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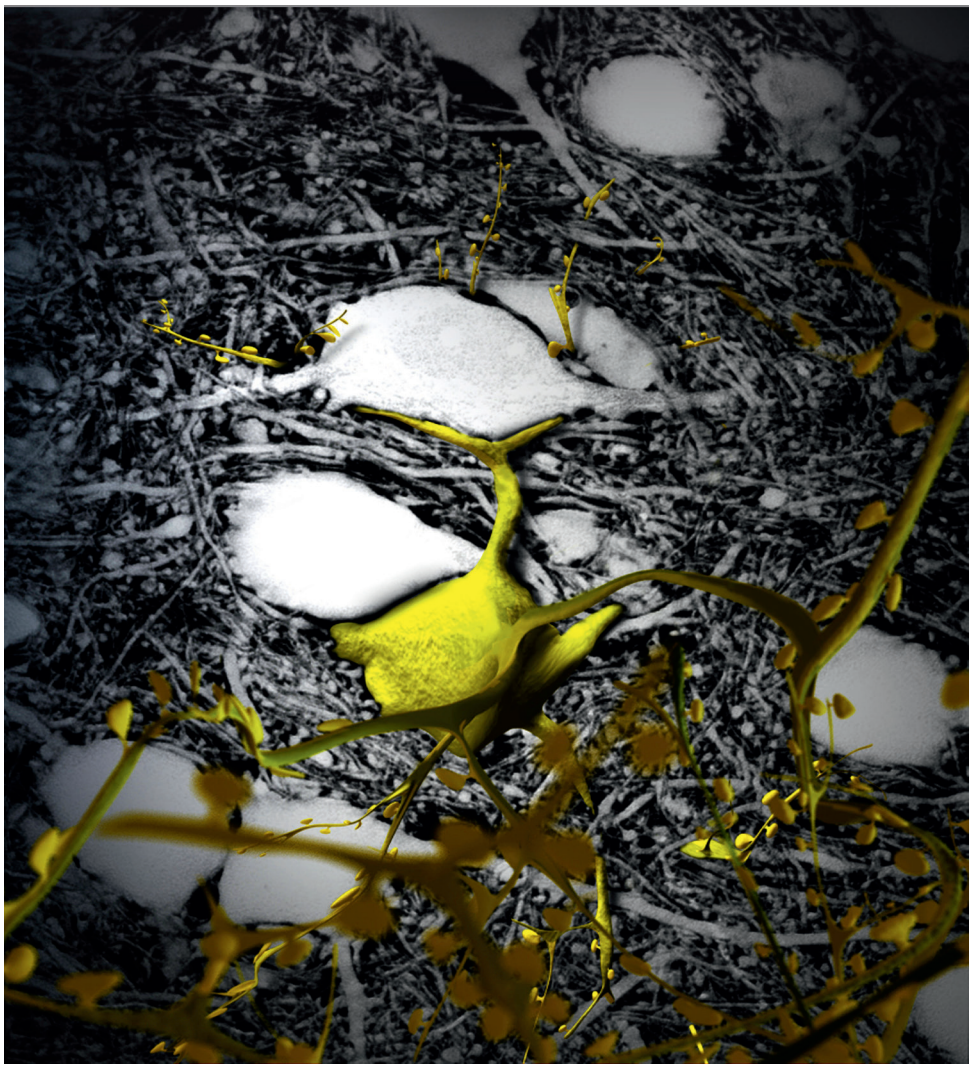

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COVER ILLUSTRATION Super-resolution shadow imaging (SUSHI) of a living brain slice, based on STED microscopy and fluorescence labeling of the interstitial fluid, providing a panoramic yet nanoscale view of brain tissue. The yellow cell was positively labeled with YFP, and artistically rendered in 3D. Cover illustration provided by M. Arizono, S. Bancelin, P. Bethge, R. Chéreau, A. Idziak, V.V.G. Krishna Inavalli, T. Pfeiffer, J. Tønnesen and U. V. Nägerl, Nanoscale imaging of the functional anatomy of the brain, (nf-2021-0004, pp. 67–77 in this issue).

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Editorial

Editorial der neuen NWG-Präsidenten zum Amtsantritt

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Mit Ende der diesjährigen Göttinger Tagung hat der neue Vorstand der NWG die Arbeit aufgenommen. Wir möchten uns an dieser Stelle zunächst bei Albert Ludolph bedanken, der die Gesellschaft in den letzten beiden Jahren engagiert geleitet hat. Wir freuen uns, dass er uns noch weitere zwei Jahre als Ehrenpräsident mit Rat und Tat zur Seite stehen wird. Auch dem ehemaligen Ehrenpräsidenten Eckhard Friauf und den nun ausgeschiedenen Sektionssprechern Petra Wahle, Melanie Wilke, Angela Richter, Benedikt Grothe und Christian Wegener sind wir zu großem Dank verpflichtet.

Die Göttinger Tagung, nach wie vor Herzstück und international sichtbares „Aushängeschild" der NWG, stand in Zeiten der weltweiten Corona-Pandemie unter besonderen Herausforderungen. Nachdem sich der Vorstand im Oktober letzten Jahres dafür entschieden hatte, die Tagung rein virtuell stattfinden zu lassen, war zunächst nicht sicher, wie gut diese Form angenommen werden würde. Nun können wir berichten, dass sie mit über 1.100 Teilnehmern unerwartet großen Zuspruch gefunden hat. Das Berliner Büro hat auch diese Herausforderung exzellent gemeistert und zusammen mit Martin Göpfert und den weiteren „Vor-Ort"-Organisatoren in Göttingen ein modernes, hervorragend strukturiertes und lebendiges Forum auf die Beine gestellt, bei dem der wissenschaftliche Diskurs klar im Vordergrund stand. Daneben boten vor allem auch die beiden Poster Sessions Gelegenheit zum Plausch unter Kollegen in der (virtuellen) Kaffeeecke. Wir freuen uns alle auf ein – dann wieder reelles – Wiedersehen auf der NWG-Tagung im Jahr 2023.

Die Präsidentschaft möchten wir mehreren entscheidenden Themen widmen. Höchste Priorität sehen wir in einer stärkeren und dedizierten Sichtbarmachung der Relevanz neurowissenschaftlicher Grundlagenforschung, der ersten Säule der NWG. Leider beobachten wir zunehmend Forderungen nach einer direkten Anwendungsorientiertheit bei verschiedenen Förderinstitutionen, nicht nur von Seiten des Bundesministeriums, sondern auch im Rahmenprogramm der Europäischen Kommission. Ein entschlossenes Eintreten für die Notwendigkeit von Grundlagenforschung, das Gewinnen öffentlicher Aufmerksamkeit für unsere Belange und Lobbyarbeit bei den politischen Entscheidungsträgern werden dabei wichtige Instrumente sein. Hierzu unter anderem werden wir uns beim German Brain Council, und damit beim European Brain Council, einbringen und die Berücksichtigung der NWG-Interessen bei der Politik einfordern.

Gleichzeitig möchten wir jedoch auch die zweite Säule der Neurowissenschaften, also die translational-klinische Forschung, noch näher an die Gesellschaft heranführen, damit beide Säulen enger vernetzt werden können. Die neurowissenschaftliche Forschung mit ihrem enormen Erklärungs- und Therapiepotential für weitverbreitete Erkrankungen des Nervensystems, wie z.B. Schlaganfall, Demenz, Hirntumore oder neuropsychiatrische Erkrankungen, wird weltweit als eine gemeinsame globale Aufgabe angesehen. Die Einbettung der NWG in die internationalen Netzwerke, wie sie in Europa durch die FENS, in Südamerika durch die FALAN oder weltweit durch die IBRO repräsentiert sind, soll weiter vertieft werden. Damit wollen wir für die hochrangige neurowissenschaftliche Forschung an unseren Universitäten und anderen Einrichtungen werben.

Mit unserer populärwissenschaftlichen Website *dasgehirn.info* stellen wir das durch unsere Forschungen erzeugte Wissen der interessierten Öffentlichkeit vor. Die Faszination für unser komplexestes Organ ist ungebrochen, wie wir an den Nutzerzahlen erkennen können. Die langfristige finanzielle Sicherung dieses wichtigen Informationskanals wird eine unserer weiteren vorrangigen Aufgaben sein.

Wie unsere beiden Vorgänger möchten wir Sie gerne auffordern, uns weitere Aspekte, denen sich der NWG-Vorstand annehmen sollte, zu nennen. Die Gesellschaft lebt durch das Engagement ihrer Mitglieder und wird durch sie maßgeblich geprägt. Diese Bitte richtet sich insbesondere auch an unsere jungen Mitglieder. Schauen Sie sich an, was die vor einiger Zeit neu gegründete Sektion „junge NWG" zu bieten hat und sprechen Sie mit uns, wie wir gemeinsam die Gesellschaft moderner und jünger gestalten können. Wir sind gespannt auf Ihre Ideen.

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Präsidentin: **Prof. Dr. Christine R. Rose**, Institut für Neurobiologie, Mathematisch-Naturwissenschaftliche Fakultät, Heinrich-Heine-Universität Düsseldorf, Gebäude 26.14.01, 40225 Düsseldorf, E-mail: rose@uni-duesseldorf.de, http://www.neurobiologie.hhu.de/

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Review article

Shirin Hosseini, Kristin Michaelsen-Preusse and Martin Korte*

Respiratory viral infections and associated neurological manifestations

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Abstract: Respiratory viruses as a major threat to human and animal health today are still a leading cause of worldwide severe pandemics. Although the primary target tissue of these viruses is the lung, they can induce immediate or delayed neuropathological manifestations in humans and animals. Already after the Spanish flu (1918/20) evidence accumulated that neurological diseases can be induced by respiratory viral infections as some patients showed parkinsonism, seizures, or dementia. In the recent outbreak of COVID-19 as well patients suffered from headache, dizziness, nausea, or reduced sense of smell and taste suggesting that SARS-CoV2 may affect the central nervous system (CNS). It was shown that different respiratory viral infections can lead to deleterious complications in the CNS by a direct invasion of the virus into the brain and/or indirect pathways via proinflammatory cytokine expression. Therefore, we will discuss in this review mechanisms how the most prevalent respiratory viruses including influenza and coronaviruses in humans can exert long-lasting detrimental effects on the CNS and possible links to the development of neurodegenerative diseases as an enduring consequence.

Keywords: central nervous system; coronavirus; influenza virus; neurodegeneration; respiratory viral infections.

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Zusammenfassung: Atemwegsviren stellen eine große Bedrohung für die Gesundheit von Mensch und Tier dar und sind eine der Hauptursachen für weltweite schwere Pandemien. Obwohl das primäre Zielgewebe dieser Viren die Lunge ist, können sie bei Mensch und Tier akute oder langfristige neuropathologische Manifestationen auslösen. Bereits nach der Spanischen Grippe (1918/20) gab es zahlreiche Belege dafür, dass neurologische Erkrankungen durch virale Infektionen der Atemwege ausgelöst werden können, da eine Reihe von Patienten Parkinsonismus, epileptische Anfälle oder verschiedene Formen einer Demenz zeigten. Auch beim jüngsten Ausbruch von COVID-19 leiden die Patienten unter Kopfschmerzen, Schwindel, Übelkeit oder vermindertem Geruchs- und Geschmackssinn, was darauf hindeutet, dass SARS-CoV2 das Zentralnervensystem (CNS) beeinträchtigen könnte. Es konnte gezeigt werden, dass verschiedene respiratorische Virusinfektionen zu schädlichen Komplikationen im CNS führen, und zwar durch eine direkte Invasion des Virus in das Gehirn und/oder indirekte Wege über eine proinflammatorische Zytokinexpression. Daher werden wir in dieser Übersicht Mechanismen diskutieren, wie die beim Menschen am weitesten verbreiteten respiratorischen Viren, darunter Influenza- und Coronaviren, negative Auswirkungen auf das CNS haben können und so eine mögliche Verbindung zur Entwicklung neurodegenerativer Erkrankungen als Langzeitfolge haben.

Schlüsselwörter: Zentralnervensystem; Coronavirus; Influenzavirus; Neurodegeneration; Respiratorische Virusinfektionen.

Background

Respiratory viral infections are one of the most important leading causes of morbidity and mortality particularly among young children, elderly and patients with immunodeficiency, imposing a massive economic burden and critical hazards for public health (Bohmwald et al., 2018). The most important viruses that cause respiratory diseases include coronavirus, influenza virus, human respiratory

syncytial virus (hRSV, *orthopneumoviruses*), human metapneumovirus (hMPV, *metapneumoviruses*) and adenovirus (Desforges et al., 2020; Nichols et al., 2008). Respiratory viral infections usually are self-limiting, involve the upper airways and cause relatively mild symptoms such as sneezing, coughing and nasal congestion. Nevertheless, these mild infections can be dangerous for vulnerable individuals, such as newborns, elderly and immunocompromised persons in that the viruses can impact the lower airways, resulting in shortness of breathing and pneumonia (Troy and Bosco, 2016). Some respiratory viruses are constantly appearing among human populations around the world every year, leading to symptoms ranging from mild to more severe manifestations requiring hospitalization (Desforges et al., 2020). In addition to the seasonal respiratory viruses, new strains emerge in the human population occasionally causing epidemics or even pandemics. These are usually RNA viruses such as influenza A subtypes and human coronavirus strains that are present in an animal reservoir, cross the species barrier selecting a new host. Zoonoses like these can be very dangerous for humans (Berry et al., 2015; Desforges et al., 2020). The latest emerging virus entitled severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) was recently identified in December 2019 in an individual located in Wuhan, China, who had severe symptoms of pneumonia. Subsequently, the world health organization (WHO) named the disease COVID-19 and declared the emergence of a global pandemic with high international concern (Desforges et al., 2020).

It is important to note that besides affecting the respiratory tract, these emerging viruses can have devastating effects also on other parts of the human body, including the central nervous system (CNS) (Table 1), thereby potentially increasing the risk for neurological disorders and neurodegenerative diseases (Bohmwald et al., 2018).

Some respiratory viruses such as neurotropic influenza A strains have the capability to invade the CNS where they can infect neurons and other resident cells and lead to neural dysfunction. However, new findings indicated that also merely peripheral infections caused by respiratory viruses can have substantial impacts on the CNS (Hosseini et al., 2018). Neurodegeneration as well as chronic neuroinflammation induced by respiratory viral infections might moreover trigger pathways involved in classical neurodegenerative disorders in humans. Supporting this, many similarities between prevalent neurodegenerative diseases such as Alzheimer's and Parkinson's and virus-mediated neurodegeneration have been identified at the cellular and molecular level (Arbour et al., 2000; Gamboa et al., 1974; Jang et al., 2009). However, the details of how respiratory viral infections affect the CNS are still incompletely understood.

Neurological manifestations associated with respiratory viral infections

Commonly when referring to virus associated neurological disorders, nonrespiratory viruses which directly invade the CNS such as *Flaviviridae* family members including Japanese encephalitis, Langat or West Nile viruses (Cornelius et al., 2020; Sips et al., 2012), while especially the latter is now a threat in Germany as well (RKI: www.rki.de), are discussed. These neurotropic viruses increase the incidence of dramatic

Table 1: The most common respiratory viruses with neurological manifestations.

Respiratory viruses	Virus description	Associated neurological sequelae	References
Human coronaviruses (SARS-CoV1, MERS-CoV, SARS-CoV2)	*Coronaviridae* family Enveloped viruses with a positive-sense single-stranded RNA genome	Encephalopathy Encephalitis Meningitis Seizures Stroke Neuromuscular disorders Anosmia and dysgeusia	Alshebri et al. (2020); Ng Kee Kwong et al. (2020); Verstrepen et al. (2020)
Influenza A viruses (H1N1, H3N2, H7N7, H5N1)	*Orthomyxoviridae* family Enveloped viruses with a negative-sense single-stranded RNA genome	Seizures Encephalopathy Encephalitis Confusion Loss of consciousness Transverse myelitis Guillain-Barré syndrome	Ekstrand (2012); Khandaker et al. (2012); Mylonaki et al. (2020); Robinson and Busl (2020)

neurological dysfunction and can even lead to respiratory deficiency induced by neuromuscular impairment (Madden, 2003). In addition, CNS pathology is intensively studied in infections caused by other well-known neurotropic viruses including measles, Varicella-Zoster and human immunodeficiency viruses (HIV) (Koyuncu et al., 2013). However, regarding the increased risk of respiratory viral infections due to spreading in an increasingly globally connected human population, more attention is necessary to also focus research on neurological manifestations induced by these infections (Bohmwald et al., 2018). The most common reported neurological complications associated with severe respiratory infections induced by influenza, coronavirus, hRSV, and hMPV are seizures mostly occurring as febrile seizures with a higher incidence in patients suffering from epilepsy (Bohmwald et al., 2018; Vezzani et al., 2016). Besides this, encephalopathy can also be observed following respiratory infections as well as an expanded spectrum of manifestations including coma with long-term morbidity or mortality and some nonsevere changed mental states accompanied by minimal-to-no sequelae. Occasionally, other neurological disorders can be associated with respiratory infections like stroke, focal neurologic defects, Guillain-Barré syndrome, acute disseminated encephalomyelitis and transverse myelitis (Ekstrand, 2012). Furthermore, respiratory viral infection can induce significant changes in gut microbiota compositions (Groves et al., 2020). A link between the gut microbiota and the brain has long been suggested. Recent findings, however, elucidate the important role that changes in the composition of the gut microbiota play in the development of behavioral disorders such as anxiety and depression (Kim and Shin, 2018).

In line with previous observations, COVID-19 patients show neurological manifestations such as headache, confusion, dizziness, nausea and vomiting as well. In a subset of these patients, stroke, and seizures have also been reported. Furthermore, other unusual neurologic signs such as a diminished sense of smell (anosmia) and taste (dysgeusia) are reported in COVID-19 patients (Paterson et al., 2020). Earlier it was shown that SARS-CoV1 is indeed able to infect the brainstem in both patients and

experimental animals (Netland et al., 2008). Increasing evidence shows that coronaviruses similar to influenza viruses do not always affect only the respiratory system but may also induce neurological consequences either by directly invading the CNS or indirectly by peripheral infection (Figure 1) (Ekstrand, 2012; Li et al., 2020). Nevertheless, in addition to the acute impacts of respiratory viral infections on the CNS, one of the earliest and most important links between respiratory infections and long-term neural dysfunction is a correlation between the 1918 Spanish flu, caused by influenza A H1N1 strain and an epidemic of neurodegenerative disease such as Parkinson's disease (PD) decades later (Henry et al., 2010). Interestingly, PD-like symptoms such as tremors in the months after seasonal influenza infection have also been reported, however, this is not associated with an increased risk of developing idiopathic PD (Toovey et al., 2011). Moreover, several studies have associated human coronaviruses (HCoV) with multiple sclerosis (MS) in which coronavirus-like particles were detected in brain tissue and cerebrospinal fluid from MS patients (Arbour et al., 2000). One of the major histopathological hallmarks of neurodegenerative diseases are misfolded or aggregated proteins associated with neurotoxicity. However, mechanistic details about the emergence of misfolded protein aggregations already at very early stages of several diseases are still mostly unknown. Recently, it was shown that disrupted lysosomal autophagy and subsequent proteostasis loss induced by respiratory viruses such as influenza and coronaviruses may be an overlooked factor in the onset of protein aggregation such as α-synuclein and β-amyloid (Jang et al., 2009; Marreiros et al., 2020; Sulzer et al., 2020). Therefore, besides acute neurological manifestations, these observations reveal that respiratory viral infections may also induce chronic neurological impairments even triggering or enhancing the development of neurodegenerative disease which represents an important threat for public health.

How can respiratory viral infection reach the CNS?

As a main controlling unit of the human body, the CNS needs to be especially protected from endogenous and exogenous threats (Louveau et al., 2015). Therefore, despite the close connection with the environment, the

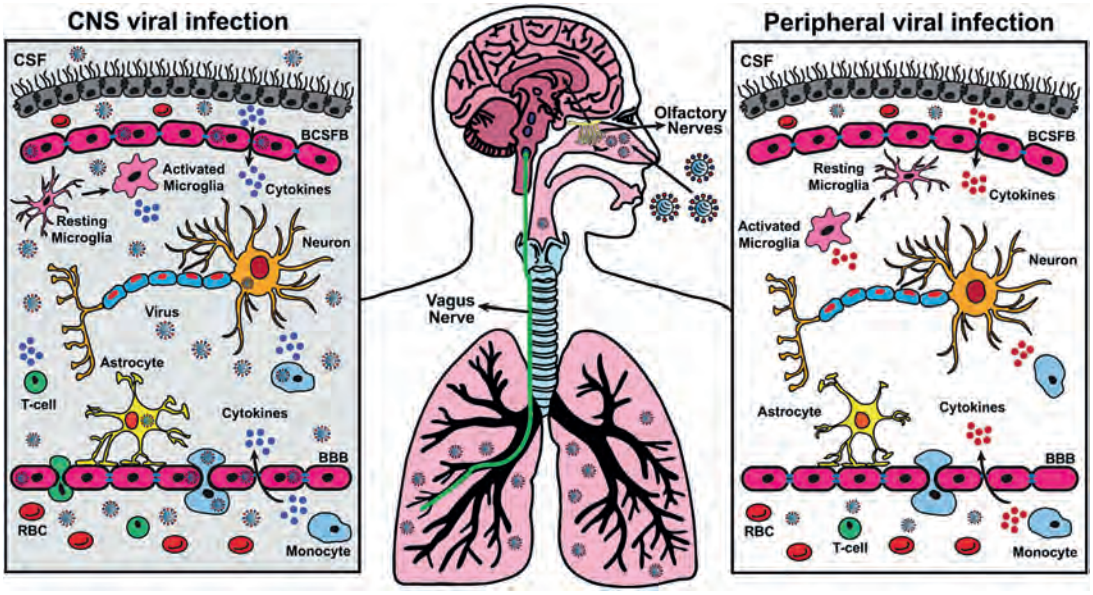

Figure 1: Respiratory viruses directly via infection of CNS or indirectly via peripheral infection might have devastating impacts on CNS. [Left panel] Neurotropic respiratory viruses can reach the CNS via direct infection of BCSF and BBB endothelial cells, via a "Trojan horse" (infected monocytes, light blue cell) or entrance via peripheral neural routes such as olfactory sensory neurons and the respiratory tract vagus nerve. The virus can spread in the brain parenchyma and infect the resident cells. This is followed by increased infiltration of peripheral monocytes (light blue cell) and T-cells (green cell) from the periphery and activation of microglia (pink cell) as resident innate immune cells in the brain. Subsequently, the local production or entry of proinflammatory cytokines (i.e., IFN-γ, TNF-α and IL-6; blue circles) from the periphery leads to neuroinflammation as a potential cause of neurological manifestations. [Right panel] Non-neurotropic respiratory viruses cannot enter the CNS, in this case proinflammatory cytokines can, however, enter the CNS (red circles) as well as the infiltration of activated monocytes (light blue cell). This then also leads to the activation of microglia (pink cell) in the brain parenchyma triggering neuroinflammation and neurological consequences.

CNS is largely protected from free entry of noxious molecules, pathogens and circulating immune cells within the blood by the blood-brain barrier (BBB) and blood-cerebrospinal fluid barrier (BCSFB) of the choroid plexus located in the ventricles of the brain. The integrity of the BBB is maintained by tight junctions between cerebral microvascular endothelium, astrocytic endfeet, pericytes and the extracellular matrix (Engelhardt and Sorokin, 2009; Kaplan et al., 2020). Nevertheless, neurotropic subtypes of respiratory viruses can disrupt the endothelial tight junctions of the BBB and subsequently infect resident cells of the CNS (Figure 1). Furthermore, these viruses can cross the BBB via direct infection of endothelial cells and pericytes using endocytic vesicles in a process called transcytosis. A different way to enter the CNS is the "Trojan horse approach" which allows neurotropic viruses to cross the BBB utilizing infected monocytes or macrophages, also termed hematogenous routes (McGavern and Kang, 2011; Swanson and McGavern, 2015). The BCSFB, unlike the BBB, is located at the epithelial level, in which capillaries are leakier and more permeable to small molecules, thus allowing rapid entry of pathogens and hazardous molecules more easily (Engelhardt and Sorokin, 2009). Some neurotropic viruses can in addition spread to the CNS through peripheral neural routes which can be sensory or motor by retrograde and anterograde neuronal transport using the motor proteins dynein and kinesins. Commonly respiratory viruses use olfactory sensory neurons, facial nerves, the trigeminal ganglion, and especially the respiratory tract vagus nerve as gates to enter the CNS (Figure 1) (Swanson and McGavern, 2015). On the other hand, most of the respiratory viral infections which are known as non-neurotropic are limited to the periphery, commonly to epithelial or endothelial cell surfaces in the airways (Figure 1) (Teijaro et al., 2011). Usually, infection of these cells initiates a cell-autonomous reaction and paracrine signaling from the infected cell to neighboring uninfected cells by secreted cytokines as part of the innate immunity (Koyuncu et al., 2013). Nonetheless, the infection can be resolved by the secretion of infection-specific antibodies and the involvement of T-cells the so-called adaptive immunity.

However, both neurotropic and non-neurotropic viruses may escape the local immune control at the primary site of infection and spread to other tissues. Robust viral replication as well as an overreacting innate immune response causing a "cytokine storm" can lead to severe consequences in patients (Castelli et al., 2020; Teijaro et al., 2011). The cytokine storm was reported following many respiratory viral infections including influenza and coronaviruses (SARS-CoV1 and CoV2) which is the major

factor underlying acute respiratory distress syndrome (ARDS) induced by these viruses (Tisoncik et al., 2012). A cytokine storm is an aberrant response of the host immune system that induces an exaggerated release of inflammatory mediators. This immunological response includes both proinflammatory (i.e., TNF-α, IFNs, ILs) and anti-inflammatory cytokines (i.e., IL-4, IL-10) as well as chemokines (CXCL10, MCP1, and MIP1α), which are secreted at very high levels in the serum leading to an intense systemic immune reaction. Indeed, the cytokine storm in fatal COVID-19 and other severe respiratory infections is represented by several pathological features such as ARDS and subsequent multiorgan failure (Figure 2). Such a reaction can have a dramatic impact on many organs including the brain, as the BBB and the BCSFB are permeable for most of the cytokines (Castelli et al., 2020).

It has been shown that although the baseline levels of inflammatory cytokines are critical for synaptic plasticity (Hosseini et al., 2020), high levels of them impair neuronal function in the adult brain by their direct effect on neurons or by indirect mechanisms mediated by non-neuronal cells such as brain resident microglia and astrocytes and infiltrating peripheral immune cells (Prieto and Cotman, 2017). Therefore, it can be hypothesized that a cytokine storm can be responsible for neuropathological conditions such as meningitis, encephalitis, meningoencephalitis, resulting even in death (Koyuncu et al., 2013). It is in this respect noteworthy that also neurotropic respiratory viruses can affect the brain in both ways including direct CNS infection as well as cytokine secretion. Therefore, given the fact that both neurotropic and non-neurotropic respiratory viruses can have substantial impacts on the CNS, the detailed mechanisms of neuronal dysfunction caused by two prevalent respiratory viruses in the human population including influenza A viruses and coronaviruses will be outlined here.

Mechanisms of neural dysfunction induced by respiratory viruses

Coronaviruses

Coronaviruses (CoV) as enveloped positive-stranded RNA viruses belong to the *Coronaviridae* family which usually causes mild-to-moderate common cold symptoms associated with upper airways infection. There are over 100 subtypes of coronaviruses that can circulate among animals and humans. Sometimes these viruses are transmitted from animals to humans in a so-called spill-over process, leading to the development of more severe symptoms. Less than 20 years ago, three new coronaviruses emerged from animal reservoirs and caused severe respiratory diseases and death in humans including SARS-CoV1, MERS-CoV, and the recent SARS-CoV2 which in March 2020 led to the global COVID-19 pandemic. It was shown that indeed several laboratory strains of coronaviruses are able to replicate efficiently in the CNS of mice and other rodents by infiltration via the nasal infection route. Among the infected cell types were particularly microglia and astrocytes, leading to a serious infection especially of the brainstem. It is noteworthy that CoV may first invade peripheral nerve terminals, and then penetrate to the CNS via so-called trans-synaptic transfer (Xu et al., 2005). In animal models, depending on the CoV strain, neurovirulence and pathology vary from mild encephalitis with subsequent clearance of the virus and demyelination to rapidly progressing fatal encephalitis (Perlman and Wheeler, 2016). In addition, a severely impaired motor function was shown following CoV infection in animal models. Interestingly, secretion of TNF-α, IL-6, IL-12, and IL-15 and associated activation of microglia play a critical role in controlling CoV in the CNS,

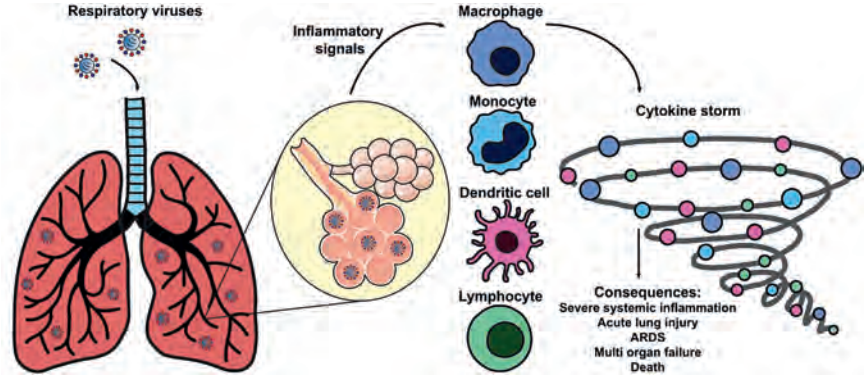

Figure 2: An exaggerated host immune response following severe respiratory viral infection can lead to a cytokine storm with severe consequences. Immune signals upon severe respiratory viral infections such as COVID-19 can induce a positive feedback activation of immune cells resulting in exaggerated release of inflammatory cytokines and chemokines also known as a "cytokine storm". This is responsible for acute respiratory distress syndrome (ARDS), multiorgan failure and eventually death.

as depletion of this cells resulted in faster viral replication and enhancement of the capacity of CoV to scape adaptive immunity (Li et al., 2004). In humans as well, the neurovirulent properties of some coronavirus subtypes have been confirmed. For instance, the RNA of human coronaviruses was isolated from autopsy samples of multiple sclerosis (MS) and encephalomyelitis patients which points toward a possible persistent infection (Arbour et al., 2000). However, MERS-CoV has never been extracted from neural tissue or fluids in infected humans (Algahtani et al., 2016). So, until now the precise capacity of CoV to penetrate and infect the CNS in humans is not well defined. Nevertheless, several neurological complications such as seizures and four-limb twitching have been reported in SARS-CoV1 and MERS-CoV patients. In addition, computed tomography (CT) observations from MERS-CoV patients indicated signs of intracerebral hemorrhage with significant brain edema and intraventricular space enlargement (Algahtani et al., 2016; Arbour et al., 2000; Bohmwald et al., 2018).

In post mortem brain samples of CoV-infected patients (especially after infection with SARS-CoV1), high levels of in particular proinflammatory IFN-γ induced chemokines such as CXCL9 and CXCL10 were observed. These CXC chemokine family members play a critical role in T cell-mediated immunity in the CNS as they promote the infiltration of CD3+ T lymphocytes in the brain parenchyma by binding to the CXCR3 receptor (Xu et al., 2005). In the brains of patients with Alzheimer's disease and respective animal models, a high concentration of CXCL10 was found which can be associated with plaque formation and cognitive deficits, suggesting a neuropathogenic role for this chemokine and its receptor (Krauthausen et al., 2015). Moreover, earlier studies revealed a high expression of granulocyte-macrophage colony-stimulating factor (GM-CSF) in the periphery and brain of CoV patients which shows significant activation of myeloid cells invading other organs especially the brain. The high expression of GM-CSF in the brain with known proinflammatory functions plays a pivotal role in the development of autoimmune and inflammatory diseases such as autoimmune encephalomyelitis (Li et al., 2016).

In addition to the previous coronaviruses, in the recent outbreak of novel SARS-CoV2, neurological manifestations such as headache, myalgia, nausea, anosmia, ageusia, psychomotor agitation, encephalopathy, acute cerebrovascular disease and even impaired consciousness have been observed in several patients (Moro et al., 2020; Paterson et al., 2020). Although a large number of case reports with neurological manifestations following COVID-19 have been published, it seems yet too early to determine the precise incidence and prevalence rate of these complications in COVID-19 patients. So far studies indicated various prevalence rates for neurological manifestations in different affected countries. For example, in Wuhan, China approximately 36% of COVID-19 patients showed neurological complications, however, in Europe neurological symptoms were documented in 49% of patients. In a study in the USA only 8% of patients with COVID-19 exhibited neurological sequelae, yet neurological symptoms in 35% of COVID-19 patients were reported in Ankara, Turkey (Moro et al., 2020; Pezzini and Padovani, 2020). At the current state a rather high prevalence of neurological manifestations can be estimated in COVID-19 patients which makes it likely that SARS-CoV2 can penetrate into the CNS. In a recent study, the presence of SARS-CoV2 RNA in the nasopharynx and distinct brain regions was documented postmortem in COVID-19 patients which indeed confirms SARS-CoV2 neurotropism. Apparently, SARS-CoV2 can enter the brain via the neural–mucosal interface in the olfactory mucosa and directly spread in the respiratory and cardiovascular control centers located in the medulla oblongata (Meinhardt et al., 2021). Apart from acute neurological consequences of COVID-19, it is still too early to know whether neurodegenerative related manifestations similar to the once reported for instance following the Spanish flu and H5N1 avian flu might indeed occur (Jang et al., 2009). So far only a single case report, of postencephalitic parkinsonism was documented. Specific motor deficits have been documented in some patients as well. Therefore, it has been proposed to particularly monitor COVID-19 patients with long-term hyposmia symptoms for decades to find out the particular role of SARS-CoV2 in the onset and progression of neurodegenerative diseases such Parkinson's disease (Sulzer et al., 2020).

Mechanistically, the first evidence of the harmful effects of the COVID-19 for brain function came from the fact that the SARS-CoV2 virus similar to SARS-CoV1 utilizes the angiotensin-converting enzyme 2 (ACE2) receptor to invade and infect host cells (Baig et al., 2020). Interestingly, the widely ACE2 expression in different brain areas has been defined (Xia and Lazartigues, 2008). Therefore, it can be concluded that the interaction of SARS-CoV2 with ACE2 receptors expressed in neurons can initiate a neuronal viral replication resulting in neuronal damage and dysfunction and subsequent massive neuroinflammatory processes which even can lead to respiratory failure and death in COVID-19 patients (Baig et al., 2020).

Further laboratory experiments using the neurotropic and non-neurotropic strains of coronaviruses are needed to investigate the virus- and immune-mediated neural dysfunction, subsequent neurodegeneration, demyelination and particularly virus clearance, and/or persistence in the CNS.

Influenza A viruses

Influenza A viruses (IAV) as enveloped segmented negative-strand RNA viruses belong to the *Orthomyxoviridae* family which are circulating among animals and the human population. Despite the fact that most individuals recover from an IAV infection, the acute and long-term IAV impacts on the CNS remain mostly elusive.

Some strains of IAV (i.e., H7N7, H7N9, H5N1) are neurovirulent and can spread to the CNS through olfactory, trigeminal, vagus and sympathetic nerves and induce severe neurological manifestations (Park et al., 2002). For instance, the highly pathogenic avian H5N1 IAV can infect the CNS cells including neurons and glial and subsequently lead to neuronal damage and death acutely. Evidence is accumulated that this is induced by neuroinflammation through the activation of brain resident immune cells, microglia, who increase the local proinflammatory cytokine expression and secretion (Jang et al., 2012; Park et al., 2002). In addition, the activation of resident brain immune cells following H5N1 IAV infection leads to a significant increase in phosphorylation and aggregation of alpha-synuclein, resulting in the degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and parkinsonian symptoms (Jang et al., 2009). Investigations on other avian neurotropic IAV strains such as H7N9 revealed efficient viral replication, proinflammatory cytokine upregulation and cytopathy in the brain which can induce intensive CNS injury (Ng et al., 2018). Furthermore, in the case of H9N7 neurotropic IAV strain, a significant relationship between infection-induced neuropathology and increased levels of inflammation active factor NLRP3 and related cytokines IL-1β and TNF-α was identified (Yu et al., 2014). In addition to the acute impacts of neurotropic IAV strains on brain cells, we recently investigated the long-term effects of a mouse-adapted neurotropic H7N7 (rSC35M) IAV strain for hippocampal neuron structure and function at time points well beyond the acute phase of infection (30, 60 and 120 days post infection [dpi]) (Hosseini et al., 2018). It is noteworthy that the hippocampus is a highly plastic region in the brain which is involved in learning and memory formation processes (Korte and Schmitz, 2016). Hippocampus is especially vulnerable to neuroinflammation (Lynch, 2002; Vitkovic et al., 2000), and hippocampal neurons show negative structural changes due to the inflammatory processes as a consequence of the virus infection. This can lead to impairments in hippocampal function associated with deficits in learning and memory formation (Atluri et al., 2015). Our own findings revealed significant signs of immune cell infiltration and profound gliosis in the hippocampus of H7N7 infected mice at 30 dpi correlated to deficits in spatial memory formation, impaired long-term potentiation and reduced dendritic spine density in all principal cells of the hippocampus (Hosseini et al., 2018). The H7N7 IAV subtype did not only replicate in the CNS but the infection led to elevated levels of IFN-γ and TNF-α in the hippocampus and a disruption of the BBB. It can be speculated that this pronounced and prolonged inflammatory immune response in the CNS with activation of microglia might be the underlying cause of neuronal damage resulting in cognitive deficits (Figure 3) (Hosseini et al., 2018). Infections with neurotropic viruses have a wide economic burden on society and a wide range of morbidity and mortality worldwide. Therefore, neurotropic influenza viruses are a major challenge to human and animal healthcare systems. This mainly depends on the unique organization of the CNS with different cell types, very sophisticated structures and functions, reduced immune surveillance and limited regeneration capacity (Ludlow et al., 2016).

Interestingly, neurological sequelae induced by influenza infection are not only limited to neurotropic strains but have also been reported following epidemics and pandemics involving non-neurotropic strains, which cause the majority of human infections (i.e., H1N1, H3N2). These viruses are neither neuroinvasive nor neurovirulent and therefore cannot penetrate or replicate in the CNS but only in the respiratory tract (Atluri et al., 2015; Hosseini et al., 2018). Notably, despite this fact, they can acutely induce neurological consequences. For instance, following the influenza A (H1N1) 2009 pandemic neurological manifestations such as seizures were relatively common among infected children (Khandaker et al., 2012). An investigation in mice showed elevated expression of proinflammatory cytokines such as TNF-α, IL-1β, and IL-6, a reduction in neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF). This was accompanied by an activation of microglial cells upon H1N1 IAV (A/PR/8/34) infection as well as the altered hippocampal structure and learning deficits in mice at seven days post infection (Jurgens et al., 2012). Another study also confirmed that H1N1 IAV (CA/09) infection can induce microglial activation in parallel with a reduction in BDNF and glial cell-derived neurotrophic factor

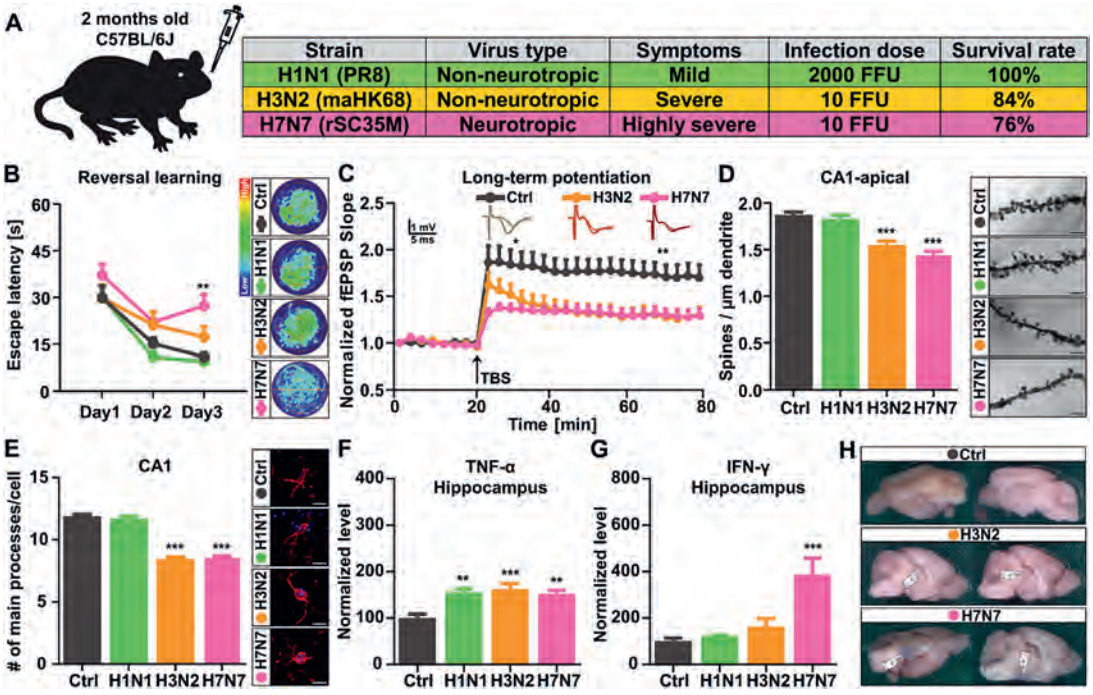

Figure 3: The destructive effects of influenza A virus (IAV) infection on hippocampal structure and function at 30 dpi.
[A] Young adult mice were inoculated with three strains of IAV with different characterizations. [B] Infection with both neurotropic (H7N7) and non-neurotropic (H3N2) IAV subtypes impaired learning ability for a new platform position in the reversal Morris water maze test. [C] Hippocampal slices obtained from H7N7 IAV infected mice exhibited significantly lower induction and maintenance of long-term potentiation (LTP) compared to control, whereas H3N2 IAV infected mice showed reduced maintenance of LTP compared to control. [D] Thirty days following infection with H3N2 and H7N7 IAVs, the spine density of apical dendrites of CA1 neurons decreased. Representative images of Golgi-stained dendritic spines in hippocampal CA1 neurons, scare bar = 2 µm. [E] The activation status of microglia was assessed by counting the number of primary processes. After infection with both H3N2 and H7N7 IAVs, the number of primary processes of microglia in the CA1 hippocampal subregion decreased at 30 dpi. Representative examples of IBA-1 + cells, scale bar = 10 µm [F-G] Levels of TNF-α and IFN-γ were elevated in the hippocampus of IAVs infected mice at 8 dpi. [H] Following injection of Evans blue dye for the assessment of the BBB integrity, at 10 dpi, the dye was well visible macroscopically only in the brain of H7N7-infected mice, whereas in H3N2-infected mice, it was only weakly visible around the ventricle; adapted from Hosseini et al. 2018.

(GDNF) levels and an elevation in the immune-modulatory chemokine (C-C motif) ligand 4 (CCL4) expression mainly in the substantia nigra pars compacta (SNpc) and the hippocampus, despite the absence of virus in the brain (Sadasivan et al., 2015).

Nevertheless, long-term impacts of infection with non-neurotropic IAV strains especially on the CNS have not been studied. Therefore, in our recent study, the effects of two different mouse-adapted non-neurotropic IAV strains including H1N1 (PR8) and H3N2 (maHK68) at 30, 60, and 120 dpi for hippocampal neuron structure and function were investigated (Hosseini et al., 2018). Our findings indicate that unlike the short-term effects reported by (Jurgens et al., 2012), H1N1 infection does not lead to long-term impairments in spatial memory formation or neuronal morphology (Figure 3) (Hosseini et al., 2018). Yet, following infection with non-neurotropic H3N2 IAV, immune cell infiltration and signs of gliosis were indeed observed in the hippocampus of infected mice albeit to a lesser extent compared to the neurotropic IAV strain (Hosseini et al., 2018). Moreover, 30 days post H3N2 infection impaired spatial memory formation and long-term potentiation, as well as a reduced spine number, were detected. The H3N2 IAV strain is not able to replicate in the brain, however, a leaky BBB and even locally elevated secretion of TNF-α in the hippocampus and also an increase in the number and activation status of microglia were found (Figure 3) (Hosseini et al., 2018). Although activated microglia are crucial for the host defense against pathogens, prolonged or aberrant activation can have damaging effects on neurons and adversely affect synaptic transmission and structure (Riazi et al., 2015). It was shown previously that activated microglia play a role in synaptic remodeling and plasticity in the infected brain (Vasek et al., 2016).

Therefore, the most likely explanation for the destructive effects of non-neurotropic IAV infection on the CNS lies in processes of neuroinflammation particularly caused by the indirect activation of microglia as the local effectors of the brain innate immunity (Barbosa-Silva et al., 2018; Santos et al., 2016).

Nevertheless, in our study, young adult mice showed partial and full recovery at 60 and 120 days, respectively, post H3N2 and H7N7 IAV infection. This investigation provides evidence that neuroinflammation induced by IAV infection can cause longer-lasting, virus-specific alterations in neuronal connectivity that are still detectable one month after infection and are associated with impairments in spatial memory formation. Interestingly, the immune response promoted by IAV infection can be caused even without CNS viral replication (Hosseini et al., 2018).

IAV infection in humans may therefore not only lead to short-term responses in infected organs but may also trigger neuroinflammation and associated chronic alterations in the CNS. As mild-to-moderate cognitive impairments in humans might be compensated in everyday life these consequences may have been overlooked so far. It will thus be important to study whether similar or even more pronounced impairments would be observed in aged individuals as a more vulnerable group. Our recent preliminary findings suggest that the effects of both neurotropic and non-neurotropic IAV strains are significantly more destructive in older individuals than in the young ones. However, the detailed mechanisms of how peripheral inflammatory responses can lead to the activation of microglia and subsequently cognitive deficits need to be examined more closely.

Conclusions

So far, the origin of many neurological disorders, especially neurodegenerative diseases, remains poorly understood. On the other hand, several common human respiratory viruses with or without neuroinvasive capacity can trigger or exacerbate neuropathological manifestations, particularly in vulnerable individuals. Therefore, nowadays respiratory viruses are considered as important agents responsible for CNS pathologies. Influenza viruses (IAV) and coronaviruses (CoV) are key candidates among the respiratory viruses associated with neurological complications (Table 1) (Nichols et al., 2008). A deeper understanding of the underlying mechanistic details of neuroinvasion of respiratory viruses is needed. In addition, the interaction of peripheral immune reactions triggered by these viruses with the CNS (Figure 1) is critical to evaluate potentially pathological short- and long-term consequences.

Our own investigations indicate that influenza infection in young adult mice with neurotropic (H7N7) and even a non-neurotropic (H3N2) virus, can initiate inflammatory cascades via microglia activation in the brain leading to long-term consequences and therefore most likely increases the likelihood to develop neuropsychiatric and neurodegenerative disorders during a life-time. It needs to be emphasized that also the host immune response triggered by the H3N2 IAV subtype in the periphery was able to impair hippocampal function in our mouse model. More strikingly, IAV without direct replication in the brain resulted in prolonged activation of microglia with the detrimental outcomes for cognitive functions (Hosseini et al., 2018). Neuroinflammation in this respect might well be a central mechanism contributing to the generation and progression of a number of neuropsychiatric and neurodegenerative disorders including Alzheimer's disease, especially in vulnerable individuals. Our unpublished findings confirmed the hypothesis by showing the far more destructive effects of influenza viruses on the hippocampal structure and function in the elderly and genetically Alzheimer's mouse models. In addition to IAV, several pieces of evidence revealed that coronaviruses with neurotropic properties were isolated from the brain autopsy obtained MS patients and animal mouse models accompanied by neurological manifestations such as motor function deficits. This indicates that some respiratory viruses such as CoV can be added to the growing list of viruses that persist in the CNS. Interestingly, seasonal coronavirus patterns fit the observed occurrence of MS exacerbations in the human population (Arbour et al., 2000). Therefore, by identifying the exact mechanistic details of CNS and peripheral infections following respiratory viruses in the future, novel approaches to modulate the neuroimmune interaction may provide a strategy to prevent deleterious acute and long-term effects of neurotropic and non-neurotropic respiratory viral infections on brain function and integrity, especially in highly susceptible patient groups. Moreover, by investigating the life-time history of a person and the respiratory viral infections they have been exposed to, it might be possible to unravel the mystery of the unknown origin of neurodegenerative diseases and steps can be taken to reduce the risk of their occurrence, for example, via vaccination.

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Bionotes

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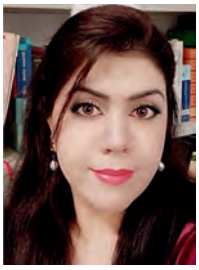

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Review article

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Nanoscale imaging of the functional anatomy of the brain

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Abstract: Progress in microscopy technology has a long history of triggering major advances in neuroscience. Super-resolution microscopy (SRM), famous for shattering the diffraction barrier of light microscopy, is no exception. SRM gives access to anatomical designs and dynamics of nanostructures, which are impossible to resolve using conventional light microscopy, from the elaborate anatomy of neurons and glial cells, to the organelles and molecules inside of them. In this review, we will mainly focus on a particular SRM technique (STED microscopy), and explain a series of technical developments we have made over the years to make it practical and viable in the field of neuroscience. We will also highlight several neurobiological findings on the dynamic structure-function relationship of neurons and glia cells, which illustrate the value of live-cell STED microscopy, especially when combined with other modern approaches to investigate the nanoscale behavior of brain cells.

Keywords: extracellular space; glial cells; SMLM; STED; super-resolution microscopy; synapse.

Zusammenfassung: Fortschritte in der Mikroskopie-Technik haben in der Vergangenheit immer wieder große Durchbrüche in den Neurowissenschaften ausgelöst. Die superauflösende Fluoreszenzmikroskopie, berühmt für die Durchbrechung der Beugungsgrenze der Lichtmikroskopie, bildet hier keine Ausnahme. Sie ermöglicht beispiellosen Zugang zum anatomischen Aufbau und der Dynamik von Nanostrukturen, die mit konventioneller Lichtmikroskopie nicht auflösbar sind, von der ausgefeilten Anatomie der Nerven- und Gliazellen bis hin zu den Organellen und Proteinen in ihrem Inneren. In diesem Überblicksartikel werden wir hauptsächlich auf die STED-Mikroskopie eingehen und eine Reihe von technischen Neuerungen erläutern, die wir im Laufe der Jahre anwendungsspezifisch dafür entwickelt haben. Wir werden dabei einige unserer neurobiologischen Untersuchungen und Resultate über Synapsen, Gliazellen und den Extrazellulär-Raum vorstellen, wo die ‚live-cell' STED-Mikroskopie in Kombination mit anderen modernen Ansätzen einen entscheidenden Beitrag leisten konnte.

Schlüsselwörter: Extrazellulärer Raum; Gliazellen; SMLM; STED; Super-Resolutions-Mikroskopie; Synapsen.

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Introduction

Progress in microscopy technology has a long history of triggering major advances in neuroscience, most prominently with Golgi's staining technique in the 1870s, electron microscopy (EM) in the 1950s, confocal microscopy, 2-photon microscopy, fluorescent proteins, and optogenetics in recent times. Synergistic and self-amplifying, these innovations have dramatically accelerated the symbiotic progress of technology and biology, the discovery of biological luminescence and the runaway success of GFP-based biosensors being a prime example.

In fact, one of the great controversies in neuroscience history exemplifies the role that new tools and technology play for scientific progress. Enabled by technical breakthroughs in staining and viewing samples of human brain tissue, the Spanish neuroanatomist Ramon y Cajal made seminal observations about the shape and arrangement of brain cells (DeFelipe, 2009). Against the reigning 'reticular theory' promoted by Camillo Golgi, who thought of the brain as a diffuse network of anastomosing neurons, Cajal proposed the 'neuron doctrine' where discrete, physically separated cells (neurons) transmit electrical signals at special microscopic junctions (chemical synapses) formed by dendritic spines. Both of them were partly right in the end, sharing a Nobel Prize in 1906, because neurons have synapses and gap junctions that mediate stochastic-quantal and gradual-analogue electrical communication, respectively, as since proven by more modern cell biology techniques.

In the perpetual cycle of innovation and discovery, the advent of super-resolution microscopy (SRM) is a recent milestone. It refers to fluorescence imaging techniques that cleverly exploit the 'on–off' behaviour of fluorophores to resolve features in a sample that remain obscure to conventional light microscopy. Recognized by the Nobel Prize in 2014 (shared by Stefan W. Hell, William E. Moerner and Eric Betzig) for breaking the diffraction barrier of light microscopy (which is around 200 nm), SRM opens a new window on the "nanocosm" of biological life.

Indeed, SRM methods are on track to offer single-digit nanometer spatial resolution, unearthing ever more data on the molecular organization and dynamics of cells and tissues. SRM is a powerful tool, especially in neuroscience, because it can capture the extremely elaborate morphology of neurons and glial cells, as well as the crowded arrangement of organelles and molecules inside of them (Figure 1) (Tønnesen and Nägerl, 2013). As the anatomical designs and dynamics of these nanostructures are tightly linked to brain functions, there is a huge interest to develop and apply SRM. Accordingly, SRM is becoming a mainstay in biology departments and core facilities around the world only a few years after their principles and prototypes were developed by a handful of bio-photonics labs.

In this review article, we will explain the basic principles of SRM and highlight several methodological innovations and neurobiological applications we have driven over the last few years.

SRM basics

To understand how super-resolution can be achieved, we first need to appreciate why the resolution of conventional microscopy is limited. Photons that are emitted by a point source of light (such as a single fluorophore) are diffracted by the optics of the microscope, causing them to be projected into a blurry spot instead of a nice and crisp point on the retina, camera screen or other light detector. The size of this spot (Δr) corresponds to the 'diffraction limit of light microscopy' or the 'spatial resolution' of the microscope, which is incarnated by Abbe's simple formula $\Delta r = \lambda/2{\cdot}NA$, where λ denotes the wavelength of the light and NA the numerical aperture of the microscope objective.

Importantly, if there is just one fluorophore, it can be localized very precisely by calculating the geometric center of the spot. However, if there are too many fluorophores that are too close to each other (closer than Δr), this localization step becomes impossible and the fluorophores can no longer be distinguished as their images merge into a blurry whole. This is the case of conventional fluorescence microscopy where basically all fluorophores emit photons at the same time, making the image irredeemably fuzzy.

There are mainly two ways to get around this problem and achieve a resolution that is 10 times or even a hundred times better than Δr (Figure 2). In both cases, the

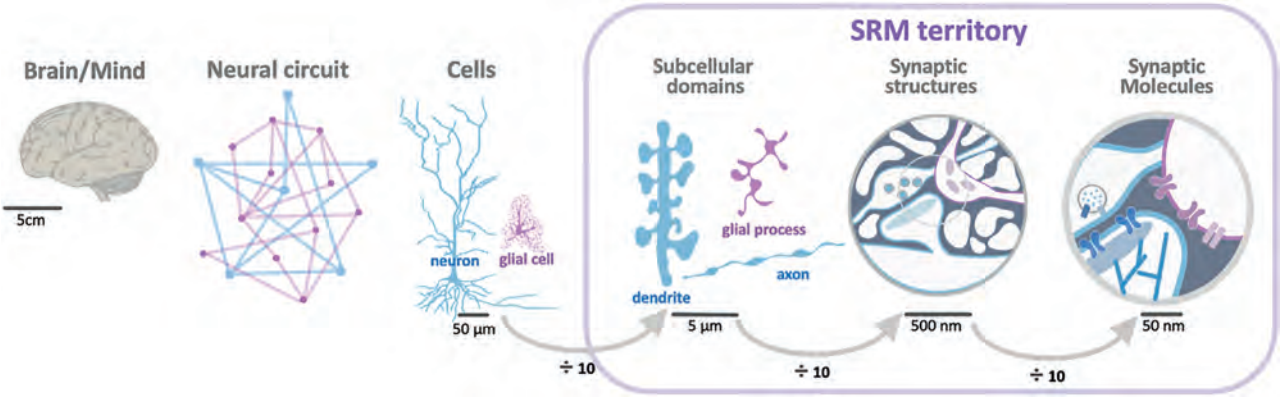

Figure 1: Super-resolution microscopy opens a window into the nanocosm of the brain.
SRM can capture the extremely elaborate nanoscale anatomy of neurons and glial cells, as well as the way organelles and proteins are arranged inside of them.

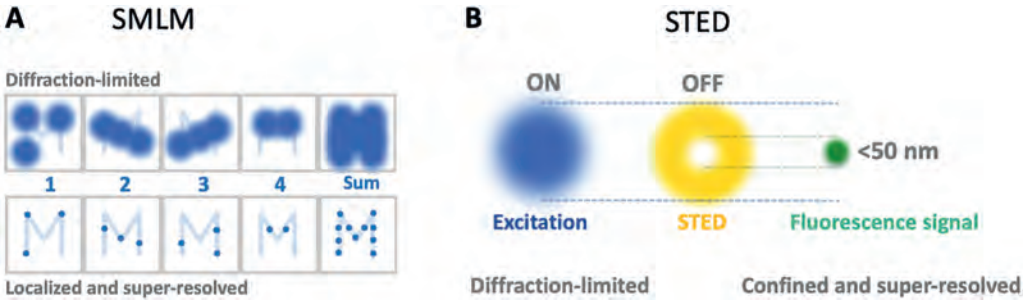

Figure 2: Two major 'tricks' to crack the diffraction limit of light microscopy.
(A) In SMLM, only a sparse subset of fluorophores is stochastically turned on at a given time, making it possible to localize each of them very precisely. By repeating this cycle many thousands of times, a super-resolved image can be constructed by merging all the individual localizations. (B) In addition to an excitation laser, a STED microscope is also equipped with a second laser with the purpose of de-exciting the molecules. By shaping this laser like a donut, it can strongly suppress the fluorescence on the edge of the excitation spot, thereby increasing the spatial resolution.

fluorescent dye molecules, and the ability to control their photophysical state with light, take centre stage.

On the one side, one can find methods that are based on the detection of single molecules (such as PALM, STORM and uPaint) (Fürstenberg and Heilemann, 2013). Instead of exciting many fluorophores at the same time, only a sparse subset is stochastically turned on at a given time, using a special switching mechanism. Under such conditions, it is possible to determine very precisely the location of individual fluorophores, to 'localize' them, assigning each of them a spatial coordinate. By repeating this cycle many thousands of times, each time turning on a different subset of fluorophores, a super-resolved image can be constructed by merging all the individual localizations (Figure 2A).

By analogy, single-molecule localization microscopy (SMLM), as it is commonly referred to, is like drawing a picture in pointillist style, but only after shrinking down all the little dots that collectively produce the composite image. While SMLM is the method of choice for imaging nanoscale protein distributions in cells because of its unrivalled spatial resolution (<10 nm) and ability to provide quantitative information on the number and diffusion of single molecules, its overall temporal resolution is quite slow (on the order of minutes per image).

On the other side, there are methods that reduce the fluorescence spot in laser-scanning microscopes (such as STED and RESOLFT) (Hell, 2007). This reduction is achieved by a second laser (the STED laser), which can de-excite, or 'turn off', molecules by stimulated emission, well known from laser physics. By shaping the STED laser like a donut, it can suppress the fluorescence on the edge of the excitation spot, while leaving it untouched in the middle of the donut, effectively increasing the spatial resolution of the microscope (Figure 2B).

Acquiring a STED image then is like drawing with a pencil that is mounted in front of two closely spaced erasers so that the pencil marks left behind become much thinner. While STED imaging generally offers less spatial resolution (~20–30 nm) than SMLM, it can be relatively fast (on the order of seconds per image) and is well-suited for volumetric imaging of diffusible cytosolic fluorophores to reveal nanoscale cell morphology.

Not only does SRM cost extra time and money, it also comes at the price of technical challenges and setbacks due to its more stringent requirements and taxing conditions compared to conventional microscopy. With SRM, it is typically more challenging to obtain sufficient signal/noise ratios, depth penetration, sample stability. SRM techniques are also more prone to phototoxicity and photobleaching. Hence, for many years, its application was limited to imaging chemically fixed samples very close to the coverslip and remained disconnected from other experimental approaches or measurements. This immaturity was a far cry from the wide scope and effectiveness of well-established fluorescence techniques, such as 2-photon microscopy or simple wide-field imaging.

Fortunately, numerous incremental technical improvements cumulatively have made a big difference for SRM performance, from sample labelling (engineering tags that are brighter and more photostable, smaller, more specific and less invasive) to microscope instrumentation and optics (with tighter engineering tolerances, digital control and automation) to image processing and analysis (with more computing power and better algorithms). Having come of age, SRM is now an indispensable tool for cellular and molecular neuroscience.

In the following, we will describe our journey to making STED microscopy easier to use and more impactful, explaining a series of innovations and tweaks we have introduced over the years.

STED microscopy in living brain tissue

After the demonstration that STED microscopy can greatly improve live-cell imaging of neurons in brain slices (Nägerl et al., 2008), properly resolving their morphological details for the first time with photons instead of electrons, it became desirable to make STED a more useful tool for neurobiologists.

To image in multiple colours is essential for distinguishing different cellular structures (e.g. presynaptic axons, postsynaptic dendrites, glial processes). While this is a given for conventional fluorescence microscopy, it is more difficult to achieve for STED microscopy where the STED laser constrains the available spectral bandwidth. Sidestepping this problem, we came up with a robust method for two-colour STED imaging of neuronal morphology (Tønnesen et al., 2011). By using spectrally similar fluorophores (e.g. GFP and YFP), it is possible to get away with a single pair of excitation and STED lasers to simultaneously image both fluorophores at super-resolution. The two overlapping fluorescence signals can be spectrally separated by simple image processing ('linear unmixing'). This solution avoids the cost and complexity of adding lasers to address each fluorophore separately and rules out chromatic errors to boot.

Many neurobiological questions can only be addressed inside live brain tissue, which demands a certain amount of tissue depth penetration. Unfortunately, the quality of the STED donut degrades rapidly with imaging depth inside biological tissue, obliterating spatial resolution and image contrast. With early STED microscopes, which were designed for oil-immersion objectives, it was only possible to image a few microns into the tissue because of a large mismatch in refractive index between the oil–sample interface. This causes spherical aberrations, which blur out the excitation and STED laser spots. Switching to a glycerine-immersion objective (which has a smaller mismatch and a correction collar to reduce aberrations), proved to be a simple and effective remedy. It significantly extended the depth penetration of STED, making it possible to resolve cellular actin structures as thin as 70 nm at depths of 80 µm below tissue surface (Urban et al., 2011).

In another tack, we developed a new combination of 2-photon and STED microscopy, aiming to combine the unique benefits of both techniques. It enabled us to image in acute brain slices beyond the debris and damaged cells on the surface from cutting the slices (Bethge et al., 2013). We have also adopted an approach to preserve the STED donut by shaping the wavefront of the STED laser beam (Bancelin et al., 2021). It is based on 'adaptive optics', a technique originally developed by astronomers to counteract the optical aberrations from the Earth's atmosphere (Rodríguez and Ji, 2018). When combined with modern computational tools like machine learning, it is possible to optimize the adaptive parameters on the fly, which will greatly facilitate maintaining a good donut deep inside heterogenous tissue.

Another way to achieve higher depth penetration in fixed tissue samples is to modify the optical properties of the sample itself. Recently, we demonstrated that embedding brain slices in a refractive index-matching medium renders them transparent and suppresses the spherical aberrations at the oil–sample interface (Angibaud et al., 2020).

Armed with these technical improvements, we set out to address several interesting neurobiological questions about the morphological dynamics and plasticity of neurons and glial cells. In essence, STED microscopy could solve the classic impasse, where light microscopy can do live-cell imaging but doesn't have enough resolution, while EM has enough resolution but can't do live-cell imaging.

Experiments were usually—unless stated differently—performed in cultured organotypic hippocampal slices, which is a very stable and accessible experimental preparation that retains the main anatomical relationships and synapto-physiological properties of the intact hippocampus.

Spine neck plasticity regulates synapse compartmentalization

Dendritic spines, the tiny dendritic membrane protrusions that Cajal famously observed and drew, are the postsynaptic structural compartments of excitatory synapses in the brain. Despite intense investigations for more than a century, these beautiful structures are still quite enigmatic (Figure 3A). Conspicuously shaped, with a prominent head and elongated neck, spines transform synaptic signals through chemical and electrical compartmentalization (Adrian et al., 2014; Yuste, 2013). However, the impact of spine morphology on synapse compartmentalization remained difficult to assess, because spines, especially their necks, are so small and difficult to resolve. Enabled by a combination of STED and modern electrophysiological and biophysical techniques, we could illuminate the relationship between the nanoscale structure and function of spines (Tønnesen et al., 2014).

We demonstrated that spine necks become substantially wider and shorter after the induction of functional

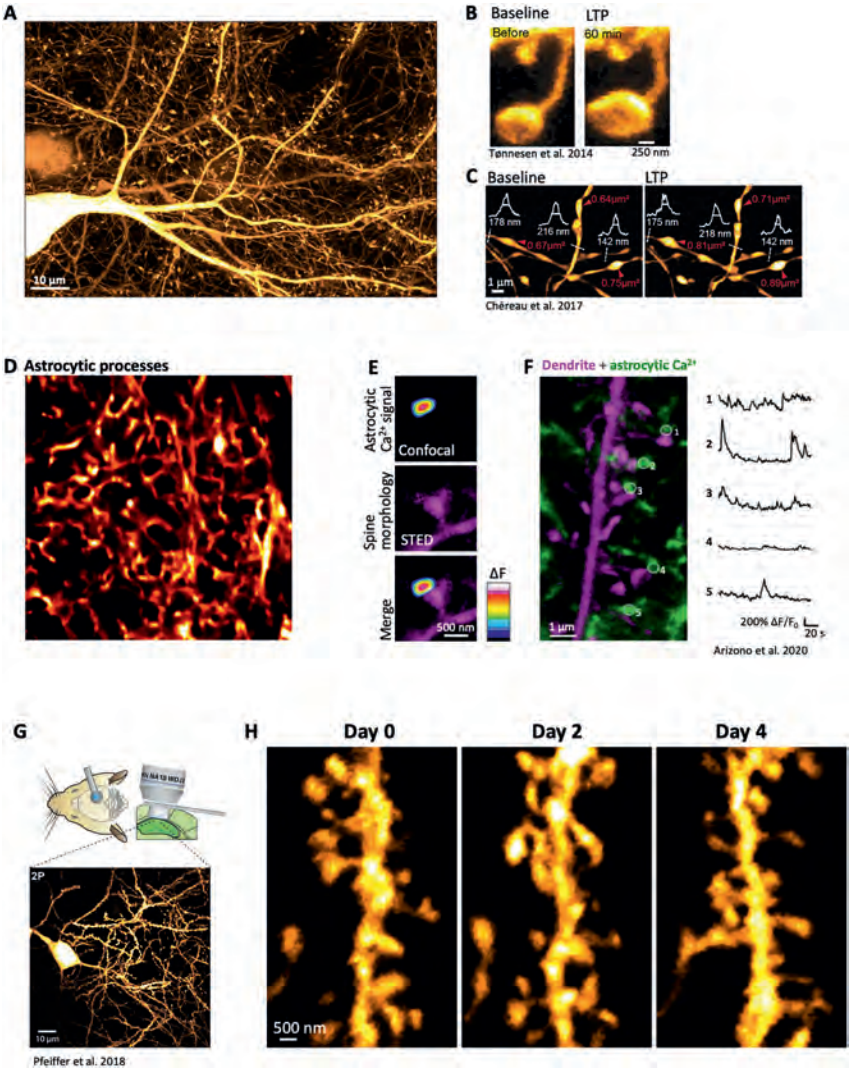

Figure 3: Dissecting the functional nano-anatomy of the brain using live-cell STED microscopy.
(A) A typical pyramidal neuron in the brain, which projects elaborate dendritic and axonal arbors. Experimental induction of synaptic plasticity (LTP) resulted in spine head enlargement/spine neck widening (B) and transient enlargement of axonal boutons (C). (D) Astrocytic processes exhibit a reticular organization in their hyperfine processes. (E) Mapping the Ca^{2+} signals onto the super-resolved morphology showed astrocytic Ca^{2+} activity associated with single synapses. (F) Unique astrocytic Ca^{2+} patterns associated with individual synapses. (G) The combined use of the hippocampal window preparation and a long working distance objective (top) gives access to CA1 hippocampal neurons *in vivo* (bottom). (H) *In vivo* chronic super-resolution imaging (2P-STED microscopy) reveals a high turnover rate of dendritic spines in the hippocampus.

synaptic plasticity induced by glutamate uncaging. These changes could reflect a structural mechanism to modify the strength of synapses (Figure 3B), because any changes that reduce the electrical resistance of the spine neck (which is what neck widening would be expected to do) will decrease the amplitude of excitatory synaptic potentials (EPSP) in the spine head.

Counterintuitively, this reduction in EPSP would actually potentiate the synapse by preventing spine voltages from reaching the Nernst (reversal) potential of the synaptic conductance, where the ionic current into the spine ceases to flow. For this disinhibition effect to be physiologically noticeable, the synaptic conductance and neck resistance would have to be high enough for spine EPSPs to approach the reversal potential, which is likely to be the case for spines with large heads and long or thin necks (Tønnesen and Nägerl, 2016).

Axon plasticity tunes conduction speed of action potentials

Several studies over the 20 years have punctured the classic view of axons as electro-anatomical cables that faithfully conduct action potentials (AP) in an all-or-none fashion to downstream synaptic targets (Debanne et al., 2011; Rama et al., 2018). It was shown that axons have a variety of sophisticated ways to regulate AP conduction (Sasaki et al., 2011) and synaptic transmission (Alle and Geiger, 2006), and thus the timing of signal processing in the brain. While AP conduction speed in unmyelinated axons depends strongly on axon diameter, it was unknown whether AP conduction speed could be dynamically regulated by activity-dependent changes in this biophysical parameter. Again, given the minute

dimensions of the structures involved, this question could not be addressed by conventional light microscopy.

Enabled by time-lapse STED imaging paired with electrophysiology in hippocampal brain slices, we showed that high-frequency AP firing induced physical enlargement of axons, where axonal boutons showed a transient increase, which was followed by a sustained widening of the intervening axonal shafts (Figure 3C). These structural dynamics were mirrored by bidirectional changes in AP conduction speed. A causal link between the nano-structural and functional changes was also supported by pharmacological experiments and mathematical modelling, which closely predicted the effects on AP conduction. Our findings revealed a novel structural plasticity mechanism that tunes the timing of fast electrical signalling (Chéreau et al., 2017).

Astrocytic nanostructures generate calcium signals at tripartite synapses

If conventional light microscopy struggles to resolve neuronal morphology, it totally fails for astrocytes, a type of glial cells in the brain, which has an even more elaborate morphology than neurons. Their nanoscale processes wrap around synapses, forming so-called tripartite synapses, whose elements are thought to be all in close communication to tune synaptic transmission and plasticity. Perisynaptic astrocytic processes are responsible for glutamate uptake from the synaptic cleft and appear to release neuroactive substances that can modulate synaptic transmission. But because everything looks so fuzzy under a normal microscope, it has been difficult to witness how astrocytes interact with synapses (Rusakov, 2015).

To overcome this problem, we turned to 3D-STED microscopy and combined it with confocal Ca^{2+} imaging and FRAP experiments to assess their signalling activity and biophysical properties. We observed that astrocytic processes form a reticular meshwork of nodes and shafts that were frequently arranged as rings (Figure 3D–F). The nodes gave rise to spontaneous Ca^{2+} signals, which tended to stay confined, but could also spread to neighbouring nodes via the shafts. FRAP experiments indicated that nodes can effectively compartmentalize diffusible signals by virtue of their structural design. Mapping the Ca^{2+} signals onto the STED-resolved morphology showed that astrocytic Ca^{2+} activity was associated mostly with single synapses, consistent with the idea that astrocytes can communicate 'privately' with many different synapses at the same time.

Altogether, our study shines new light on the nanoscale organization of astrocytes in live brain tissue, identifying astrocytic nodes as the elusive anatomical structure that may regulate neuronal communication at tripartite synapses (Arizono et al., 2020).

Two-photon STED microscopy reveals turnover of hippocampal spines *in vivo*

Rewiring neural circuits through synapse formation and elimination is thought to be a key mechanism of learning and memory. While experience-dependent spine plasticity has been extensively studied in superficial cortical areas using 2-photon microscopy, little is known about it in the hippocampus, despite its outsize importance for memory processing. This knowledge gap was mainly due to difficulties in gaining optical access to this deeply embedded brain structure, and the fact that 2-photon microscopy struggles to correctly report hippocampal spine density (Attardo et al., 2015; Gu et al., 2014), which can be 10 times higher for hippocampal than cortical neurons (Holtmaat et al., 2006).

In this context, we set out to develop a super-resolution approach to monitor spine plasticity over extended time periods in the hippocampus *in vivo*, developing further our 2-photon STED microscope. To gain optical access, we surgically removed a piece of cortex above the hippocampus and implanted a metal cylinder into the space created. We also retrofitted our 2-photon STED microscope with a long-working distance objective to optically reach the hippocampus below the cortical surface. Performing repeated 'chronic' imaging of fluorescently labelled hippocampal neurons in anesthetized mice, we monitored their spine density and spine turnover over a few days (Pfeiffer et al., 2018).

Because of the high acuity of our imaging approach, the measured spine density was more than twice as high as the values reported by previous 2-photon studies, in good agreement with the gold-standard EM literature. Enabled by this high spine detection efficiency, we could follow individual spines through time. We observed that a stunning 40% of them turned over (i.e. were lost or replaced, while their total number, or density, stayed constant) during four days of observation (Figure 3G and H). Our study provides direct evidence for a high level of circuit remodelling in the hippocampus, supporting the view that hippocampal

synapses serve as transient buffers and dynamic relays for newly formed memory traces.

Super-resolution shadow imaging (SUSHI) of the extracellular space

Despite all of its strong points, fluorescence microscopy has the distinct disadvantage that you only see what you label, leaving you literally in the dark about the rest.

To get a non-biased and truly comprehensive view, we have developed an 'inverted' strategy to label brain tissue. Instead of marking individual cells, we simply label and image the spaces between the cells, using a highly diffusible but membrane-impermeable fluorescent dye and a homemade 3D-STED microscope. Collectively, these in-between spaces are called the extracellular space of the brain (ECS), taking up roughly 20% of the volume of the brain and containing cerebrospinal fluid and the extracellular matrix.

We named the technique 'super-resolution shadow imaging' or SUSHI (Tønnesen et al., 2018) because all cells appear as dark shadows in a bright sea of fluorescence (Figure 4A). SUSHI generates a super-resolved negative imprint of the space occupied by membrane-bound

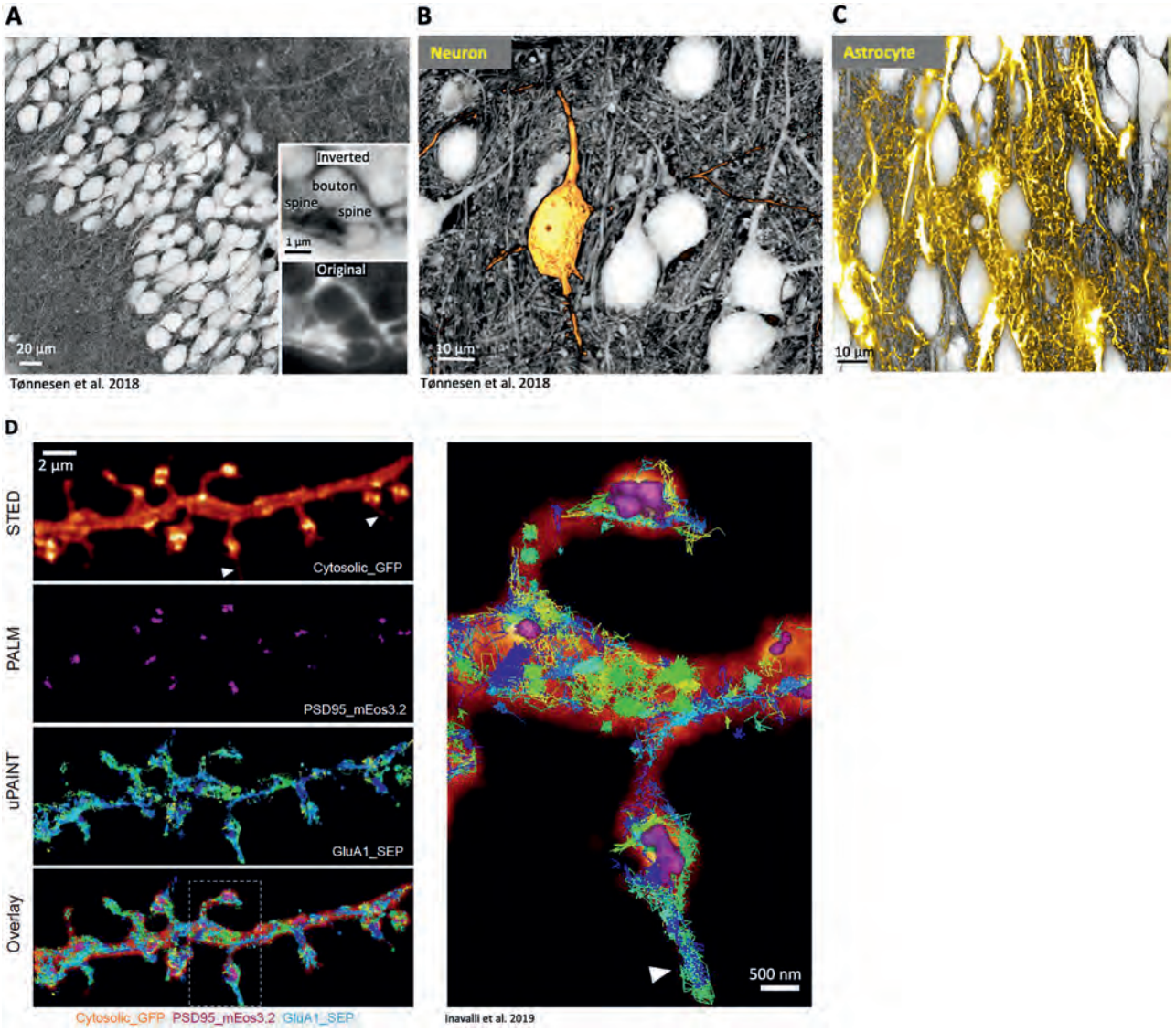

Figure 4: New applications for STED microscopy.
(A) An inverted SUSHI image showing imprints of all brain cells in the tissue. This can be combined with positively labelling of a particular cell type such as neurons (B) and astrocytes (C). (D) Combination of STED and PALM makes it possible to image nanoscale dendritic spine morphology (orange, STED) together with scaffolding proteins (pink, PALM) and receptor dynamics (blue, uPAINT) (left). White arrow indicates 'spinules', a type of 'mini-spine' extending from dendritic spines, where receptors are especially dynamic (right).

cellular structures. As in regular photography, the negative image holds the same structural information as the positive image, making it possible to view the anatomical organization of live brain tissue in a sweepingly panoramic, yet exquisitely detailed way.

Even though the labelling is inherently unspecific, different cell types can readily be distinguished based on their shape. It is even possible to discern synaptic clefts, owing to the nanoscale spatial resolution and favourable contrast conditions, where the super-thin but brightly labelled extracellular fissures stand out against the pitch-black cellular structures that Sandwich them (Figure 4A).

Labelling the ECS rather than individual cells comes with several practical advantages. It is easy to apply, and is much more resistant to photobleaching and phototoxicity. This is because bleached dye molecules get continuously replenished via diffusion and toxic photoreaction products don't build up inside the cells but wash away rapidly.

Not only is SUSHI—especially in combination with positively highlighted cells (Figure 4B and C)—useful for imaging cells and their anatomical relationships, it can also reveal the complex nano-architecture of the ECS. Surrounding all cells, the ECS is the obligatory transit station for extracellular signalling molecules and therapeutic substances, influencing neuronal communication and the efficiency of drug treatments.

EM and MRI have been used to reveal the ECS, but they provide only grossly distorted/static or imprecise/macroscale views, respectively. In fact, the ECS shrinks down to a uniformly thin layer after chemical fixation for EM, bearing little resemblance with its live version, which is actually very voluminous and heterogenous.

Physiologically regulated (Xie et al., 2013) and highly sensitive to experimental stimulations (Arizono et al., 2021; Tønnesen et al., 2018), the ECS provides a dynamic and biophysically influential three-dimensional stage, where neurons and glia cells perform in concert. As a versatile technique, SUSHI can be readily applied to other tissues and organs, from tumours to salivary glands (Stolp et al., 2020).

SRM^2 to image the molecular and morphological organization of live cells

Over the last few years, we have seen a growing diversification and cross-fertilization of SRM techniques, towards more quantitative, multiproperty and integrated analyses of ever more complex biological samples. While SRM offers wonderful opportunities to unravel nanoscale structures and events, current SR microscopes do not offer a good way to reveal both protein distributions and the morphological shape of cells. It meant either one or the other, but not both.

Recently, hybrid SRM modalities were introduced that incorporate optical motifs of STED to enhance the spatial precision of SMLM, such as MINFLUX (Balzarotti et al., 2017) and LocSTED (Puthukodan et al., 2020), but they remain essentially single-molecule imaging techniques.

We have recently overcome this problem by combining fully-fledged versions of SMLM and STED on a single platform, offering a 'best-of-both-worlds' solution (Inavalli et al., 2019). It places the molecular information in the context of the morphological organization of the cells, which is crucial for deciphering cellular nanobiology.

In essence, the new platform makes it possible to closely correlate, in space and time, the data from both imaging modalities. Based on an optimized workflow, one can rapidly and repeatedly switch back and forth between the PALM and STED modes without undue spectral crosstalk and bleaching of the fluorescent probes of the respective modalities.

Using this new approach, we could resolve the distribution and diffusional mobility of several prominent synaptic proteins, such as glutamate receptors (subunits of AMPA receptors, GluA1 and GluA2) and scaffolding proteins (PSD95), within distinct dendritic microstructures in dissociated neuronal cell cultures. We observed that GluA1 molecules are basically arrested inside PSD95 clusters in the spine head but diffuse around rapidly in spinules, which are tiny protrusions projecting from the spine heads (Inavalli et al., 2019), giving us intriguing new insights into the nanoscale dynamics of the molecular machinery of synapses.

Modular and flexible by design, the new platform also incorporates other SRM techniques, such as uPAINT and SUSHI, thereby opening a doorway to important discoveries in cellular biology and neuroscience (Figure 4D).

Outlook

Progress in neuroscience will continue to be shaped by advances in optical microscopy, coming from molecular biology, physics, chemistry, engineering and computer sciences. The new neurophotonics technologies will in time eclipse everything we currently know in terms of speed, precision and gentleness to record and manipulate the key players of brain function from genes and molecules to cells and circuits.

It's probably the right time to start dreaming about linking *in vivo* brain nano-structure, including the ECS, with

nano-physiology and even higher brain functions such as memory and sleep, breaking down the barriers between the different scales and concepts.

To achieve this ambitious goal, we will need more technology 'mash-ups', combining fluorescence SRM with more macroscale and label-free imaging modalities like photoacoustic imaging, MRI or Raman spectroscopy. This would produce complementary and correlative data for a given biological system or give each of the techniques a leg up, opening experimental access to more key parameters on wider temporal and spatial scales.

All this will require the creative imagination of stubborn pioneers and the swarm intelligence of the scientific community, who come up with stimulating controversies and keep the cycle of innovation and discovery turning, very much in the spirit of Cajal and Golgi!

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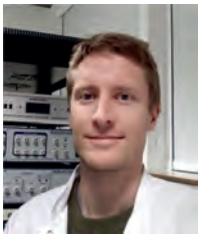

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Review article

Martin Brüne*

Mental health and biological evolution: implications for psychiatry and psychosomatic medicine

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Abstract: Psychiatric disorders are common and seem to increase in prevalence worldwide. Most scientific approaches for this phenomenon fail to explain why the majority of mental disorders, unlike most somatic diseases, manifest in early adulthood, why individuals are not more resilient, and why some genes increasing the risk for mental disorders have not been selected against. In this article, an evolutionary perspective on mental health and disorder is taken. This perspective suggests that mismatches between ancestral and contemporary environments contribute to the risk for mental disorders. In addition, predictions from attachment theory and life history theory can explain individual differences with regard to the risk of developing a psychiatric or psychosomatic disorder. Insights from evolutionary approaches to psychiatric and psychosomatic disorders may contribute to improve the prevention and treatment of mental disorders.

Keywords: attachment; differential susceptibility; gene-environment interaction; mismatch; vulnerability.

Zusammenfassung: Psychische Störungen sind häufig und scheinen in der Prävalenz weltweit zuzunehmen. Die meisten wissenschaftlichen Ansätze können nicht schlüssig erklären, warum viele psychische Erkrankungen, anders als die meisten körperlichen Erkrankungen, im frühen Erwachsenenalter auftreten, warum Individuen nicht resilienter sind, und warum manche Gene, die für das Auftreten psychischer Störungen disponieren, nicht negativ selektiert worden sind. In diesem Beitrag wird eine evolutionsbiologische Perspektive vertreten, die argumentiert, dass das Risiko für psychische Störungen zum Teil mit der Verschiedenheit anzestraler Lebensbedingungen von heutigen erklärt werden kann. Darüber hinaus lassen sich individuelle Unterschiede im Hinblick auf das Risiko, eine psychische oder psychosomatische Erkrankung zu entwickeln, auf der Basis bindungstheoretischer Ansätze und der „life history theory“ vorhersagen. Diese Einsichten aus dem Blickwinkel der Evolution können dazu beitragen, die Prävention und Therapie psychischer Störungen zu verbessern.

Schlüsselwörter: Bindung; differentielle Empfindlichkeit; Gen-Umwelt Interaktion; „mismatch“; Vulnerabilität.

Introduction and objectives

Psychiatric disorders are remarkably prevalent around the world. As regards depression, for example, the World Health Organization (WHO) predicts for the year 2030 that depression will constitute the second most burdensome disease as measured in “disability-adjusted life years”, only exceeded by HIV-associated diseases including AIDS, but figuring before cardiovascular disease (Mathers and Loncar, 2006). Yet in contrast to cardiovascular disease, cancer and many other diseases, psychiatric disorders usually manifest at people’s prime of life. Why is this so? Is happiness an elusive ideal, as the evolutionary psychiatrist Randolph Nesse once put it (Nesse, 2004)? Why are mood disorders so frequent that in developed countries about one in four adults at some point will suffer a depressive episode? How can we explain that most psychiatric disorders occur at an age where the influence of selection is greatest, i.e. near the peak of reproductive potential? Why are human beings not more resilient against the experience of adverse life events? After all, can we dare to ask the question, whether low mood could be good for something?

This is not the usual way neuroscience and psychiatry enquire about the nature of mental illness. Instead, in keeping with the WHO ideal of mental health, defined as “a state of well-being in which every individual realizes his or her own potential, can cope with the normal stresses of life,

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can work productively and fruitfully, and is able to make a contribution to her or his community", research into the origins of psychiatric conditions readily equate mental health with the presence of positive emotions as a marker for a good quality of life, whereas the presence of negative emotions is likened to the concept of mental disorder. It is certainly a truism that in the economically developed countries societies have succeeded in reducing many causes of suffering, including hunger, pain, infectious diseases, and premature death. However, there is little indication that this has led to a general increase of happiness (Nesse, 2004). Even high income seems to be largely unrelated to emotional well-being (Kahneman and Deaton, 2010). Therefore, we need to choose a different approach to the understanding of psychiatric disorders.

From an evolutionary point of view, the questions referred to above can be reframed in the following ways: Why is the human mind apparently vulnerable to dysfunction in spite of millennia during which natural selection has operated on our species' behavioural, emotional and cognitive endowment? Why has natural selection failed to eliminate negative emotions, in light of their potentially deleterious influence on health? How can we resolve the dissonance between an adaptationist perspective suggesting that some signs and symptoms of common psychiatric disorder may be adaptive under specific circumstances, and the fact that many psychiatric disorders are associated with poor biological fitness?

Even though these questions seem to suggest that an evolutionary approach to mental health is reductionist, this article seeks to emphasize that it is rather in full accordance with George Engel's proposition of a bio-psycho-social model of health and disease (Engel, 1960; Fabrega, 1974), and can serve as a unifying conceptual framework for psychiatry and neuroscience.

A conceptual framework for the understanding of behaviour

A full understanding of any physiological, anatomical or behavioural trait requires the analysis of that trait on four levels. Two of them refer to so-called "proximate" or immediate explanations, namely (1) ontogeny of the trait, and (2) its underlying physiological or molecular mechanisms. The other two, referred to as the "ultimate" or evolutionary explanations concern (3) the phylogeny of the trait, and (4) its adaptive value. This framework was put forth by Nikolaas Tinbergen, emphasizing that all four levels need to be addressed for a full comprehension of any feature (Tinbergen, 1963). Importantly, the proximate causes are modifiable during an individual's lifetime and strongly depend on gene-environment interaction, including epigenetic regulation, as we now know (Roff, 2007). The evolutionary levels entail the exploration of similarities and dissimilarities between species (comparative method), and the analysis of the ecological contingencies shaping a given trait by selection (Tinbergen, 1963).

The heuristic value of Tinbergen's framework was long ignored by the life-sciences, including medicine, because pathological variation seemed to be precluded from Tinbergen's approach, given their maladaptive nature by definition. This has changed in the last few decades, for reasons outlined in the following paragraphs (Brüne, 2014, 2016; Nesse, 2013; Nesse and Stearns, 2008).

Evolutionary inquiry into the nature of human nature acknowledges several basic principles. First, contemporary *Homo sapiens* is a product of evolution by natural selection, and most adaptations (physiological, anatomical or behavioural) evolved in our ancestral past as hunter-gatherers, which does not preclude mounting evidence that our species continues to evolve (Stearns et al., 2010). Second, selection operates on phenotypic variation, conferred by genes, whereby unfavourable traits are usually eliminated from the gene pool of a population, as long as the trait has consequences for an individual's reproductive fitness and does not escape selection (which can be the case, if the consequences manifest after the reproductive period). Some exceptions to this rule involve positive (as opposed to negative) selection of genes that supposedly convey fitness advantages, for example, the ability for creative thinking. Such genes have been assigned a potential role in the aetiology of schizophrenia (Crespi et al., 2007). Importantly, as selection operates on survival and maximization of reproductive fitness (referred to as "inclusive fitness"; Hamilton, 1964), individual well-being is not targeted by selection. Instead, some traits that promote reproductive success can even be deleterious for survival and/or longevity, a process known as antagonistic pleiotropy. Some forms of dementia may represent a consequence of this kind of trade-off (Bufill and Blesa, 2006; Finch and Stanford, 2004). In addition, many sexually selected genes may also fall into the category of antagonistic pleiotropy; for example, genes conferring fitness advantages in terms of mating may come at the cost of stress-related disorders in the long run. A third evolutionary principle concerns the observation that selection does not produce traits that are optimal by design. Instead, like all organisms the human body is composed of many design compromises. One well-known example is bipedalism which comes at the expense of giving birth to immature

offspring (called the "obstetrical dilemma"; Washburn, 1960; Wells et al., 2012). Moreover, increasing brain size probably contributed to the obstetric dilemma, because the maternal placenta could not supply the brain's nutritional demand beyond nine months of gestation (Campbell, 2010). These circumstances, in turn, created new selective pressures on parenting and mating. Immaturity at birth necessitated particular adaptations in mother-infant bonding. Moreover, as mothers were less capable of foraging when caring for immature babies, there was a need for increasing paternal and close kin investment to successfully raise human offspring (Burkart et al., 2009). A fourth principle suggests that no sign or symptom of psychiatric conditions is qualitatively distinct from a statistical norm. Instead, they can either be considered as outliers that have become dysfunctional due to their abnormal frequency, intensity or inappropriateness in the current context (Brüne et al., 2012). This may become intuitively plausible when considering fear responses to real or imagined threats. Fear is an adaptive response that occurs in situations posing a threat to the individual's inclusive fitness. In natural environments, such situations comprise threats by predators, social status by conspecifics etc. Accordingly, fear responses arise a relatively low thresholds, because it is "cheaper" to produce false alarms (i.e. a fear response that in retrospect was unwarranted) than to run the risk of a fatal attack. In some ways, fear responses thus seem to follow the technical logic of smoke detectors (Nesse and Ellsworth, 2009). It is less clear if other psychological mechanisms adhere to the same principle, but Signal Detection Theory (Green and Swets, 1966) suggests that this might be the case. One may wonder, for instance, if suspiciousness could make a case in this regard, because from an inclusive fitness point of view, it may be "cheaper" not to trust others than to be fooled or cheated, at least in dangerous environments.

A final point that needs to be emphasized concerns differences between ancestral environments and contemporary living conditions. Many human traits, including ones that are relevant for mental health, evolved in the "Environments of Evolutionary Adaptedness" (EEA), a term coined by John Bowlby (1969). The EEA is not a single one environment, but comprises a set of environmental conditions that were pervasive enough to leave anatomical or behavioural marks on the species (Tooby and Cosmides, 1990).

It is undisputed that anatomically modern humans have lived 99% of the existence of the species as hunters and gatherers in stoneage-like environments. Cultural evolution is a relatively modern event that has lasted for not much more than 10,000 years or so. It has progressed much more rapidly than biological evolution, causing a "mismatch" of ancestral adaptations and modern environments (Nesse and Stearns, 2008). These drastic differences between ancestral and contemporary lives are relevant for virtually all branches of medicine. It is pertinent to the understanding of modern disease to know these differences, because this approach opens new avenues to identify risk factors of "modern" diseases. Readers interested in "Evolutionary Medicine" may be referred to the Oxford Handbook of Evolutionary Medicine (edited by Brüne and Schiefenhövel, 2019).

Common mismatches relevant for psychiatric disorders comprise the exposure to social stress. Indeed, the incidence of psychotic disorders is significantly higher in urban compared to rural areas (Vassos et al., 2012). Moreover, migration to a different culture is a risk factor for psychosis (van Os et al., 2010). In fact, it could be that modern environments contribute to the aversion of outgroup members in vulnerable individuals who may develop persecutory delusions (Abed and Abbas, 2011). Another example of a mismatch between adaptations to ancestral conditions and modern environments concerns the dramatic change in exposure to pathogens. In fact, the contemporary pathogen landscape is vastly different from ancestral ones, thanks to hygiene, such that a lack of exposure to certain infectious agents during childhood may actually increase the risk for dysfunction of immunoregulatory mechanisms, which in turn may contribute to the rising prevalence of allergies and autoimmune diseases (Strachan, 1989), and may even play a role in mental health by increasing the risk for depression (Rook and Lowry, 2008). Along similar lines, modern environments differ vastly from ancestral ones regarding the presence of man-made toxic substances that pose novel challenges to physical and mental health (Trumble and Finch, 2019). For example, Bisphenol A, a now ubiquitous environmental toxin from plastic, disrupts endocrine pathways, which may impact on sexually dimorphic traits (reviewed in Palanza et al., 2016).

In sum, Tinbergen (1963) suggested that for a full understanding of animal anatomy, physiology and behaviour, it would be necessary to address four levels of causality, including adaptation and phylogeny. As shown above, this is also true for human psychological traits. In terms of mental health, a specific interest concerns those evolved mechanisms that mediate between biological imperatives such as survival and reproduction, and the subjective evaluation of one's individual mental health in terms of well-being, realization of one's potential, ability to cope with stress, and to contribute to one's community. These mechanisms emerged as adaptations to ancestral environments, but are still relevant for mental health in contemporary conditions. The plasticity of the developmental trajectories that contribute to the phenotypic

expression of these psychological mechanisms (including their maladaptive variants) is dealt with in the next section.

Anatomical and psychological evolution are two sides of the same coin

For about 300,000 years, anatomically modern humans have lived in small, kin-based and mostly patrilocal social groups of around 50 to 150 people. Recent studies in contemporary hunter-gatherer societies suggest that individuals have played active roles to maintain complex social networks characterized by mutual exchange (Apicella et al., 2012). Ancestral communities were probably much more egalitarian than societies after the Neolithic Revolution, where the possession of personal goods became much more common (Ehrlich, 2000). Western scholars consider the "nuclear family" comprising father, mother and children as the primeval model of the smallest functional unit within ancestral societies. However, comparative research suggests that this was not everywhere the same. In many hunter-gatherer societies female exogamy seemed to be common, that is, young women left their original tribe to live with their husbands' families. One striking feature of *Homo sapiens* was that they helped each other in raising children, known as "cooperative breeding" (Hrdy, 2000). This gave early humans a decisive advantage over other primates, because humans were able to significantly shorten inter-birth intervals to 3–4 years (whereas in chimpanzees, our closest extant relative, the interval is about 5–6 years; Hrdy, 2000).

This advantage in population growth notwithstanding, a problem for human mothers that remained was how to successfully raise immature offspring. As already noted, antedating human birth has been perhaps the anatomical design compromise with the furthest-reaching consequences for human social life. Upright walking evolved in hominoids approximately two million years ago, long before brain size increased. In other words, our distant ancestors were bipedal apes, such that parturition was not a problem despite the narrower birth canal of these australopithecine species. As the brain started to increase in size after the human lineage split from the larger tree of ape-like species, presumably due to increasing social selection pressures, referred to as the "Social Brain" hypothesis (Brothers, 1990; Dunbar, 2003), giving birth became more dangerous for both mother and offspring. Selection thus operated on antedating parturition, i.e. early human mothers gave birth to immature infants. In fact, if babies of anatomically modern humans were comparably mature to extant ape infants, pregnancy in humans would last about 20 months, perhaps even longer. Interestingly, the human brain continues to grow post-partum at the same speed as ante-partum for another 13 months, as if babies remained in the mother's womb for this extended growth period. In terms of psychological adaptations to this unique design compromise, the immaturity and dependency of human newborns, favoured the selection of strong dyadic relationships between mother and infant, known as "attachment" on the infant's side (Bowlby, 1969), whereas the mother's emotional ties to the baby is referred to as "bonding" (which develops more slowly that attachment; Hrdy, 2000). The quality of this dyadic relationship has been decisive for infant survival and for its psychological well-being. In addition to the mother-infant dyad, the mother herself became more dependent on others in terms of protection and provision with food. In contrast to extant ape mothers who more or less rear their offspring alone (with some help from older daughters or aunts), human mothers started to help each other, a behaviour that has been termed "cooperative breeding" (Burkart et al., 2009). Moreover, the infant's immaturity also impacted on the involvement of the father, who, more than in any other ape, contributed protection and nurturance in support of both mother and infant. It could well be that "concealed ovulation", that is, the invisibility of signs of oestrus in women, evolved secondary to the design compromise, because only close proximity and vigilance of men secured their fatherhood, a somato-psychic constellation that is unique to humans (Alexander and Noonan, 1979).

Attachment

In the psychological literature, attachment theory is barely acknowledged as the first evolutionary framework for the understanding of human development and mental health. Indeed, John Bowlby experienced profound objections against his ideas from his own (psychoanalytic) community, such that he sought advice from ethologists who were much more open to his scientific inquiry (Bowlby, 1991). Today, it is undisputed that healthy human development—both physical and mental—critically depends on the quality of the emotional relationship between infant and caregiver (most often the biological mother). It was Bowlby's discovery that human infants, like other primates, are biologically preprogrammed to seek physical proximity and emotional warmth, ultimately to secure survival (Bowlby, 1969). As Harlow's (in retrospect heartless) experiments with Rhesus monkeys later confirmed, the formation of a strong dyadic relationship is primarily

driven by the affectional bond between caregiver and child, not food supply (Harlow and Zimmermann, 1959). More recent human research has corroborated these observations, showing that mothers (and fathers) are highly responsive to their babies' needs, whereby parental responsivity is physiologically regulated by the neuropeptide oxytocin (Feldman et al., 2010). The ability and willingness to bond with her baby, on the mother's (and father's) side, in turn, is less unequivocal than the infant's attachment behaviour; it depends on the availability of resources, including social support from the partner and kin. In poor circumstances lacking social support, neonaticide or abandonment of the newborn may occur, even in modern societies.

Following the establishment of a dyadic relationship, infants develop emotional and cognitive representations of their caregivers and of themselves, which Bowlby termed "internal working models". The nature of this internal working model determines if a child experiences the environment as safe or unsafe. Only in safe conditions can the child dare to explore the environment, whereas in times of insecurity it will prefer to cling to the mother. Bowlby distinguished secure from insecure attachment. Secure attachment develops if the caregiver is available to emotionally resonate to the infant's needs. In contrast, unresponsive or unavailable caregivers promote the development of insecure attachment, where infants perceive the world as unreliable, untrustworthy and potentially dangerous. A particularly unresolvable problem for young infants occurs, when caregivers are not just unresponsive to the infant's needs, but act in abusive ways. An infant growing up under such circumstances may be caught in the ambivalent situation to attach to caregivers who, at the same time, are a source of threat and danger. While fear of abandonment causes intense proximity-seeking, threatening behaviour causes withdrawal. If pervasive over prolonged periods of time, this may result in disorganized attachment, the most pathological form of insecure attachment (other forms of insecure attachment are not necessarily pathological; see below).

Life history strategies and biosocial goals

For Bowlby, secure attachment was the evolved blueprint for healthy (and adaptive) child development. He thereby ignored (or could not know at his time) that mental health has never been a direct target of selection. This insight is perhaps one of the most bittersweet aspects of evolutionary thinking in medicine, because medical treatment always concerns well-being and health as an overarching goal, and may hence be at odds with the "goals" set by natural selection (i.e. survival and reproduction). However, evolutionary research utilizing behavioural ecology (or "life history theory"; Stearns, 1992) as a frame of reference suggests that insecure attachment styles are not necessarily pathologies (Belsky, 1999). Instead, fluctuations in ancestral environmental conditions in terms of resource availability selected for behavioural flexibility to ultimately promote reproductive fitness by choosing the optimal strategy to accomplish important biosocial goals (Simpson, 1999).

For example, in harsh environmental conditions, which may include scarcity of food or poor emotional availability of caregivers, an individual is more likely to develop an internal working model suggesting that the world is unsafe, the availability of future resources uncertain, such that immediate resource extraction might be the best strategy. Arguably, such a situation may also predispose to exploit others and to act opportunistically. What is more interesting and much less known is that early adversity can accelerate biological maturation, a fact that has been replicated several times, but seems to be more robust for girls than boys (Belsky et al., 2007). Thus, from an attachment point of view, this suggests that insecure attachment can serve as a proximate adaptive strategy to ensure survival and to maximize reproductive success under unpredictable environmental conditions. It is difficult to swallow for clinicians and therapists that such a solution or strategy may be adaptive in the biological (reproductive) sense, but also associated with low mood and negative affect. Thus, the term "adaptive" has a double meaning here, as low mood and mood disorders are certainly not adaptive.

Research suggests that father absence accelerates menarche, especially if fathers have left their families before the girl's onset of puberty. This relationship is less clear for adrenarche. Part of this reproductive strategy, then, is to engage in multiple short-term relationships, early reproduction (which in industrialized societies includes teenage pregnancies), and to invest relatively little in own children (Ellis, 2013; Nettle et al., 2010). There is evidence to suggest transgenerational transmission of rearing styles, where mothers who as children were exposed to neglect or abuse have greater difficulties in bonding than unaffected mothers (Muzik et al., 2013). Evolutionary psychologists have termed this biosocial strategy "fast", to which the opposite is "slow". "Fast" strategies not only impact on mating behaviour and sexual maturation. Life history theory also posits that an organism cannot allocate a limited amount of resources to reproduction and body growth and maintenance at the same time (Stearns, 1992). In other words, if reproductive effort is on the agenda, body maintenance is low.

Accordingly, consequences of "fast" strategies entail a faster accumulation of "allostatic load", that is, somatic costs of chronic stress, such as hypertension, chronic inflammation and premature ageing (McEwen, 2020).

A "slow" life history strategy is characterized by beneficial early rearing conditions, i.e. spousal harmony, emotional availability of caregivers, low levels of stress and adequate (financial) resources. Under such favourable circumstances it is likely that children develop a trustful internal working model and secure attachment (Bowlby's adaptive model). Securely attached individuals tend to mature later, that is, menarche (and adrenarche) is delayed (relative to individuals adopting a "fast" strategy). Consequently, securely attached people have more stable intimate relationships, and tend to invest more in their own children. Again, the logic behind all this is that early environmental conditions coin expectations regarding future resource availability in many ways, financial, emotional, and environmental. "Slow" strategies are consequently also associated with less allostatic load (McEwen, 2020).

It is thus clear that individuals differ in their ways to attain biological goals in terms of reproduction, depending on environmental contingencies. Beyond reproduction, however, there are other important biosocial goals in life that indirectly impact on one's reproductive success, at least in ancestral environments. They concern the opportunity (and the ability) to elicit care and to provide care, to form cooperative alliances, to find a mate and to attain an acceptable rank in the social hierarchy (Gilbert, 1998). Achieving these goals is indirectly linked with subjective well-being, however, whenever the arrival at one of these goals is thwarted, mental health can deteriorate in the long run. Common psychiatric disorders that may arise from chronically unattained biosocial goals include depression, anxiety, substance dependence, and personality disorders. But humans also differ in coping with adversity. Some are deemed resilient, that is, relatively unresponsive to environmental contingencies, while others are highly susceptible. This leads us back to one of the initial questions. Why are mental disorders so common, and why has selection not operated on those genes that seem to predispose to psychiatric and psychosomatic disorders?

The role of genes

Individual differences in susceptibility to adverse events are crucially linked to the activity of genes, or their allelic variants. In psychiatric genetics, the prevailing model of explaining vulnerability to mental disorder is known as the "diathesis-stress-model". Accordingly, some individuals are at increased risk of developing a psychiatric condition, when carrying a certain allelic variant in association with the experience of an adverse event, i.e. gene-environment interaction. The diathesis-stress model is, however, insufficient, because it fails to explain why many genetic variants that cause vulnerability have undergone recent positive selection in recent human evolution. In other words, natural selection would not have favoured the persistence of alleles that predispose to psychopathology, given the maladaptive nature of most psychiatric conditions, including reproductive success (Brüne et al., 2012). Instead, if genes prevailed in the human genepool that may enhance the risk for psychopathology, there must be a compensatory advantage of maintaining them at the population level, otherwise they should have been selected against. One of the most compelling theories to explain this conundrum, now supported by numerous studies, has been termed the "differential susceptibility hypothesis" (Belsky et al., 2009; Boyce and Ellis, 2005). The differential susceptibility hypothesis posits that while certain alleles can predispose to developing a psychiatric condition under adverse environmental conditions such as childhood neglect, abusive parenting or loss of an important attachment figure, the very same variants predispose to a superior outcome, when the carrier of these variants grows up under favourable conditions, including parental warmth and emotional availability of caregivers. This is not the same as resilience, as resilience means unresponsiveness to environmental variation. Instead, carriers of plasticity genes are better off than average when growing up under positive circumstances, that is, the risk of developing a psychiatric condition is lower than the population average. Consistent with this proposition, several lines of research have provided empirical support of the "differential susceptibility hypothesis". For example, the low-activity variant of the MAO-A coding gene, which predisposes in combination with early adversity to the development of antisocial personality disorder, is also associated with lower than average prevalence of antisocial personality when early environmental conditions were supportive (Widom and Brzustowicz, 2006). As regards the serotonin system, the s-allele of the 5-HTTLPR gene may increase vulnerability to depression in individuals who grew up under unfavourable rearing conditions. The same allele confers lower risk for depression when experiences with early caregivers were positive (Taylor et al., 2006). In addition, in another study the s-allele selectively moderated the impact of childhood maltreatment on empathic perspective taking, with low scores in childhood trauma being associated with superior perspective taking. Homozygous carriers of the l-allele, in contrast, were unresponsive to environmental

conditions in this regard, suggesting that the s-allele confers "differential susceptibility" (Flasbeck et al., 2019). Another example concerning the dopaminergic system has shown that children who possess the seven-repeat variant of the DRD4 gene are at risk of developing ADHD and externalizing problems, if their mothers are emotionally unresponsive and rejecting, whereas the same variant bares a reduced risk for ADHD, if mothers' are emotionally supportive (Bakermans-Kranenburg and van Ijzendoorn, 2006).

A final example concerns the oxytocin receptor gene (OXTR). Here, it was found that individuals with borderline personality disorder who experienced childhood maltreatment and were carriers of at least one A-allele rated psychological pain as more intense compared to controls. No such difference occurred in GG carriers of the OXTR. Together, these findings suggested that the A-allele of the OXTR was more response to environmental impact than the G-allele, and that early adversity influenced empathy for another's pain in genetically susceptible individuals (Flasbeck et al., 2018).

Together, this line of research offers novel insights to questions about how and why natural selection has shaped behavioural flexibility, and how this may explain the persistence of genes that predispose to psychiatric conditions. However, the search for "risk" alleles has been criticized for methodological reasons, and it needs to be emphasized that the heritability of mood disorders is polygenic. Thus, individual genes contribute only a small amount to the variation in phenotypic expression. These objections notwithstanding, any research into gene-environment interaction needs to be framed in a Darwinian perspective, particularly to prevent false conclusions in relation to psychopathology.

Summary

Evolutionary approaches are indispensible for the understanding of how nature has shaped the human mind. In fact, most of our psychological mechanisms, emotional responses and interpersonal behaviours emerged in our distant past, at least long before sedentary lifestyles and the explosion of cultural evolution came into being. Since modern environments are different from ancestral ones, there are many evolutionary "mismatches" that contribute to the risk of somatic and psychiatric diseases. Group size and encounters with people who are not from one's ingroup are two examples that may contribute to an unphysiological activation of the stress axis. People therefore struggle to cope with loosing familial ties, and uncertainty about one's social role in the community (Gilbert, 1998). In addition, the emotional availability of early caregivers coins an individual's psychology in terms of his or her ability to form trustful and reciprocal relationships with peers, partners, colleagues and additional significant others. Life history theory explains individual differences in the timing of biological maturation, mating, and the quality of parenting. The relationship between the "pace of life" and risk of accumulating somatic consequences of suboptimal stress coping mechanisms (i.e. allostatic load) has only begun to be better understood (McEwen, 2020), including its relevance for psychosomatic medicine.

Nutrition is another example that constitutes an important factor in the dramatic rise of "non-communicable diseases", including cardiovascular disease, overweight, obesity, and musculoskeletal diseases (see chapters in Brüne and Schiefenhövel, 2019). Moreover, the exposure to a changing pathogen landscape is another issue that deserves more attention. Ironically, the lack of exposure to ancestral pathogens may cause problems in modern environments, especially concerning the over-reactivity of the immune system, which may cause autoimmune disease or allergies, but perhaps also contribute to the "depression pandemic" (Rook et al., 2017). Conversely, we now see modern health systems unprepared and overburdened by a virus pandemic, which predictably was only a matter of time to occur (Barnes, 2005). The behavioural consequences in terms of both, avoidance of infection, and sickness-associated behaviour have a profound impact on how such health crises are handled. Importantly, evolutionary approaches to such events can help make predictions about the course of the pandemic (Brüne and Wilson, in press).

In any event, no organism is optimal by design. That is, selection is "thrifty", with adaptations being just good enough for survival and reproduction, but not for longevity, for instance. Instead, defence mechanisms that evolved to cope with adversity may be vulnerable to dysfunction. Cough and fever, for example, are useful defences against microbial attacks, but may become dysfunctional if excessive. Similarly, low mood and anxiety are useful in conflicts when biosocial goals are unattainable. They can help protect the individual from an escalation of the conflict, but may come at the cost of poor subjective well-being (Nesse, 2004).

Flexibility, creative thought and gregariousness have made *Homo sapiens* an evolutionary success story, at least in the short run. No single one feature separates our species from the rest of the animal kingdom, however. Thus, "medicine without evolution is like engineering without physics", as Randolph Nesse once put it. Evolutionary medicine can certainly help prevent, diagnose and treat medical conditions of all kinds. It is time to

consider this in the development of curricula for medical schools.

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Bionote

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Martin Brüne was born in Dortmund, Germany, in 1962. He graduated in medicine at the Westphalian Wilhelms University in Münster in 1988. He completed his neurology training in 1993, and his psychiatry training in 1995. His subsequent training included a Visiting Research Scientist fellowship at the Centre for the Mind, a joint venture of the Australian National University and University of Sydney. He is currently Professor of Psychiatry and Head of the Division of Social Neuropsychiatry and Evolutionary Medicine at the LWL University Hospital, Ruhr University Bochum, Germany. Dr. Brüne has authored more than 250 articles and book chapters. He has also authored the Textbook of Evolutionary Psychiatry and Psychosomatic Medicine: The Origins of Psychopathology (2nd edn. Oxford University Press, 2016). Recently, he edited (together with Prof. Wulf Schiefenhövel) The Oxford Handbook of Evolutionary Medicine (Oxford University Press, 2019). His current clinically oriented research projects include the analysis of social cognition in psychosis and in personality disorders, the association of social cognition with social functioning and non-verbal behaviour, the behavioural performance of psychiatric populations in evolutionary game-theoretical scenarios, the effect of oxytocin on social perception and cognition in psychiatric disorders and social cognitive training in patients with psychosis, as well as non-verbal interaction in therapeutic settings. His research approach

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Review article

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Neurons interact with the microbiome: an evolutionary-informed perspective

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Abstract: Animals have evolved within the framework of microbes and are constantly exposed to diverse microbiota. Microbes colonize most, if not all, animal epithelia and influence the activity of many organs, including the nervous system. Therefore, any consideration on nervous system development and function in the absence of the recognition of microbes will be incomplete. Here, we review the current knowledge on the nervous systems of *Hydra* and its role in the host–microbiome communication. We show that recent advances in molecular and imaging methods are allowing a comprehensive understanding of the capacity of such a seemingly simple nervous system in the context of the metaorganism. We propose that the development, function and evolution of neural circuits must be considered in the context of host–microbe interactions and present *Hydra* as a strategic model system with great basic and translational relevance for neuroscience.

Keywords: antimicrobial peptides; evolution; *Hydra*; metaorganism; nerve nets.

Zusammenfassung: Tiere sind in einer Welt voller Mikroben entstanden und sind ständig verschiedenen Mikrobiota ausgesetzt. Mikroben besiedeln die meisten, wenn nicht gar alle tierischen Epithelien und beeinflussen die Aktivität vieler Organe, einschließlich des Nervensystems. Jede Betrachtung der Entwicklung und Funktion des Nervensystems ohne Berücksichtigung des Mikrobioms bleibt daher unvollständig. Hier fassen wir das aktuelle Wissen über das Nervensystem von *Hydra* und insbesondere seine Rolle in der Wirt-Mikrobiom-Kommunikation zusammen. Wir zeigen, dass moderne molekulare und bildgebende Verfahren ein umfassendes Verständnis der Leistungsfähigkeit eines solchen scheinbar einfachen Nervensystems im Kontext des Metaorganismus ermöglichen. Wir schlagen vor, künftig die Entwicklung, Funktion und Entwicklung neuronaler Schaltkreise im Kontext von Wirt-Mikroben-Wechselwirkungen zu betrachten und präsentieren *Hydra* als strategisches Modellsystem mit großer grundlegender und translatorischer Relevanz für die Neurowissenschaften.

Schlüsselwörter: Antimikrobielle Peptide; Evolution; *Hydra*; Metaorganismus; Nervennetz.

Introduction: neurons interact with the microbiome

Nervous systems allow animals to perceive signals from the environment and to respond to them. Novel technologies including sequencing and imaging has unveiled that an important component of the immediate environment of many if not all organisms is a coevolved and resident microbiota (Baquero and Nombela, 2012; Blaser et al., 2016). Microbes shaped the Earth since billions of years before the “invention” of any nervous system, and they continue to shape the Earth. In animals, including humans, microbes are colonizing all epithelia. Animal evolution therefore appears intimately linked to the presence of microbes. Considering organisms as “metaorganisms” or “holobionts” (Bosch and Mcfall-Ngai, 2011, 2021) incorporates this impact of the microbial world and attempts to drive the neurosciences to the next level of enquiry.

Previous studies on germ-free (GF) animals, i.e., organisms treated with broad-spectrum antibiotics to completely eliminate their microbes or animals born and raised in absolutely axenic conditions, show that specific microbiota can impact central nervous system (CNS) physiology and neurochemistry (Sharon et al., 2016). GF mice that are devoid of associated microflora exhibit neurological deficiencies in learning, memory, recognition, and emotional behaviours (Foster et al., 2017; Gareau, 2014). In developing mice embryos, proliferation of neurons in the dorsal

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hippocampus is greater in GF mice than in conventionalized mice. However, post-weaning exposure of GF mice to microbial clones did not influence neurogenesis, suggesting that neuronal growth is stimulated by microbiota at an early stage (Ogbonnaya et al., 2015).

It is now well established that microbiota not only affect the CNS but also influence the enteric nervous system (Cryan et al., 2019). For example, mice kept under sterile conditions show reduced excitability of enteric neurons, resulting in slower gut peristalsis and protracted intestinal transit time. Interestingly, colonization of adult GF mice with microbes taken from the intestine of animals kept under standard laboratory conditions restores the peristaltic activity to normal levels (De Vadder et al., 2018; Obata et al., 2020), indicating that the gut monitors continuously the contents of the lumen and responds to potential changes. It also has been shown that intestinal microbiota directly affects transcriptional programs in enteric neurons (Obata et al., 2020). These observations are medically relevant because changes in the composition of microbiota (known as dysbiosis) are also observed in common gastrointestinal disorders, including those characterized by changes in intestinal motility, such as irritable bowel syndrome (De Palma et al., 2017).

Most if not all of these studies were done in laboratory mice. How relevant are they for our understanding of neurobiology in general? From our evolutionary point of view, the discovery of an interaction of microbes with the mouse nervous system(s) comes as no surprise. Below we show that similar interactions between the microbiota and the neurons are in place already at the beginning of animal evolution, suggesting that animal–bacteria interactions are likely as ancient as animals themselves.

Hydra, a model to study neuron–microbiome interactions

Hydra, a member of the animal phylum Cnidaria, is close to the earliest animals in evolution that had nervous systems (Figures 1, 2A and B). Cnidaria occupy a sister phylogenetic position to bilaterians. The fact that they encode most of the gene families found in bilaterians makes them a suitable model to study the "genetic tool kit" present in the cnidarian–bilaterian ancestor. This includes their repertoire of ion channels, synaptic proteins, small neurotransmitters, receptors and the corresponding processing machinery. In *Hydra*'s simple tube-like body structure, the single layer of ectodermal epithelial cells covered by a multilayered glycocalyx represents a physical barrier toward the environment, whereas a single layer of endodermal epithelial cells separates the body from the content of the gastric cavity. Very much to our surprise, and made possible by novel sequencing technologies, we discovered very early that *Hydra*'s ectodermal epithelial surface is densely colonized by a stable multispecies bacterial community (Fraune and Bosch, 2007) (Figure 2C). Since that discovery, *Hydra* has proven itself as an excellent model for studying host–microbe interactions and how metaorganisms function *in vivo* (Bosch, 2013, 2014; Klimovich and Bosch, 2018; Schröder and Bosch, 2016). The presence and composition of *Hydra*'s microbiota is critical for the tissue homeostasis and health of the polyps (Rathje et al., 2020). Remarkably, each *Hydra* species supports long-term associations with a different set of bacteria, suggesting that the host imposes specific selection pressure onto its microbiome (Franzenburg et al., 2013; Fraune and Bosch, 2007). Both, ecto- and endodermal epithelial cells produce a rich repertoire of antimicrobial peptides that regulate the microbiome (Franzenburg et al., 2013).

In addition to ectodermal and endodermal epithelial cells, *Hydra* has an anatomically simple nervous system (Figures 1, 2D–G) which consists of approximately 3000 neurons in an adult and 70 neurons in a newly hatched polyp (Klimovich and Bosch, 2018; Martin et al., 1997). Although in the early studies, we had considered the epithelial cells as prime regulators of the microbiome (Bosch, 2013,

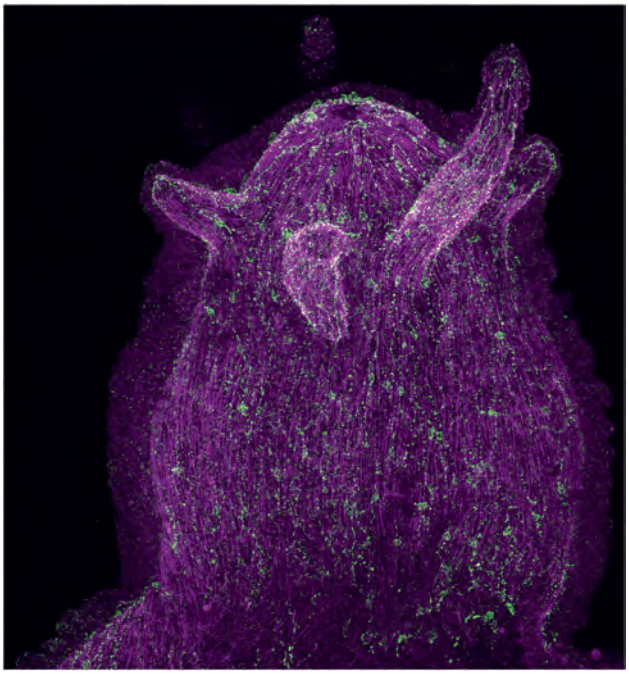

Figure 1: The nervous system of *Hydra* is a diffuse nerve net. Here, a population of neurons expressing a *Hydra*-specific Hym355 neuropeptide (green) and muscular fibers of epithelial cells (magenta) are visualized in a juvenile polyp.

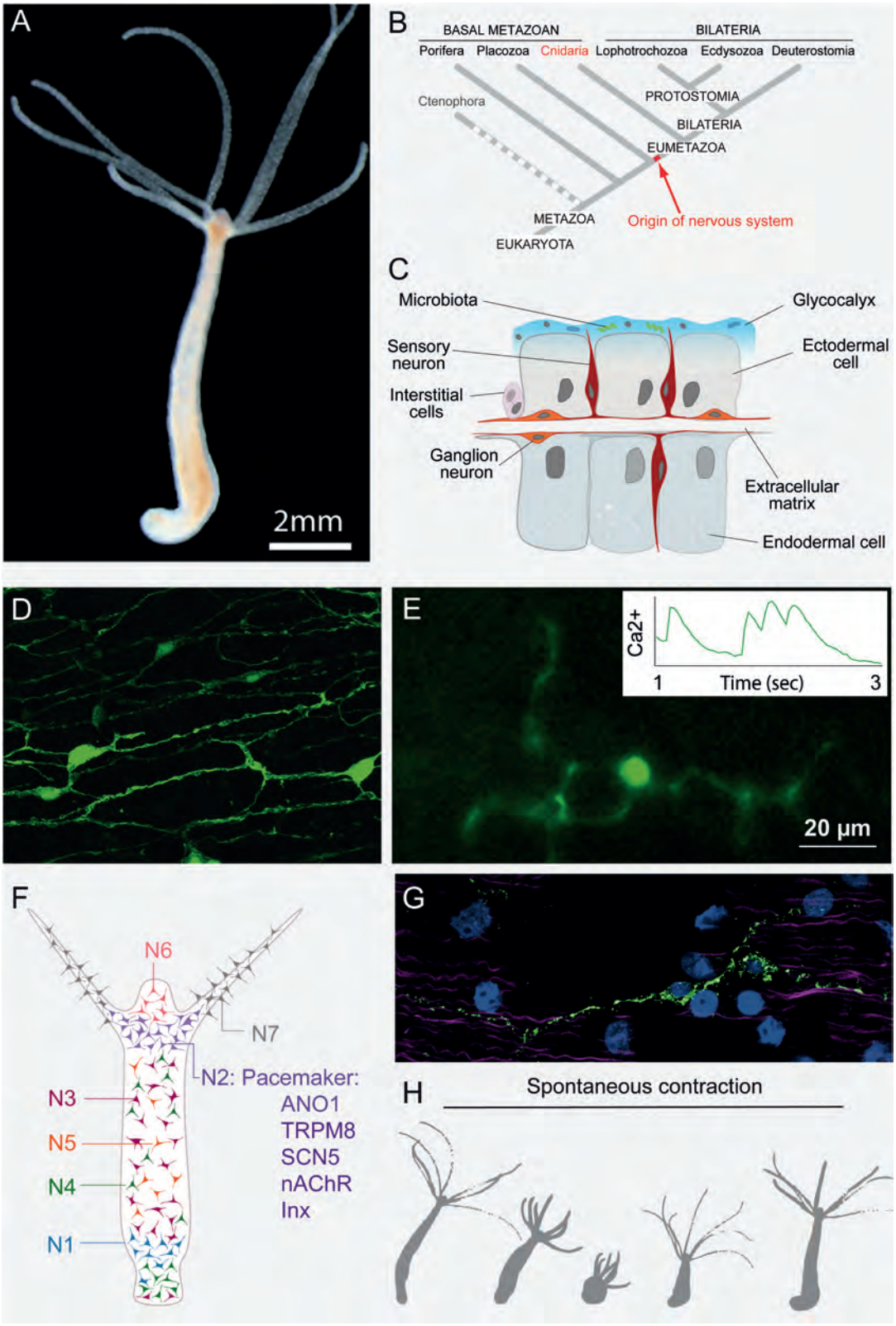

Figure 2: *Hydra* as a model to study neuron–microbe interactions.
A. An adult polyp contains a nervous system comprising approximately 3000 neurons. **B.** *Hydra* belongs to the phylum Cnidaria, the sister group to the Bilateria. Their common ancestor developed the first nervous system. **C.** The tissue structure of *Hydra* with the microbiota in the glycocalyx. **D.** The nerve net of *Hydra*. **E.** *In vivo* recording and quantification (inset) of neuronal activity using a genetically-encoded Ca^{2+}-sensor GCaMP expressed specifically in neurons in transgenic *Hydra*. **F.** The spatial distribution of the seven distinct neuronal populations in *Hydra*. N2 as the pacemaker population with the conserved signature of ion channels. **G.** A pacemaker neuron of *Hydra,* visualized using an antibody against SCN5-like channel (green). Nuclei are stained with TO-PRO (blue) and actin filaments of epitheliomuscular cells are stained with Phalloidin (magenta). **H.** Schematic illustration of the spontaneous contraction behaviour.

2014), we recognized over time that neurons per se are involved and that they somehow interact with microbes. When assessing antibacterial activity in *Hydra*, we observed a strong correlation between the number of neurons present and the antibacterial activity (Kasahara and Bosch, 2003). Moreover, when we removed all neurones from the epithelium, we observed significant changes in *Hydra*'s microbial community (Fraune et al., 2009). Based on these observations, meanwhile, we have established an experimental platform to investigate the neuron–microbe interactions in *Hydra* not only at a descriptive level, but also to uncover the underlying molecular mechanisms (causalities).

What neuronal circuits do in *Hydra*

Nervous systems are commonly interpreted as information processing input–output devices. They receive environmental information from their sensors as input, subsequently process or integrate this information, and use the result to control effectors, providing some kind of output. Although this interpretation seems beyond dispute, from an evolutionary perspective, it requires some clarification and reflection. First, neuronal circuits evolve by the Darwinian processes of variation and selection. Given the extremely high costs of building and maintaining nervous systems, selective optimization seems to shape neuroanatomy rather than neutral evolutionary processes (Jékely, 2011). Second, in evolutionary ancient neuronal circuits, input is provided by sensory cells having receptors for neurotransmitters, neuropeptides and other signaling molecules in the neural membrane which may still have been incompletely genetically individualized compared to more complex animals (Schlosser, 2018). In animals such as *Hydra*, the few neuronal cell types are multifunctional, and later during a long evolutionary history may have diversified and specialized for different sensory modalities and larger and more complex sense organs. Third, as emphasized by Jékely (2011), behaviour evolved before nervous systems. Various single-celled eukaryotes (protists) and the ciliated larvae of sponges devoid of neurons can display sophisticated behaviours, including phototaxis, gravitaxis or chemotaxis. Fourth, animal behaviour allows individuals to adapt to the environment at a time scale that is much faster than natural selection, and therefore drives the rapid evolution of the nervous system (Anderson and Perona, 2014). Last, there is increasing evidence that human and animal's social behaviour, hyperactivity and maybe even anxiety are influenced by microbes (Bruckner et al., 2020; Vuong et al., 2017).

Hydra behaviour has been studied for centuries. It was first described by Trembley (1744) and consists of both spontaneous and stimulus-evoked, reactive behaviours (Trembley, 1744). Spontaneous behaviours include the rhythmic spontaneous body contractions that are correlated with a specific electrophysiological activity termed contraction bursts and are modulated by light, among other stimuli (Passano and McCullough, 1964). The stereotypical feeding response, a typical reactive behaviour induced by food-associated stimuli consists of three distinct stages: tentacle writhing, tentacle ball formation and mouth opening (Koizumi et al., 1983; Lenhoff, 1968). This reactive and elaborate reflex-like behaviour is fundamental to the survival of *Hydra* and sensitive to its needs: well-fed animals do not appear to show feeding behaviour when exposed to a food stimulus (Grosvenor et al., 1996; Koizumi and Maeda, 1981; Loomis, 1955). In addition, feeding behaviour can be robustly induced by small molecules, such as glutathione (Lehoff, 1961). Mounting evidence suggests that all these behaviours represent a motor output of neuronal circuits that may comprise sensory and ganglion neurons which are controlling the effectors, i.e. the multifunctional epitheliomuscular cells. However, the architecture of these circuits, the principles of neuronal connectivity and signal transduction within the *Hydra* nerve net and the neural mechanisms underlying the behaviour changes under environmental, physiological, nutritional or pharmacological manipulations are still largely in the dark.

Ontogeny, architecture and activity of *Hydra*'s nervous system

In a *Hydra* embryo, the first neurons appear to develop relatively late and just before hatching (Martin et al., 1997). A juvenile polyp (hatchling) emerges with a few dozens of neurons. After hatching, the growth of a polyp is accompanied by a gradual increase in the number of neurons, which reaches approximately 3000 two weeks after hatching. Since *Hydra* proliferates asexually continuously by budding, in an adult *Hydra*, neurogenesis also takes place continuously to maintain tissue homeostasis. The simplicity and difference in neural architecture between an embryo and an adult polyp offer great potential for understanding the basic design principles and minimal size of a nervous system to still perform basic sensory information processing tasks.

Currently, it is unknown which level of neuronal organization is required for *Hydra*'s spontaneous and stimulus-evoked, reactive behaviour. Moreover, we do not know the essential components of the nerve net that enable

spontaneous and reactive behaviour as an indication of functional neuronal circuit growth. A rich repertoire of methods including *in vivo* labelling and tracking of transgenic neurons, cell cycle analysis and expression analysis at the protein and transcriptome level is available to explore how neuronal circuits are established and maintained by continuously integrating stem-cell-derived migratory neuronal precursor cells into the nervous system. In addition, improved imaging techniques enable neuroscientists to observe the entire activity of certain nervous systems at a glance, providing completely new insights in neural circuit architecture and functioning (Figure 2E). This becomes obvious in the recent work by Dupre and Yuste (Dupre and Yuste, 2017) who demonstrated by calcium imaging technology in *Hydra* the existence of multiple circuits within these nerve nets. They proposed that three major functional networks extend through the entire animal and are activated selectively during longitudinal contractions, elongations in response to light, and radial contractions. From these and others studies, it is obvious that the advent of novel imaging technologies leverages the great potential of *Hydra* as a model system to get in-depth insight into the functional sophistication of apparently simple nerve nets.

Rhythmic spontaneous body contractions require both pacemaker cells and the presence of microbes

Spontaneous contractions of the digestive tract play an important role in almost all animals. From simple invertebrates to humans, there are consistently similar patterns of movement, through which rhythmic contractions of the muscles facilitate the transport and mixing of the bowel contents. The triggers for the spontaneous contractions of the muscle tissue are so-called pacemaker cells of the nervous system. In a specific rhythm and without any external stimulation, they emit electrical impulses, that ultimately reach the smooth muscles of the intestinal wall, and cause them to contract. Although the impulses as such occur autonomously, their frequency, regularity and intensity are subject to external influences. The factors underlying the control of these impulses are not known yet.

Hydra turned out to be a very suitable system for understanding the control of this simple spontaneous behaviour and the underlying neuronal circuits. An undisturbed adult *Hydra* polyp will contract spontaneously with a frequency in the order of 5–10 contractions per hour (Figure 2H). The regularity and frequency of these contractions are highly sensitive to environmental conditions—such as light intensity and spectrum, presence of food, and osmolarity (Benos and Prusch, 1973; Kanaya et al., 2019, 2020; Passano, 1963; Rushforth et al., 1963; Yamamoto and Yuste, 2020). The contractions are electrically induced by central pattern generator neurons or pacemaker cells (Figure 2F and G). Previous extracellular electrophysiological recordings (Passano and McCullough, 1964) suggest that the pacemaker cells operate at a higher intrinsic frequency than the contraction burst frequency, and thus imply existence of an additional mechanism or cell type that relays their motor output. To identify additional components of the control machinery, we remembered that the *Hydra* epithelium is colonized by a specific microbiota, and compared normal *Hydra* which had typical bacterial colonisation with those that had their microbiome completely removed (Murillo-Rincon et al., 2017). In comparison, organisms without bacterial colonisation exhibited a reduction in contractions by about half. At the same time, the rhythm of the movements became disrupted, and some of the breaks between the contractions were much longer. Thus, the absence of the specific microbiome in *Hydra* compromised the peristaltic movements in the body cavity. In a further step, we restored the specific bacterial colonisation in the germ-free organisms. Initially, we introduced each of the five most common bacterial species found in the *Hydra* microbiome individually back into the sterile polyps. It turned out that this individual bacterial colonisation has no appreciable effect on the frequency and timing of contractions. Only the joint reintroduction of the five main representatives of the microbiome led to a marked improvement in peristalsis, although even then, the pattern of contractions was not fully normalised. The point was made even stronger by the fact that an extract produced from the colonising bacteria had a similarly positive influence (Murillo-Rincon et al., 2017). Taken together, these observations indicate that only the natural and complete *Hydra* microbiome is indispensable for regular spontaneous contractility. Not yet identified molecules secreted by the bacteria can intervene in the control mechanism of the pacemaker cells. As such, bacterial metabolites or signals can have a decisive effect on the pattern of spontaneous peristaltic contractions. In sum, the microbiome appears to have an indispensable function in the frequency and timing of tissue contractions.

The molecular signature of pacemaker cells

Based on the differential expression of transcripts encoding neurotransmitter receptors, ion channels, neuropeptides, and transcription factors, the neuronal population of *Hydra* can be subdivided into distinct clusters that are likely to include neurons with unique functions (Klimovich et al., 2020; Siebert et al., 2019). By using cluster-specific transcripts as molecular markers, certain neuronal classes were found to be restricted to specific domains in the *Hydra* body column. One such neuronal subpopulation is located at the base of the tentacles and expresses nicotinic acetylcholine receptors as well as genes encoding SCN-like sodium channels, ANO1-like chloride channels and TRPM-like cation channels (Figure 2F and G). When we blocked the activity of these genes in *Hydra*, this immediately led to a drastic reduction in rhythmic body contractions. Modulation of the activity of these "pacemaker" channels disturbed both the rhythm and the frequency of the spontaneous contractions of the *Hydra* body, indicating that they depend on the unique combination of ion channels. For this reason, we are convinced that these neurons are indeed the pacemaker cells that control the peristalsis; and that they are able to perceive signals from microorganisms and react to them. Interestingly, the human orthologs of these channels are expressed by the intestinal pacemaker cells in mammals (first identified by Ramón y Cajal and called interstitial cells of Cajal) and linked to the pathogenesis of irritable bowel syndrome (Beyder et al., 2014; Mazzone et al., 2019; Strege et al., 2018). This evolutionary connection can be stretched even further since the unique molecular architecture of pacemakers appears to be conserved between *Hydra* neurons, the pharyngeal pacemaker complex of *Caenorhabditis elegans* and the above mentioned enteric nervous system of the mouse. The peristaltic activity of the gut turns out as an evolutionarily ancient neurogenic behaviour dependent on microbial signals and essential for life.

Bidirectional communication between pacemaker neurons and the symbiotic bacteria

Our studies uncovered that *Hydra* neurons not only receive signals from the microbiome, but also actively affect the composition of the associated microbiota. A detailed molecular genetic analysis of *Hydra's* individual nerve cells using single cell RNA sequencing technology showed (Klimovich et al., 2020) that distinct subpopulations of neurons exert a direct influence on the density and composition of the symbiotic bacteria using the tools of the innate immune system. Distinct neuronal types, including the pacemakers, produce neuropeptides that display highly selective antimicrobial activity and alter the composition and spatial distribution of the microbial communities on *Hydra* body (Augustin et al., 2017; Klimovich et al., 2020). In addition, neurons in *Hydra* produce many components of microbe-associated molecular pattern (MAMP) receptors, such as Toll-like receptors, NOD-like receptors, C-type lectin, etc., indicating that neurons in *Hydra* are immunocompetent cells with critical roles in immune signalling function (Klimovich et al., 2020). Emphasizing further the role of *Hydra* neurons in immunity, bioinformatics and machine learning algorithms revealed that a large fraction of neuronal genes unique to this genus (so called taxonomically restricted genes), are capable of encoding antimicrobial peptides (Klimovich et al., 2020). To our surprise, we uncovered that a number of *Hydra*-specific neuropeptides known to mediate neuroeurotransmission and motor control have a second function; they act as antimicrobial peptides and shape the microbiome (Augustin et al., 2017). Intriguingly, a bidirectional interaction between neurons and microbes can also be observed in vertebrates. While defensin family AMPs are expressed in the murine enteric neurons (Klimovich et al., 2020), a plethora of other peptides, produced in the mammalian brain, may also play a role in controlling resident beneficial microbes (Holzer and Farzi, 2014). Moreover, similar to dual-function neuropeptides of *Hydra*, a neuropeptide PACAP known to regulate neurodevelopment, emotion and stress responses in the mammalian brain has been recently identified as an antimicrobial peptide (Lee et al., 2021). Strikingly, antimicrobial peptides have structural features that make them prone to aggregation into plaques similar to those characteristic for the amyloids in the brain (Lee et al., 2020). Even more intriguingly, the β-amyloid protein also has antimicrobial potential and may normally function in the innate immune system (Soscia et al., 2010). These observations provide an exciting perspective that the accumulation of amyloid, considered a toxic waste product, may in fact be an immune reaction of the brain to the presence of microbes or their products (Abbott, 2020). Taken together, these observations uncover the existence of a common evolutionary conserved principle and support an emerging paradigm that the communication between the nervous system(s) and the microbiota are indeed bidirectional. The nervous system receives signals from the gut (gut–brain axis) affecting host behaviour and

development; and on the other hand is producing neuropeptides with antimicrobial activity and a possible role in controlling the microbiota.

Conclusions, open questions, and future perspectives: a new way of exploring neuronal circuits

Here we have reviewed that nerve cells are involved in controlling resident beneficial microbes in the early emerging metazoan *Hydra*, and that microbes affect the animal's behaviour by directly interfering with neuronal receptors. Recent progress in molecular and imaging analysis allows us to present *Hydra* as a powerful system for studying neural interactions and neural circuit formation which allows easy access to combined genetic, cell biological, molecular, and biocomputational tools. It is increasingly evident that bidirectional interactions exist in many vertebrates among the gastrointestinal tract, the intestinal microbiota and the enteric and central nervous systems.

The path taken so far enables us to address specific and evolutionary informative questions with regard to the evolutionary origin of host neuron–microbe interactions. Open questions include:

- How do microbes affect innate behaviour such as *Hydra*'s feeding reflex?
- What are the microbial taxa involved and the responsive neuron populations?
- How different are these signals and factors closely related but different *Hydra* species? Preliminary observations point to a surprising difference in neuroanatomy in closely-related and apparently similar *Hydra* species; yet functional consequences of these differences remain unclear.
- Does the resident microbiota influence neurogenesis in embryos and/or in adults?
- Is the resident microbiota involved in educating neuronal precursor cells/stem cells which, in turn, influence the composition of the microbiota?
- How do the commensal microbiota support the development of the complex nerve net made of distinct spatially restricted neuronal populations (Figures 3 and 4)?
- Ample histochemical, biochemical and functional data has been accumulated, indicating the presence of different small molecule neurotransmitters such as catecholamines, serotonin, acetylcholine, glutamate and GABA in *Hydra*. Do the resident microbes contribute to the repertoire of neurotransmitters?

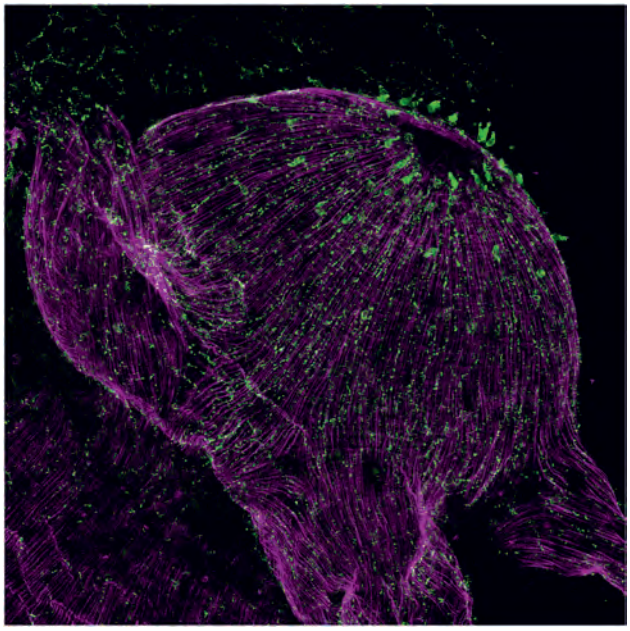

Figure 3: The nerve net of *Hydra* is composed of at least seven distinct spatially restricted neuronal populations. Here, one of them – a population of neurons expressing the RF-amide neuropeptide (green) in the hypostome of a polyp are visualized using specific antibodies. Muscular fibers of epithelial cells (magenta) are counterstained with Phalloidin.

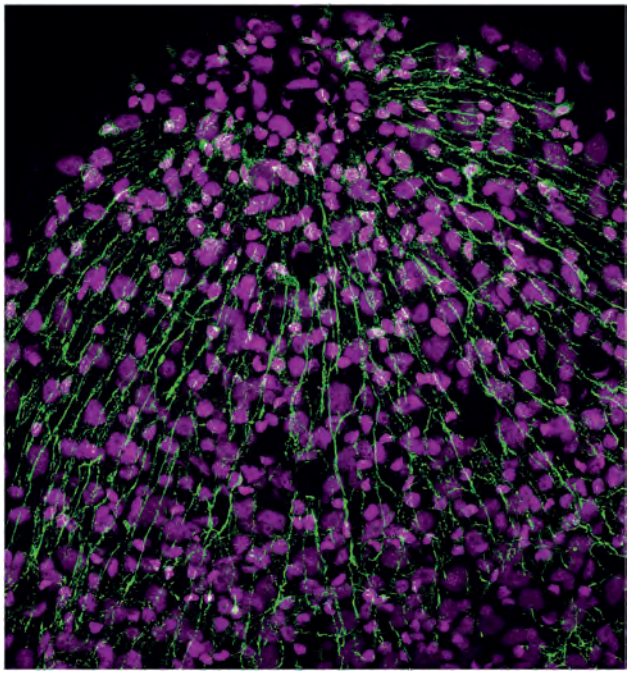

Figure 4: Modern microscopy technologies allow analysing the complex anatomy of the *Hydra* nerve net with unprecedented resolution. Here, the cell bodies and neurites of RF-amide-positive neurons in the hypostome (green) are visualized using a specific antibody. Cell nuclei are counterstained with TO-PRO (magenta).

– Last: what are the fundamental principles of the nerve net topology, dynamics and function that allow the simple nervous system of *Hydra* to be highly effective, multifunctional and energy-efficient? Understanding these basic rules of network design, implemented in the simple nervous systems of *Hydra* and other models, will be instrumental for development of highly efficient yet less energy-demanding microprocessors and computers (Bosch et al., 2017; Dupre and Yuste, 2017; Martinez and Sprecher, 2020).

Some of these questions are already under study in laboratories around the globe, but a more focused effort is required. The fascinating perspective is that these efforts will assist our understanding of how all of the parts of a living organism operate together within the metaorganismic framework. The comprehensive elucidation of the neural code for behaviour in an experimental system where one can have in principle access to either connectivity or functional data from every single neuron also enables the rigorous modeling of neural circuits, with simulations that are constrained completely in terms of the number of neurons, connections between the neurons and activity patterns. Model systems such as *Hydra* therefore may open new pathways to mimic basal neuronal mechanisms by electronic systems. Such studies will have relevance for understanding neural circuits in all animal species. In conclusion, the evidence is now irrefutable that "from so simple a beginning" (Charles Darwin) the neurobiology of animals has been, and is being, shaped by interactions with the microbial world.

Glossary

Antimicrobial peptides (AMPs): Small molecular mass proteins with broad spectrum antimicrobial activity against bacteria, viruses and fungi. These peptides are usually positively charged and have both a hydrophobic and hydrophilic side that enable the molecule to be soluble in aqueous environments yet also enter lipid-rich membranes.

Axenic condition: Condition of animal culture, in which only a single species of organism is present and entirely free of all other contaminating organisms. This state is achieved by sterilizing the housing equipment, supplied food and air. Axenic culture is an essential tool for studies on symbiotic interactions in a controlled environment.

Commensal microbe: A bacterial, viral, fungal or archaeal organism that under normal circumstances resides in or on host tissue, does not cause disease, and forms a symbiotic relationship with the host in which one derives some benefit, while the other is unaffected.

Conventionalized host organisms: Carrying the full (undefined) load of organisms usually associated with this species.

Dysbiosis: An altered state (or disbalance) of microbiota associated with a change in species composition, abundance and/or spatial distribution and typically associated with a disease.

Germfree: Host organisms that are devoid of any other living germs or microorganisms.

Holobiont: The cnidarian host organism and all of its symbiotic algae and stably associated microbiota. While the term "meta-organism" defines a superordinate entity that is applicable to all kinds of interdependent associations, the term "holobiont" is constrained to specific taxonomic groups.

Metaorganism: An association composed of a uni- or multicellular macroscopic host and diverse microorganisms, including bacteria, Archaea, fungi, viruses, and various other microbial eukaryotic species including algal symbionts.

Microbes: Microbial life forms including bacteria, archaea, fungi and viruses.

Microbiota: Microbial life forms within a given habitat or host.

Microbiome: The totality of microorganisms and their collective genetic material present in or on the body of a macroscopic host organism or in another environment.

Symbiotic interactions: A close and usually obligatory association between two or more different organisms of different species that live together, often but not necessarily to their mutual benefit.

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Presentation of scientific institutions

Peter Walter*, Wilfried Mokwa and Sven Ingebrandt

Innovative retinal interfaces for optimized artificial vision – a new DFG funded Research Training Group

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Introduction

Blindness caused by end stage progressive degenerative diseases of the retina is untreatable. In early stages of such diseases, gene therapy as demonstrated for Leber's Congenital Amaurosis (LCA), a homozygote early manifest RPE65 defect, may be helpful (Dias et al., 2018). In end stage disease with profound blindness, electrical stimulation at various levels of the visual system has been discussed as a useful approach to restore basic visual functions (Ayton et al., 2020). In the last years, two retinal implants were approved as implantable devices to electrically stimulate remaining neurons in the retina. Approximately 400 patients were implanted worldwide. However, the success was limited to phosphene perception and only in very rare cases pattern and forms were perceived by the implant recipients (Schaffrath et al., 2019). In some cases, also surgical complications occurred after placement of the devices inside the eye (Gekeler et al., 2018; Rizzo et al., 2020).

Although the basic concept of substituting the missing function of photoreceptors by electrical stimulation of postsynaptic cells in the retina was a straightforward approach, still many biological and technological challenges exist. Most importantly, the new concepts need to be adaptive and personalized to address the dynamics of the progressing neurodegenerative disease and the individual situation of each patient.

Last year the DFG confirmed the funding of a new Research Training Group RTG 2610 InnoRetVision with the goal to further analyze the underlying mechanisms preventing the success of local electrical stimulation in the visual system and to elaborate novel concepts to overcome these challenges.

Aims of the RTG

The RTG will perform basic research on major topics of local retinal or cortical stimulation with the aim to overcome the limitations of the currently available implant technology. Novel concepts will address the biological implications originating from retinal remodeling during the degeneration process or functional cortical rearrangements associated with long-term blindness.

At the same time the RTG will provide strong interdisciplinary teaching in the fields of Electrical Engineering, Biophysics, Material Sciences, Neurobiology, Image Processing, and Ophthalmology, especially Vitreoretinal Surgery.

It is not intended to construct and fabricate a new retinal prothesis. This RTG will work on foundations for new ideas removing roadblocks for the realization of upcoming concepts. It will teach and train a new generation of researchers and experts in neuroengineering.

Research working fields and projects

Three working fields were defined to group projects with a very strong cooperation and exchange between each project. The cooperation between the working fields is the main interdisciplinary component of the RTG (see Figure 1).

In Working Area A entitled *Next Generation of Stimulation and Recording Electrodes for Retinal Implants* we will work on new concepts for very high density electrode designs based on nano-needles (A1, Karsten Seidl, Department for Electronic Devices and Circuits, University Duisburg-Essen) and 2D materials such as Graphene (A2, Joachim Knoch, Institute of Semiconductor Electronics,

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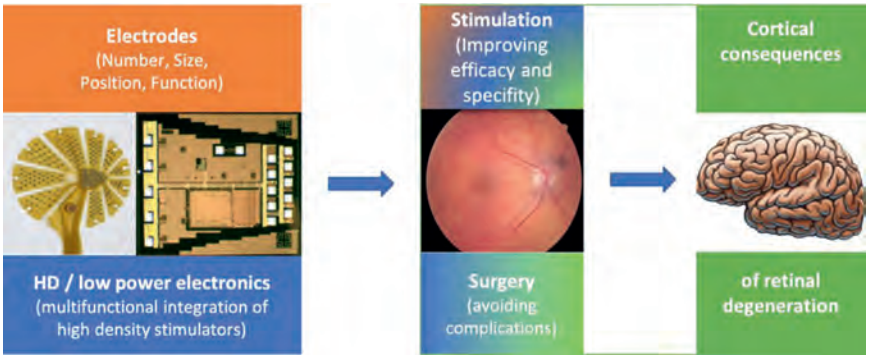

Figure 1: Working Areas and topics of the Research Training Group RTG 2610. Working Area A (orange) evaluates the *Next Generation of Stimulation and Recording Electrodes for Retinal Implants*), Working Area B (blue) contributes to *System Components for Retinal Implants*, and Working Area C (green) helps for a further *Understanding Retinal Degeneration and Improving Surgical Interventions*.

RWTH Aachen). These projects should solve the problem of the very low resolution obtained with implants of current technology and small numbers of electrodes. Another bottleneck of current retina implant technology is the use of surface electrodes and the distance between such electrodes and the targeted neurons in the retina, which limits the achievable resolution. We will examine flexible, three-dimensional electrode stacks, which can be inserted into the retina to get the electrodes as close as possible to their target cells (A3, Andreas Offenhäusser, Institute of Biological Information Processing, Bioelectronics (IBI-3), Forschungszentrum Jülich). We will also develop concepts for multifunctional implants capable of recording electric activity within the retina, recording of biophysical parameters and local genetic modification of cells by electroporation (A4, Sven Ingebrandt, Institute of Materials in Electrical Engineering I, RWTH Aachen).

Working Area B is entitled *System Components for Retinal Implants*. Here we will solve major limitations in resolution by integrating thousands of electrodes on a very small, flexible substrate with integrated electronics (B1, Wilfried Mokwa, Institute of Materials in Electrical Engineering I, RWTH Aachen). We will also realize the electronic circuits necessary to drive thousands of possibly multifunctional electrodes (B2, Rainer Kokozinski, Department for Electronic Devices and Circuits, University Duisburg-Essen). Further functions will be integrated on a substrate such as the recording of local field potentials or ganglion cell responses to local light stimulation (B3, Florian Merget, Institute of Integrated Photonics, RWTH Aachen). We will also explore, how camera images can be analyzed and processed e.g. with tunable spatial and temporal filters or with real time feature extraction algorithms to optimize the stimulation algorithms (B4, Dorit Merhof, Institute of Imaging and Computer Vision, RWTH Aachen). The information from cameras and the information for stimulation pulses can be sent to any implant by means of RF circuits. Optoelectronic measures are much faster and more efficient especially when phased array transmitters are used. We will determine, if this technology may also help to provide complex information to high-density implants in real time (B5, Jeremy Witzens, Institute of Integrated Photonics, RWTH Aachen).

In Working Area C (*Understanding Retinal Degeneration and Improving Surgical Interventions*) the biological and surgical topics are grouped. We want to further understand the cellular network in the degenerated retina and improve the stimulation efficacy in an animal model of Retinitis pigmentosa by blocking diseased intrinsic activity by pharmaceutical silencing (C1, Frank Müller, Institute of Biological Information Processing, Molecular and Cellular Physiology (IBI-1), Forschungszentrum Jülich) or by means of genetic modulation obtained with local electroporation (C2, Sandra Johnen, Department of Ophthalmology, University Hospital RWTH Aachen). In projects C3 and C4, we want to take a closer look at the visual cortex after long standing retinal degeneration by means of innovative multimodal imaging to understand anatomic (C3, Antje Willuweit, Institute of Neuroscience and Medicine, Medical Imaging Physics (INM-4), Forschungszentrum Jülich) and functional resources (C4, Björn Kampa, Institute of Biology II, RWTH Aachen) in the brain for restoring visual perception. The implantation of any device into the eye requires an in-depth understanding and planning of the anatomic structures especially if the implant is of significant size and the eye is small. Therefore, we want to generate 3D data sets for microscopic and surgical eye anatomy of different species (C5-1, Sabine Baumgarten), we want to design instruments for a less invasive implantation procedure (C5-2, Tibor Lohmann), and we want to test all this in project C5-3 (Kim Schaffrath, all Department of Ophthalmology, University Hospital RWTH Aachen). These three project topics are addressed by medical doctoral students, which will be supervised by clinician scientists in this highly interdisciplinary RTG.

Teaching activities

At the same time as doctoral students are working on their PhD thesis projects, we offer intensive interdisciplinary courses covering all the important disciplines of the RTG. In the beginning, the cohort of PhD students will be very divers with a discipline orientated background, e.g. with master degrees in neurobiology or in electrical engineering. In an intensive curriculum, the PhD students will be trained in all the complementary disciplines with basic introduction courses and advanced special courses in a later phase of the RTG program. Towards their practical education, each student is participating in a lab-rotation program to get a hands-on training in their complementary disciplines. In many project, we organized the scientific supervision by two senior researchers coming from different disciplines.

Career building

Throughout the RTG time, we will also provide skills necessary for the individual career development. We will encourage all students to build their own professional network. The students will be connected to the career building measures of the hosting universities and we will introduce our young researchers during conferences and meetings to other senior researchers in the field. We will invite internationally renowned colleagues for specialized seminar talks and to our bi-annual ***Artificial Vision Symposium*** series to Aachen. We will also provide a network of important companies in the field of Neuroengineering and Medical Technology with possibilities of visits and internships.

More Information:

available at www.rtg2610.org

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Presentation of scientific institutions

Elisabeth Binder* and The ALBA Network

ALBA Network – towards diversity and equity in brain sciences

https://doi.org/10.1515/nf-2021-0010

The ALBA Network was founded in 2018 by a group of international scientists to promote equity and diversity in brain sciences. It is led by the ALBA team composed of international brain scientists involved in research, education, communication and advocacy. ALBA provides a global network for sharing best practices and providing better visibility, networking and mentoring opportunities to scientists from underrepresented groups. The Network founding members are the Federation of European Neuroscience Societies (FENS), the International Brain Research Organization (IBRO) and the Society for Neuroscience (SfN). The Brain Prize (Lundbeck Foundation) is a supporting member of ALBA.

As a major step toward promoting a fair and inclusive research community, the ALBA Network released the ALBA Declaration on Equity and Inclusion this January 2021. The ALBA Declaration aims to raise awareness of challenges faced by underrepresented groups in science and academia and provide a concrete set of actions that individuals and institutions can commit to making their organisations and research communities at large more inclusive. The Declaration focuses specifically on overcoming two specific barriers to equity: implicit biases and workplace cultures. More than 190 major scientific organisations and more than 380 individuals worldwide already endorsed the ALBA Declaration.

Another key activity of ALBA is to highlight role models through Awards. The ALBA-FKNE Diversity Prize highlights a scientist or group that has made outstanding contributions to promoting diversity in brain sciences and is a partnership between the ALBA Network and the FENS Kavli Network of Excellence (FKNE; network of early and mid-career European Neuroscientists), with the support of the FENS-CHET (Committee of Higher Education and Training of the Federation of European Neuroscience Societies). This Prize is awarded annually at either the FENS Forum or the FENS Regional Meetings (FRM). The Prize was awarded for the first time in 2020 to Prof Erin Shuman for her exceptional accomplishments in promoting gender equality in neuroscience, and celebrated at the FENS Virtual Forum 2020 (watch the celebration video at: http://www.alba.network/alba-fkne-diversity-prize-2020-winner).

The call for the 2021 Prize winner was open until 22 March 2021 and the ALBA-FKNE Diversity Prize 2021 winner will be celebrated at the FENS Regional Meeting 2021.

You can find more information about the ALBA Network activities at: http://www.alba.network/activities. Read and sign the ALBA Declaration

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on Equity and Inclusion at: http://www.alba.network/declaration.

Prof Elisabeth Binder (Member of the ALBA Board of Directors) – "We need to increase diversity at the leadership level of institutions and professional societies. Doing this should improve the quality of science and ensure greater diversity on all levels."

Prof Carmen Sandi (Chair of the ALBA Network) – "It is important that we join forces and work together to increase diversity and ensure equity in the way we deal with science. The ALBA Network tackles these goals at a global level by launching and regrouping initiatives for diversity in brain sciences under one umbrella. Our ambition is to create a network to help all brain scientists to have equal opportunities to thrive."

Andreas Gumbert and Ileana L. Hanganu-Opatz*

Nachruf Dr. Jan Kunze (1968–2021)

https://doi.org/10.1515/nf-2021-0014

In der Woche vor Ostern hat uns die Nachricht von Jan Kunzes Tod erreicht. Gemeinsam und aus zweierlei Perspektive wollen wir erkennbar machen, was Jan Kunze persönlich für uns und für die Neurowissenschaften bedeutet hat.

Jan Kunze als Wissenschaftler, Kollege und Freund

Der Tod von Jan Kunze erfüllt uns mit tiefer Trauer. Jan war für uns ein wissenschaftlicher Mitstreiter und Freund. Getrieben von Neugier und Begeisterung für die belebte Natur, hat Jan sich an Projekten beteiligt, die ihn in entlegene Regionen der Welt geführt haben, vom Regenwald bis in die Wüste. Als passionierter *bird watcher* und guter Pflanzenkenner liebte er besonders die Forschung in der freien Natur unter Einsatz der ganzen Person und mit modernen Methoden.

Jan Kunze, ca. 1999, beim Blütenstudium in Griechenland. Copyright Andreas Gumbert.

Jan promovierte in seiner Heimatstadt Berlin an der Freien Universität im Bereich der Blüten- und Bestäubungsbiologie und verband ökologische Fragestellungen mit Aspekten des Lern- und Sammelverhaltens der Bestäuber, deren Farbensehen und Duftwahrnehmung. Er hatte eine ansteckende Art, interdisziplinär zu denken und zu arbeiten und Themenfelder der Botanik, Freilandbeobachtungen, kontrollierte Verhaltensexperimente, spektroskopische Analysen von Blütenfarben, die Modellierung der Farb- und Formwahrnehmung durch die Bestäuber, die chemische Analyse von Düften und deren neuronale Verarbeitung wie selbstverständlich zu verbinden.

Zudem beteiligte sich Jan an einer Reihe von Gemeinschaftsprojekten zur Navigation von Bienen im Freiland. Diese Freilandarbeiten bereiteten ihm enormen Spaß auch unter zuweilen extremen Bedingungen, Vergnügen an der Gemeinschaft, und bedienten seine Faszination für anspruchsvollste wissenschaftliche Arbeit. In der Tat waren auch Abenteuergeist, Lust am sportlichen Wettstreit miteinander und der Mut, Neues zu wagen, immer dabei.

Jan hat uns immer wieder mit seiner Begeisterung, seinem scharfen Humor und seinem Ideenreichtum beflügelt und uns durch seinen Sinn für Fairness beeindruckt. Als Programmdirektor für Neurowissenschaft bei der DFG hat er sein Wissen und diese Talente der Förderung der Wissenschaft, und ganz besonders den jungen Leuten in der Wissenschaft, gewidmet, und dies auch nach seiner Rückkehr nach Berlin als Abteilungsleiter für Strategische Kooperationen und Forschungsförderung am Max-Delbrück-Centrum für Molekulare Medizin so gehalten.

Jans Tod hinterlässt für uns eine tiefe Lücke. Unsere Gedanken sind bei seinen geliebten vier Kindern und seiner Familie.

Andreas Gumbert (Brüssel) (E-mail: andreas.gumbert@gmx.net) Lars Chittka (Queen Mary University London), Giovanni C. Galizia (Zukunftskolleg Universität Konstanz), Bertram Gerber (Leibniz Institut für Neurobiologie Magdeburg), Martin Giurfa (CNRS Université Paul Sabatier Toulouse), Frank Hellstern (Lautenbach im Renchtal), Randolf Menzel (Freie Universität Berlin), Silke Sachse (Max-Planck-Institut für Chemische Ökologie Jena)

Jan Kunze als Mentor der Neurowissenschaften

Meine erste Begegnung mit Dr. Jan Kunze fand in einer Ausnahmesituation statt: Ich wartete auf mein „Vorsingen“ für eine Emmy Noether-Förderung in den Räumlichkeiten

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Andreas Gumbert, Brüssel, Belgium, E-mail: andreas.gumbert@gmx.net

der Deutschen Forschungsgemeinschaft. Wir hatten zwar häufiger telefoniert, da er der zuständige Programmdirektor im Bereich Neurowissenschaften bei der DFG war, getroffen hatten wir uns bis zu diesem Zeitpunkt noch nie. Nach der tiefen Stimme am Telefon zu urteilen, habe ich Herrn Dr. Kunze in die Schublade „alte ernste Herren" geschoben. Als er vor mir stand, kaum älter als ich, sportlich und freundlich, war ich so überrascht, dass meine gesamte Nervosität beim kurz darauffolgenden Betreten des „Vorsingen-Raums" verflogen war. Jan Kunze rief mich am nächsten Tag an und teilte mir die freudige Nachricht mit: Ich hatte die Förderungsempfehlung, die für mich das Bleiben auf dem akademischen Weg bedeutete, erhalten.

Jan Kunze ca. 2020, Copyright privat.

Seit dieser Begegnung habe ich viele Male mit Jan Kunze gesprochen: Wenn es Unklarheiten zu einer Antragsstellung gab, er bearbeitete sie ruhig, sachlich und kompetent. Oder wenn die Frage aufkam, ob man einen Antrag zu einem Thema bei der gegebenen Expertise, Datenlage usw. überhaupt stellen soll, er hatte das fachliche Know-how und den Überblick, um immer eine schnelle Hilfestellung zu leisten. Bei der Planung einer Verbundinitiative, wenn man im Chaos zu versinken drohte, er wusste immer wo und wie man anfängt und welche Schritte am sinnvollsten sind. Oder wenn fachliche Fragen zu einem Thema aufkamen, er kannte die deutsche Neuro-Szene wie kein anderer und wusste immer, wer die richtige Ansprechperson ist. Auch wenn schonungslose, ehrliche Meinung zu einer wissenschaftlichen Idee nötig war, er konnte die Wahrheit vermitteln ohne zu verletzen und man bekam während des Gespräches einen „Spiegel", um die eigenen Denkfehler zu erkennen und verbessern.

Jan Kunze war Biologe und studierte und promovierte an der FU in Berlin. Bevor er 2018 als Abteilungsleiter „Strategische Kooperationen und Forschungsförderung" zum Max-Delbrück-Centrum für Molekulare Medizin in Berlin wechselte, war er 17 Jahre bei der DFG. In all diesen Jahren und für viele Neurowissenschaftler war Jan Kunze „die DFG", Immer bereit, dem Nachwuchs zu helfen und vor allem zu unterstützen, um selbst Lösungen zu finden und über sich hinaus zu wachsen. Er wusste, wie man solch ehrgeizigen Nachwuchs dazu bringt, zusammen zu arbeiten. 2009 schaffte er es etwa, dass infolge eines zweiwöchigen Austauschs mit der Japanischen Neurowissenschaftlichen Gesellschaft aus neun damaligen Emmy Noether- und Heisenberg-Stipendiaten, die sich vorher nicht oder kaum kannten, bis zum heutigen Tag Freunde wurden. Es war vielleicht seine sachliche, unaufgeregte und dennoch so herzliche Art, die all diesen Nachwuchswissenschaftlern und Nachwuchswissenschaftlerinnen zeigte, wie man gemeinsam mehr als alleine erreicht. Es war vielleicht auch seine intrinsische Neugier und Begeisterung für die Wissenschaft, die ihn über Zugvögel am Rhein plaudern ließ und die uns faszinierte. Es war auch die Mischung aus Offenheit, Humor und Lebensfreude, die uns auch beim Karaoke-Singen in Nagoya veranlasste, ihm Respekt zu zeugen.

Ich habe mich häufig gefragt, warum Jan Kunze sich, bei seiner Begeisterung und Freude an der Wissenschaft, bei seinem Wissen und seiner Betreuungsgabe, gegen eine akademische Laufbahn entschieden hat. Als Professor wäre er eine Bereicherung für jede deutsche Universität gewesen. Ich habe ihn nie gefragt, weil die Antwort doch offensichtlich war: Jan Kunze hat sehr früh erkannt, dass man nicht nur einer, sondern vielen deutschen Universitäten helfen kann, indem man die Neurowissenschaften vorantreibt, stärkt und lenkt, indem man junge Nachwuchstalente auf ihrem Weg betreut und Networking auf Basis von Aufrichtigkeit und Menschlichkeit betreibt.

Die deutsche Neurowissenschaft wird Dich vermissen, Jan!

Ileana L. Hanganu-Opatz (Zentrum für Molekulare Neurobiologie, Universitätsklinikum Hamburg-Eppendorf) (E-mail: hangop@zmnh.uni-hamburg.de)

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Nachrichten aus der Gesellschaft

https://doi.org/10.1515/nf-2021-0013

Who is who im Vorstand der Neurowissenschaftlichen Gesellschaft – die neuen Vorstandsmitglieder stellen sich vor

Prof. Dr. Constance Scharff

Sektionssprecherin „Entwicklungsneurobiologie/ Neurogenetik“

Foto: © Thomas Berg

Akademischer und beruflicher Werdegang

seit 2004
C4-Professorin für Verhaltensbiologie, Freie Universität Berlin
2002–2007
Associate Professor, Max-Planck-Institut für molekulare Genetik, Berlin
1998–2001
Assistant Professor, Rockefeller University, New York, USA
1994–1998
Postdoktorandin (bei Prof. Fernando Nottebohm), Rockefeller University, New York, USA
1991–1993
Wissenschaftliche Mitarbeiterin (bei Prof. Nicole Le Douarin), Paris, Frankreich
1986–1991
Promotion, Rockefeller University, New York, USA
1982–1986
Graduate Studies in Neurobiology and Behavior, Adelphi University, New York, USA
1982
Vordiplom Biologie, Philipps-Universität Marburg

Funktionen in wissenschaftlichen Gesellschaften und Gremien

seit 2019
Mitglied, Max Planck School of Cognition (MPS-Cog), Leipzig
seit 2019
Mitglied, Senatsausschuss Wettbewerb (SAW), Leibniz-Gemeinschaft
seit 2016
Mitglied, Stiftung Elsa-Neumann-Stipendium (NaFöG) zur Promotionsförderung
seit 2016
Mitglied, Rat der Berlin-Brandenburgischen Akademie der Wissenschaften (BBAW)
2016–2017
Mitglied, Stiftungsrat, Schering Stiftung
2005–2017
Mitglied im Vorstand Sonderforschungsbereich „SFB 665: Entwicklungsstörungen im Nervensystem“
seit 2015
Gründungs- und Vorstands-Mitglied, Einstein-Zentrum Neurowissenschaften
2014–2018
Kassenprüferin der Neurowissenschaftlichen Gesellschaft
2013–2015
Präsidentin, Deutsche Zoologische Gesellschaft (DZG)
seit 2012
Mitglied, Scientific Committee, College for Life Sciences, Wissenschaftskolleg zu Berlin
2011–2013
Geschäftsführende Direktorin, Institut für Biologie, Freie Universität Berlin

Projektkoordination, Mitgliedschaft in Verbundprojekten

seit 06/2020
DFG „Optimization and testing of new methods for the generation of zebra finch transgenics“
2016–2019
HFSP Förderung „Seeing voices: the role of multimodal cues in vocal learning“
2013–2016
DFG-Exzellenzcluster EXC 257: „NeuroCure“
2013–2017
DFG-Sonderforschungsbereich „SFB 665: Entwicklungsstörungen im Nervensystem“

2009–2015
„Bernstein Fokus Neuronale Mechanismen des Lernens motorischer Sequenzen"
2005–2013
DFG-Sonderforschungsbereich „SFB 665: Entwicklungsstörungen im Nervensystem"
2008–2010
DFG-Exzellenzcluster „EXC 302: Languages of Emotion"
2001–2006
National Institute of Mental Health RO1 „Functional recovery after induces neuronal death"

Forschungsschwerpunkte
Neuroethologie mit Schwerpunkt Neurogenetik. Erforschung der molekularen Netzwerke, die für das Erlernen von Lautäußerungen (Sprache, Vogelgesang) Voraussetzung sind, sowie der neuralen Schaltkreise, in denen diese molekularen Netzwerke aktiv sind. Mechanismen und der Funktion der erwachsenen Neurogenese.

Auszeichnungen und verliehene Mitgliedschaften
seit 2019
Mitglied der Nationalen Akademie der Wissenschaften Leopoldina
seit 2012
Mitglied der Berlin-Brandenburgischen Akademie der Wissenschaften
2008
Preis für gute Lehre, Institut für Biologie, Freie Universität Berlin (erneut 2016)

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Dr. Sophie E. Seidenbecher

Sektionssprecherin „Junge NWG (jNWG)"

Education & Work Experience
currently
on parental leave
2020
Faculty Recruitment Tenure Track
Wissenschaftliche Referentin, Technical University Munich
2020
Scientific Coordinator, Leibniz Institute for Neurobiology LIN Magdeburg (3 month)
2018
Research Visit, DRCMR, Hvidovre Hospital Copenhagen (3 month research visit with Prof. Ollie Hulme)
2015–2019
PhD in Molecular Biology and Genetics
"Modeling foraging decisions in fruit flies" with Prof. D. Kvitsiani, DANDRITE, Aarhus University
2012–2015
Master of Science in Physics
"Stimulus-dependent drift-diffusion model for perceptual decision making processes in the brain", with Prof. E. Schöll, Prof. S. Kiebel (MPI CBS Leipzig, TU Berlin)
"Stimulus-dependent drift-diffusion model for perceptual decision making processes" (MPI CBS Leipzig, TU Berlin)
2007–2012
Bachelor of Science in Physics
"Structure and spectroscopy of charged flavin complexes", with Prof. O. Dopfer, Prof. T. Möller (Technical University Berlin)

Scientific Interest
My interests in neuroscience are mainly in the field of behavior and decision-making. I enjoy beautiful models, research that studies behaviour across different species and (re-)discovering classic research papers from 60–70 years ago.

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Prof. Dr. Christiane Thiel

Sektionssprecherin „Kognitive Neurowissenschaften“

Werdegang

2010
Gastprofessur, Department of Psychiatry, Vanderbilt University School of Medicine (USA)

2005–2011
Professur für Kognitive Neurobiologie, Universität Oldenburg

2000–2005
Post Doc, Kognitive Neurologie, Institut für Medizin, Forschungszentrum Jülich

1997–2000
Post Doc, Wellcome Department of Imaging Neuroscience, UCL, London (UK)

1997
Promotion in Biologischer Psychologie, Universität Düsseldorf

1988–1994
Studium der Psychologie und Neuroscience, Universität Koblenz-Landau, Düsseldorf und Sheffield (UK)

Weitere berufliche Aktivitäten und Auszeichnungen

seit 2020
Mitglied im DFG Fachkollegium Psychologie

seit 2018
Mitglied des Cluster Boards des Exzellenzclusters „Hearing4all“

2016–2019
Forschungsdekanin Fakultät für Medizin und Gesundheitswissenschaften, Oldenburg

2015–2018
Mitglied des Direktoriums des Forschungszentrums Neurosensorik

2013–2016
Vorsitzende der Ethikkommission der Universität Oldenburg

seit 2009
Mitglied des Senats der Carl von Ossietzky Universität Oldenburg

2013
Ruf an die Universität Düsseldorf (abgelehnt)

2005
Ruf an die LMU München (abgelehnt)

Wissenschaftliche Schwerpunkte

Ich beschäftige mich mit den Mechanismen visuell räumlicher und auditorischer Aufmerksamkeit sowie anderer kognitiver Funktionen im menschlichen Gehirn. Darüber hinaus untersuchen wir, wie cholinerge und dopaminerge Neurotransmission an diesen Prozessen beteiligt ist. Methodisch benutzen wir hauptsächlich die funktionelle Magnetresonanztomographie. Langfristiges Ziel ist ein besseres Verständnis kognitiver Veränderungen in verschiedenen Patientenpopulationen, wie beispielsweise bei Schwerhörigen oder Patienten mit Hirntumoren.

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Sektionssprecher „Molekulare Neurobiologie“

Foto: © Uni Ulm

Current Position

Director, Institute of Anatomy and Cell Biology, Ulm University, Professor W3, Head, DZNE Collaboration Group, Translational Biochemistry

University training and degree

1990
Approbation, Medical License

1983–1989
Medical School, Münster University, Germany, University of Washington, Seattle, USA; University of Otago, Wellington, New Zealand

Advanced academic qualifications
since 2003
Full Professor and Head of the Institute of Anatomy and Cell Biology, Ulm University
1998
Habilitation, Münster University (Anatomy and molecular Neurobiology
1991
Promotion Dr. med. (scl), Münster University
Postgraduate professional career
since 2019
Head of a Collaboration Group, DZNE, Ulm site
since 2019
Elected member of the Leopoldina, Academy of Sciences, Halle
since 2016
Board Member of the Neuroscience Panel, DFG
since 2010
Dean of Studies and member of the faculty board, Ulm University
2012
President of the Anatomische Gesellschaft
2006–2018
Offer of Professorships of the Universities Munich, Heidelberg, Freiburg, Göttingen and Magdeburg (LIN, Leibniz Professorship)
1997
Guest researcher at the Leibniz Institute for Neurobiology, Magdeburg (Prof. Gundelfinger)
1996
Board Certification Anatomy
1992–2002
Stipend at the MPI for Experimental Medicine (Göttingen) and Postdoc at the Institute of Anatomy at Münster University
1991–1992
AiP Nephrology, Münster University
1992
Medical License (Approbation)

Research interests
Molecular structure of excitatory synapses, molecular mechanism in neurodegenerative and neuropsychiatric diseases

Other
Stipend of the Cusanuswerk, Thesis – Prize, Münster University, Bargmann Prize of the Anatomische Gesellschaft
Köhler Prize for Rare diseases, WoS researcherID: V-9948-2017 orcid-id: 0000-0002-1486-8535

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Prof. Dr. Heidrun Potschka

Sektionssprecherin „Neuropharmakologie/-toxikologie“

Beruflicher Werdegang
seit 10.2006
Lehrstuhlinhaberin und Universitätsprofessorin (W3) Institut für Pharmakologie, Toxikologie u. Pharmazie Ludwig-Maximilians-Universität (LMU) München
2004–2006
Juniorprofessorin und Privatdozentin, Tierärztliche Hochschule Hannover, gefördert im Rahmen des Dorothea-Erxleben-Programmes (MWK-Niedersachsen),
1997–2004
wissenschaftliche Mitarbeiterin/Assistentin, Tierärztliche Hochschule Hannover, gefördert im Rahmen des Dorothea-Erxleben-Programmes (MWK Niedersachsen)
1996–1997
wissenschaftliche Mitarbeiterin (Justus-Liebig-Universität Gießen)
1994–1996
Promotionsstudium, Justus-Liebig-Universität, Gießen; gefördert durch ein Stipendium im Rahmen der Graduiertenförderung des Landes Hessen
1988–1993
Studium der Veterinärmedizin, Justus-Liebig-Universität, Gießen

Wissenschaftliche Auszeichnungen
Zuwahl in die Nationale Akademie der Wissenschaften Leopoldina
Falk Medical Research Trust Award (US-amerikanische Stiftung CURE)

Internationaler Preis der Michael-Stiftung für die beste Publikation auf dem Gebiet der Epilepsieforschung
Förderpreis der Akademie für Tiergesundheit
Best Bursary Award der European Epilepsy Academy
Förderung im Rahmen des Dorothea-Erxleben-Programmes des Ministeriums für Wissenschaft und Kultur des Landes Niedersachsen

Editor und Editorial Board (Bsp.)
seit 2015
Editorial Board "Neurobiology of Disease"
seit 2015
Editorial Board "Veterinary Neurology and Neurosurgery"
seit 2013
Associate Editor "Epilepsia"
2007–2012
Editorial Board Member "Epilepsia"
2006–2015
Editorial Board Member "Recent patents on CNS drug therapy"
2006–2017
Editorial Board Member "Epilepsy Research"

Tätigkeit in Kommissionen und Gremien (Bsp.)
seit 2020
Tierschutzkommission des Bundesministeriums für Ernährung und Landwirtschaft
seit 2017
Mitglied der Bf3R-Kommission für den Schutz von Versuchstieren
seit 2014
Translational Task Force der International League against Epilepsy & American Epilepsy Society
2012–2020
DFG-Fachkollegiat (2016–2020 als Sprecher) im Fachkollegium 207
2012–2017
Vorstandsmitglied der Deutschen Gesellschaft für Epileptologie
seit 2009
Kuratoriumsmitglied der Akademie für Tiergesundheit
2008–2020
Deutsche Forschungsgemeinschaft: Senatskommission für Tierexperimentelle Forschung

Forschungsschwerpunkte
- Pathophysiologie und Pharmakologie von Epilepsien: Identifizierung neuer Zielstruktur- und Biomarkerkandidaten; präklinische Validierung neuer therapeutischer Ansätze
- Identifizierung von Parameters präklinischer Studienqualität
- Evidenz-basierte Belastungseinschätzung und Refinement in der neurowissenschaftlichen Forschung

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Prof. Dr. Ileana Hanganu-Opatz

Sektionssprecherin „Systemneurobiologie"

Foto © Prof. Dr. Ileana Hanganu-Opatz

Werdegang
2009
Habilitation und Erlangung der Venia legendi für das Fach Physiologie an der Johannes Gutenberg-Universität Mainz
1999–2002
Promotionsarbeit am Institut für Neurophysiologie der Heinrich Heine-Universität Düsseldorf
1997–1998
Diplomarbeit am Universitätsklinikum Hamburg-Eppendorf (UKE)
1994–1998
Studium der Biologie und Biochemie an der Universität Bukarest

Tätigkeiten
2002–2005 & 2007–2008
Wissenschaftliche Angestellte am Institut für Physiologie und Pathophysiologie der Johannes Gutenberg-Universität Mainz
2005–2006
Postdoktorandin (DFG-Stipendiatin) am Institut de Neurobiologie de la Méditerranée (INMED, INSERM), Marseille (Frankreich)

Leitungspositionen
seit 2020
Direktorin des Institutes für Entwicklungsneurophysiologie am Zentrum für Molekulare Neurobiologie (ZMNH) des UKE
seit 2015
W3-Professorin für Entwicklungsneurophysiologie am UKE, Hamburg
2009–2015
Leiterin einer unabhängigen Nachwuchsgruppe im Emmy Noether-Programm der DFG
W2-Professorin für Entwicklungsneurophysiologie am UKE, Hamburg
2008–2015
Leiterin einer unabhängigen Nachwuchsgruppe im BMBF Programm „Selbständige Forschungsgruppen in den Neurowissenschaften“

Funktionen
seit 2020
Mitglied des Advisory Board des Excellence Cluster „Brain Links Brain Tools“, Freiburg
2016–2020
Mitglied des FENS Committee for Higher Education and Training (CHET)
2013–2019
Koordinatorin des DFG-Schwerpunktprogrammes 1665
seit 2010
Vorstandsmitglied und Stellvertreterin des Vorstandvorsitzenden (seit 2021) des Hamburg Center of Neuroscience
2011
Beraterin des Wissenschaftsrates zum Thema „Anreizsysteme in der Wissenschaft“
2009–2011
Wissenschaftliche Koordinatorin der DFG-geförderten Initiative zur Stärkung der deutsch-japanischen Zusammenarbeit auf dem Gebiet von Neurowissenschaften

Preise und Auszeichnungen
seit 2014
Gründungsmitglied des FENS-Kavli Network of Excellence
2015
ERC Consolidator Grant
2009
Du Bois-Reymond-Award of the German Society of Physiology

Wissenschaftliche Schwerpunkte
Entwicklung und Funktion neuronaler Netzwerke
Uni- und multisensorische Verarbeitung und Ontogenese
Pathophysiologie neurologischer und neuropsychiatrischer Erkrankungen
Kommunikation zwischen dem Nerven- und Immunsystem während der Entwicklung

Adresse:
Universitätsklinikum Hamburg-Eppendorf
Institut für Entwicklungsneurophysiologie
Falkenried 94
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Email: hangop@zmnh.uni-hamburg.de
Homepage: www.opatzlab.com

Prof. Dr. Martin Göpfert

Sektionssprecher „Verhaltensneurowissenschaften“

Akademischer und beruflicher Werdegang
seit 2009
W3-Professor für Zelluläre Neurobiologie, Universität Göttingen
2009
W2-Professor für Biophysik und Molekularbiologie Sensorischer Systeme, Universität Köln
2003–2008
VolkswagenStiftungs-Nachwuchsgruppe, Universität Köln
2001–2003
Royal Society University Research Fellow, University of Bristol
2001–2003
Leopoldina Forschungsstipendiat, Bioacoustics lab (Dr. Daniel Robert), University of Bristol
1998–2001
DAAD und Leopoldina Forschungsstipendiat, Universität Zürich
1998
Promotion, Universität Erlangen-Nürnberg
1994–1998
Doktorand, Zoologie, Universität Erlangen-Nürnberg
1988–1994
Studium der Biologie, Universität Erlangen-Nürnberg

Funktionen in wissenschaftlichen Gesellschaften und Gremien

seit 2021
Stellvertretendes Mitglied, Senat, Universität Göttingen
seit 2018
Finanzdekan, Fakultät für Biologie und Psychologie, Universität Göttingen
seit 2019
Forschungsdekan, Fakultät für Biologie und Psychologie, Universität Göttingen
2012–2014
Dekan, Fakultät für Biologie und Psychologie, Universität Göttingen
2012
Geschäftsführender Direktor, Inst. Für Zoologie und Anthropologie, Universität Göttingen
seit 2011
Stellvertretender Sprecher, SFB 889 „Cellular Mechanisms of Sensory Processing", Universität Göttingen

Forschungsschwerpunkte

Martin Göpfert ist Zoologe mit Schwerpunkt Sinnesbiologie, wobei die mechanosensorischen Systeme von *Drosophila* im Vordergrund stehen. Martin Göpferts Forschung hat zum Verständnis der neuronalen und molekularen Grundlagen von Gravitationssinn und Hören bei *Drosophila* beigetragen. Verblüffende Parallelen zwischen Wirbeltier- und Insektenhören wurden aufgedeckt, von aktiver mechanischer Verstärkung bis hin zu Schall-Transduktion, mechanosensorischer Adaptation und hör-relevanten Genen. Für visuelle Sehpigmentproteine, Opsine, wurden mechanosensorische Funktionen belegt – ohne Opsine kann *Drosophila* weder hören noch krabbeln weil mechanosensorische Ionenkanäle fehl-lokalisieren und mechanosensorische Zilien degenerieren. Grundlagen des mechanischen Öffnens des NOMPC Mechanotransduktionskanals wurden charakterisiert, und TRP Ionenkanäle wurden als Zielproteine von Insektiziden identifiziert.

Neben molekularen und biophysikalischen Aspekten beschäftigt sich Göpferts Forschung mit der Evolution von Sinnesorganen und der neuronalen Steuerung tierischen Verhaltens – von Bewegungskoordination bis hin zur Aggression.

Auszeichnungen und verliehene Mitgliedschaften

2019
Preis für gute Lehre der Fachschaft für Biologie, Universität Göttingen
2005
„Biologie-Preis" der Göttinger Akademie der Wissenschaften
2003
VolkswagenStiftungs-Nachwuchsgruppe
2003
Walther-Arndt Forschungspreis der Deutschen Zoologischen Gesellschaft
2002
Royal Society University Research Fellowship
2000
Leopoldina Forschungsstipendium
1999
DAAD Postdoc-Stipendium
1992
Stipendium der Studienstiftung des Deutschen Volkes
1991
Stipendium der Friedrich-Ebert-Stiftung

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Tel: +49-551-39-177 955
Email: mgoepfe@gwdg.de
Homepage: http://www.cellneuro.uni-goettingen.de/

NeuroWissenschaftliche Gesellschaft e.V.

Protokoll der Mitgliederversammlung
Montag, 22. März 2021
Zoom
im Rahmen der virtuellen 14. Göttinger Jahrestagung der Neurowissenschaftlichen Gesellschaft e.V.

Versammlungsleiter ist der Präsident der Neurowissenschaftlichen Gesellschaft, Prof. Dr. Albert C. Ludolph.

Protokollführer ist der Generalsekretär der Neurowissenschaftlichen Gesellschaft, Prof. Dr. Christian Steinhäuser.

Die Zahl der zugeschalteten Mitglieder beträgt 43.

Die Versammlung wurde satzungsgemäß einberufen, die Tagesordnung war den Mitgliedern bei der Einberufung mitgeteilt worden.

Beginn: 15:30 Uhr
Ende: 17:00 Uhr

Tagesordnung:
(1) Begrüßung durch den Präsidenten
(2) Bestätigung des Protokolls der letzten Mitgliederversammlung
(3) Bericht des Schatzmeisters/Bericht der Kassenprüfer
(4) Mitteilungen
(5) Aktivitäten der Gesellschaft
(6) Bericht zur Göttinger Jahrestagung 2021
(7) Wahl des neuen Vorstandes
(8) Verschiedenes

1 Begrüßung durch den Präsidenten

Albert Ludolph begrüßt die Anwesenden und eröffnet die Sitzung. Ergänzungen zur Tagesordnung werden nicht gewünscht.

2 Bestätigung des Protokolls der letzten Mitgliederversammlung

Das Protokoll der letzten Mitgliederversammlung vom 22. März 2019 ist in der Ausgabe 3/2019 von Neuroforum erschienen. Ergänzungen werden nicht gewünscht. Es wird mit 43 Ja-Stimmen, 0 Enthaltung und 0 Nein-Stimmen angenommen.

3 Bericht des Schatzmeisters / Bericht der Kassenprüfer

Ansgar Büschges erläutert die Jahresabrechnung der NWG zum Ende 2020 im Vergleich zu den Vorjahren und kommentiert einige Posten. Wie immer zeigt die Jahresabrechnung der NWG die zweijährigen, durch die Göttinger Tagung bedingten Schwankungen, d.h. in den geraden Jahren fließen die Teilnehmergebühren auf das NWG-Konto, und in den ungeraden Jahren wird das Geld für die Göttinger Tagung wieder ausgegeben. Der Anstieg der Personalkosten über die Jahre resultiert daraus, dass das administrative Personal inzwischen zu hundert Prozent von der NWG finanziert werden muss. In früheren Jahren konnte zum Teil auf Personal aus der Arbeitsgruppe Kettenmann am MDC zurückgegriffen werden, was nun nicht mehr der Fall ist. Seitdem die Klaus Tschira Stiftung die Finanzierung von dasGehirn.info übernommen hat, gehen auch diese Einnahmen und Ausgaben direkt über die NWG und nicht mehr über den Sponsor, wie zu Zeiten der Hertie-Finanzierung.

Die Einnahmen und Ausgaben der NWG im Jahr 2020 wurden am 23. und 24. Februar 2021 von den Kassenprüfern Jens Dreier und Helmut Kettenmann geprüft. Die Kassenprüfer bestätigen eine korrekte Kontenführung und empfehlen der Mitgliederversammlung, den Schatzmeister zu entlasten.

Der Vorstand schlägt der Mitgliederversammlung als Kassenprüfer für die Prüfung der Jahresabrechnung 2021 Christian Rosenmund, Berlin, vor, da Jens Dreier nicht noch einmal zur Verfügung steht. Helmut Kettenmann ist bereit, die Kassenprüfung 2021 nochmals zu übernehmen. Die Mitgliederversammlung stimmt dem Vorschlag mit 43 Ja-Stimmen, 0 Enthaltung und 0 Nein-Stimmen zu. Albert Ludolph dankt Christian Rosenmund für seine Bereitschaft.

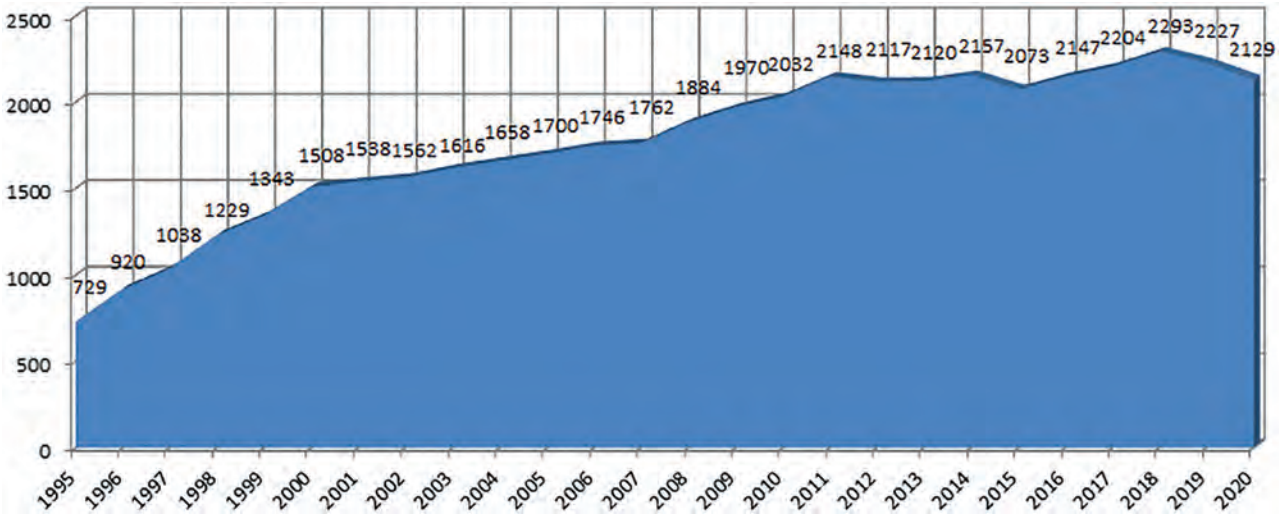
Die Mitgliederversammlung entlastet den Schatzmeister auf der Grundlage des Berichts der Kassenprüfer mit 42 Ja-Stimmen, 1 Enthaltung und 0 Nein-Stimmen.

Constanze Seidenbecher stellt den Antrag, dass die Mitgliederversammlung den Vorstand entlastet. Die Mitgliederversammlung entlastet den Vorstand mit 43 Ja-Stimmen, 0 Enthaltung und 0 Nein-Stimmen.

4 Mitteilungen

4.1 Mitgliederzahlen

Die Mitgliederzahlen stagnieren, liegen aber seit 2010 konstant über 2.000. Dennoch gibt es, wie vor allem die Teilnehmerstatistiken der Göttinger Tagung zeigen, noch ein großes Potential für neue Mitglieder.



Entwicklung der Mitgliederzahlen von 1995 bis 2020

Christine Rose berichtet, dass der Vorstand sich Werbestrategien für die Mitgliedergewinnung überlegen wird. Eckhard Friauf bemerkt, dass er den Eindruck hat, dass in den ungeraden Jahren immer mehr Neueintritte zu verzeichnen sind. Dies kann auch daran liegen, dass neben der Registrierung für die Göttinger Tagung auch die Anmeldung für das FENS Forum in die geraden Jahre fällt. Eine Möglichkeit, Mitglieder auch längerfristiger zu binden, wurde schon auf der Tagungswebsite 2021 umgesetzt, nämlich eine Mitgliedschaft für zwei Jahre zur Gebühr für ein Jahr anzubieten, wenn jemand während der Tagung beitritt. Eine weitere Idee wurde diskutiert, nämlich die Möglichkeit zur Teilnahme an der Göttinger Tagung von einer Mitgliedschaft in der NWG abhängig zu machen, so wie es bei der Society for Neuroscience der Fall ist. Davon wurde aber Abstand genommen, weil das der internationalen Ausrichtung der Tagung entgegensteht und zudem unnötigen Druck auf die Teilnehmer ausübt. Vielmehr wurde vorgeschlagen, den Unterschied zwischen dem Tagungsbeitrag für Mitglieder und Nichtmitglieder deutlich zu erhöhen, um damit eine Mitgliedschaft attraktiv zu machen. Außerdem sollte auf nationaler Ebene stärker geworben werden, indem Vorstandsmitglieder persönlich gezielt bekannte Wissenschaftler an ihrem Arbeitsort, die noch nicht Mitglieder sind, anschreiben.

Die Verteilung der Mitglieder auf die Sektionen ist fast unverändert.

4.2 FENS

Die NWG hat die Teilnahme am virtuellen FENS Forum mit 13 Stipendien in Höhe der Teilnehmergebühr unterstützt. Stefan Treue wird die NWG beim CARE (Committee for Animals in Research) Meeting im April 2021 vertreten.

4.3 German Brain Council

Christine Rose vertritt die NWG (und damit auch die Grundlagenwissenschaften) im German Brain Council. Ziel des GBC ist es, die Interessen von Neurowissenschaftlern ins Bewusstsein von Parlamentariern zu rücken. Dafür wird im Moment ein „German Brain Plan“ entwickelt mit dem Ziel, Förderung für Hirn-Gesundheitsforschung zu erhalten. Das Dokument wird dann der NWG als Mitglied des GBC zugänglich sein.

4.4 Leopoldina

Die NWG hatte für das siebte deutsch-israelische Neuroscience Inter Academy Symposium neue Stipendien zur Verfügung gestellt, coronabedingt konnte dieses allerdings nicht stattfinden.

4.5 DFG Fachkollegienwahl

Die NWG war bei der Fachkollegienwahl 2019 in 12 Fachkollegien vorschlagsberechtigt, in 7 dieser Fachkollegien wurden insgesamt 19 NWG-Mitglieder gewählt. Die Fachkollegienwahl 2023 ist in Vorbereitung und die NWG wird wieder vorschlagsberechtigt sein. Dazu fand im Dezember 2020 ein Zoom-Gespräch mit Vertretern der DFG statt.

5 Aktivitäten der Gesellschaft

5.1 Methodenkurse

Das Methodenkursprogramm 2020 mit insgesamt 9 Kursen konnte bis März 2020 wie geplant durchgeführt werden, danach, also nach Coronabeginn, wurden alle Kurse von den Veranstaltern abgesagt. Für 2021 werden 8 Kurse angeboten, von denen allerdings noch keiner stattfand. Eine Aussage, ob weitere Kurse 2021 stattfinden können, kann derzeit nicht getroffen werden.

5.2 Lehrerfortbildung

Das gleiche Bild zeichnet sich für die Lehrerfortbildungsveranstaltungen ab, im Schuljahr 2019/2020 fanden alle Veranstaltungen bis auf die letzte im März 2020 statt, im Schuljahr 2020/2021 fanden bisher drei Veranstaltungen als Zoom Webinar statt, die anderen sind ausgefallen bzw. wurden ins nächste Schuljahr verschoben.

5.3 NWG-Website auf Englisch

Seit September 2020 ist die NWG-Website auch auf Englisch verfügbar.

5.4 dasGehirn.info

Die Förderung der Klaus Tschira-Stiftung für dasGehirn.info läuft im August 2022 aus. Bisher konnte noch kein Hauptsponsor als Nachfolger gefunden werden. Der jährliche Finanzbedarf liegt bei ca. 175.000 Euro. Deshalb steht im Moment die Suche nach innovativen Lösungen für die weitere Finanzierung des Projektes, z. B. durch Internationalisierung der Website (d.h. Übersetzung ins Englische) oder eine Allianz mit der Industrie, im Vordergrund und dies wird sowohl im NWG-Vorstand wie auch im Lenkungsausschuss diskutiert. Albert Ludolph betont, dass diese Situation aber auch als Chance, neue Aspekte auf die Seite zu bringen, gesehen werden kann. Wichtig ist bei allen Überlegungen, dass die Seite unabhängig bleibt. Dafür steht auch der Chefredakteur des Portals, Arvid Leyh, als treibende Kraft der Website besonders ein. Er entwickelt und gestaltet die Seite maßgeblich und ist für deren Fortbestand essentiell. Christine Rose stellt fest, dass es keine grundsätzliche Ablehnung gegenüber Industriepartnerschaften gibt. Frank Kirchhoff erläutert als weitere Möglichkeit zur Finanzierung die Imagefilme von neurowissenschaftlichen Instituten, die für diese eine gute Selbstdarstellung sind und für die Rekrutierung genutzt werden können. Diese Möglichkeit wird auch schon ausgeschöpft, hier gibt es aber noch Potential.

5.5 Neuroforum

Nach fast anderthalb Jahren krankheitsbedingtem, personellem Engpass, der allerdings keine Auswirkungen auf die hohe Qualität und breite Vielfalt der Artikel in Neuroforum hatte, läuft die redaktionelle Arbeit wieder in geregelten Bahnen. Die NWG wird den Vertrag mit dem de Gruyter-Verlag um drei Jahre verlängern. Wie immer sind Vorschläge für Themen und Autoren für weitere Beiträge willkommen.

Albert Ludolph dankt Petra Wahle für ihren hervorragenden Einsatz als Chefredakteurin.

5.6 Junge NWG (jNWG)

Die jNWG hatte sich vor zwei Jahren konstitutiert mit dem Ziel, junge Wissenschaftler auf ihrem Weg in die Zukunft zu unterstützen. Wegen Corona konnten allerdings die Aktivitäten nicht wie geplant oder nur eingeschränkt stattfinden. Sophie Seidenbecher fasst diese kurz zusammen. Das jNWG Symposium ist nun für November 2021 geplant. Die jNWG ist auch wieder an der Auswahl für die Breaking News Preise auf der virutellen Tagung beteiligt. Für Ende März ist ein Virtual Career Pitch geplant, der über Berufsperspektiven für junge Neurowissenschaftler informiert.

5.7 NWG-Preise

Der Schilling-Forschungspreis 2021 wurde an Katrin Franke, Tübingen, für ihre Arbeiten zu funktionalen Charakterisierung von Informationskanälen in der Netzhaut verliehen. Der NWG-Vorstand hat die Ausschreibungskriterien für zukünftige Preise in Bezug auf die Altersbegrenzung

überarbeitet. In Zukunft wird die Bewerbungsfrist auf 5 Jahre nach der Dissertation unter Berücksichtigung individueller Lebensumstände entsprechend den DFG-Richtlinien festgesetzt.

6 Bericht zur Göttinger Tagung

Die Göttinger Tagung 2021 findet aufgrund der Covid-19-Pandemie erstmals als virtuelle Tagung statt. Die Beteiligung ist mit etwas über 1.100 Registrierungen erfreulich hoch und liegt damit nicht dramatisch unter der Zahl der letzten Tagung. Albert Ludolph dankt der Geschäftsstelle für die erfolgreiche Organisation. Der Trend zur jungen Tagung ist weiter ausgeprägt, Studenten und junge Wissenschaftler unter 30 Jahren machen die stärkste Teilnehmergruppe aus. Auch die Beteiligung aus dem Ausland ist mit Anmeldungen aus 32 Ländern erfreulich hoch.

7 Ergebnis der Wahl des neuen NWG-Vorstandes 2021–2023

Der neue Vorstand wurde zum Stichtag 31. Januar 2021 gewählt, die Wahlbeteilung (25,63 %) war etwas geringer als beim letzten Mal, aber im Rahmen. Albert Ludolph heißt die neuen Vorstandsmitglieder willkommen und gratuliert Christine Rose zu ihrer Wahl zur Präsidentin der Gesellschaft.
Christine Rose dankt Albert Ludolph für sein Engagement für die NWG während der letzten beiden Jahre und begrüßt es, dass er als Ehrenpräsident noch weitere zwei Jahre die NWG mit seiner Erfahrung und seinem Wissen unterstützen wird. Sie dankt auch den anderen scheidenden Vorstandsmitgliedern und begrüßt die neuen. Frank Kirchhoff dankt Albert Ludolph ebenfalls und sieht es als positive Entwicklung, dass auch in Zukunft ein klinisch arbeitender Neurologe im Vorstand vertreten sein wird.

8 Verschiedenes

Es werden keine weiteren Diskusssionspunkte gewünscht.

Ende der Sitzung: 16:45 Uhr

Prof. Dr. Albert Ludolph
(Präsident)
Protokollführer
Prof. Dr. Christian Steinhäuser
(Generalsekretär)

NEU auf dasGehirn.info

Im ersten Quartal 2021 standen erneut die Themenschwerpunkte *Im Kopf der anderen* und das Thema **Schmerz** im Mittelpunkt. Bei letzterem handelt es sich um eine Themenpartnerschaft mit dem SFB 1158. Beide Themenkomplexe werden auf der Webseite mit etwa zehn Artikeln und mehreren Multimediabeiträgen, mit Videointerviews und Infografiken erschlossen.

In der Rubrik **Krankheiten** wurden die Themen *Alzheimer* und *Schlaganfall* um die folgenden Videobeiträge ergänzt, die eine Zusammenarbeit von Urania Berlin und Charité Universitätsmedizin Berlin sind und vom Einstein-Zentrum für Neurowissenschaften, dem Exzellenzcluster NeuroCure, dem Max-Delbrück-Centrum für Molekulare Medizin in der Helmholtz-Gemeinschaft (MDC), dem Sonderforschungsbereich 1315 (SFB1315), dem Centrum für Schlaganfallforschung Berlin (CSB) und dem Bernstein Zentrum für Computational Neuroscience Berlin (BCCN Berlin) präsentiert werden:

Gefahr fürs Gehirn – Den Ursachen von Alzheimer auf der Spur
Morbus Alzheimer ist vermutlich die bekannteste Form der Demenz. Wie sie entsteht, wie sie erforscht wird und was man sonst noch wissen muss, beschreiben Prof. Dr. Thomas Willnow und Dr. Anna Löwa vom Max-Delbrück-Centrum für Molekulare Medizin (MDC) in einer Live-Veranstaltung – inklusive Hörerfragen.

#BerlinBrains2021: Geschichten aus der Neurointensivmedizin
Erkrankungen des Nervensystems können nicht nur schwere Behinderungen verursachen, sondern auch lebensbedrohlich sein. Die Intensivmedizin zielt darauf ab, lebensbedrohliche Zustände zu überwinden. Die Frage nach einer langfristigen Prognose der Lebensqualität ist für Betroffene mit großen Ängsten verbunden. Wir geben einen Einblick in die Arbeitsweise, in moderne Verfahren zur Therapie und Prognostik sowie in neuartige Forschungsansätze, die Menschen den Weg zurück in ein lebenswertes Dasein ermöglichen können. Denn auch, wenn man vom Schlimmsten ausgehen muss, ist noch nicht alle Hoffnung verloren.

In dem Format **Frage an das Gehirn** beantworten Experten regelmäßig Fragen unserer Leser. Die folgenden Fragen wurden jüngst beantwortet:

Beeinflussen die Corona-Maßnahmen das Gehirn?
Ich habe seit einiger Zeit vermehrt Konzentrationsstörungen, mein Kurzzeitgedächtnis leidet. Kann dies mit Covid-19 bzw. den Maßnahmen zusammenhängen?

Wie wirkt die Menopause auf das Gehirn?
Stimmungsschwankungen, Konzentrationsstörungen, Vergesslichkeit: Was machen die Wechseljahre im Gehirn? Und kann hier die Hormonersatztherapie auch helfen?

Wie hängen Lesegeschwindigkeit und IQ zusammen?
Der Weltrekord im Schnelllesen liegt derzeit bei 4251 Wörtern pro Minute. Stimmt es, dass jeder normal intelligente Mensch das durch Üben erreichen kann?

In der Rubrik **Neues aus der Wissenschaft** macht dasGehirn.info im März 2021 auf die folgenden Pressemeldungen aus den Instituten aufmerksam:

Astrozyten im Fokus der Epilepsieforschung | Heinrich-Heine Universität Düsseldorf (02.03.2021)

Lernen und Gedächtnis mit Willenskraft verbessern | Ruhr-Universität Bochum (02.03.2021)

Auch bei Astrozyten gibt es nicht nur Schwarz und Weiß | Heinrich-Heine Universität Düsseldorf (05.03.2021)

Dem Gehirn beim Lernen zusehen | Georg-August Universität Göttingen (08.03.2021)

Loslösung aus der Matrix: Befreite Nervenzellen verarbeiten mehr Information | Leibniz-Institut für Neurobiologie (11.03.2021)

Wie das Gehirn sich selbst reguliert | Max-Planck-Institut für Biologische Kybernetik (15.03.2021)

Das Hirnareal, mit dem wir die Welt interpretieren | Max-Planck-Institut für Kognitions- und Neurowissenschaften (26.03.2021)

Dem Boten auf der Spur | Max-Planck-Institut für Hirnforschung (27.03.2021)

DasGehirn.info gibt neurowissenschaftlichen Lehr- und Forschungseinrichtungen Gelegenheit, sich und ihre Arbeit in einem Videoportrait vorzustellen:
Institut für Neurobiologie, Mathematisch-Naturwissenschaftliche Fakultät an der Heinrich-Heine Universität Düsseldorf

Möchten Sie eine Pressemeldung an dasGehirn.info weitergeben oder Ihr Institut vorstellen, wenden Sie sich bitte an Arvid Leyh (a.leyh@dasgehirn.info).

Neueintritte

Folgende Kolleginnen und Kollegen dürfen wir als Mitglieder der Neurowissenschaftlichen Gesellschaft begrüßen:

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Emad Amini (Würzburg)
Anna Antoniou, Dr. (Bonn)
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Der Mitgliedsstand zum 01. April 2021 beträgt 2.115 Mitglieder.

Ausblick

Ilia A. Solov'yov
Navigation of migratory songbirds: a quantum magnetic compass sensor

Karl-Wilhelm Koch
The secret natures of cryptochromes: From Photoreceptors, Clock proteins, and Magnetic sensing

Karin Dedek
The retinal circuitry for magnetoreception in migratory birds

Dominik Heyers
The neuronal correlates of the avian magnetic senses

Miriam Liedvogel
Endless skies and open seas - how birds and fish navigate

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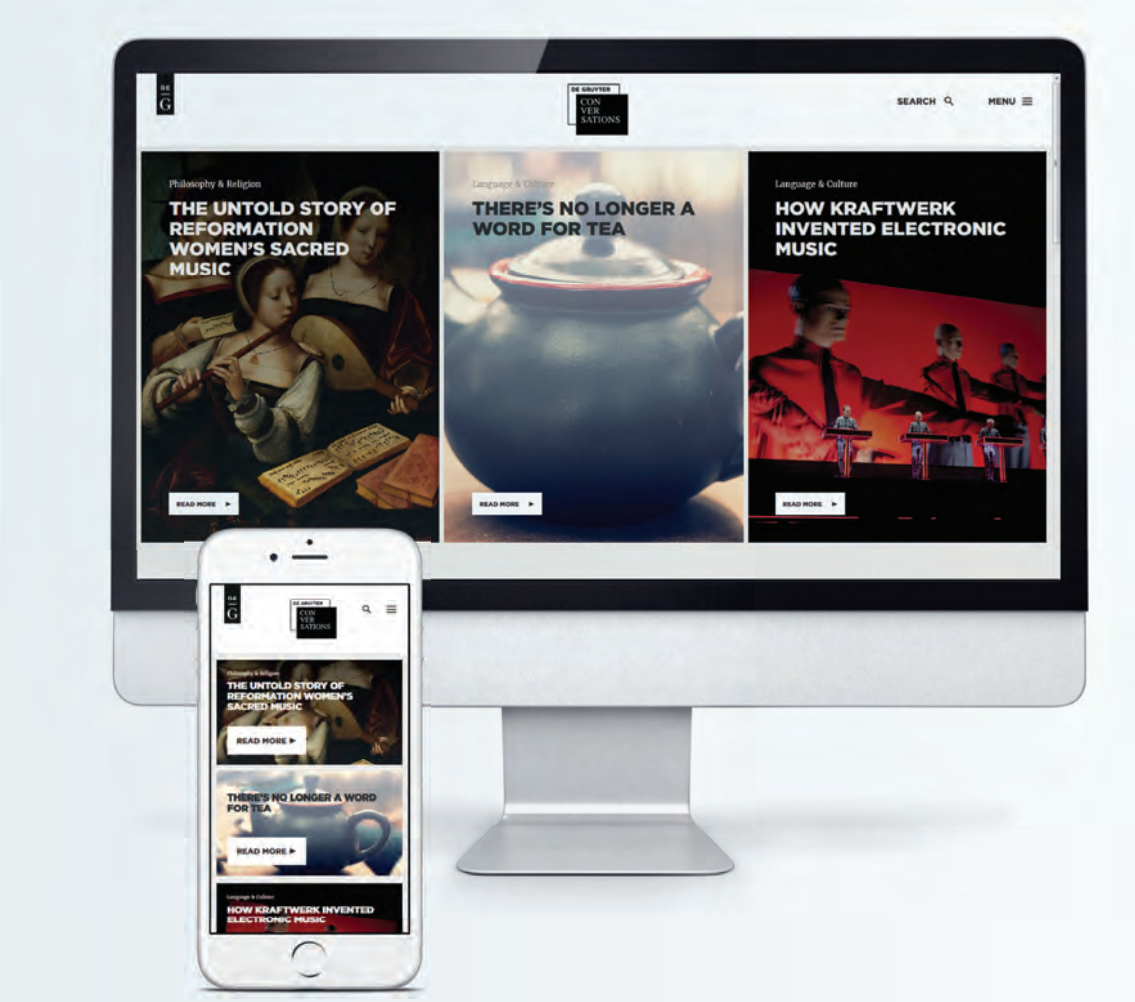

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Hiermit erkläre ich meinen Beitritt zur Neurowissenschaftlichen Gesellschaft e.V. (NWG).

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Bitte senden Sie Ihren Antrag an die Geschäftsstelle der NWG:

Stefanie Korthals
Neurowissenschaftliche Gesellschaft e.V.
MDC
Robert-Rössle-Str. 10
13092 Berlin
Email: korthals@mdc-berlin.de
Tel.: +49 30 9406 3127

Ich optiere für folgende 2 Sektionen:

- ☐ Computational Neuroscience
- ☐ Entwicklungsneurobiologie/Neurogenetik
- ☐ junge NWG (jNWG)
- ☐ Klinische Neurowisschenschaften
- ☐ Kognitive Neurowissenschaften
- ☐ Molekulare Neurobiologie
- ☐ Neuropharmakologie und -toxikologie
- ☐ Systemneurobiologie
- ☐ Verhaltensneurowissenschaften
- ☐ Zelluläre Neurobiologie

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