“Hiding within those mounds of data is knowledge that could change the life of a patient, or change the world”

- Atul Butte

"The goal is to turn data into information, and information into insight"

- Carly Fiorina

Foreword

Dear reader,

In front of you lies the 24th issue of the Journal of Neuroscience and Cognition with the main theme 'Big Data'. I enjoyed witnessing the development of this issue from up-close for two reasons. First of all, the contributors put a lot of effort and passion in this journal, and as a former N&C Master student I know how hectic it can be to combine your research project with other demanding activities.

In addition, the editors have chosen a timely and important theme, because 'Big Data' has the potential to drastically change the field of neuroscience; not only in the answers it can bring but also in they way researchers collaborate. For 'Big Data' projects to be a success, researchers have to work together; this can be a challenge within the current academic model, where researchers tend to work on hypotheses relatively independent of their peers and there is the need to distinguish yourself. Therefore 'Big Data' will not only revolutionise the way neuroscientists can answer their research questions, it also challenges the efficiency of the conventional academic system.

I hope this issue will inspire you, next generation of neuroscientists, to think about what role big data plays in your current research project and how it will in the future. After all, you decide whether the big data wave is here to stay.

Dr Estrella Montoya
Senior Advisor Journal of Neuroscience & Cognition

Editorial

Dear reader,

I proudly present to you the first issue of this year's Journal of Neuroscience and Cognition. This issue is the product of many brainstorm sessions, email conversations and efforts on behalf of the editorial board, our contributors and our reviewers. Even though we had a bit of a troubled start, everyone quickly settled into their respective roles and it was a surprisingly smooth editing process from there on. The true kickoff came, when we immediately agreed on the topic for this issue: 'Big Data'!

The goal of the journal is, of course, to inform you on the developments in our field of research. We believe that Big Data remains an enigmatic subject for many people, even though it is gaining more and more importance throughout the field of neuroscience and cognition. In this first issue, we aim to shed some light on the mystery surrounding Big Data.

For this, we interviewed two leading experts on the topic; Jan Veldink and Floor Schepers. Both researchers took the time to enlighten us on the application, importance and complexity of Big Data in our field. They told us about their team, their daily work and their involvement in projects (from which we concluded that both Jan and Floor are highly skilled multi-taskers). In order to take this information to a present-day level, we highlighted two of the Master's profiles that are relevant in the field of Big Data. Also, one of our fellow students, who is currently doing an internship in line with our theme, wrote a method section. Thereby giving a very practical example of the application of Big Data in neuroscience.

Deflecting slightly from our theme, but just as relevant are the three review/research articles by Coen, Dennis and Tuomas, who show us what is new in the field of neuroscience and cognition. Complementary to that, we provide you with several experiences from fellow students who went abroad, attended a congress, came to the Netherlands or obtained a PhD grant.

On behalf of the editorial board 2017/2018 I wish you all the best for the upcoming time and hope you enjoy the read!

Yours sincerely,
Maaike Dubbeldam
Editor in Chief

A shift of focus: Are astrocytes' reduced supportive functions at the basis of Alzheimer's disease?

Van Deursen, C.B.J.[1]

[1] Department of Translational Neuroscience, UMC Utrecht Brain Center Rudolf Magnus, the Netherlands

Alzheimer's Disease (AD) is a neurodegenerative disease characterised by dementia, cognitive impairment, and two histopathological hallmark lesions: neurofibrillary tangles and β-amyloid (Aβ) protein aggregates, both potentially neurotoxic. AD research is mostly focused on neurons, but astrocytes have become implicated in AD more often. Astrocytes are involved in synaptic transmission and also fulfil many homeostatic support duties in the brain, such as providing metabolic support for neurons. Astrocytes can become immunoactive and obtain a pro-inflammatory phenotype (astrogliosis) after damage to the central nervous system has arisen or protein aggregates such as Aβ start to appear. Although there is evidence that astrogliosis arises very early in AD pathology, it remains unclear whether it could actually be the cause of AD. When astrogliosis is chronically triggered such as in AD, astrocytes can become part of the problem. Their properties can become curses and their chronic shift of focus to their immunoactive role will cause lower supportive activities. This can eventually lead to neuronal atrophy or even neuronal loss. Since study outcomes do not show a consensus on the time of onset of astrogliosis in AD and its impact on pathology, no verdict can be given on these matters at this time.

Keywords: Alzheimer's Disease, astrocytes, astrogliosis, supportive functions, GFAP

Alzheimer's Disease (AD) is a neurodegenerative disease that starts with the deterioration of short-term memory, followed by other cognitive functions. After diagnosis, AD patients will likely die within 3 to 9 years (Querfurth & Laferla, 2010). Alois Alzheimer described the first case of AD in 1907, but sadly to this day its cause and mechanics are still not fully understood and no treatment option has yet become available. During life, a definite diagnosis of AD cannot be made. By using the patient's medical history, a thorough mental and physical examination and by performing tests to exclude other potential conditions, a patient can be given a probable diagnosis of AD. Only with a post-mortem examination of the brain for AD hallmarks, a conclusive diagnosis of AD can be given. The two well-known histopathological hallmarks that can be discerned in AD are neurofibrillary tangles (NFTs) and senile plaques (Querfurth & Laferla, 2010). These lesions are used to diagnose AD but the reason for their appearance and their cause are unclear.

NFTs consist mostly of a hyperphosphorylated form of the tau protein, a microtubule-associated protein that assembles and stabilises microtubules in neurons of the central nervous system (CNS). Tau is phosphorylated under many circumstances and in multiple conditions and accumulates during aging as well, which would suggest that NFTs formation could be a sign of neuronal damage or neuronal death instead of a characteristic or the cause of AD (Drachman, 2006). Senile plaques or amyloid plaques are extracellular plaques in the brain's grey matter. They are aggregates of proteins, dystrophic synapses and neurites, but they are mainly made up of β-amyloid (Aβ). Aβ is the resulting protein of an alternative cut of the transmembrane amyloid precursor protein (APP). This APP cleaving is normally performed by the enzyme alpha-secretase, but in AD the protein is cut by beta-secretase 1 (BACE1), producing Aβ, which is prone to aggregation (Castellani, Rolston & Smith, 2010). AD can be divided in two categories based on the age of onset: early-onset AD (EOAD, also known as familial AD), in which the age of onset is before 65 years of age, and late-onset AD (LOAD, also known as sporadic AD), in which the disease reveals itself later than 65 years of age. Both types of AD have the same clinical manifestation, but the progression of EOAD pathology tends to be quicker (Reitz & Mayeux, 2014). EOAD only accounts for 1-6% of total AD cases, but unlike LOAD, it has a strong genetic cause. Three genes are implicated in EOAD: APP, presinilin 1 (PSEN1) and presinilin 2 (PSEN2). These genes are often not involved in LOAD pathology, but their (dys)functions in EOAD have helped to understand possible mechanisms underlying LOAD pathology (Bekris, Yu, Bird, & Tsuang, 2010).

Neurons and neuronal loss have long been the focus of AD research, which is not entirely strange since cognitive impairment is a characteristic of AD. Up until rather recently neurodegenerative and other neurological diseases were investigated from a purely neuronal

approach and supporting glial cells such as astrocytes were deemed less important. These assumptions changed when research into the roles of astrocytes in normal brain physiology as well as pathology showed significant impact of astrocyte functions, making glial cells a topic of interest in many neurological disorders nowadays, including AD (Sofroniew & Vinters, 2010).

Astrocyte biology and physiology

Astrocytes are star-shaped glial cells with characteristic processes which are found in the CNS. They have a wide variety of supportive roles in the brain (Figure 1) and are connected to each other by gap junctions, forming astrocytic syncytia. Astrocytes have been found to be involved in synaptic transmission, a process that was previously believed to only be influenced by the pre- and postsynaptic neuronal element. Recent evidence shows that astrocytes perform multiple tasks at the synapse, leading to the tripartite synapse hypothesis. This hypothesis states that surrounding glial cells play an important role in synaptic signalling, next to the pre- and postsynaptic neurons (Araque, Parpura, Sanzgiri, & Haydon, 1999).

By releasing gliotransmitters like purines, GABA and glutamate, astrocytes can alter the neuronal excitability (Sofroniew & Vinters, 2010). Astrocytes are also regulators of neurotransmitter homeostasis, especially the excitatory neurotransmitter glutamate. Perisynaptic processes of astrocytes prevent glutamate excitotoxicity by taking up excessive glutamate from the synaptic cleft and returning it to synaptic vesicles. Furthermore, in the event of an increasing neuronal firing rate, astrocytes can release energy substrates such as lactate for their surrounding neurons (Verkhratsky, Olabarria, Noristani, Yeh, & Rodriguez, 2010). They also store substantial glycogen reserves and during hypoglycaemia or high energy demand this will help neurons to preserve their synaptic transmission levels (Sofroniew & Vinters, 2010). The endfeet of fibrous astrocytes are connected to blood vessels in the brain, which puts them in a perfect position to influence the brain's blood flow. Local increases in neuronal firing can be sensed by astrocytes, which will lead to a Ca2+ wave to the astrocyte endfeet, leading to an increased blood flow. In this way, astrocytes function as a bridge between neurons and the brain's microcirculation (Zonta et al., 2003).

These diverse tasks show that normal functioning astrocytes are pivotal for a healthy CNS and their potential contribution to neurodegenerative diseases is considerable. When the focus of astrocytes starts to shift to other tasks, this could prove highly destructive for the brain.

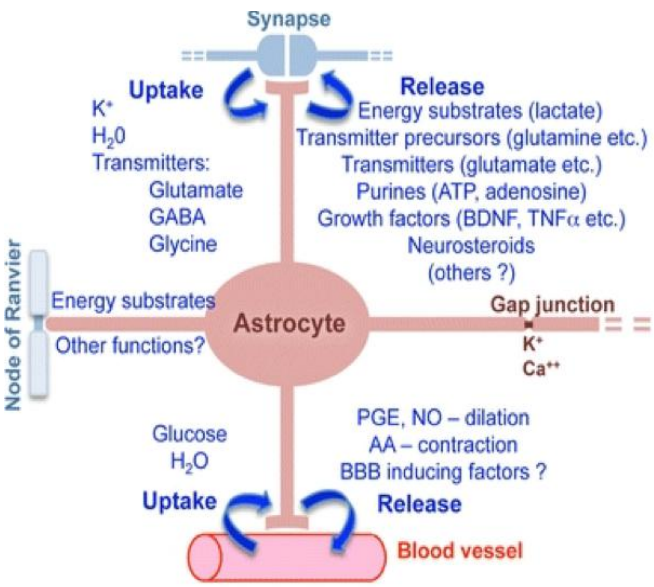

Figure 1 | Astrocyte functions in healthy CNS. *Astrocytes are connected to each other via gap junctions in the tips of their distal processes. They have an impact on synapse functioning, brain blood flow and provide energy substrates for neurons. Image adapted from Sofroniew & Vinters (2010).*

Astrogliosis and its functions

Next to their physiological functions, astrocytes possess inflammatory and immunoactive properties once they go into a reactive state called astrogliosis or reactive gliosis. When astrocytes become reactive, their gene expression, functions and morphology change (Lian & Zheng, 2016). These changes are triggered by a variety of CNS insults, such as focal, acute injuries as well as neurodegeneration and make astrocytes primary responders to neuronal damage and diseases. Molecular triggers are for example cytokines like interleukin-6 (IL-6) or leukaemia inhibitory factor, certain neurotransmitters (glutamate or noradrenalin), and reactive oxygen species (Sofroniew, 2009).

Two of the most well-known characteristics of reactive astrocytes are hypertrophy of the astrocytic processes (Figure 2) and a strong upregulation of glial fibrillary acidic protein (GFAP). GFAP is the intermediate filament protein in astrocytes and as such, it is the most used biomarker for astrocytes. Because of its strong increase in astrogliosis, it is especially helpful to visualise reactive astrocytes (Hol & Pekny, 2015). Other intermediate filaments are upregulated in reactive astrocytes as well, such as vimentin and nestin. Without GFAP or vimentin expression, astrocytes do not become hypertrophic and glial scar formation is reduced as well. Research showed that this has a negative effect on the containment of neuronal damage, meaning astrogliosis can prove beneficial in the event of CNS damage (Pekny, Wilhelmsson & Pekna, 2014; Hol & Pekny, 2015). Furthermore, the expression of many proteins normally involved in normal astrocytic functions such as regulating ion homeostasis and energy reserves changes

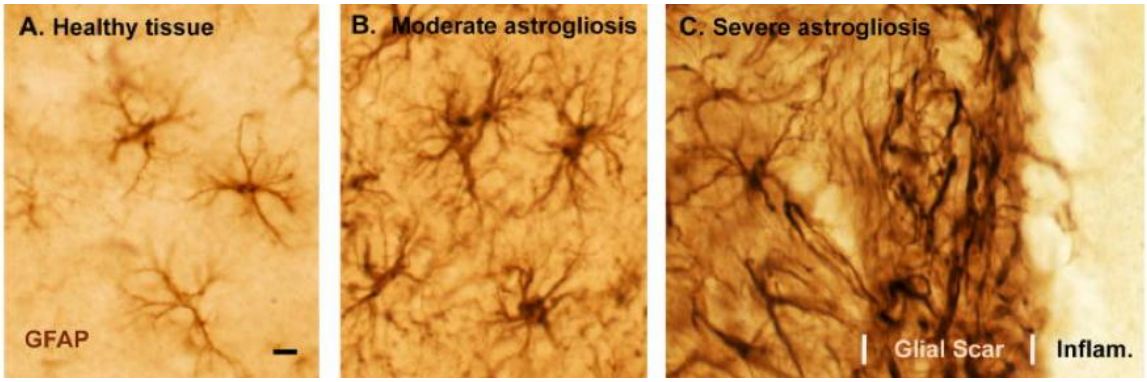

Figure 2 | Comparison of astrocytes in healthy tissue with different gradations of reactive astrocytes.
Immunohistochemically stained glial fibrillary acidic protein (GFAP) in black in astrocytes of wild type mice. (A) Normal appearing astrocytes in healthy cortical tissue of a wild type mouse brain. (B) Following an intracerebral injection of lipopolysaccharide (LPS), moderate astrogliosis has arisen. The astrocytic processes do still not overlap. (C) Inflammation (Inflam.) and severe tissue injury has caused severe astrogliosis and the formation of a glial scar. Astrocytic processes do overlap heavily in this stadium. Scale bar equals 8 µm. Image adapted from Sofroniew (2009).

during reactive gliosis (Sofroniew, 2009). This indicates that the astrocytes switch towards a more immunoactive profile and may have an impact on the normal astrocytic functions, such as the glutamate/glutamine shuttle (Ortinski et al., 2010).

Astrogliosis is not a heterogeneous state, it has a general as well as a disease-specific response (Hol & Pekny, 2015). Depending on the trigger and its severity, astrocytes change their cellular state and molecular output. If the intensity of the tissue damage or danger increases, the astrogliosis form will increase as well. When the reaction is mild to moderate, the astrocytic response might prove enough to resolve any issues and astrocytes appear to return back to a healthy physiological state. In these levels of astrogliosis, astrocytes still maintain their own domains in the brain and do no overlap (Sofroniew, 2009). However, if the neuronal damage or inflammation is too severe, reactive gliosis can trigger astrocytic scar formation. Proliferating astrocytes and pericytes form a barrier between the damaged tissue and the healthy parts of the brain (Pekny et al., 2014). The downside of this solution is that axonal regrowth in the affected area is inhibited. Unlike in a healthy or mildly reactive state, astrocytes will start to overlap when forming an astrocytic scar, as can be seen in Figure 2c (Sofroniew, 2009).

The primary function of astrogliosis is neuronal protection. If injuries occur in the brain, it is the astrocytes' task to decrease neuronal damage and loss and to keep the lesions as small as possible. Sometimes, this also means that they will inhibit the response of immune cells such as microglia to lesions to a certain extent (Pekny et al., 2014). Next to their neuroprotective duties, reactive astrocytes also help defend against harmful factors like oxidative stress or excitotoxic glutamate (Sofroniew, 2009). Scar formation is only seen in cases of severe damage, where extreme astrogliosis occurs. The physical barrier that is formed by newly proliferating cells seals away the damaged tissue, as well as inflammatory cells, from the surrounding healthy tissue. By isolating the healthy tissue, toxic or damaging influences can be sustained and potentially cleared by entering immune cells (Pekny et al., 2014).

Astrogliosis can be a helpful mechanism to prevent the spread of damaging factors in neural tissue. However, dysfunction of this mechanism or chronic injuries might lead to detrimental side effects of astrogliosis, which might be the case in AD (Sofroniew, 2009). This could mean that dysfunctioning astrocytes might cause problems for their surrounding neurons and disrupt the micro-environment with a more immunoactive profile. Moreover, the time of onset of astrogliosis in AD remains unclear, but there is evidence for a leading role for astrogliosis in its pathogenesis. This review will thus focus on the question whether it could be that astrogliosis is actually at the basis of AD, as an effect of a switch in astrocyte functioning.

Astrocytes and astrogliosis in AD

The role of astrocytes in many neurological diseases was dismissed until relatively recently. The same can be said about astrocytes in AD, even though Alois Alzheimer himself already observed astrocytes accompanying the plaques, which he described in 1907 (Alzheimer, 1907). However, in the last three decades, more insights into the functions of astrocytes in health and disease have been gained, as well as their possible implications in AD.

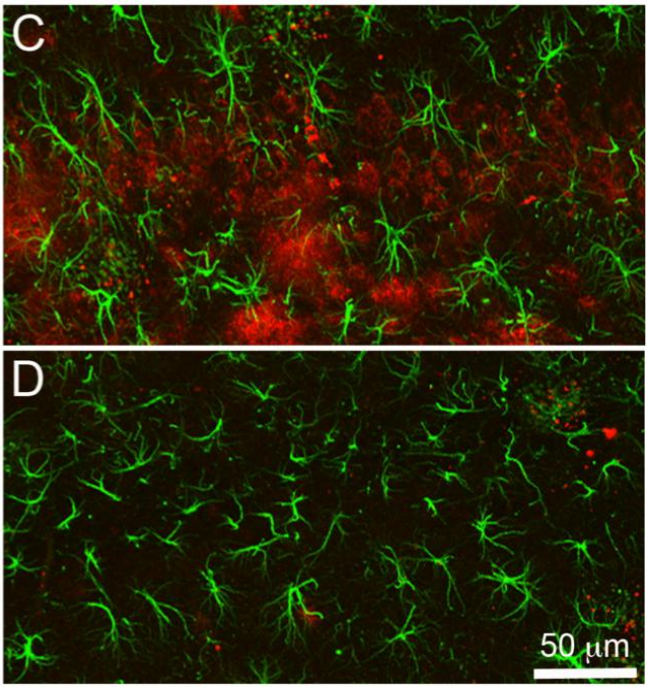

Figure 3 | Astrogliosis arises in the presence of Aβ plaques in mice.
Immunohistochemical staining of reactive astrocytes (GFAP, green) and Aβ plaques (Aβ, red) in a hippocampal section of an 18-month-old 3x TG-AD mouse. There is a clear difference in hypertrophy and GFAP expression displayed in astrocytes in the presence of Aβ plaques (above) when compared to astrocytes in an Aβ plaque free environment (below). Image adapted from Rodríguez-Arellano et al. (2016).

Astrocytes, neuroinflammation and AD

The inflammatory status of the AD brain seems to have shifted from a neutral resting state towards a pro-inflammatory state leading to neuroinflammation (Heneka et al., 2015). Neuroinflammation is a very broad term used to describe any inflammatory response in the CNS as a result of CNS injury. This response can be both innate immune-driven or adaptive immune-driven. The inflammatory reaction in neurodegenerative diseases such as AD is mostly an innate immune-driven neuroinflammation. In this type of neuroinflammation astrocytes and microglia play the biggest role, with additional monocytes migrating into the CNS to assist. Thus, astrogliosis is only an aspect of an innate immune-driven neuroinflammation and is not a term that is interchangeable (Heppner, Ransohoff & Becher, 2015). In AD an inflammatory response to lesions such as Aβ plaques is present and astrocytes are clearly in a reactive state, since hypertrophy and an increase in GFAP is reported. Thus, astrogliosis is identified as a hallmark of AD (Osborn, Kamphuis, Wadman, & Hol, 2016). Localisation of reactive astrocytes near Aβ plaques can be identified by using immunohistochemical stainings for GFAP and Aβ, as seen in Figure 3 (Orre et al., 2014). Research by Mathur et al. (2015) shows that human reactive astrocytes are affiliated with both diffuse and compact Aβ plaques, but also that this association correlates with cognitive impairment. This could imply a causal role for reactive astrocytes in AD.

Glial cells, and especially microglia, have an important regulatory function in the inflammatory response in the brain. But astrogliosis is also partly to blame for the new pro-inflammatory state of the AD brain (Avila-Muñoz & Arias, 2014). Reactive astrocytes and activated microglia are a source of pro-inflammatory cytokines like tumour necrosis factor α (TNF-α) and IL-6 in AD. A definitive answer as to what the exact function of neuroinflammation in AD is cannot yet be given, but evidence suggests it comes into play at an early time in AD pathology and thus has a part in its appearance (Heneka et al., 2015).

It is debatable whether astrogliosis has a positive or negative effect on AD pathology. Furman et al. (2012) inhibited the calcineurin-dependent dephosphorylation of nuclear factor of activated T-cells (NFAT) in APP/PS1 transgenic mice, a process that can be responsible for activation of a neuroinflammatory response. This resulted in less astrogliosis and Aβ depositions in the mouse brain and improved cognition. However, suppressive effects of astrogliosis on Aβ plaque load in the AD brain have also been observed. Research in APP/PS1 AD mice crossed with GFAP-/- Vim-/- mice by Kraft et al. (2013) showed an increased Aβ plaque load compared to controls. The expression of GFAP and vimentin are needed for the functioning of a reactive astrocyte, without these intermediate filaments astrocytes will become less hypertrophic and neuronal repair following varying CNS injuries is attenuated (Pekny et al., 2014). Less physical interaction between the astrocyte processes and Aβ depositions in the GFAP-/- Vim-/- APP/PS1 mice was also observed. This would indicate that reactive astrocytes can lower the Aβ plaque load in APP/PS1 mice, but physical interaction is required (Kraft et al., 2013).

What triggers astrogliosis in AD?

Astrogliosis is not the default astrocytic state; an astrocyte needs a trigger for it to become reactive. There are multiple factors that can evoke astrogliosis in AD, these are visualised in Figure 4. One such trigger is the direct consequence of CNS injury. Upon damage infliction, CNS cells will die, resulting in the release of intracellular substances. Additionally, dying or dead cells that are still intact express danger-associated molecular patterns. These factors give a warning signal to their surroundings, a signal that triggers astrogliosis. This inflammatory response depends on the displayed factors, which can indicate the severity of the inflicted

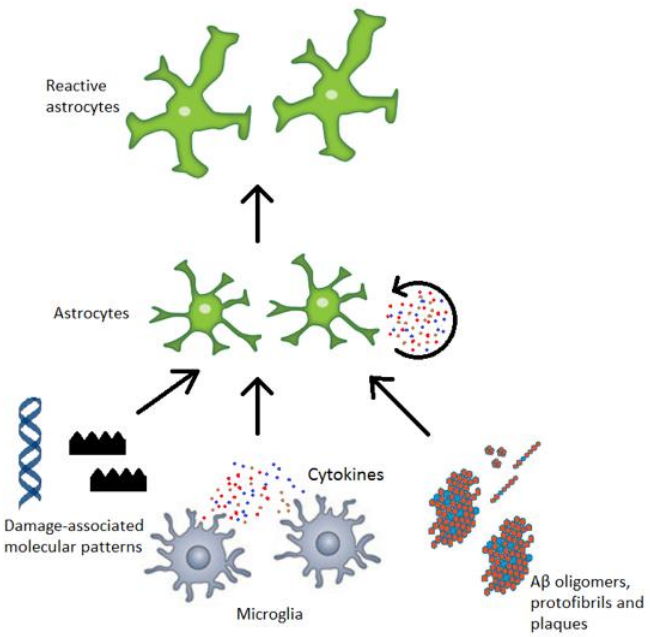

Figure 4 | Triggers for astrogliosis in AD.
This overview shows the different triggers for astrocytes to become reactive in AD. Firstly, CNS tissue damage can be recognised by damage-associated molecular patterns, for example DNA or cellular fragments. Secondly, cytokines released by both microglia and astrocytes themselves such as IL-1 and IFN-ɣ can prompt astrogliosis. Finally, proteins depositions, like Aβ oligomers, protofibrils and plaques in AD, can make astrocytes become reactive. Image made with elements from Hefti et al., 2013; Perry, Nicoll, & Holmes (2010); Stephan, Barres, & Stevens (2012).

damage. In AD, dying or dead neurons can promote astrogliosis via this route (Burda & Sofroniew, 2014; Verkhratsky et al., 2010).
Furthermore, tissue damage also activates microglia, which will release multiple cytokines upon activation. This will result in a pro-inflammatory environment, which can be neurotoxic if sustained for a longer period of time (Heneka, O'Banion, Terwel, & Kummer, 2010). Cytokines produced by microglia, which produce the biggest amount of cytokines in a damaged CNS, will also promote astrogliosis in AD (Buffo, Rolando & Ceruti, 2010). Cytokines that are known in AD pathology to trigger astrocytes to become reactive are for example interleukins IL-1 (Sheng et al., 1996) and IL-6 (Chakrabarty et al., 2010a), but also interferon-ɣ (IFN-ɣ) (Chakrabarty et al., 2010b) and TNF-α (Chakrabarty, Herring, Ceballos-Diaz, Das, & Golde, 2011). Communication between astrocytes and microglia is not a one-way street. Studies in AD rodent models have found that once triggered, reactive astrocytes can affect microglia functioning as well, in both seemingly good and bad ways. On the one hand, reactive astrocytes negatively influence the phagocytic ability of Aβ by microglia, causing microglia to take up less Aβ (Dewitt, Perry, Cohen, Doller, & Silver, 1998). On the other hand, attenuated astrogliosis shows an increase in microglial proliferation and plaque infiltration, however, there is still a higher total Aβ plaque load (Kraft et al., 2013). These examples show that after astrocytes become reactive, they can have either a positive or negative impact on AD pathology and that activation, crosstalk and cooperation of these glial cells are delicate processes. Finally, astrocytes are also able to produce pro-inflammatory cytokines themselves, which can work in an autocrine or paracrine fashion. This way, astrocytes can maintain a reactive state for a longer period of time (Selinfreund, Barger, Pledger & Van Eldik, 1991; Buffo et al., 2010).
Aggregated proteins, like Aβ in AD, are also a signal that cellular functioning is not up to standards. Reactive astrocytes are often found alongside Aβ plaques and Aβ plaques have been shown to trigger astrogliosis (Dewitt et al., 1998; Hu, Akama, Krafft, Chromy, & Van Eldik, 1998). However, not all Aβ plaques are surrounded by reactive astrocytes in humans (Simpson et al., 2010). Current findings now point to Aβ oligomers or (proto) fibrils as triggers for astrogliosis in AD (Alberdi et al., 2013; Craft, Watterson, Frautschy, & Eldik, 2004; White, Manelli, Holmberg, Van Eldik, & LaDu, 2005). Which form of Aβ is a trigger and the exact mechanism behind this activation is not yet evident.

The function and dysfunction of astrogliosis in AD

Astrogliosis and neuroinflammation as a whole can be helpful mechanisms to combat threats to the CNS and protect its integrity. This is especially beneficial in acute injuries like trauma or ischemia, where astrogliosis will promote isolation of the damaged area, clearing the way for wound repair relatively quickly (Burda & Sofroniew, 2014). On the other hand, when astrogliosis lasts longer and the particular damage and its cause cannot be dealt with swiftly, as is the case in a more chronic and neurodegenerative disease like AD, the properties of reactive astrocytes can have detrimental effects on their surroundings (Heneka et al., 2010; Pekny et al., 2014). A decent balance between neurosuppression, focussing on tissue repair, and neuroinflammation, focussing on ridding the area of harmful stimuli, is always needed for proper reactions to CNS injuries (Avila-Muñoz & Arias, 2014). Most physiological functions and properties of reactive astrocytes can cause negative effects in AD pathology, although some might have a positive effect.

Neuroprotective barrier and axon regeneration

Whereas astrogliosis will lead to glial scar formation when severe neuronal damage occurs, this is not the case in AD, since there are numerous smaller lesions that do not elicit this response (Burda & Sofroniew, 2014;

Sofroniew & Vinters, 2010). Although they do not form glial scars, reactive astrocytes are located in the vicinity of Aβ, as described previously. They form a dense layer of astrocytic processes around the plaques, in order to prevent exposure of Aβ to healthy tissue as much as possible. Some processes even penetrate the cores of Aβ plaques (Kato et al., 1998). This neuroprotective barrier function is dependent on the upregulation of astrocytic intermediary filaments such as GFAP as seen in astrogliosis. When this upregulation is not present, the astrocytes will not surround Aβ plaques to form a barrier (Xu, Malouf, Messing, & Silver, 1999).

The barrier formation seen after CNS damage could also have an inhibiting effect on axonal regeneration if astrogliosis continues too long (Fitch & Silver, 2008; Pekny et al., 2014). In GFAP-/- Vim-/- mice, the activity of reactive astrocytes was greatly reduced and axonal regeneration and functional restoration after spinal cord injury was significantly greater when compared to controls (Menet, Prieto, Privat, & y Ribotta, 2003). These studies might suggest that astrogliosis has a chronic negative effect on the recovery from AD, since it blocks restoration of functional connections. However, the blocking of regeneration by reactive astrocytes might also mean that the environment is just not yet deemed safe enough for axons to start regrowing (Osborn et al., 2016). Unfortunately, no research on this function or dysfunction in AD has yet been performed. Further research is needed to investigate if reduction of astrogliosis leads to axonal regeneration in AD.

Uptake and degradation of Aβ

Reactive astrocytes are thought to play a role in the clearance of Aβ plaques, both by uptake and degradation, but this is under discussion. Reactive astrocytes with internalised Aβ, including monomers, oligomers and fibrils, have been found in human post-mortem AD tissue (Thal et al., 2000). Mouse astrocytes from healthy mice have been shown to degrade Aβ in vitro. Dysfunctional astrocytes in AD were also observed, since astrocytes from the APP AD mouse model did not succeed in degradation of Aβ (Wyss-Coray et al., 2003). It can thus be concluded that there might be differences in the ability of reactive astrocytes to degrade Aβ in AD when compared to a healthy CNS, but the exact role of astrocytes in this process is not fully understood at this time.

Synaptic dysfunction: glutamate and GABA

One of the most important roles of an astrocyte in the healthy brain is its function in regulating neurotransmitter homeostasis for synaptic transmission. One component of this regulation is the glutamate/glutamine cycle. Extracellular glutamate is brought into the cell by glutamate transporters like excitatory amino acid transporter 2 (EAAT2). In AD however, Simpson et al. (2010) reported that the expression of these EAAT2 transporter proteins is decreased in reactive astrocytes. Furthermore, a decrease in the expression of glutamine synthetase (GS), the protein that converts glutamate into glutamine in astrocytes, is observed as well. This is seen in both APP/PS1 mouse (Orre et al., 2014) and human astrocytes (Ortinski et al., 2010). A proper glutamate/glutamine cycle is crucial for synaptic transmission and plasticity and an imbalance in this cycle can have negative effects. The reduced expression of both EAAT2 and GS will lead to an increase in glutamate that is left behind in the synaptic cleft, which could be a source of major excitotoxicity that possibly leads to the observed neuronal loss in AD. For example, in Wernicke encephalopathy and amyotrophic lateral sclerosis this excitotoxic glutamate has been shown to be at least partly responsible for neuronal loss (Rodríguez-Arellano, Parpura, Zorec, & Verkhratsky, 2016).

Not only glutamate homeostasis is deregulated in AD, reactive astrocytes also struggle with the regulation of homeostasis of other neurotransmitters, like GABA. GABA-related abnormalities in reactive astrocytes have been reported, for instance that expression of GABA and GABA transporter 3/4 was elevated in reactive astrocytes close to Aβ plaques in 5xFAD mice (Wu, Guo, Gearing, & Chen, 2014). Next to these findings, tonic inhibition in the areas where GABA levels were increased was also found. This could lead to a disruption in the balance between excitation and inhibition in the brain towards inhibition, which can have disastrous effects on neuronal function and cognition.

Aberrant calcium signalling: oxidative stress and blood flow

The astrocytic syncytia are formed by the gap junctions connecting astrocytes. Ca2+ ions can pass through these gap junctions and act as second messengers. These Ca2+ signals are for instance used for communicating with surrounding neurons (Avila-Muñoz & Arias, 2014) and gliotransmitter release (Verkhratsky et al., 2010). It has been reported that Aβ can cause changes in the frequency of Ca2+ oscillations in cultured astrocytes (Abramov, Canevari & Duchen, 2003). In reactive APP/PS1 mouse astrocytes near Aβ plaques, changes in the internal Ca2+ levels and frequency of Ca2+ oscillations have also been observed. In these astrocytes the internal Ca2+ levels were elevated and spontaneous Ca2+ waves that spread to nearby astrocytes appeared more frequently (Kuchibhotla, Lattarulo, Hyman, & Bacskai, 2009). These aberrant Ca2+ waves caused depletion of the antioxidant glutathione in both neurons and astrocytes, which could lead to vulnerability to oxidative stress. Indeed, 24 hours after the Ca2+ oscillations had been induced by Aβ, half of the cultured neurons had died (Abramov et al., 2003).

Ca2+ waves are also used in the signalling to surrounding blood vessels, to induce vasodilatation or vasoconstriction (Sofroniew & Vinters, 2010). In the 3x Tg-AD AD mouse model, astrocytes with a higher frequency of spontaneous Ca2+ oscillations were

associated with an unstable vasculature (Takano, Han, Deane, Zlokovic, & Nedergaard, 2007). Changes in the regulation of blood flow to neurons could lead to problems. Functional hyperaemic neurons have a higher blood flow demand for instance, but because of aberrant Ca2+ waves, the appropriate response in surrounding blood vessels might not be elicited. Ca2+ anomalies in reactive astrocytes could thus lead to a decrease in astrocytic supportive functions and even neuronal loss.

Disrupted glucose metabolism

The brain has a high glucose demand: with around 20% of the body's glucose derived energy usage it is the body's biggest user of glucose. The brain's glucose metabolism supplies it with this required energy (Mergenthaler, Lindauer, Dienel, & Meisel, 2013). In AD, it appears that the glucose metabolism in the brain and reactive astrocytes is affected. Pedrós et al. (2014) observed glucose intolerance and changes in expression of genes involved in glucose metabolism already early in AD pathology. More specific for astrocytes, it was shown that the glucose metabolism of in vitro astrocytes in the direct vicinity of Aβ was affected as well. These changes in glucose metabolism had a negative influence on the viability of co-cultured neurons (Allaman et al., 2010). Finally, research demonstrated that the glucose transporter 1 expression was lowered significantly in astrocytes in the arcAβ AD mouse model (Merlini, Meyer, Ulmann-Schuler, & Nitsch, 2011). This evidence all points towards a disrupted glucose metabolism in reactive astrocytes and suggests once again that the reactive state of astrocytes as induced by Aβ can have negative effects on neuronal survival.

Aβ production by reactive astrocytes

It is generally accepted that neurons are responsible for the production of Aβ, since they possess all the necessary molecular machinery like BACE1 in healthy conditions, unlike astrocytes (Verkhratsky et al., 2010). In AD pathology however, this may change. Various researchers showed that reactive astrocytes of Tg2576 AD mice near Aβ plaques exhibited BACE1 activity and this was also reported to be true in human reactive astrocytes (Hartlage-Rübsamen et al., 2003; Rossner, Apelt, Schliebs, Perez-Polo, & Bigl, 2001). Cytokines, for instance TNF-α and IFN-ɣ, are also able to induce activation of BACE1 in reactive wild type mouse astrocytes (Zhao, O'Connor & Vassar, 2011). Although this Aβ production by reactive astrocytes is likely not the primary source of Aβ in the AD brain (Rossner et al., 2001), it can definitely add to the Aβ plaque load and is certainly not helping in combatting the detrimental effects of Aβ in AD patients.

During an acute and short inflammation, the above-mentioned astrocytic properties or functions could prove beneficial. However, these same properties or functions can have severely negative effects in a situation where the brain is not able to rid itself of the inflammation and inflammatory stimulus. The balance between the helpful and damaging effects of astrogliosis is a thin line.

DISCUSSION

In the previous paragraphs the functioning of astrocytes has been discussed in health and in AD. Their versatile role as both a supportive cell and an immune cell and their ability to switch rapidly between these two, make astrocytes a very interesting cell type. Concerning AD, the available research suggests that reactive astrocytes have mostly detrimental effects on neuronal tissue, since they disregard their homeostatic functions and maintain a chronic inflammatory state. It remains unclear whether this switch in astrocyte functioning could actually be at the basis of AD, or if it is a reaction to AD pathological hallmarks.

Alterations of gene expression in reactive astrocytes during AD

Astrocytes are invaluable to the wellbeing of their surrounding cells. They have the properties to maintain balance in a healthy brain, but also to help combat an imbalance. However, in chronic disease such as progressive neurodegeneration as seen in AD, the changes astrocytes undergo can have quite the opposite effects. This can be seen in the reactive astrocytic functions that take a wrong turn or underperform in AD, such as described in 'The function and dysfunction of astrogliosis in AD'. Studies that looked into these differences between astrocytic functioning in the healthy brain and the AD brain on the level of gene expression have come up with some interesting results. Microarray analysis of the transcriptome of post-mortem astrocytes of AD patients revealed certain changes in gene expression. In the limbic stage of AD, Braak stages III-IV, deregulation of transcription of genes involved in apoptosis, proliferation, ubiquitin proteolysis and cytoskeleton could be seen in these astrocytes. This stage of AD is generally not associated with dementia or any other major symptoms of AD, but shows remarkable changes on the level of gene expression. Furthermore, in the isocortical stage of AD, Braak stages V-VI, changes in transcription of intracellular signalling pathways such as mitogen-activated protein kinase and insulin genes were also observed. These transcription differences lead to alterations in intracellular signalling pathways (Simpson et al., 2011). Next, Orre et al. (2014) reported that APP/PS1 mouse astrocytes in AD indeed obtain a pro-inflammatory state and an increase of immune-related gene transcripts. This is accompanied by a decreased expression of genes involved in neuronal communication and neuronal support. Moreover, these transcriptional gene changes to a more pro-inflammatory state were comparable to changes observed in a human astrocytic dataset, showing a common mechanism. Finally, inhibition of astrogliosis with the aminopyridazine

derivative compound MW01-070C in wild type rats after they had received successive Aβ infusions, lead to a decrease of inflammatory cytokine levels. Moreover, the levels of markers indicating synaptic dysfunction returned to the same levels as the controls and the number of Aβ plaques decreased. Thus, attenuating astrogliosis can have a positive effect on the welfare and functioning of the brain (Craft et al., 2004). These studies show that astrocytes have a greatly altered gene expression in AD and their switch to an inflammatory profile with the subsequent functional changes can have detrimental effects on neuronal survival.

Evidence for changes in astrocytes and astrogliosis before Aβ plaques formation

According to the amyloid cascade hypothesis, Aβ depositions are at the very source of AD pathology. In recent years however, increasing evidence has been gathered that questions this hypothesis. For instance, changes have been observed in mental capacities of animals before Aβ plaques were formed. Moreover, in an APP mutational mouse model synaptic loss was observed long before the formation of AD lesions (Redwine et al., 2003). Furthermore, Leon et al. (2010) showed that significant cognitive decline had already occurred in three month-old McGill-R-Thy1-APP mice, a transgenic model which they generated for this study. This cognitive decline could be seen before the extracellular aggregation of Aβ, which first started around six months. Additionally, in a human prospective cohort study it was found that ten years or more before the clinical diagnosis of AD dementia, changes in abstract thinking and information retention could already be distinguished (Elias et al., 2000). These studies suggest that mental capacities could be affected long before lesions arise in the brain or noticeable AD symptoms reveal themselves.

The amyloid cascade hypothesis also states that neuroinflammation, of which astrogliosis is a part, is the result of lesions such as Aβ plaques. However, this viewpoint is disputed more and more as well. Firstly, overexpression of S100β, indicative of astrogliosis, was reported in APPV717 mouse astrocytes already before Aβ plaques could be seen (Sheng et al., 2000). Secondly, Heneka et al. (2005) noticed this as well in the same mouse model but with GFAP overexpression. Furthermore, a rise in reactive astrocytes was seen in an APP/PS1 mouse model with orphan nuclear receptor Ear2 knock-out which does not produce Aβ proteins, when compared to the APP/PS1 mouse itself (Kummer et al., 2014). The appearance of astrogliosis even despite the absence of Aβ is more evidence that astrogliosis is not purely triggered by Aβ plaques. These studies indicate an alternative order of events in the early phase of AD.

Despite these studies, a side note should be placed here. There is still the possibility that the smaller Aβ oligomers or fibrils are the real culprit. In the above mentioned study by Heneka et al. (2005), the astrogliosis in the vicinity of neurons with activated BACE1 could also mean that the recently produced smaller fragments of Aβ trigger astrogliosis, instead of the other way around. Most studies focus on the manifestation of Aβ plaques, but do not look at the moment these smaller Aβ fragments begin to form. Oligomers and fibrils have been shown to be very neurotoxic and can be the trigger for astrogliosis. However, Krstic et al. (2012) reported that both wild-type and 3x Tg-AD mice would develop AD-like pathology, such as astrogliosis and formation of APP deposition and phosphorylated tau aggregation, following strong immune challenges either prenatally or in adulthood. This does again show a role for inflammation in the onset of AD, apart from the formation of Aβ.

CONCLUSIONS

Astrocytes have long been a neglected cell type in AD, but this is no longer the case. Their implications in the disease are far from fully understood, but impressive advances have been made in recent years and our knowledge of their properties and functions will continue to grow.

Astrocytes fulfil the tremendously important task of being a supportive cell type in the brain and they have many properties at their disposal to do so. Once the focus on this task wavers for a short amount of time, the brain will cope. This can be the case during a small infection of the CNS, in which astrocytes will return to their supportive duties relatively quickly. However, if a progressive trigger such as AD causes astrogliosis, the astrocytes can undergo a more chronic switch and stick to their immunoactive phenotype. This shift of focus that astrocytes undergo causes them to neglect their supportive role for the surrounding neuronal tissue. The change that is seen in astrocytes in AD can actually exacerbate AD pathology and prove disastrous for the brain.

The exact onset mechanism of AD is still not understood. Many have looked at the amyloid cascade hypothesis as the answer, but the foundations of the hypothesis are shaking. Despite the criticism on the hypothesis, there are still many questions before the hypothesis can be rejected, especially since the discoveries that Aβ oligomers and fibrils could be the compounds that are toxic and able to trigger neuroinflammation. Thus, at this time, no clear conclusions can be drawn on the order of events regarding astrogliosis and Aβ. However, an interesting AD hypothesis focused on astrocyte dysfunction has been suggested by Verkhratsky et al. (2010) (Figure 5). They hypothesise that atrophic astrocytes and the following supportive coverage reduction and dysfunction leads to synaptic loss. When Aβ arises in the later stages of AD, it activates both astrocytes and microglia, which become immunoactive. These glial cells will then start to release pro-inflammatory cytokines

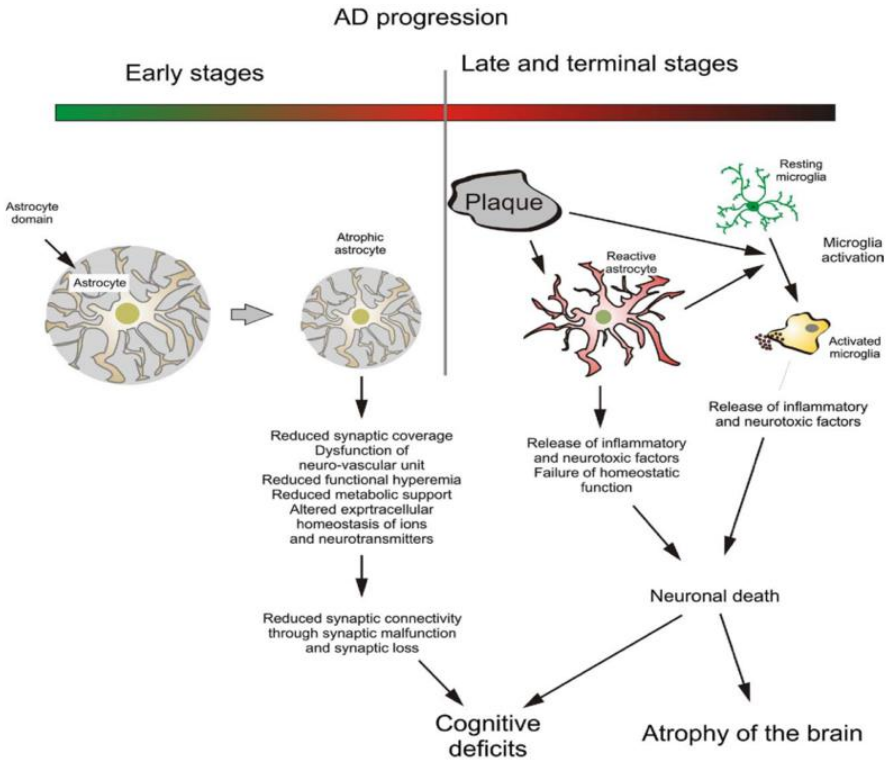

Figure 5 | An astrocytic hypothesis of AD.
A proposed hypothesis of AD, with astrocytic dysfunction at the centre. Atrophic astrocytes have a smaller coverage area and are accompanied by astrocytic dysfunctions, which will result in synaptic loss. In later stages of AD, Aβ comes into play and activates astrocytes and microglia. This causes release of inflammatory cytokines and further astrocytic dysfunction, leading to neuronal death and ultimately the characteristic cognitive impairment of AD. Image from Verkhratsky et al. (2010).

and become even less invested in their homeostatic tasks. This will lead to neuronal atrophy and death, finally resulting in the typical cognitive decline seen in AD. Although this theory is certainly alluring, more knowledge on the role of astrocytes is needed before it can be adopted. Astrocytes surely play an important role in AD pathology, but the present evidence is not enough to claim that either astrocytic hypertrophy, atrophy, or even both could precede Aβ formation and stand at the very origin of AD.

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CONFLICTS OF INTEREST

The author reports no conflicts of interest.

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Single cell RNA sequencing

The improved characterisation of cellular heterogeneity

Hulsebos, M.J.[1]

[1] Graduate School of Life Sciences, UMC Utrecht Brain Center Rudolf Magnus, Utrecht, the Netherlands

A common principle of cell biology is that each cell is unique in its (epi)genetic regulation, metabolic activity and in- and extrinsic cellular responses. Despite the fact that cell biologists have known this principle for quite some time, they had no way of distinguishing individual cells based on their transcriptome. Methods like fluorescence assisted cell sorting (FACS), next-generation sequencing (NGS), and the discovery of unique biological markers paved the way to describe cell types within an otherwise seemingly morphologically homogenous tissue.

Fortunately, a relatively new technique has become available: single cell RNA sequencing (scRNAseq). This technique enables researchers to distinguish individual cells based on their RNA profile (transcriptome). The general principle of scRNAseq is roughly equal across the board. However, there are many variations in each step, each with their unique advantages and disadvantages. Generally speaking, scRNAseq consists of isolating single cells, labeling these cells with an unique identifier and subsequent intermediate steps to generate single cell cDNA libraries by reverse transcription (Kolodziejczyk, Kim, Svensson, Marioni, & Teichmann, 2015). In this project, such technique will be applied in order to characterise ependymal cells generated from human iPS cells/mouse ES cells or organoids (Figure 1).

The advantages of scRNAseq are quite apparent. Finally, scientists are able to zoom in on tissue and capture the dynamics of a single cell more precisely. It allows one to delineate different cell types never described before. Though, this property should be evaluated very critically, as infinitely many cell types can be described on the basis of one or more up- or downregulated genes. The numbers of cell types that can be defined are thus quite arbitrary and the biological relevance of results must be considered when doing so. Another caveat is the amount of transcriptome data coming from ~20,000 genes for each cell. This results in large

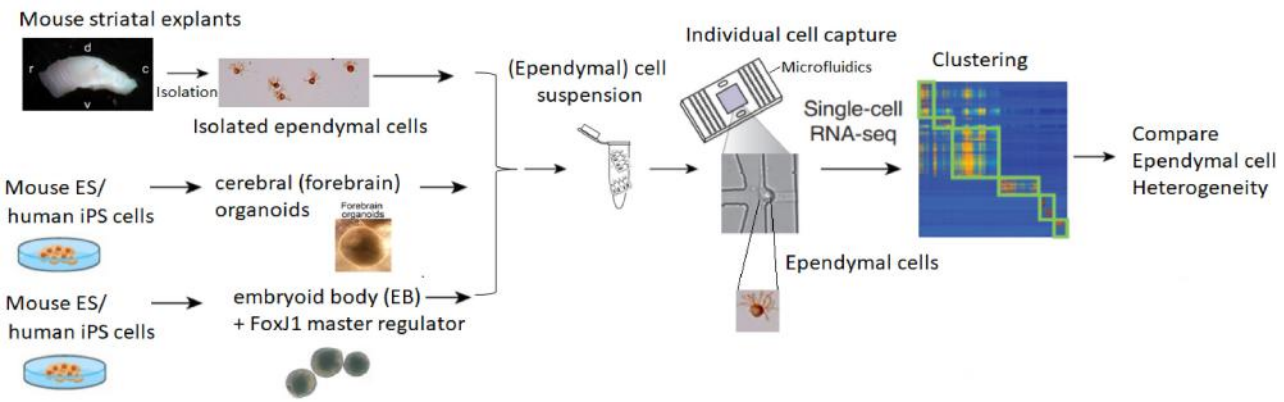

Figure 1 | Flowchart for the generation and characterisation of ependymal cells.
Left: three different approaches to acquire ependymal cells (1) isolation from primary brain tissue (2) isolation from cerebral organoids (3) generation via overexpression of a putative ependymal master regulator. All three approaches lead to the characterisation of these cells via scRNAseq to study cell heterogeneity, validate different model systems and to better understand molecular pathways implicated in stem-cell properties, specification and differentiation (Adapted from Zeisel et al., 2015).

amounts of data, even if the analysis only contains 100 cells. This data also needs to be processed, analysed and stored.

After processing the data with several quality control steps, the data has to be analysed. This portion of scRNAseq takes a considerable amount of effort. With the final dataset consisting of ~ 1,000 cells, which can be analysed in several ways, depending on the question being posed by the researcher. A common way to begin analysis is to use clustering. Clustering uses an algorithm to optimally rearrange the rows and columns of the data matrix. The generated clusters consist of a subset of rows, which exhibit a similar expression profile across a subset of columns. The generated clusters can be described as different cell types (classes), which can be divided into sub-cell types (subclasses). Two commonly used algorithms are hierarchical and k-means clustering. The hierarchical method is based on finding the nearest neighbor of a data point in 2D space, whereas k-means clustering clusters observations closest to the mean of that cluster. These correlated rows and columns can be visualised using a heatmap profile, showing correlation values represented as a colour hue (Figure 1).

However, the high dimensional data matrix space cannot be easily visualised and understood, due to the large number of genes. Therefore, dimension reduction algorithms are used to visualise and identify cell types on a 2D plane. Two methods generally used are: principal component analysis (PCA) and t-distributed stochastic neighbour embedding (t-SNE). Both methods use algorithms that minimise the number of variables that explains the maximum variation. Important to note is that different algorithms identify completely different cell types, therefore its biological meaning must always be taken into account.

The scRNAseq technique enables the single cell level to be as accurately described as never before. Naturally, the implementation of this technique has posed new challenges, like those of data handling and the determination of biological relevance of the obtained results. However, when scRNAseq matures and becomes widespread, it will surely enhance our understanding of the mechanisms for generating and maintaining cellular diversity.

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Big on Big Data

Floortje Scheepers

Prof. Dr. Floortje Scheepers is head of the department of Psychiatry of the UMC Utrecht. Aware of the complexity of the field, she is working in a patient-oriented innovative approach that implements Big Data as a crucial tool. Her goal: help patients in a realistic and practical way.

As the head of the department of Psychiatry of the UMC, you are in charge of both the care and education, but also the research part. How do you manage that?

"Yes, it is a lot of work, but I have a very strong management team. For example, in the care part, we divide our work in four departments: acute psychiatry, psychosis, developmental disorders and treatment resistant psychosis & severe depression. All four have two people in charge. So, even though I do visit the patients, I mostly supervise the people in charge of the departments."

You studied medicine, which is more clinically oriented. How did you end up doing research as well?

"I was always involved in research, care and education all combined, so when I did my PhD about psychosis I really had the idea that I could finally help patients with my research. I ended up a bit disappointed, because my topic was very fundamental and didn't yield clinical insight. After my PhD, I thought: 'This is not going to help people'. Psychiatry is about behaviour, cognition and emotions, and therefore too complex to reduce it to just one neurotransmitter or one structure in the brain. So, I changed my focus on more clinical research, and I asked myself: 'What kind of research would really help psychiatry improve? What kind of innovation is going on around us? And how is the world developing?'. That is the moment that I ran into the book of Viktor Mayer-Schönberger and Kenneth Cukier; *Big Data: a revolution that will transform how we live, work, and think*. His approach inspired me to think of new ways of using data from

daily practice; not the typical 'selected clear-cut bias patients' normally used in research, but the 'real ones', the ones from my doctor's room."

Is that when you started with projects like PsyNet and Big Data?

"Yes. Until five years ago, the way the different parts of the care chain worked together was not very efficient. Patients had to go from one organ-

isation to another, and there were problems like duplication of records and a lack of well-organised communication. We needed innovation to change that, and that is when PsyNet was born. It is a digital tool to connect all organisations in this region. Psychiatrists, general practitioners and social worker teams – for example – can communicate with each other through PsyNet. The patient and even informal caregivers – for example the mother of the patient – can be involved in it as well. They can all communicate together in the platform.

The project of Big Data is another one, and we do it at our department. We use all kinds of data from the electronic patient files – from the lab, questionnaires, texts, etc. – and we try to re-use it. In order to replicate and validate we also built a consortium, called 'compute visits data consortium', with three other psychiatric organisations: the Technische Universiteit Eindhoven and the beta faculty of the UU – because we needed a lot of data scientists and technicians in this project –, Mental health hospital (GGZ) in Eindhoven, Antonius Ziekenhuis in Utrecht, and Antes GGZ, a mental health care facility in Rotterdam."

> ***"We want to find the topics that we do not ask about but are still very important for psychiatric patients."***

Can you explain how you are processing this information?

"A lot of people think big data is only combining data in one big data pool and then try to analyse it. We do not want to connect data in one pool, because of patients' privacy and also because we think that we could use these separate data pools to replicate and validate our findings.

What we actually do is 'visit' the different data pools with the computer/tooling/algorithms/output. By placing the computer in another hub instead of bringing data together, we can try to replicate our findings and share knowledge. We do this a third time, and a fourth, and so on. It is like a carrousel; we re-do everything. Every time we are in another hub, we try to optimise our algorithms."

And did you find a lot of replication when you used the algorithms in other groups of patients?

"The consortium has just started, and up until now we only have output from our own department. However, we just got a grant to continue with the project, and we are already doing scrum sessions at our own department. In those sessions a data scientist, a psychiatrist, a nurse and a manager get together and look at all the data. Also, anyone who is interested and who has a question from practice can join the sessions. We visualise the data in a clear way, trying to make sense and value of it. When we find something interesting, we zoom in looking for missing data, mistakes in statistical analysis, etc. And then we do it all over again. It is really co-creation, a learning loop. It never stops!"

Do you specifically hire data scientists for this type of work? Or do people from the psychiatry department learn how to do it?

"We normally get them from external groups. It is very difficult to find good data scientists who want to commit themselves to care organizations though, as they prefer companies like Google or Facebook, where they can be creative…"

So, would you say that somebody from the Neuroscience & Cognition Master could specialise in this field as well? Could they contribute as data scientists?

"Yeah! We have Master students all the time. From all kinds of studies: medical, social, etc. We are organised in a way that the clinician of the ward poses a question during the scrum session, and then the rest of the group – data scientists, but also Master and even Bachelor students – works together to see if the answer can be found with the data we have.

We need people who know how the brain works and how the person behaves."

Your approach sounds really humanistic and practical.

"I will tell you about another project, also related to big data. It is called 'The Story Bank'. It is a digital platform where patients and informal caregivers share their life story. Also, professionals add their experiences. Those stories can be analysed with machine learning and text mining by some of the researchers here. A philosopher and a language skill post-doc then do the same, but manually. We want to know, whether there are differences when you do the analysis in a manual way or with a computer. To add to that we want to see if there are distinctive patterns that emerge from these stories. And lastly, we would use that information for daily treatment. Because we want to find the topics that we do not ask about but are still very important for psychiatric patients.

Big data is not always about "BIG data" and volume. It is also about the complexity and variety of data. You have the *five Vs of Big Data*... Can you name them?"

No! What are they?

"Big data is *volume*, of course. Everybody knows that. But it is also *variety*, combining different sources of data. It is *velocity*, the speed at which you can collect data – big data of one person can be collected if you have a wearable device that monitors, for example, your blood pressure seven days a week, 24 hours a day. Big data is *validity*, how representative the data is for real life – whether it really tells us something about this person. This is a problem that occurs when you collect data in a more old-fashioned way, like a questionnaire. You get an answer of one fixed moment in time. But it does not tell you anything about how the patient's feeling fluctuated throughout time. The last "v" is *value*, how you create significant results from this mix of information."

Could you give us an example of clinical use of big data on which you are working at the moment? And is it already being put in practice?

"We are now looking at aggression. Aggression is a really big burden for patients, but also for professionals, particularly nurses. Our goal is to reduce aggression. However, it is really difficult to predict. We are trying to find clues, predictive profiles for an aggressive episode in order to prevent it.

We found a lot of signs already. For example, if nurses report 150 words or more in the electronic patient files for two days in a row, the third day there is more than 85% chance of aggressive behaviour. Nurses can use this knowledge: on day three, they could take the patient for a walk, or sit with them for a cup of coffee, thereby maybe avoiding the traumatic episode. These findings can be implemented right away in the clinical setting!"

> ***"A lot of important things in care are not measurable."***

What will be the consequences of this way of working?

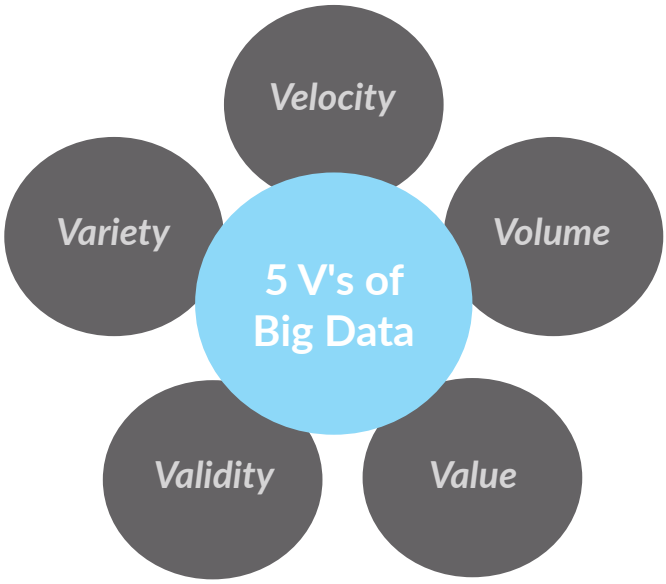
"Doctors have their theoretical knowledge and experience with patients. In the nearby future the aggregated data-knowledge from the electronic patient files could be presented to the doctor through a 'decision support system'. The information will be customised for each patient. It is clearly visualised for both doctor and patient, which makes it possible to discuss and make further decisions together. The experience of the patient, the professional experience of the doctor and the data combined have more value. This system may be 'the doctor of the future'."

So, it will not replace the doctor's opinion, but it serves just as a helpful tool.

"Yes! A lot of important things in care are not measureable. Data is fixed points in time, and what you feel in the room is dynamic. You could name this "emergence". Complex systems (like human beings) are not to be understood if reduced to separate particles. However, together they have a new dimension."

Is the brain itself comparable with big data?

"Big data can provide answers on how complex sys-



tems work. The brain does not work solitary; it is in constant interaction with everything around us, and with everything in your body. Every step we take has an influence on how the brain is reacting upon it. It is a complex system, and these systems need complexity science. The term "exposome" defines the dynamics of our surroundings – air, pollution, all the things that interplay around us - that have an effect on our health and the way we think. I do not think we will find a solution, but with big data we may be able to understand better how it all works.

This makes us understand how modest we need to be in our research."

> ***"Complex systems (like human beings) are not to be understood if reduced to separate particles."***

Will big data be a big breakthrough in psychiatry?

"Yes, but beware! It is not the golden egg. It is not about great breakthroughs, it is about tiny steps in daily practice, about learning how we can improve. Big data does not solve the problem of complexity. Since big data can take all aspects of psychiatry into account, it is a better fit to the real patients we see every day."

Is big data expensive in this field?

"Compared to fundamental research, big data is actually very cheap. However fundamental research is still very necessary. Because sometimes you have to zoom into specific things to understand how it works, and then zoom out again to better understand the process with the help of big data."

Is science changing with all this innovation?

"Absolutely. Frank Miedema, from the University Hospital here in Utrecht is carrying out a project called 'Science in transition'. It started around five years ago, and it tries to transform science into more impact and societal science, in order to help society solve big problems. Now, five years later, we are almost at a turning point where a lot of people feel that science also has a responsibility towards society. Science should not be focused on complete freedom in creativity anymore but rather show results that help us design the future in a sensitive way. Innovation in technology is going so fast, and we do not even realise what the impact will be. We have to step down and think: 'What are the major problems in the world that we have to solve?'. We need to work together and solve these problems, instead of speeding towards the future, which may be very scary if you read the book '*Life 3.0*'!" ■

Floortje recommends you these books:

Big Data: a revolution that will transform how we live, work, and think
by Viktor Mayer-Schönberger & Kenneth Cukier

The future of professions
by Richard Susskind & Daniel Susskind

Life 3.0
by Max Tegmark

We are Big Data: The Future of the Information Society
by Sander Klous

Het nieuwe brein van de dokter
by Erik-Jan Vlieger

Big on Big Data

Jan Veldink

Prof. Dr. Jan Veldink is an example of working interdisciplinary: he is both a clinical neurologist and principal investigator of Project MinE. By sequencing genomes of 15,000 patients with Amyotrophic Lateral Sclerosis (ALS) in an extensive international study, he hopes to unravel the genetic architecture of this disease.

What is your background?

"I started with studying medicine in Utrecht, since it is so diverse and has a bit of everything: psychology, math, sociology and biology. Back then, education was combined for medical and biomedical students in the first two years. From the start I knew I wanted to do research as well, I really liked and still like the combination."

What are the advantages of combining research and the clinical work?

"This combination creates more diversity in the work and makes me less vulnerable. It is nice to switch between numbers and the occasional emotional work. I think I would get bored if it is only one of them. Furthermore, working in the clinic has its benefits. Problems that are faced and questions that patients have sometimes lead to a research question. Moreover, for Project MinE, patients are participating in my study by filling out questionnaires, giving blood samples and showing up for measurements. But sometimes, patients with a specific profession such as IT or consultancy, are even willing to involve their company or their own expertise. That is amazing and can be very helpful."

At what point of your career did you start focussing on ALS?

"It was clear during my study of medicine that I wanted to become a neurologist because of the complexities of the nervous system and the characteristic clinical reasoning in neurology. It is the combination of knowledge and logical thinking that is important in neurology. As a neurologist, first you localise the problem of a patient in the nervous system, and then start to come up with a differential diagnosis. During my training as a neurologist, I came in contact with the subject of ALS. This is a lethal neurodegenerative disease, in which motor neurons in the brain, brainstem and spinal cord progressively deteriorate and die, leading to progressive muscle weakness."

Since ALS is such a devastating disease, what is it like for you? Is this hard sometimes?

"It is a well-known phenomenon for neurologists,

nurses, physiotherapists and other people who work with ALS patients, that they can get depressed or lose their enthusiasm. It can be very hard, if you only see ALS patients. If it is a bad day, we bring news to seven people that they are diagnosed with ALS. That is why the combination with research helps. So yes, it can be though, interruptions can then make the work easier."

> ***"We store all this data on SURFsara, a 'super computer' in Amsterdam. Data is coming in automatically as we speak."***

Can you tell us a bit more about Project MinE, this big project on ALS that you are currently involved in?

"Project MinE was initiated by patients. The start of the project was during a tour in our research lab that we regularly give to inform our patients about the process of ALS research. We organise these tours in order to show patients, their relatives and other stakeholders what we do in the lab. Two patients, Bernard Muller and Robert Jan Stuit, attended the tour. Wouter van Rheenen, a PhD student, showed DNA samples in the freezer. Bernard Muller asked: 'What are you doing with these samples?' 'Nothing much, we are just collecting and storing them, waiting for better times' said Wouter. Bernard asked: 'Why are you not sequencing them? This is waiting for an answer!' Wouter replied: 'Yes, but that costs a lot of money. It is pretty expensive to sequence a genome or do a chip.' And then Bernard, who is an entrepreneur and made a lot of money in his life, responded: 'Okay, that is a clear assignment. For me, for us. That is what we are going to arrange and pursue to get this DNA sequenced.' And he did. Also, at that time, by coincidence, the Ice Bucket Challenge came around. That was, of course, not organised by Bernard Muller, but raised obviously a lot of money in many countries. That helped as well to get this project started. The data is already there, you can mine it and look for associations. That is the term of Project MinE. You can extract this genomic information forever and integrate it with other data later."

How far does project MinE spread? Do you sometimes experience cultural differences between the countries?

"There are now 17 countries involved. Most are Western European countries: the United Kingdom, France, Ireland and the United States, but also Turkey, Russia, Slovenia, and India are involved. And yes, we do see a lot of important differences. For example: some countries do not allow transportation of DNA to other countries. Then, you must get the blood samples and sequence the DNA locally, which is a challenge. Meetings can be very political as well, like the European Union. You sit around the table with 17 partners, who all have their opinions and backgrounds. For example, in the beginning, several partners tried to be the prime site for data collection, as that might result in more control over the data. Also, coming up with a consensus regarding the specific clinical data we collect, took months. I experience that to be difficult sometimes, but also a challenge."

How do you store all this international data?

"We store all this data on SURFsara, a 'super computer' in Amsterdam. We convinced the sequencing company Illumina to liaise with SURFsara, leading to a direct data connection between Illumina and SURFsara. So, data is coming in automatically as we speak. The unique thing about SURFsara is that it can store a huge amount of data, but it also has a great computing power to process the data. We currently have 10,000 profiles: 7,000 ALS cases and 3,000 controls of roughly 100 GB per sample. Furthermore, it is crucial that researchers remain fully in control of their data and samples. It is not that they deliver it to Project MinE and lose control of it. For example, someone from Spain, can log onto their account, and see the Spanish sequenced data. If they would like to access the rest of the data, then it is a simple request that we send around to all the principal investigators. You can allow people to access all data."

> *"The people in my research group in Utrecht all have this inclination for bioinformatics, but with different backgrounds as well: psychology, biomedical sciences and biology."*

How long do you think that you need to finish this project?

"We currently have 10,000 profiles sequenced, we aim for 22,500 (15,000 patients and 7,500 controls). The strategy right now is to get Project MinE connected to other projects that sequence ALS genomes. We should be realistic, there is no Ice Bucket Challenge right now. In the near future, less money will be invested in sequencing new genomes as there was in the beginning. Luckily, there are other projects going on throughout the world, such as in Australia and the US. My focus now, is to get those on board and combine their data with ours, hopefully using SURFsara of course."

What will be the next step with this data?

"We are not going to wait to do the analyses until we have all the profiles. We already did quite some analyses on the data that we already have and discovered some genes and mutations linked to ALS, including *NEK1*, *TBK1*, and *KIF5a*. The goal is to get a clue what the problem is, since there is currently no therapy for ALS. We hope that in the end a few percent of the patients, those with the same variant, have their own specific advanced gene therapy. For the most common genetic abnormality, the *C9orf72* mutation, there will be a start of a phase 1 study this year, targeted at this mutation. If it works, this will be an example of how gene therapy could work for other mutations causing this disease. There are indications that ALS is not a simple disease; you need a few mutations to get it. One of the most important benefits of having all these data together and scattered around the globe, is that you can look at combinations of mutations. You do not always get sick if you have one variant, probably because there is a second or a third variant needed. Therefore, analysing the architecture of ALS is one of the most important aspects."

Why do you think big data is useful for genetic research, and generally in research?

"There are many forms of big data. There can be a big sample of many patients but with little individual data or a few but very rich samples. Project MinE is both: you have many samples and huge amounts of data per sample. This determines what you can do with it. If the disease is complex, you need huge samples to detect homogenous subgroups or patterns in data. If you really think about the future, we will probably end up using other statistical techniques than we do now, such as deep learning and machine learning. Deep learning includes trying to detect linear and non-linear combinations in big data, in order to test if these patterns have predictive value. These patterns cannot be recognized by human beings—many compute cores are needed. For that, you really need these rich well-structured datasets. For example, you could have a deep learning model based on 100,000 genomes, 'Project MinE 4.0'. This can be used to see if a patient suspected of ALS has the disease or can be used to predict the chances of survival. That is sort of the 'long long long term' prospect."

To analyse all this data, what kind of programming languages do you currently use?

"I think it is good to realise that for Project MinE, we are not so much programming ourselves, it is usually being able to use non-standard algorithms and tools that have been programmed by other people. Sometimes we co-develop new tools. For example, we developed a tool to detect this repeat expansion in *C9orf72*, which is not a standard thing you can look at in the whole genome sequencing data. There is not only one programming language that we use. Mostly we use R for scripting, Pearl and some Java-based programmes. So, it is very diverse."

What kind of people are in your research group?

"For this workflow, people should be able to use parallel computing efficiently and adequately—they have to do many jobs at the same time to find a quick answer. This means that people need to be able to work with 'HPC': high-performance computing, which typically involves some cloud solution of many compute cores without standard operating systems like Windows or Mac OS, but more like Unix or Linux based operating systems. The background of the international research group is diverse: some are Doctors of Medicine like myself, some are PhD students and others have a neurology background. The core of this group is made up of people with an expertise in bioinformatics. They are always there to educate and help the rest and will remain in the research group. When PhD students or Postdocs move away again, this core group still knows what to do and where the data can be found. The people in my research group in Utrecht all have this inclination for bioinformatics, but with different backgrounds as well: psychology, biomedical sciences and biology. When I am hiring people, the most important aspect is that they are interested in and open for using bioinformatics and programming to answer research questions. I believe that they need to be intrigued by this way of working, it is not so important what they have previously programmed. People are very accustomed to Excel and tend to see all their data in columns and rows. For this, you need to learn to work with data objects that are hidden in your computer. If you like that sort of game, then you are welcome!"

> ***"Realise that science can be tedious, without glory, and sometimes even unfair. It is, therefore, crucial to have a strong intrinsic motivation."***

Finally, do you have tips for students who are just starting their scientific career?

"First ask yourself if you really want this and why. Is it an intrinsic curiosity that is driving you, or some desire for fame and impact? Or maybe a bit of all of this? Realise that science can be tedious, without glory, and sometimes even unfair. It is, therefore, crucial to have a strong intrinsic motivation, larger than fame or impact alone. In addition, realise that people will not automatically recognise your quality, there is a bit of 'selling yourself' to the outside world needed (giving talks and interviews!)." ■

Outbound...

United States of America

"The researchers here are extremely friendly and helpful, and criticism after presenting your data is always constructive."

NAME

Christy-Joy Kolsteeg

HOST INSTITUTION

Harvard Medical School/Massachusetts General Hospital, Boston, USA

TOPIC

The role of tumour-derived extracellular vesicles in modification of the brain microenvironment.

During my first internship in the Pasterkamp group, I met Lieke van de Haar, a PhD who just came back from an internship in Boston. She was very positive about her experience and referred me to the lab of the American professor Xandra Breakefield and Dutch neurosurgeon/PhD Marike Broekman. Marike interviewed me over the phone, and she told me with great enthusiasm about Boston and the Breakefield Laboratory. The laboratory's expertise mainly lies in extracellular vesicles released by tumour cells, a relatively new and exciting field. As I had been working on ALS and neurons during my previous internship, this topic seemed very interesting, because it was something completely different. I personally think it's wise to explore different top-

ics during your Masters, because it can help you find out which career path you want to take in the future.

Some mailing back and forth and two reference letters later, I received the great news from Marike: I could come to Boston! After a few days of joy, it became clear to me that planning this internship would be a lot of work. For example, I had to arrange my visa, a time-consuming job due to all the paperwork, and I had to write my own research proposal for the GSLS. Moreover, I had to apply for scholarships, as Boston is one of the most expensive cities of the USA. Raising funds may sound like a tough job, but I'm convinced that if you have good grades and great motivation, anyone from N&C should be able to do it. On top of that, Lieke and Marike were always available to help me, and they made this process a whole lot easier on me.

October last year the moment had come to move to Boston. I first stayed in an Airbnb so I could look for a room from there and explore the city. It is possible to look for a room from home via the internet, but because the rents are so high I preferred to look at some places first and then make a well-considered decision. Besides, moving

to a new city brings about a lot of impressions and excitement, and therefore it's good to have a little time to settle down. In the beginning, I was a bit nervous about starting my internship at Harvard because I expected some fierce competition. However, the opposite was true. The researchers here are extremely friendly and helpful, and criticism after presenting your data is always constructive. Xandra Breakefield is an amazing leader with a warm personality, who, even after years of experience, still looks with the greatest care at every little graph you show. I also noticed soon that I get a lot of freedom here to perform my research, and that there are a lot of experts around in Boston, which together make the possibilities endless.

In addition to conducting your research, it's important to relax after work. Boston is a relatively small, but lively city with loads of fun bars and restaurants. Boston has multiple universities and hospitals, which brings together students and researchers from all over the world. Especially during this era of social media, it's easy to join a get-together or a sports team in order to get to know new people. Already during my first week, I made an amazing group of friends whom I hang out with multiple times a week and share every experience with. In conclusion, doing your second internship in Boston will be an unforgettable experience, which will result in a lot of professional and personal growth. I can highly recommend it to anyone! ■

Scotland

"I would certainly advise to choose your internships in different areas to learn as many techniques as possible, of course about topics you like."

NAME

Eline Feenstra

HOST INSTITUTION

Centre for Regenerative Medicine

Edinburgh, University of Edinburgh,

Scotland

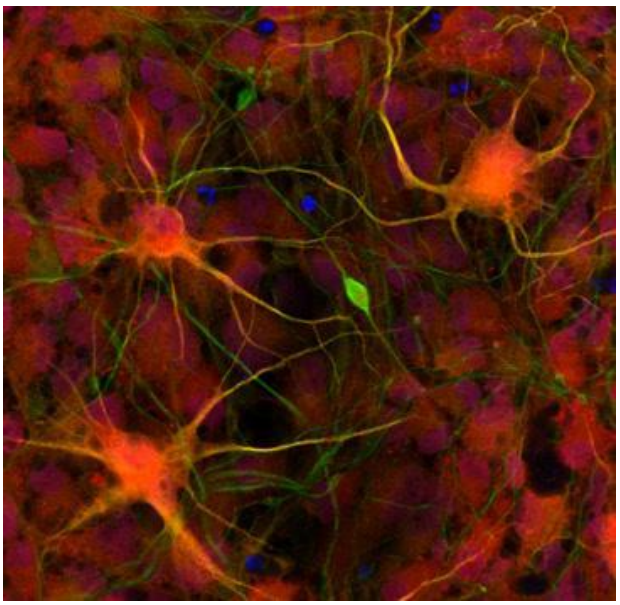
TOPIC

Axonal regeneration

At the start of the masters Neuroscience & Cognition, during the introduction course, students told us about their experiences abroad. One of the girls presenting that day showed her work on axonal regeneration and pictures of her stay in Edinburgh. I was immediately appealed by the research topic and the city, so I wrote down her name, just in case I would need it someday.

Time passed, and I started my major internship in Amsterdam at the Netherlands Institute for Neuroscience. I really liked my time there working on visual plasticity in mice, but kept the idea of Edinburgh in mind and I decided to write to the Centre for Regenerative Medicine. After arranging a skype session they invited me to come for one day and night in April to meet the lab. It took only an hour by plane to get to Edinburgh and the first thing I noticed after entering the city centre were the beautiful old buildings and cosy live-music pubs (of which the latter immediately encouraged me to play myself). In the evening, I had dinner with the lab members in a nice restaurant in town.

The next day we met early in the lab and I gave a presentation about my internship in Amsterdam. The rest of the day I went to lab meetings and spoke to many people to get an idea of the



Human embryonic stem cell derived neurons

research going on. After a last walk to the Edinburgh castle, I went home, really enthusiastic about the perspective of going back to Edinburgh for six months in October.

After finishing my major internship in Amsterdam and writing for funding, I took a few weeks off to arrange my stay in Edinburgh. It took me a month of searching before I found the perfect room in the city centre near the Meadows, together with four lovely housemates. I went to Edinburgh by boat and car to take all my stuff with me, including my guitar. My first week in Edinburgh consisted mainly of meeting my flatmates and being a tourist, including visiting all the highlights in Edinburgh and whisky tasting. The easiest way to get to know people in a new city is to find a house with other students. Furthermore, I have been on different international student trips, for example to Loch Ness, Inverness and St Andrews. The second week I started my internship focussing on axonal regeneration, using human embryonic stem cells. I am still working on this project and I will stay in Edinburgh until the end of April. I have really liked my time here so far and enjoyed the big differences between my internships (animal vs cell culture). I would certainly advise to choose your internships in different areas to learn as many techniques as possible, of course about topics you like. I would definitely recommend going abroad. It is an incredibly cool experience to get out of your comfort zone and have the opportunity to meet new people and visit amazing places, especially Edinburgh. ■

...and inbound!

The Netherlands

"Outside the context of America, it is impossible to be 'Docky' without also being 'Docky the American'."

NAME

Docky Duncan

HOST INSTITUTION

AttentionLab, Eperimental Psychology, Utrecht University, Utrecht, The Netherlands

TOPIC

Inattentional context effects on visuospatial short term memory

"OUT OF CONTEXT"

I never really felt American until I left America. I spent the first 17 years of my life in the United States (US), and when I left to do my Bachelor's abroad it was in no small part to escape from what I saw as a sort of toxic nationalism. In the US, "Feeling American" has been highly commoditized in a million beer commercials and political slogans as a mix between tenacious nationalism, youthful overestimation and the desire to buy things, usually trucks. "Feeling American" is derived from the sense of American exceptionalism, which is so difficult to explain to Europeans; a sense which carries with it the implication that if America is the greatest country filled with the greatest people in the world, then why would any reasonable person ever choose to leave? And so I was very surprised when I found that it was this very unpatriotic act of leaving that was the catalyst to my own feelings of national belonging.

It is in the question "Where are you from?", a common question everywhere in the world and a question which essentially has one answer, and yet my answer to that question changes depending on where and to whom I am speaking. In California I would probably say I was from San Jose, in other states I would probably just say California, or maybe San Francisco to sound cooler. But here in the Netherlands where I currently live, that information usually appeals to empty references, and so, even though 99% of the US is as familiar to me as say Namibia, my normal response is that I am from America. All of it.

In the borders of my home country it is easy to disassociate myself from my national identity, but outside the context of America it is impossible to be "Docky" without also being "Docky the American." And while many people have strong impressions of the US, I feel most American when I meet someone that does not and maybe only knows what can be learned about the US from watching television and movies. To them I may be the realest thing they have ever encountered from that part of the world, and they eagerly take my personal experiences as representative of some larger "Americanness." If I am funny, sad or rude, then it is taken that all Americans are funny, sad or rude. And though I share about as much in common with all 323 million Americans as any other group of people, this representation connects me to all of them.

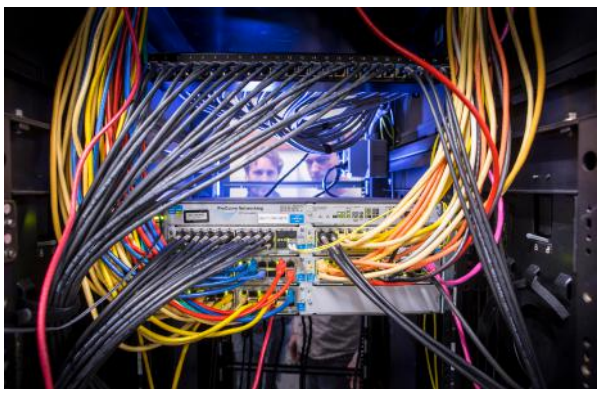
This is what I mean by "feeling American"; it's being unable to represent myself without also representing my country. This is a feeling of national connection that you too will feel if you ever have the opportunity to take your studies and your life abroad; a feeling much more meaningful than the idealized beer commercial brand of nationalism I knew before I had left America. It changes the way you think of your country because it changes the way you think of yourself. And while there is a real and sometimes catastrophic debate in my home country about who is and is not really American, abroad it is much simpler – to be American is just to be myself. It affords me the opportunity to emphasize the parts that I think are best about my country, but also to talk critically about its many problems without fear of being called "un-American" for upsetting someone's idealized view of our nation. And through this experience of being abroad, our individual differences are muted in comparison to the very many small things we share as compatriots; subtle similarities which become meaningful abroad and go on to make up my own definition of "Americanness." Things often look different from the outside, and it's good to spend some time out of context. ■

What is a "Profile"?

Within the Graduate School of Life Sciences, several profiles are offered that can replace your minor research project. In this section, we highlight two of the interdisciplinary research focused profiles. These two profiles are involved in the use and development of computational science and relate to the theme of 'Big Data'.

Bioinformatics Profile

Bas van Breukelen



Probably everyone has heard about the big data wave that is flooding our proverbial beaches. In almost every corner of research and especially in life sciences, massive amounts of data are produced in every single experiment. Suddenly you, as a researcher, find out that it is almost impossible to analyse your data in Excel and that there is a need for better and more advanced data processing, analyses and visualisation. This is where the field of bioinformatics comes into view.

Bioinformaticians are scientists that have learned to apply computational techniques from the fields of data sciences, mathematics, statistics and many more to delve deeper into the data produced in biological experiments, such as genomics - in which the DNA of one or multiple subjects are sequenced and compared to find certain changes in the DNA sequence - and proteomics - in which the complete proteome with all its modifications is recorded and compared. On top that, all these already massive datasets can be combined and integrated to obtain even more insight in biological processes. To find the factors that cause a certain phenotype, these data can in turn be combined with other population data, such as for example that of patient cohorts with neurological diseases.

The Utrecht Bioinformatics Centre, ubc.uu.nl, has created a Master's profile that can be planned as a part of your minor and electives. This bioinformatics profile has a goal to teach the future scientist to be able to analyse his/her own large datasets, rather than being completely dependent on bioinformaticians. Although it is not possible to train you as a full fletched bioinformatician, as this is a Master's on its own, you will be better able to talk to a bioinformatician for additional help when things become too complicated. The bioinformatics profile has two forms; a 'short' 33 EC version, that has 15 EC of bioinformatics courses and an 18 EC bioinformatics project and a 'big' 45 EC version that has 12 EC of courses and a 33 EC bioinformatics internship. We recommend the last version, as an internship is really beneficial for your further career as a scientist. An internship allows for a much more in depth, hands-on, training in bioinformatics and looks good on your CV as well. As a bonus, you are allowed to go abroad to another country to do your internship!

Are you interested in our bioinformatics profile and would you like to learn more about its background and our courses? Contact the UBC bioinformatics profile coordinator, Dr Bas van Breukelen, b.vanbreukelen@uu.nl for an appointment. ■

Complex systems Profile

Kirsten ten Tusscher

The term complex systems is used for systems composed of many interacting particles, where the properties of the system as a whole depend not only on the properties of the individual particles but also strongly depend on the complicated manners in which these different particles interact. Examples of complex systems range from termite mounds and ecosystems to the weather and climate systems, the economy, social systems and the world wide web. Clearly, the human brain with its many complex interactions amongst neurons is such a complex system.

Independent of whether one is studying a social interaction network or the human brain, typical questions for complex systems are what happens if one or a few particles in the network fail, e.g. a neuron that dies or a friend that is moving abroad, and how this depends on the position of this particle in the network and the number of interactions with other particles it has. Other typical questions are how the emergent properties of the system, for example cognition, can be understood from the interactions amongst particles, i.e. the network and processing properties of the brain.

Answering these types of questions requires an interdisciplinary approach, with an important role for mathematical modelling and computer simulation techniques. Mathematical and computational modelling approaches have traditionally played an important role in neurosciences, and have helped elucidate how action potentials are generated via the famous Hodgkin-Huxley model, or led to the Hebbian learning rule suggesting that learning involves strengthening of specific neural interactions. With the increase of computer power, larger and larger networks of neurons, with individual neurons simulated in more details are being investigated (e.g. the blue brain project).

The goal of the complex systems profile is to learn to use such an interdisciplinary approach, learn how this same approach can be applied across a wide variety of disciplines dealing with complex systems problems, and apply it to life science problems. Students will get an understanding of the various models used in the complexity field and the dynamics (i.e. transitions, predictability) that play an important role. Students applying for this Master's profile should have an affinity for this quantitative approach.

The Complex System's profile consists of electives and a thesis on a complex systems topic. In order to stimulate the interdisciplinary approach of the profile, at least two supervisors from different departments or faculties should be involved in the thesis. Students can choose electives on complex systems topics like computational biology or toy models. All students receive a certificate upon completion of the profile. Students can apply by sending an email to the profile coordinator, Prof. Kirsten ten Tusscher (K.H.W.J.tenTusscher@uu.nl). ■

NVP Winter Conference 2017

Sanne Böing

December 14, 2017. A harsh freezing wind caused my overdressed legs to tremble and my hair to get wrapped around my head. All clotted together we stood there excited, waiting for the bus that would take us to the long-awaited biannual Winter Conference 2017 of the 'Nederlandse Vereniging voor Psychonomie' (NVP; Dutch Association for Psychonomics), that would last for three days. The conference was held in Egmond aan Zee and offered a variety of topics presented in various settings: poster presentations, parallel sessions and keynote lectures. Subjectively, the waiting felt like hours. But maybe that was just our own stupid fault: we were standing on the wrong side of the station.

After a short introduction by the organising committee, all scientists were unleashed to attend their parallel session of preference, which were grouped by category. All topics fit in the field of scientific research in psychology, with a focus on studying laws in human behaviour and the underlying biological processes. Since my internship is about multisensory integration in spatial perception and several researchers of the department of Experimental Psychology presented here, I preferred attending the sessions about perception. The parallel sessions were really informative and doable, because they consisted of four short presentations of 15 minutes. What is striking, yet comforting to notice as a student, is that even experienced scientists sometimes have difficulty putting only the most relevant information in a comprehensive talk. Or to not talk too fast.

During the poster presentations I encountered a study on misophonia, which refers to a condition in which specific sounds - mostly produced by other people - yield enormous feelings of irritation and abomination. It really drew my attention, since I hate the sound of my mom eating a cookie or swallowing her coffee. Now I have learned that the aversion to the sound is not a physical auditory property per se, but that it probably has something to do with the social component. Well, I immediately tried to relate to some of these findings during dinner, which was amazing. The best part was when the cooks came in with sparkles put on ice cakes, accompanied by Robbie William's 'Let me entertain you'.

The conference was not only very informative and insightful in how scientific community shares ideas and findings, it was also very fun. Never before did I have the chance to get to know researchers in such an informal way. Who could have guessed that our own CN track coordinator is a fantastic DJ, who even got the stiffest researchers dancing on the lighted, coloured dance floor? Britney Spears requests were frequently submitted – they never made it. A glass of wine at dinner loosened the tongues and resulted in a very amusing discussion about artificial intelligence taking over. The conference also offered a great opportunity to get to know the other Neuroscience and Cognition students somewhat better (yes, we had shared rooms, so we could wake each other up for breakfast by shouting 'GOOD MORNING' too enthusiastically) and a good moment to gain muscles and some fresh air over a short stroll on the beach.

The NVP conference is known for its informal character. I know that not all conferences will be like this, but for sure, this first encounter made an indelible impression! ■

Erratum volume 11, edition 2 – October 2017

We would hereby like to report on an erroneous printing of the abstract of the article "Smart drugs: fuel your brain!" by Jet Termorshuizen in edition 2 of volume 11 of this journal as published October 2017. Please find the correct version below and disregard the previous.

With our sincerest apologies,

The Editorial Board of the Journal of Neuroscience and Cognition 2017-2018

Smart drugs: fuel your brain!

Jet Termorshuizen[1]

[1] Master student, Graduate School of Life Sciences, Utrecht University, Utrecht, The Netherlands

Have you ever heard of smart drugs? Cognitive enhancers? Nootropics? 'Fuel your brain with the latest in neuroscience!' 'Improve memory with smart drug supplements!' To be honest, I had never heard of these kinds of drugs. My roommate told me about this phenomenon, and he said that people in Silicon Valley routinely take this drug 'to get ahead'. He also told me that types of these drugs are sold in supermarkets in the Netherlands, called 'Study Buddy' – 'Boost your concentration, thé healthy alternative for coffee and energy drinks'! It claims to directly raise your concentration and, 'of course – it's 100% natural'.

I want to know everything about these 'smart drugs'. And, most of all: is there a scientific foundation for the message coming from the media and the internet? Do these drugs really make you smart? In this short article, I will summarize claims found on the internet, whilst also doing this for scientific publications about smart drugs. Let's find out what's true according to the media, and according to science.

Thank you to our contributors

Authors:
Tuomas ten Cate
Coen van Deursen
Dennis Trommelen
Christy-Joy Kolsteeg
Eline Feenstra
Docky Duncan
Matthijs Hulsebos
Bas van Breukelen
Kirsten ten Tusscher
Sanne Böing
Vera Wielenga

Reviewers:
Dorien Huijser
Katerina Kalamari
Mats van der Heide
Coen van Deursen
Nadia Leen
Mirjam Adams

Interview:
Floortje Scheepers
Jan Veldink