomic particles that can explain the quality of wetness or the substantial appearance. It should not at all be surprising or even upsetting, then, that when we ask about the fundamental nature of our own mind, we don’t get a satisfying answer either. We can only ask questions about reality and its objects, including our own minds. If a model is able to give, predict and connect these answers, it truly serves its purpose as a model. There is, quite literally, nothing more to ask for.

6. CONCLUSIONS

1. The strength of cognitive theories comes from their ability to make testable claims on conscious processes based on contrastive analysis

The appeal of cognitive theories of consciousness is that they stay close to the functions of consciousness without being bothered by questions of ontology on the one side and neurophysiology on the other side. Starting from functional differences that differentiate conscious from unconscious processes, such as wide dynamic range and integration of multimodal and cross-temporal input, these theories aim at explaining expansive collections of psychological data. However, the time has come for cognitive theories to produce hard neuroscientific hypotheses that stand the scrutiny of high quality imaging techniques.

2. Global Workspace Theory remains influential thanks to its local-global description

Global Workspace Theory has withstood the test of time very well. Currently, its influence can be seen in many modern theories and hypotheses of consciousness, most directly in Global Neuronal Workspace Theory. Although the idea that local-global interactions underlie the differences between conscious and unconscious cognitive processes is well established now, many questions about the materialization of a global workspace reside. The idea of specialized, unconscious microprocessors as basic functional units is one of the strengths at the core of GWT, but they might not be so easy to define neuroscientifically.

3. There are many candidates for basic functional units of the Global Workspace, but none of them can justifiably be called the “fundamental operating level”, largely owing to the complexity and autonomy of individual cells

Cortical (micro)columns seem to be a good candidate at first because of their clear anatomical segregation as well as the specificity to input displayed by some microcolumns, such as slope-specific microcolumns in the visual cortex. However, cross-columnar connections, gradual columnar boundaries and evidence from comparative neuroscience cast doubt upon the role of cortical columns as segregated functional units. Other candidates for this role are the clusters and hubs in a small world neuronal network and the corticothalamic loop, which come from network science and electrophysiology respectively. However, the autonomy and complexity of single neurons and glial cells should not be underestimated. The complex rules of cellular and synaptic plasticity and homeostasis might be so fundamental that they leave little room for simplification on a higher level.
Still, one might hope results from connectome analysis, a deeper understanding of electrophysiology and localization of function in the cortex can lead to at least some simplifications on the spatial scale. To this end, the Global Neuronal Workspace account serves as a useful guiding framework to look for the ways groups of neurons fulfil specific functions. These functions include integration of past, present and evaluative input.

4. Conscious events depend on complex dynamics that crosses multiple time scales, but the GW does seem to have a minimal cycle time required for binding and broadcasting

Considering temporal resolution of a neuroscientific GW model, two questions need to be addressed: how is information encoded by diverse neurons and specialized microprocessors and how is it shared? Much is still unknown about this topic, but firing behaviour and synaptic plasticity receive increasing attention and a breakthrough might at once make sense of the complex dynamics of brain activity such as spike timing, resonance, phase locking and cross frequency correlations. Some empirical observations are well established though, especially from cognitive psychology and psychophysics. For example, an input seemingly has to last for some minimum duration (~100 ms) to consciously arise, which might be the time needed to broadcast (“ignite”) information globally and suppress unrelated activity. These observations continue to steer the full, detailed account of the dynamics of the global workspace.

5. Complex systems studies might be the key to understand the underlying principles of organization and dynamics

An interesting and promising take on the matter comes from the field of complex systems studies. The concept of criticality aligns well with the principles and functions of the global workspace and can help understand how it functions efficiently on multiple length- and time scales. This field is concerned with finding basic descriptions and characterizations of large, complex systems. For instance, understanding the properties of small world networks can shed light on the complex anatomy of the thalamocortical system. An advanced interdisciplinary approach of neuroscience and complex systems studies might help to produce a solid mathematical application of the global workspace theory.

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CONFLICT OF INTEREST

The author has no conflict of interest to declare.

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‘Up-and-coming neuroscientific developments: Four UU-researchers about their aspirations’

In these interviews, four researchers and employees of Utrecht University will enlighten you with their personal stories on what has inspired them to choose their path of research. Prof. Dr. Dennis Schutter works at the department of experimental psychology and will tell you more about affective cerebellar research, and the promising features it beholds. Dr. Jaco Zwanenburg will thereby share some information regarding his work on development of new MRI methods which help to measure the interaction between the brain and the vascular system. Prof. Dr. Maarten Kole, as head of the department of Axonal Signalling, further tells you more about his dedication to address fundamental questions regarding axonal functioning and how this is affected in multiple sclerosis. And last but not least, Dr. Vanessa Donega, who is located at the department of translational neuroscience, discusses her motivation to further unravel the questions within the field of brain regeneration.

Photo from www.tijdschriftdepsycholoog.nl

‘Affective cerebellar research’

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COULD YOU PROVIDE US WITH A SHORT INTRODUCTION ON YOUR FIELD OF RESEARCH?

The mainstream sciences concerned with the neurobiological and functional foundations of emotion and motivation mainly work with cortico-limbic-centred theories and models. Breaking with the longstanding dogma of the cerebellum being exclusively involved in motor-related functions, there is increasing empirical evidence that the little brain is directly involved in affective and cognitive processes. Affective cerebellar neuroscience is a rapidly growing field of multidisciplinary research aimed at establishing the cerebellar correlates and mechanisms associated with normal and abnormal processes underlying motivation and emotion. My own research currently focuses on the cerebellar pathways of anger and aggression in healthy and clinical populations.

WHAT HAS INSPIRED YOU TO DIG DEEPER INTO THIS FIELD OF RESEARCH?

I developed a keen interest in philosophy and psychology during senior high school and went to Utrecht University to study psychology. I majored in theoretical psychology, but my interests shifted to experimental research. During my internship, I worked in a group of brilliant and enthusiastic scientists and was introduced to non-invasive brain stimulation and, at the time, a new emerging field called affective neuroscience. This internship was decisive for me in terms of wanting to further develop myself as a researcher. I started my academic career working on the role of the prefrontal cortex in the regulation of motivational tendencies and emotions in healthy and clinical populations. Through extensive reading of the neuroscientific and psychological literature, several lines of evidence pointed towards the involvement of the cerebellum in emotion and motivation. Due to the cortico-limbic centricity in conjunction with the dominant cognitive view of understanding human behaviour, not many scientists considered

the cerebellum a particularly important region of the emotion-dedicated neural circuitry. This is what sparked my interest to explore the role of the human cerebellum in emotion and emotional disorders.

WHAT WOULD YOU SAY IS THE MOST RECENT ADVANCEMENT IN YOUR FIELD OF RESEARCH AND DOES THIS CONTRADICT PREVIOUSLY ADOPTED SUGGESTIONS?

The most recent advancement in the field of cerebellar neuroscience is about two major points: (1) The widely held view by scientists and clinicians that the cerebellum is a brain structure primarily involved in balance, posture and motor coordination is outdated; (2) The cortico-limbic theories of emotion and emotional disorders are incomplete. In addition to conceptual, evolutionary and anatomic reasons (Schutter, 2020), a wealth of empirical data shows cerebellar co-activation during the experience and regulation of emotions.

> Yet, cerebellar coactivation is often simply ignored or its significance is downplayed by researchers. The good news is that this view is gradually changing.

HOW DID YOU EXPERIENCE THE PROCESS OF APPLYING FOR A SCIENTIFIC FELLOWSHIP/GRANT?

Applying for fellowships and grants for your ideas comes naturally when you as a researcher aspires to develop your unique line of research. It is not something you need to do, rather it is something you want to do. The part of the process I personally enjoy most is the scientific writing itself. However, applying for grants is highly competitive, time-consuming and can be very stressful. Furthermore, the process of applying requires a strong ability to deal with disappointments, because most of the grant applications will ultimately get rejected. So to make a long story short, my personal experience can be summarized by the following keywords: competitive, rejections (many!!), perseverance and success. And lastly, having a little luck!

WHAT DO YOU THINK THE FUTURE BEHOLDS FOR YOUR FIELD OF RESEARCH AND WHAT WOULD BE THE NEXT STEP TO REALIZE THIS?

The growing appreciation of the cerebellum in social cognitive and affective neuroscience will not only broaden our knowledge about the cerebellum in non-motor related functions but will contribute to the future development of novel treatment options, such as non-invasive brain stimulation techniques, in neurology and neuropsychiatry. Currently, transcranial magnetic stimulation (TMS) over the prefrontal cortex is medically approved for the treatment of major depressive disorders in many countries, including the Netherlands. However, several lines of research also point to antidepressant effects of cerebellar TMS, although this hypothesis still needs to be tested in a randomized controlled trial (RCT). Furthermore, transcranial direct current stimulation (tDCS), which is a technique that administers weak electric currents to polarize underlying nerve tissue, is increasingly used to modulate cerebellar activity. In collaboration with the Radboud UMC we are currently running an RCT in which we apply cerebellar tDCS to improve cognitive and affective functions in patients with spinocerebellar ataxia. The formation of more national and international collaborations and consortia of cerebellum researchers from various disciplines including neuroscientists, neurologists, psychologists, psychiatrists, physicists and engineers is the next step towards understanding the workings of the cerebellum and developing clinical applications for cerebellar neuromodulation. And this is exactly what's currently starting to happen.

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'Measuring how the heart beats the brain'

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Department of Radiology, University Medical Center Utrecht, Utrecht, The Netherlands

COULD YOU PROVIDE US WITH A SHORT INTRODUCTION TO YOUR FIELD OF RESEARCH?

As an MR physicist, I aim to create dedicated MRI techniques that break new grounds for assessing disease in humans. I've mostly worked on MRI methods for assessing vascular function in the brain, and currently, I focus on new MRI methods for measuring the interaction between pulsatile blood flow, brain tissue motion, and cerebral spinal fluid flow.

Blood flow to the brain has been studied extensively with a focus on blood flow as a means to supply the brain with oxygen and nutrients. What has received much less attention over time, is how the pulsatile nature of blood flow induces subtle brain tissue deformation, and subsequent flow in the interstitial fluid, and in the cerebrospinal fluid that surrounds the brain. However, it seems unlikely that nature puts energy into maintaining this pulsatile motion if it has no physiological relevance.

One hypothesis in the field is that the pulsatile brain deformation causes mixing and stirring of the interstitial fluid, which contributes to waste clearance. The brain is a metabolically active organ, and clearance of waste products is essential for maintaining homeostasis. Think of, for example, the pileup of amyloid-beta in Alzheimer's disease. The effect of brain tissue pulsatility on waste transport might be similar to moving your teabag up and down in a cup of hot water: the tea will distribute much quicker over the cup than would happen with just passive diffusion.

WHAT HAS INSPIRED YOU TO DIG DEEPER INTO THIS FIELD OF RESEARCH?

During my PhD, I read a paper in which the potential of MRI to study motion was illustrated by showing that MRI has the sensitivity to detect the subtle brain tissue deformations that are induced by the heartbeat. I was truly amazed. This deformation leads to a shift between two neighbouring voxels of only a few micrometres. Even though this motion is so small, MRI can measure it non-invasively in humans. Once I realized the potential relevance of these brain pulsations, I decided to dig deeper into the challenge of measuring this phenomenon.

> I find it inspiring that such a basic, purely mechanical process as brain pulsation is still understudied and potentially highly relevant for understanding brain disease.

WHAT WOULD YOU SAY IS THE MOST RECENT ADVANCEMENT IN YOUR FIELD OF RESEARCH AND DOES THIS CONTRADICT PREVIOUSLY ADOPTED SUGGESTIONS?

Recently a new theory on the pathways behind waste clearance has been put forward, which has created a new interest in this field and vivid discussions. This development highlights that there are quite some aspects of the brain that we still don't understand. Getting rid of your waste might sound simple, but it isn't.

HOW DID YOU EXPERIENCE THE PROCESS OF APPLYING FOR A SCIENTIFIC FELLOWSHIP/GRANT?

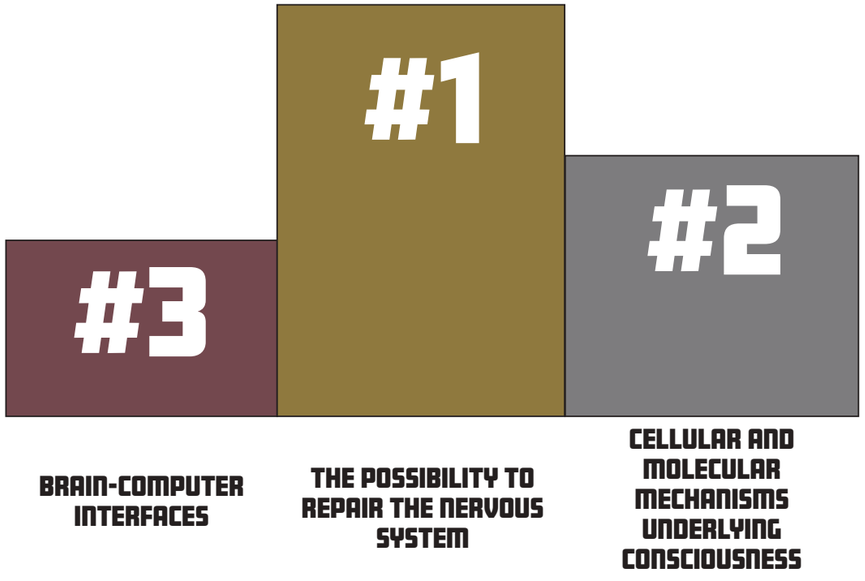
It is exciting to breed new ideas and to plan new research in a well-designed grant proposal, but it is equally frustrating if those plans don't make it due to fierce competition and limited financial resources. However, perseverance pays off, and it is fruitful to team up with scientists from other disciplines. Multi-disciplinary research is needed in challenging problems like brain diseases.

WHAT DO YOU THINK THE FUTURE BEHOLDS FOR YOUR FIELD OF RESEARCH AND WHAT WOULD BE THE NEXT STEP TO REALIZE THIS?

Increasing computer power has continuously led to new possibilities, not only for developing new MRI acquisition techniques and related demanding image reconstructions but also for image processing and computational modelling, including artificial intelligence. The combination of artificial intelligence with MRI has just begun and will significantly impact the field.

POLL #4

What future vision of neuroscience excites you the most?



'Biology of cable transmission'

Prof. Dr. Maarten H. P. Kole
Department of Axonal Signaling, Netherlands Institute for Neuroscience, Royal Netherlands Academy of Arts and Sciences, Amsterdam, The Netherlands
Department of Biology, Cell Biology, Faculty of Science, Utrecht University, Utrecht, The Netherlands

COULD YOU PROVIDE READERS WITH A SHORT INTRODUCTION ON YOUR FIELD OF RESEARCH?

In the axonal signalling group at the Netherlands Institute for Neuroscience, we investigate axons at the cellular and biophysical level. By doing so, we use techniques including two-photon imaging, optogenetics and electrophysiology in order to probe the activity and the structure-function properties of axonal membranes. To understand axons, one also needs to consider the biology of glia cells, including oligodendrocytes that produce myelin, we therefore often take an integrated 'neuron-glia' approach in our research. One of the aims is to understand how axons and networks of neurons are affected in multiple sclerosis when large regions of the brain lose myelin. For this we work together with experts in the field of multiple sclerosis research and use animal models of demyelination.

WHAT HAS INSPIRED YOU TO DIG DEEPER INTO THIS FIELD OF RESEARCH?

Already during my time as an undergraduate student I was fascinated by the detailed drawings of axons and dendrites from Ramón y Cajal.

> However, to study the biology of axons has in part also been a path of coincidences.

For example, by doing a certain research project or by having a discussion with colleagues about data or what we need to know and what is technically feasible has helped me in finding this new research direction. Exchanging ideas is in my opinion incredibly important to develop such new research directions, and at some point I made a sharp turn from dendrites to axons since there are so many new and fundamental questions which need to be addressed and, moreover, can be addressed today.

WHAT WOULD YOU SAY IS THE MOST RECENT ADVANCEMENT IN YOUR FIELD OF RESEARCH AND DOES THIS CONTRADICT PREVIOUSLY ADOPTED SUGGESTIONS?

Myelination of axons was thought to be some sort of fixed material which, once being developed, remained in place to insulate axons. However, what has been discovered by many research groups over the last decade is that myelination is rather plastic; it changes dynamically and is highly dependent on neuronal activity. In fact, changing the levels of myelination is even required for learning and memory. This conceptual advancement further underlines what I mentioned before, namely, that understanding normal brain functions demands an integrated neuron-glia approach.

HOW DID YOU EXPERIENCE THE PROCESS OF APPLYING FOR A SCIENTIFIC FELLOWSHIP/GRANT?

I have been going through all possible types of experiences, ranging from disappointment to exhaustion and up to exhilaration. I've also been at both sides of the table, as an applicant keeping my fingers crossed that my application was successful and as a committee member responsible for making decisions. It is an interesting academic process to apply for grants; one starts with a singular idea and then needs to envision, in detail, how research will look like in years from now. I personally believe the process improves the quality of research.

WHAT DO YOU THINK THE FUTURE BEHOLDS FOR YOUR FIELD OF RESEARCH AND WHAT WOULD BE THE NEXT STEP TO REALIZE THIS?

Cellular research into axons has a great future since the technical possibilities of today are already uncovering more and more detail and becoming more precise. There are seemingly endless technical possibilities with, for example, super resolution imaging or observing myelin live in the brain. The big problems in the field which tries to understand the basis of various diseases, requires nonetheless much more research and may require integration of approaches and combination of research fields. For example, chemists working together with biologists, immunologists with cognitive neuroscientists. These steps are happening already in the Netherlands and I'm looking forward to see what we will learn.

'On a journey to regenerate the brain'

Dr. Vanessa Donega

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

COULD YOU PROVIDE US A SHORT INTRODUCTION ON YOUR FIELD OF RESEARCH?

I have been working on brain regeneration since 2010 when I started my PhD. The field of neuroregeneration is relatively new. Before the '70s, scientists believed that neurogenesis stopped at birth. This dogma was proven wrong by pioneering work from Altman and Das in the early '60s. For their groundbreaking work, they used BrdU (a thymidine analogue, which is incorporated by the DNA of dividing cells) to show that neurogenesis continues throughout adulthood in the subventricular zone aligning the lateral ventricles and the dentate gyrus of the hippocampus in the mammalian brain. It gave hope that in the future we may be able to stimulate endogenous neural stem cells in the adult brain to produce new neuronal and glial cells to repair the brain. It started a new era, and in the early '90s, adult neurogenesis and regeneration became booming research fields in neuroscience. However, to date, the field is still divided on the question of whether or not neurogenesis takes place in the human dentate gyrus, despite numerous studies showing evidence of a small number of newborn neurons in this region.

WHAT HAS INSPIRED YOU TO DIG DEEPER INTO THIS FIELD OF RESEARCH?

During my PhD, I determined the potential of mesenchymal stem cell (MSC) treatment through the nose as a novel therapeutic strategy to treat brain injury in the neonate. My project was preclinical, and the results in the mouse model were very promising, which has led to a clinical trial at the UMCU to assess the efficiency and safety of this strategy in neonates with brain damage. When I analysed the mouse brain tissue and saw that up to 30% of the brain tissue was lost, and that giving MSCs through the nose decreased lesion size, and improved cognition and motor behaviour.

> I just had to keep on working in the regeneration field to understand the mechanisms that regulate regeneration in the mammalian brain.

WHAT WOULD YOU SAY IS THE MOST RECENT ADVANCEMENT IN YOUR FIELD OF RESEARCH, AND DOES THIS CONTRADICT PREVIOUSLY ADOPTED SUGGESTIONS?

It would be the work of Altman and Das that broke the dogma raised by Ramón y Cajal that neurogenesis stopped at birth (For a mini review please see: Kempermann et al., 2018). This shows how important it is to think outside the box and that the lack of evidence for something does not necessarily mean that it does not exist.

HOW DID YOU EXPERIENCE THE PROCESS OF APPLYING FOR A SCIENTIFIC FELLOWSHIP/GRANT?

I really enjoy the whole process of having an idea and seeing it grow into a full-sized project. It is also exciting to look forward to building a team of enthusiastic researchers who will work together on solving another piece of the puzzle. Besides the scientific part of the grant, and depending on the grant type, there is also a section on implementation and impact (so why is your research important to society and the scientific field, and how will it be implemented in the society in the future). For some grants, you will also need to write a response to the reviewer's comments and/or give a presentation to a panel of reviewers. There are many passionate scientists working on important research questions, but unfortunately, the available funding is limited. It is a very competitive environment and you need to get used to not always receiving the grant you have applied for.

WHAT DO YOU THINK THE FUTURE BEHOLDS FOR YOUR FIELD OF RESEARCH, AND WHAT WOULD BE THE NEXT STEP TO REALIZE THIS?

Developing tailor-made approaches to regenerate the mammalian brain. This is really far in the future, and before that we still need to, among other things, better understand the biology of neural stem cells.

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THE FUTURE OF SCIENCE IS OPEN

Science is a field that continuously changes and develops. In recent years we have seen many incredible discoveries and creations, with many yet to come. In the future, the dynamic innovation of scientific research will continue. In this section, another important aspect of the future of science will be discussed, namely how we communicate with other researchers and the public, and how we can take part in open science. Two researchers will share their ideas and insights on open science communication and collaboration. They will shed light on the challenges of communicating science to the public, and will discuss how we can make an effort to implement open science already during our studies.

'How to make the future Open Science?'

Dr. Anna-Lena Lamprecht

Department of Information and Computing Sciences, Utrecht University, Utrecht, The Netherlands

Dr. Anna-Lena Lamprecht is an assistant professor in the Software Technology group at the Department of Information and Computing Sciences at Utrecht University. She is also the Faculty Ambassador of the Open Science Community Utrecht (OSCU) at the Faculty of Science. As OSCU Faculty Ambassador, she works on promoting the adoption of Open Science practices among her colleagues, for example through the organization of faculty symposia and other events around the topic of Open Science. In these events, participants discuss principles and practices of Open Science and share ideas about actions to make science more open. The goal is to connect researchers and help them exchange experiences and best practices. In this article, we discuss making the transition to Open Science. The article is based on an interview with Dr. Anna-Lena Lamprecht, who taught us some interesting insights about Open Science.

Open Science is the future. It aims to make science more accessible for other researchers, society and the economy. To perform research in an Open Science manner, we have to understand the many different aspects that Open Science entails and how we can apply them to our research. Thus, ***how can we, as students, already promote open science during our internships?*** Of course, this highly depends on which research group you are conducting your internship with, and how open they are to Open Science. In an ideal situation, you would learn a lot of Open Science practices from your research group, because they are already practicing Open Science. However, this is not yet the case for many research groups. Many groups are positive about Open Science and acknowledge that shifting towards Open Science is a good thing. However, it may be hard to understand how to apply its principles in practice when trying to make this transition. ***Which tools and platforms are available? What, for example, is preregistration?*** If you as a student are interested in Open Science, you can discover the answer to these questions together with the research group. This requires a certain proactivity from the student's side but will be beneficial to the whole group. However, if you are doing your internship in a group that is not yet into Open Science, it can be challenging. Then you might have to convince them why this is important before you can dive into practical details.

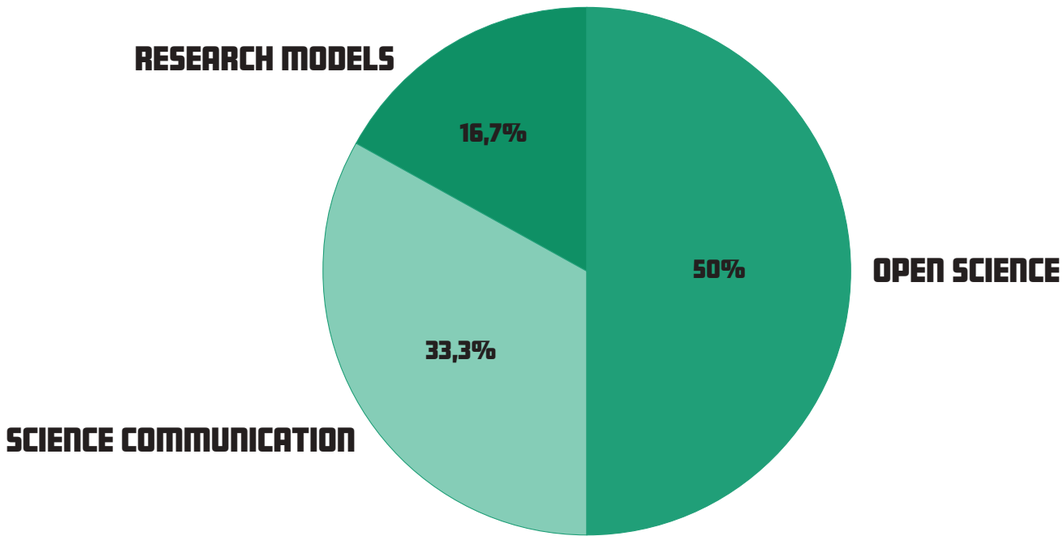
What would then be the necessary steps that should be taken to make open science more mainstream in both research and education? For researchers, it is critical to be supported by their institution and its policies. Nowadays, these policies still provide many incentives for non-Open Science behavior. For instance, if, according to promotion criteria, it is only important for researchers to publish many articles in high-profile journals, with a high impact factor, then they will rarely spend time making their data openly available. In contrast, if promotion policies would reward Open Science, people would take the time and invest in it, and it would ultimately become more mainstream. Thus, making the transition to Open Science depends on the one hand, on the skills and attitudes of researchers towards it, but on the other hand, it also needs to be supported by the policies. It is all about providing the right incentives.
Acknowledging that science happens in teams rather than it being the work of individuals is also an important aspect of open science. Life sciences are very complex, and typically many people are involved in research projects, with collaborations worldwide. Conflicting is that some prestigious grants are given to individuals rather than groups. Collaborations are facilitated by, among other things, sharing data and publications. Open Science provides tools to stimulate researchers to discuss their work and help each other. Questions to think about would be: ***How do we share data? Are we going to do it as openly as possible?***

An attempt to transition to open science can often most easily be made at the beginning of a research project. For instance, before starting a new experiment, one might ask themselves: ***what would be the Open Science way to do this?*** As the internship period is a learning environment, as a student, you can already try different Open Science related methods, such as preregistration or open lab notebooks, among many others. However, there are always aspects of research that you cannot influence, such as the use of open vs. closed access papers. Ideally, prestigious journals would also shift towards Open Science at some point. As they set scientific standards, that would set a great example for a global transition to Open Science. It is interesting to think about what would happen if these journals would indeed convert to open accessibility.

Finally, which tools could students use to learn about and take part in open science? Open Science consists of many components which are sometimes specific to certain research domains. We must recognize what is part of Spen Science, as it might be the case that you are already performing open science without knowing it! For students, a good introduction to what open science entails can be found on the ***Utrecht Open Science Community*** website, https://openscience-utrecht.com/what-is-open-science/. It contains a collection of links on the different topics of Open Science. It provides all kinds of information on these topics and includes some tools that students can use.
All in all, transitioning to Open Science does not happen overnight, it is an extensive process. We have to take small steps, be realistic and ask ourselves: ***what is the next thing I can do better? How can I make this more Open Science the next time?*** If we start thinking about these things now, then Open Science will indeed be the future.

POLL #5

What area of science needs to be developed in the future to better advance scientific understanding and cooperation?



‘The Corona Brain in the Media’

Prof. Dr. Stefan van der Stigchel

Department of Experimental Psychology, Helmholtz Institute, Utrecht University, Utrecht, The Netherlands

Stefan van der Stigchel is a Professor at the department of Experimental Psychology at Utrecht University, a principal investigator of the research group AttentionLab, a public speaker, and popular science writer. Not to forget, he is one of the track coordinators of the Neuroscience and Cognition master programme. In this piece, he touches on the perception of science in the media, particularly related to mental fatigue during the pandemic, or the so-called COVID-brain'.

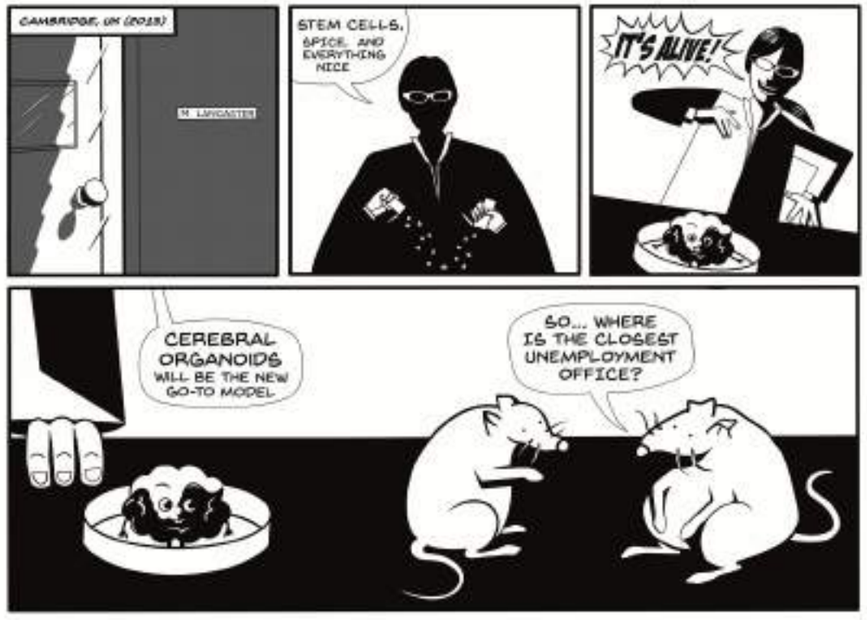
Shortly after the first peak of the Corona pandemic, I received a question from a well-known columnist of a Dutch newspaper. I had talked with her previously, and this always resulted in quite hilarious but also informative columns on issues like open office spaces and concentration in relation to social media. Given that I have written several popular science books on attention, I am used to getting questions on issues related to mental health problems due to a lack of concentration or continuous multi-tasking. She asked me about her current state of mind: she felt tired and had the impression that this was more severe than usual before the summer break. She asked me whether I thought this could be related to the current pandemic. This raised an interesting issue: what do you do? There was no data on this. We had no idea whether the level of ‘tiredness’ was different at the end of the first peak than the year before. The pandemic was so abrupt that such research was not initiated. Of course, you could release a quick questionnaire, but are people really able to judge their level of tiredness and, in retrospect, relate to their state of mind a year ago?

So what do you do? I could simply have said ‘no’ to the interview or given an honest answer, ‘we don’t know’, but I then would have missed an opportunity to inform the public about possible reasons for mental fatigue. Although there was no scientific data to show that the population is (on average) more tired than the year before, it is clear that this situation contained everything that could account for mental fatigue: the worries about the virus, combining home-schooling with working, the lack of physical movement, the absence of social interactions, just to name a few.

I decided to do the latter, unaware of the reactions this short newspaper piece would trigger. Within an hour of its release, the piece exploded on social media and my inbox was filled with reactions. The vast majority of them were positive: people recognised the problems and were happy with the ‘explanations’ provided. They were reassured by the recognition that they were not alone in their feelings and mental state. The following week, the newspaper reserved an extra page to print all the heart-warming responses. I have to admit that not all reactions were positive: there was a minority of responses in which the scientific value of the piece was questioned. Although we made sure that it was clear from the statements that we were not making scientific claims and were merely speculating about possible reasons for someone’s mental fatigue, it’s easy to see how this could be misinterpreted. It also didn’t take long for other news media to elaborate on the story and make even stronger claims and headlines (‘do we have a Corona brain?’). When other news outlets contacted me, I did not participate, as I was a bit overwhelmed by all the responses and did not want to be associated with this topic too much.

Why am I telling you this story? I feel that it’s a great example of the tension between being a scientist and doing science communication. The public is eager to know more about the brain, but sometimes scientific knowledge is lacking, and you can only make an educated guess. The decision about what to do in such instances can sometimes be difficult to make. My advice is to surround you with a critical crowd who can help you make these decisions and check your claims. Sometimes you simply have to cut corners when doing science communication (else no one will understand), as long as you stay close enough to the scientific truth. But what is close enough?

Tickle your brain



Thanks to Zuzanna Altmann

Another year of the Mind the Brain Symposium!

Science communication is multifaceted and does not necessarily revolve around writing. The distinctive characteristic of a symposium is that it allows one to engage in a two-way interaction and thus it facilitates networking and critical thinking. One of the N&C master's students and chief of the Mind the Brain committee 2020-2021, Zuzanna Altmann, shares her point of view on the organisation of a student symposium.

Are you ready to organize a symposium?

During the first MtB committee meeting, none of us knew how much we would have to overcome and learn during the organisation of such an event. We were lucky to have blueprints of the preceding editions, however, in the time of a pandemic, we had to come up with novel solutions. Our journey has not come to an end yet, as we still have to pass the responsibility of organising the Mind the Brain symposium on to a new committee. However, it is time to reflect on our work and think of future improvements. If you ever need to organise an event, try following the golden rules:

CREATE A TIMELINE AND STICK TO IT

What may appear as an obvious requirement for any group project, is especially essential for a live event, where success depends on the good timing of all the components. Use double or even triple deadlines, meaning do not set a deadline for the very last moment when something needs to be finalised. Instead, be prepared that most of the primary deadlines will not be met due to reasons you cannot always control. Better to be safe than sorry.

USE KNOWLEDGE OF YOUR PRECEDERS BUT DO NOT LIMIT YOURSELF TO IT

It is logical to use the experience of your colleagues or previous committee members since it facilitates the work and speeds up certain processes. However, it is a double-edged sword if you focus only on optimising existing solutions. It prevents you from trying new, maybe more daring options. In the Mind the Brain case, we decided to try a new platform, which was associated with facing uncertainty and putting more work into it. However, as long as the team is on board - take the risk, there is a high chance it will pay off.

FOCUS ON THE TEAM

A cohesive team is one of the necessary ingredients for success. It is widely known that people that know each other better, cooperate more effectively, even in virtual reality. Although it is more difficult to achieve it when everything is done remotely, you should never neglect this part. Use online workshops that you can follow with the whole team or organise time after one of the regular meetings to have a drink and talk or have some games. Strategic task division at the beginning of the preparations can also be very effective. Assign together team members that do not know each other so well. Encourage them to cooperate and sooner or later they will pair up without asking.

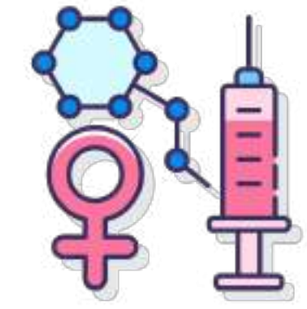
And last but not least, do not forget that in the end, **it's all about creating an enjoyable event**. During a symposium, the content is important, but it does not guarantee success. Make it a pleasure for the attendees, provide them with opportunities to connect and develop skills. As long as you as a team are having fun, the participants won't fall behind!

The Future of Neuroscience: Thoughts from the Editorial Board

Research is an ever-changing and dynamic field, and we can only wonder what is going to change in the future. As a researcher, you may hope to see certain changes in your field of interest, which you may even contribute to in your future academic career. In this article, each member of the editorial board explains what they hope will or should change in their area of research.

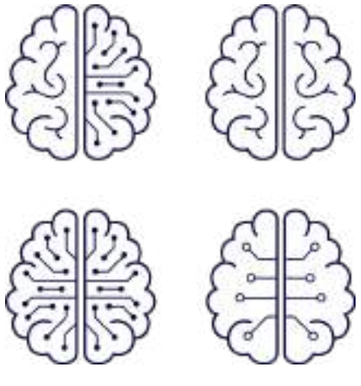
Currently, I am studying the predictive value of brain MRI in extremely preterm infants. These infants are at high risk of brain injury which can lead to impaired neurodevelopmental outcomes later in life, such as cognitive, motor, behavioural and language problems. Early intervention could improve outcome, but the problem is that neurodevelopmental impairments often only become evident from childhood onwards. Therefore, it would be helpful to predict outcome based on early brain injury, and MRI may be the right tool for this. However, researchers have not yet agreed on the predictive value of MRI. I hope that this will improve over the next few years, when more research has been done and more advanced MRI techniques have been implemented. This way, we can hopefully improve outcome of extremely preterm infants at-risk.

- VERA AALBERS



I am currently studying the role of the cerebellum in reactive aggression and how this is affected by the neuroendocrinological system. Besides the fact that the role of the cerebellum in emotion regulation is a promising field of research on its own, I believe that the role of hormones, and especially female steroids, should be acknowledged more in explaining human socio-emotional behaviour. Given the natural fluctuations and use of hormonal contraceptives, it is hard to study the role of female sex steroids, like estrogen, in a controlled manner. However, pharmacologically inhibiting these fluctuations with a GnRH agonist or day-to-day fMRI sampling allows for more experimental control and a higher measurement accuracy. Given the current widespread use of hormonal contraceptives, I think it is important that these techniques are used more often in order to study how the mental and physical well-being of females using hormonal contraceptives can be improved.

- NINA DIJKSTRA



My current field of interest is neuropsychiatry, a discipline you can read more on in this issue. One of the avenues of research that I think will develop is the diagnosis and treatment of psychiatric conditions. This field is ever-changing and has seen a lot of developments in the past century. With the help of neuroscience and various imaging techniques, I believe we can develop our understanding of current treatments with relatively high remission rates, such as electro-convulsive therapy. Based on this, new treatment options can be explored and it can be studied how to reduce adverse side-effects of such treatments. Furthermore, with the development of informative biomarkers, more personalised treatments can be incorporated in clinical practice, while also acknowledging the broader picture and role of the environment in a patient's development of psychiatric problems. Altogether, this has the potential to give insight into the various workings of the brain and most importantly help ameliorate severe clinical symptoms to improve the lives of individuals with a psychiatric condition.

- JANA HERMANS

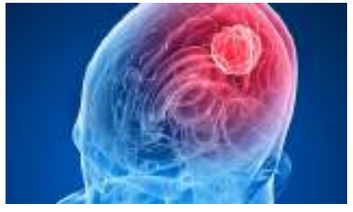
I am specifically interested in the role of the immune system in neurodegenerative diseases. In recent years, genome-wide association studies have shed light on the role of the immune system in several of these diseases, including Alzheimer's disease (AD). Over the last few months I have studied the role of astrocytes in AD pathology. While a lot of research is already being done on this topic, many aspects of the complex interplay of these immune cells and the pathogenesis and progression of AD are yet to be discovered. The question remains how immune cells may aid in AD prevention or how they may be involved in AD pathogenesis, or even both. It has also been shown that, in AD, immune cells of the brain transition from a homeostatic state into a disease-associated state, in which they are more damaging rather than helpful. If we manage to understand the underlying mechanisms, we could use this research to prevent Alzheimer's disease from developing or even find a treatment for this disease that affects so many people nowadays.

- LOTTE VAN HOUT

We need to remember that neuroscience as a discipline is still in its infancy, and many aspects of neuroscientific research will evolve in the coming decades. The most important question for me is to bridge the gap between cellular interactions and our psychological output, a question that is still, so far out of our reach. Technology is advancing our understanding of this drastically with concepts such as machine learning and artificial intelligence, mapping neural outputs and even manipulating them. Although this work is fruitful, let us not overlook our natural resources. With the taboo of substances such as psychedelics and cannabinoids being lifted as our society becomes more informed, new insights into psychological well-being are being uncovered, and many questions are being answered. Psychological well-being will be the biggest challenge we will face in the future with mental health problems only growing. This will take, not only neuroscientific research advancements, but it will take societal and scientific reform. We need to focus on making neuroscientific research reachable and beneficial for our society. Making neuroscience accessible to the masses is the key to a healthier future.

- HAYDN MERLE

I think that it is evident that facing the challenges of the current pandemic, being flexible and exploring horizons is necessary. But for the future, where I hope to work with patients with brain tumours, I believe that technology will be the best and sharpest point to address all possible issues better. Artificial intelligence will, for sure, play along all areas of neuroscience to provide and help researchers get better results. And, referring to my opening sentence, does allow for a flexible and innovative angle of approach. I don't think robots will dominate the world, but I'm confident that they will be next to us in order to help us for a long time.



- CATARINA SIMÕES PADILLA

I am currently interested in the field of neonatology, more specifically in the role of magnetic resonance imaging (MRI) in predicting neurodevelopmental outcomes of extremely preterm infants. MRI is a safe neuroimaging technique to evaluate brain injury in preterm infants and it is usually performed at term equivalent age. There are various MRI evaluation scales to evaluate the degree of brain abnormalities, but their full potential to predict long-term neurodevelopmental outcomes is yet unknown. I think that unbiased machine learning, data-driven approaches and more advanced MRI techniques will drastically improve the predictive value of MRI, which may improve outcomes and help guide early treatment of extremely preterm infants.

- SARA RAPUC

My current field of interest is sleep, more specifically, the effect of sleep on the preterm brain. It has not been long since we discovered the enormous effects that sleep can have on the body. However, a lot more research has to be done before it will be easy to convince people to actually make life changes. The first change I would like to see happen, would be made in hospitals. Hospitals are filled with the most vulnerable people of our society, including preterm infants. Improving protocols and the patient's surroundings to optimize their sleep cycle should help them recover faster and better. To achieve this, individualized sleep care is necessary, most probably with the help of algorithms that can identify the patient's current sleep state. This way, the medical care takers will have a system to help them take sleep into account during the patient's hospital stay. Hopefully, the importance of sleep will be acknowledged more by the day, making hospitals a safe place to dream.

- CHANEL SAM

Editorial Board at the Release Party of the First Issue:

Thank you to our contributors:

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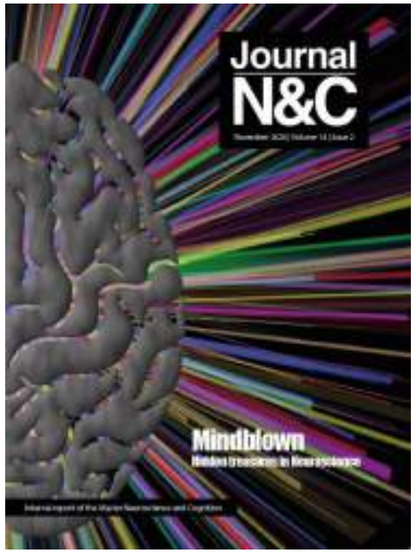
Contribute to the next issue of the journal!



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