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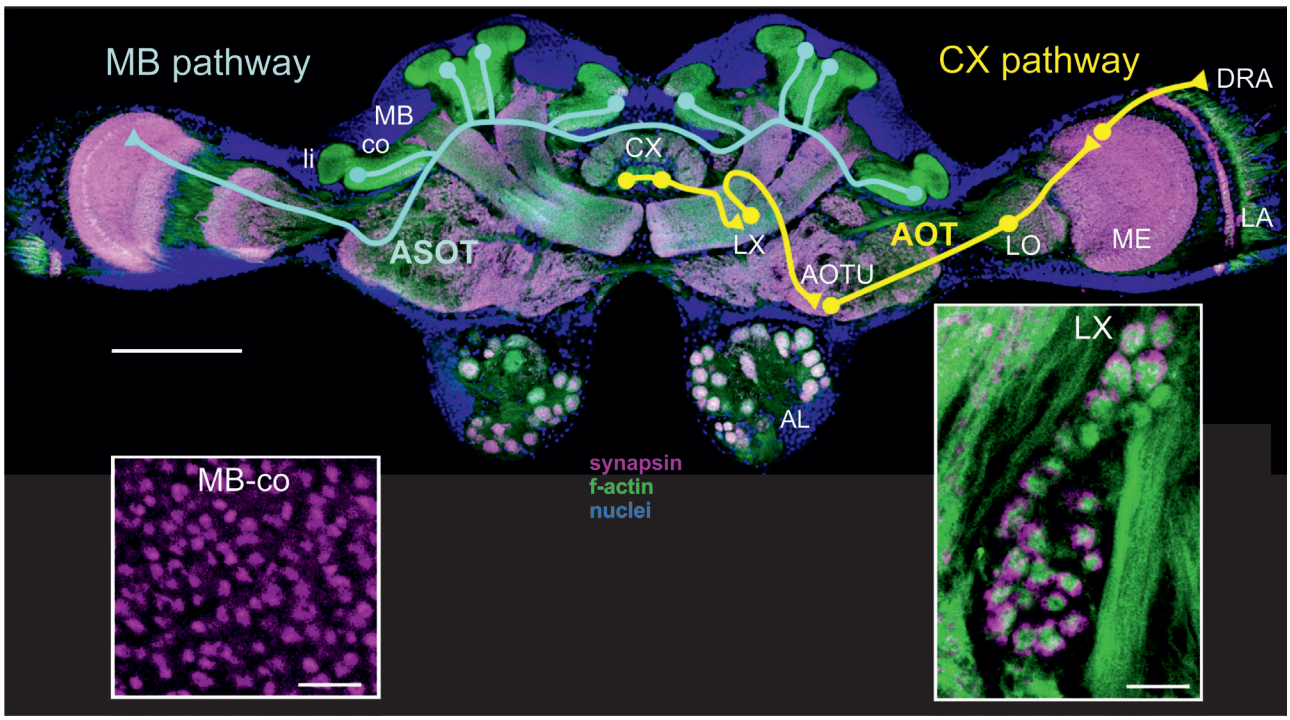

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Review Article

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Autoantibodies Against NMDA Receptors – Janus-Faced Molecules?

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Abstract: Just like the two-faced Roman god of the beginning and the end, Janus, autoantibodies against N-methyl-D-aspartate receptors (NMDAR) have dualistic effects on the human brain. In recent years, autoantibodies against the GluN1 subunit of NMDAR gained attention by physicians world-wide as a diagnostic criterion for the so-called anti-NMDAR encephalitis. Seemingly contradictory was the subsequent identification of GluN1 autoantibodies (GluN1-AB) in healthy subjects. By now, many studies analysed the abundance of GluN1-AB, their immunoglobulin classes, epitopes, and mode of action. Interestingly, GluN1-AB exert their effects by cross-linking NMDAR, which triggers their internalisation. In this review we will discuss how the resulting decrease of surface NMDAR has the potential to protect neurons from neurotoxic events during states of hyperexcitation while at the same time inducing psychosis-like symptoms upon access to the brain. Additionally, we will discuss the pathogenicity of GluN1-AB in the context of brain inflammation.

Abbreviations: AB, antibodies; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor(s); BBB, blood-brain barrier; CNS, central nervous system; CSF, cerebrospinal fluid; iGluR, ionotropic glutamate receptor(s); NMDAR, N-methyl-D-aspartate receptor(s)

Keywords: N-Methyl-D-aspartate receptor, anti-NMDAR encephalitis, NMDAR autoantibodies, GluN1 autoantibodies, ketamine-like syndrome

Zusammenfassung: Wie schon der römische Gott des Anfangs und des Endes, Janus, könnten auch Antikörper (AB) gegen N-Methyl-D-aspartatrezeptoren (NMDAR) zwei Gesichter besitzen und duale Effekte vermitteln, wenn sie Zugang zum zentralen Nervensystem erhalten. In den letzten Jahren rückten Autoantikörper gegen die obligatorische NMDAR-Untereinheit GluN1 zunehmend in den Fokus von Ärzten, da GuN1-Antikörper (GluN1-AB) in der Cerebrospinalflüssigkeit als diagnostisches Kriterium für die sogenannte anti-NMDAR-Enzephalitis genutzt werden. Jedoch sind GluN1-AB auch im Blutserum vieler gesunder Menschen vorhanden. Mittlerweile haben zahlreiche Studien die Häufigkeit, die Epitope und den molekularen Wirkmechanismus von GluN1-AB verschiedener Ursprünge und Immunglobulinklassen analysiert. Interessanterweise vermitteln GluN1-AB die Quervernetzung und Internalisierung von NMDAR. In diesem Übersichtsartikel werden wir vorstellen, wie GluN1-AB Neurone potentiell vor den neurotoxischen Prozessen einer Übererregung der exzitatorischen Neurotransmission schützen, jedoch ebenfalls psychose-ähnliche Zustände auslösen können. Zusätzlich werden wir die Pathogenität von GluN1-AB mit Bezug auf entzündliche Prozesse genauer betrachten.

Introduction

Recently, analyses of blood sera derived from more than 5000 people (>2000 healthy, >3000 patients with different neuropsychiatric diseases) showed that autoantibodies against the obligatory subunit of NMDAR (NMDAR1-AB = GluN1-AB) occur frequently in healthy as well as in neuropsychiatrically afflicted persons (Ehrenreich, 2018). To date, neither the seroprevalence nor the immunoglobulin class or epitope of naturally occurring GluN1-AB were found to be specific to any one of a set of neuropsychiatric diseases investigated, including schizophrenia, affective disorders, diabetes, Parkinson's disease, or stroke

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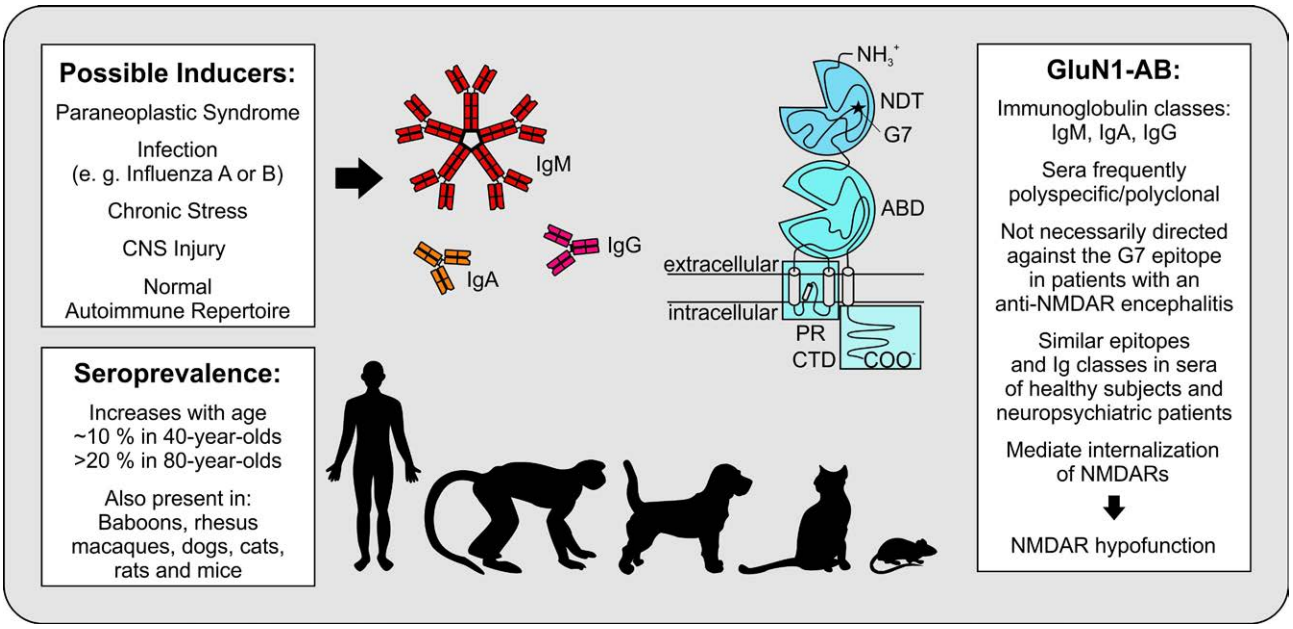

Fig. 1: Overview on naturally occurring GluN1-AB. Listed possible inducers include known correlations between GluN1-AB seropositivity and ovarian teratoma (Dalmau et al., 2011), or influenza A/B infections (Ehrenreich, 2018), as well as inducers that have been hypothesized based on experimental observations (chronic life-stress (Pan et al., 2018) and CNS Injury (Arevalo-Martin et al., 2018)). Functional GluN1-AB were frequently identified in sera of other mammals, suggesting that they may belong to the normal autoimmune repertoire of mammals (Pan et al., 2018). The indicated age-dependent seroprevalence is based on multiple studies with altogether more than 5000 human individuals (Zerche et al., 2015). These naturally occurring GluN1-AB include AB of the IgM, IgA and IgG classes recognizing epitopes that are distributed across different GluN1 domains, namely the extracellular N-terminal domain (NTD), agonist-binding domain (ABD), the transmembrane domain (PR, extended pore region), and the intracellular C-terminal domain (CTD) (Castillo-Gómez et al., 2017). Although some GluN1-AB of anti-NMDAR encephalitis patients share a common epitope (G7) (Gleichman et al., 2012), later findings suggest that GluN1-AB directed against this epitope are not necessary for the disease (Castillo-Gómez et al., 2017). Irrespective of the epitope, immunoglobulin class or origin, GluN1-AB mediate the internalisation of NMDAR (Hughes et al., 2010; Castillo-Gómez et al., 2017; Jones et al., 2018; Pan et al., 2018) resulting in NMDAR hypofunction (Hughes et al., 2010; Castillo-Gómez et al., 2017; Jones et al., 2018).

(Dahm et al., 2014; Ehrenreich, 2018). By contrast, many studies link GluN1-AB to an encephalitis that was named anti-NMDAR encephalitis due to the presence of these AB in the blood and cerebrospinal fluid (CSF) of patients (Dalmau et al., 2011). Additionally, GluN1-AB can be experimentally induced in animal models by immunization (During et al., 2000; Jones et al., 2018; Pan et al., 2018). Whereas all of these AB might differ in their origin, epitopes, titres, and immunoglobulin classes, they share a common feature, namely, the AB-mediated internalization of NMDAR from the cell surface (Hughes et al., 2010; Castillo-Gómez et al., 2017; Jones et al., 2018; Pan et al., 2018).

GluN1-AB mode of action

Generally, binding of AB to a host antigen can trigger a variety of events depending on the function and localisation of the target antigen, the epitope(s), the immunoglobulin class, the presence of cellular and/or molecular components of the immune system, or the AB concentration/titre. As the name indicates, GluN1-AB bind to the GluN1 subunit of NMDAR. In the mammalian central nervous system (CNS), functional NMDAR assemble as alternating (1–2–1–2 or 1–2–1–3) heterotetramers, with GluN1 as an obligatory component (Paoletti et al., 2013). Therefore, GluN1-AB have the potential to recognize all NMDAR unless the epitope is conformationally hidden or blocked by another subunit of the tetrameric complex. Topologically, NMDAR are composed of an extracellular N-terminal domain, an extracellular ligand-binding domain, a transmembrane domain, and an intracellular C-terminal domain (Traynelis et al., 2010). Hence, most parts of the receptor are exposed on the cell surface and can be easily recognized by AB.

Hypothetically, GluN1-AB could (a) activate the receptor by mimicking the binding of an agonist, (b) allosterically modulate the receptor kinetics, resulting in either enhanced or decreased ionic currents, or (c) inhibit the

receptor by blocking the agonist-binding site or occluding the ion pore. In addition to these effects that are measurable at the level of single receptor biophysical properties, GluN1-AB could also modulate NMDAR function at the bulk receptor expression level by (d) altering the trafficking of NMDAR to and from the cell surface, including NMDAR cross-linking and internalization events, or (e) recruiting molecular and/or cellular components of the immune system (e. g. complement proteins or brain-resident microglia). While a-c are limited to AB with distinct epitopes like the agonist binding site, d and e are less impacted by the binding site and are more affected by AB titres and immunoglobulin class. Although some studies suggest that the epitopes of GluN1-AB in anti-NMDAR encephalitis patients are limited to a distinct epitope (G7) in the N-terminal domain (Gleichman et al., 2012), not every patient carries GluN1-AB against this epitope, and epitopes of naturally occurring GluN1-AB are distributed across the entire GluN1 subunit (Castillo-Gómez et al., 2017).

Processes a-c do not appear to be involved in GluN1-AB-induced NMDAR hypofunction. This hypothesis is supported by electrophysiological experiments with GluN1-AB derived from sera of immunized mice. Whereas the slow, NMDAR-dependent component of glutamate-evoked currents in cells expressing NMDAR decrease after preincubation with GluN1-AB on a time scale of minutes that is long enough to allow endocytosis (Hughes et al., 2010; Castillo-Gómez et al., 2017; Jones et al., 2018), this effect is not present if GluN1-AB are co-applied with an NMDAR agonist acutely on a time scale of seconds (Jones et al., 2018). This strongly indicates that the GluN1-AB-induced NMDAR hypofunction is not mediated by direct blockade, activation, or allosteric modulation of the receptor (processes a-c, mentioned earlier), but by the bulk receptor level as determined through NMDAR cross-linking and internalization processes.

Excursion 1: NMDA Receptors and Excitotoxicity

NMDAR are cation channels activated by the excitatory neurotransmitter glutamate. They are expressed by neurons and glial cells throughout the central as well as peripheral nervous system and participate, together with other members of the ionotropic glutamate receptor (iGluR) family, in neurotransmission at glutamatergic synapses. At glutamatergic synapses, an incoming electrical signal (action potentials) is converted by the presynaptic terminus into a chemical signal (release of glutamate into

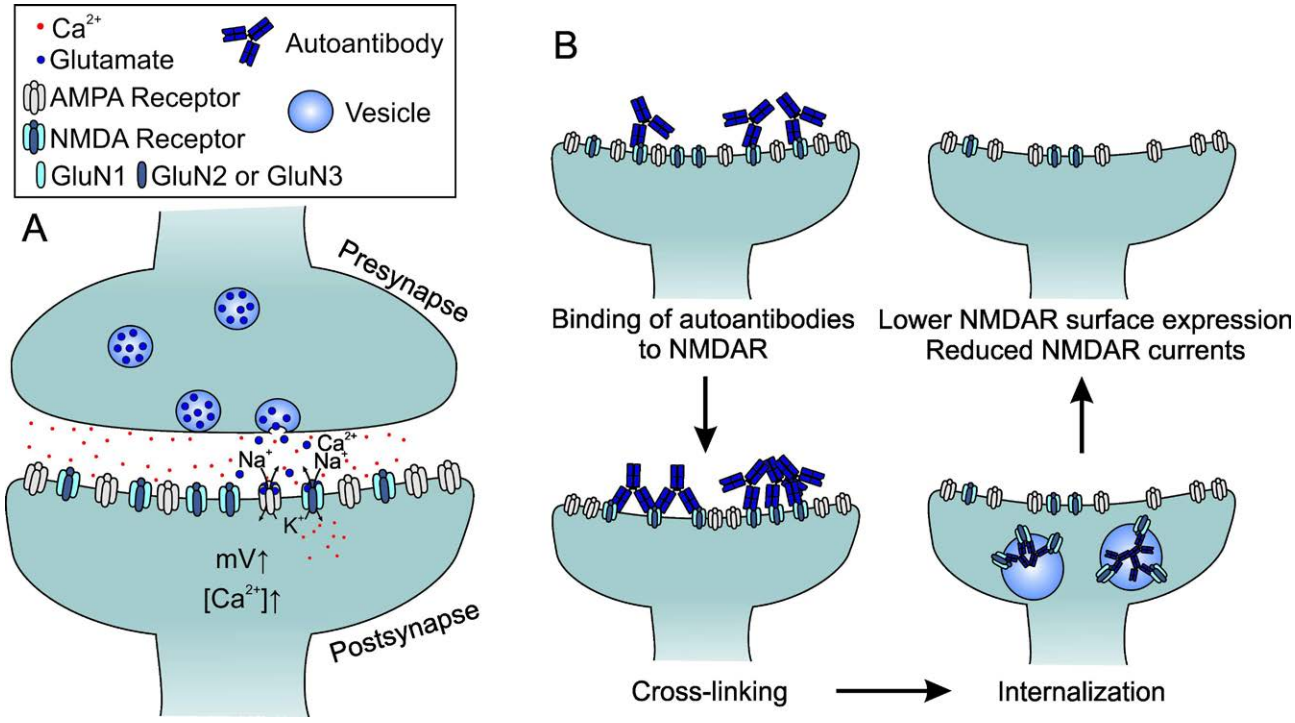

Fig. 2: Effect of GluN1-AB. A) Simplified overview of neurotransmission at a glutamatergic synapse (for further details, see Excursion 1). B) Schematic representation of the AB-mediated internalization. Binding of AB to the GluN1 subunit cross-links several NMDAR into a cluster that is removed from the cell surface by endocytosis (Hughes et al., 2010; Castillo-Gómez et al., 2017; Pan et al., 2018). This results in decreased NMDAR density in the postsynaptic membrane and hence a reduction of the slow, NMDAR-dependent component of glutamate-evoked postsynaptic currents (Hughes et al., 2010; Castillo-Gómez et al., 2017; Jones et al., 2018). The mechanism by which the receptors are cross-linked still needs elucidation. Since each NMDAR consists of two GluN1 subunits, bivalent or multivalent GluN1-AB have the potential to cross-link NMDAR on their own. However, cross-linking of the AB by accessory proteins might also contribute to GluN1-AB-mediated clustering.

the synaptic cleft), which is re-converted into an electrical signal by glutamate receptors within the postsynaptic membrane (Figure 2). In the case of iGluR, this re-conversion occurs by the opening of an ion pore within the receptor upon binding of extracellular glutamate. The iGluR channels are selective for Na^+, K^+ and in some cases Ca^{2+}. Hence, opening of these receptors results in depolarization of the postsynaptic membrane potential. If this depolarization reaches a certain threshold, voltage-gated sodium channels open and generate action potentials, which transduce the electrical signal along the postsynaptic neuron. Dependent on which iGluR is present within the postsynaptic membrane, the generated excitatory current comprises a fast component, typically mediated by AMPA receptors, and a slightly delayed but more sustained current mediated by NMDAR. This slow component is characterized by a high Ca^{2+} conductivity. Hence, NMDAR activation causes an increase in the intracellular Ca^{2+} concentration. This increase triggers additional downstream signalling cascades involved in physiological processes that are important for brain plasticity, such as long-term synaptic modulation. Therefore, it is not surprising that regulatory mechanisms exist which can alter receptor expression levels, ion channel properties and receptor kinetics as well as the trafficking and anchoring of iGluR to the postsynaptic membrane in response to specific activity patterns. By these mechanisms, which fine-tune the postsynaptic response to a certain presynaptic stimulus, synaptic neurotransmission gains another layer of complexity that theoretically contributes to higher cognitive function. Malfunction of these processes are thought to be associated with a variety of neurological diseases (Traynelis et al., 2010; Paoletti et al., 2013).

In addition to these mechanisms, the release and reuptake of glutamate is also tightly regulated. In the mammalian CNS, glutamate is the major excitatory neurotransmitter and activates iGluR in the low µM range (Traynelis et al., 2010). To facilitate efficient neurotransmission, a low basal glutamate concentration is established in the brain by the blood-brain barrier (BBB, Excursion 2), which pre-

vents passive diffusion of glutamate from blood plasma, in combination with secondary active transport mechanisms that regulate uptake of glutamate into cells (Abbott et al., 2010). In the context of neurotransmission, excitatory amino acid transporters on astrocytes are of major importance for clearance of glutamate from the synaptic cleft (Murphy-Royal et al., 2017).

Under certain neurological conditions like an ischemic stroke or an epileptic seizure, these processes become dysregulated. The resulting high concentrations of extracellular glutamate have severe side effects and can trigger or intensify epileptic seizures, as well as neuronal cell death through glutamate receptor-mediated hyperexcitation. To describe the neurotoxic effect of this excitatory neurotransmitter, the term excitotoxicity was introduced in the 1960s. Although the neurotoxic effect of glutamate has been recognized for almost 50 years, the mechanisms mediating neurotoxicity and the contribution of excitotoxicity to the tissue damage observed in many types of neurological dysfunction remain controversial. However, it is well established that influx of Ca^{2+} ions through iGluR and downstream Ca^{2+} signalling pathways play a key role in excitotoxicity. In particular, NMDAR are thought to contribute to excitotoxicity as they have the highest permeability for Ca^{2+} ions among iGluR. Additionally, Ca^{2+} binding proteins within the protein complex that is attached to the CTD of NMDAR, might contribute to their role in excitotoxicity (Szydlowska and Tymianski, 2010).

The Neuroprotective Face of GluN1 Autoantibodies

To date, many clinical studies that used NMDAR antagonists to inhibit excitotoxic processes (Excursion 1) during ischemic stroke failed due to adverse side effects and a relatively short therapeutic window. To circumvent problems associated with classical antagonists, During et al. vaccinated rodents against the GluN1 subunit and analysed the impact of GluN1-AB on experimentally-induced ischemic strokes and epileptic seizures. Their hypothesis was that GluN1-AB would circulate in the blood of immunized individuals and not cause harm under normal circumstances. Only if the BBB is disrupted (Excursion 2), for instance by an ischemic insult or a kainate-induced epileptic seizure, would GluN1-AB enter the CNS and impair NMDAR function. This was particularly intriguing, as they had already hypothesized the antagonizing effect of GluN1-AB in 2000, years before the first studies on GluN1-AB function or anti-NMDAR encephalitis were published.

Although During et al. did not directly test functionality of the AB, they found an anti-epileptic and neuroprotective effect of the vaccination against GluN1. This is well in line with the subsequently identified GluN1-AB mode of action, namely, to trigger AB-mediated internalization and a decrease of surface NMDAR. Hence, GluN1-AB can potentially counteract some neurotoxic processes by downregulation of hyperexcitation and Ca^{2+} signalling. In 2015, a clinical study investigated the impact of GluN1-AB on the evolution of stroke-associated tissue damage in humans. The study included 464 patients that had an acute ischemic insult in the middle cerebral artery territory. The investigators monitored evolution of the lesion size from day 1 to day 7 post-stroke by diffusion tensor imaging as a readout for tissue damage and compared four groups: carriers/non-carriers of naturally occurring GluN1-AB and APOE4 (associated with chronic BBB dysfunction). Most importantly, they found that patients with a hitherto normal BBB (APOE4 negative) who were carriers of GluN1-AB had the least expanding lesions (Zerche et al., 2015). This further strengthened the idea of a neuroprotective effect of GluN1-AB during states of hyperexcitation.

Excursion 2: The blood-brain barrier (BBB)

For many years, the brain was recognized as an immune-privileged site, because classical immune cells like macrophages, B cells, T cells, or NK cells are scarce in the healthy CNS. The reason for this is the BBB, a network of tightly connected endothelial cells, pericytes, and astrocytes. Interactions between endothelial transmembrane proteins, so called tight junctions, seal the network and prevent paracellular diffusion of most hydrophilic molecules, ions and macromolecules, including AB. Therefore, the BBB acts as physical barrier for neurotoxins or damaging substances from the periphery. The influx of essential solutes and metabolites is regulated by transport mechanisms that can be fine-tuned and adjusted to optimally respond to CNS needs (Abbott et al., 2010).

Some of the mechanisms enabling temporal and/or spatial alterations in BBB integrity are influenced by substances secreted from immune cells of the periphery as well as CNS-resident cells like microglia. Therefore, the inflammatory processes that occur during an encephalitis compromise the BBB, enabling GluN1-AB diffusion into the CNS. The BBB is also transiently breached, e. g. during epileptic seizures and disrupted upon ischemic stroke (Abbott et al., 2010). Apart from the depicted, sometimes transient, entry routes, GluN1-AB when present in the CNS may chronically modulate brain function. If the BBB is overcome by NMDAR-autoreactive B cells, as for instance in the so-called anti-NMDAR encephalitis, intrathecal synthesis may start and specific AB will be directly secreted into the interstitial fluid and abundantly bind to NMDAR. Unbound AB ('spill-over') will be drained into the CSF and be detectable at potentially high levels.

Anti-NMDAR Encephalitis and Novel Autoimmune Models

Contrasting sharply with its potentially neuroprotective face, GluN1-AB might also have a devastating side. In 2007, Dalmau et al. introduced the term anti-NMDAR encephalitis to characterize an encephalitis that is associated with autoantibodies against NMDAR and in particular against the GluN1 subunit. Initially, it was thought that this disease is a paraneoplastic syndrome resulting from ovarian teratomas expressing NMDAR. But later findings demonstrated that the disease is not limited to patients with ovarian tumour and was also diagnosed in men. The typical course of symptoms includes psychosis and memory deficits, progresses towards language disintegration, seizures, or in worse cases, states of unresponsiveness, autonomic instabilities, and death. If treated with anti-inflammatory drugs in combination with a tumour resection (if a tumour is present) patients often recover and the symptoms disappear in an inverse order. These findings suggested an immune-mediated disorder rather than a neurodegenerative disease (Dalmau et al., 2011). This and similarity of the symptoms to those induced by NMDAR antagonists like ketamine, frequently led to the rash interpretation that GluN1-AB cause the encephalitis. An alternative interpretation, namely that GluN1-AB shape the symptomatic phenotype of a differently-induced encephalitis, only recently gained attention, due to the discovery of naturally occurring GluN1-AB in healthy individuals (Ehrenreich, 2018).

Furthermore, the encephalitogenic role of GluN1-AB was challenged by an autoimmune model comprising immunized mice that produce functional GluN1-AB. AB access to the CNS was modelled by cohorts that had chronic BBB dysfunction. Although GluN1-AB caused a behavioural phenotype in mice with chronic BBB dysfunction, consistent with an NMDAR hypofunction, they did not cause inflammation in the CNS (Pan et al., 2018). However, in another autoimmune model, behavioural alterations and immune cell invasion into the CNS were observed irrespective of a chronic BBB dysfunction (Jones et al., 2018). Interestingly, functional GluN1-AB were present in both autoimmune models and mediated NMDAR inter-

nalisation. In the latter model, mice were immunized with close to native NMDAR that were reconstituted into liposomes, instead of an immunization with short peptides derived from the GluN1 subunit. Additionally, the adjuvant and site of application differed, which may further diversify the resulting immune response. The diverse immunization strategies, together with the striking similarity of the AB molecular mode of action, suggests that the difference of these seemingly contradictory autoimmune models is based on the provoked immune response rather than on differences between the GluN1-AB. Nevertheless, a unique influence on brain inflammation of a subset of GluN1-AB that recognize specific conformational or glycosylated epitopes, cannot yet be fully excluded.

Summary

In general, experimental evidence strongly underpins both the pathogenic and neuroprotective potential of all GluN1-AB, as they mediate the internalization of NMDAR, which results in a decrease in the slow, NMDAR-dependent component of glutamate-evoked ionic currents. Therefore GluN1-AB can, on the one hand, counteract excitotoxic processes during states of NMDAR hyperfunction while, on the other hand, induce NMDAR hypofunction and psychosis-like behaviour upon access to the healthy brain. To fully uncover the role of GluN1-AB in brain inflammation, more research is needed, and close attention should be paid to the underlying immune response. Some interesting, yet unanswered questions are:

- Do GluN1-AB modulate symptoms during an underlying brain inflammation?
- How, where, and why do autoreactive B-cells gain access to the brain?
- Do GluN1-AB/B-cells play any role in directing other immune cells, microglia, or complement proteins towards NMDAR-expressing neurons or other brain cell types?
- Is there a subset of GluN1-AB that is encephalitogenic on its own, or do these AB play a syndrome-shaping role in any kind of underlying encephalitis?
- How are NMDAR-expressing non-neuronal cells (e. g. astrocytes and oligodendrocytes) affected by GluN1-AB?

Glossary

Antibody Titre Relative value describing the abundance of AB in serum or CSF: The higher the titre, the more AB are present in a defined volume. Titres are highly dependent on the test assay. Hence, comparisons between different studies are difficult.

Encephalitis Inflammation of the neural tissue in the central nervous system. A hallmark of encephalitides is infiltration of peripheral immune cells into the CNS.

Epitope An epitope is part of an antigen and refers to the site that is recognized by the AB. Typically, even minor changes in this region will hugely impact the binding affinity of the AB to its antigen.

G7 Epitope G7 refers to the seventh N-glycosylation site (N368) on GluN1. The epitope is located within the extracellular N-terminal domain. It has been described by Dalmau and colleagues to be recognized by GluN1-AB in CSF or sera of anti-NMDAR encephalitis patients and claimed to be pathognomonic.

Ischemic Stroke A neurological condition in which the cerebral blood flow is compromised. The accompanying lack of oxygen and glucose triggers a variety of neurotoxic events resulting in cell death and loss of neurons.

Microglia Microglia are brain-resident immunologically competent cells with functions similar to macrophages.

Nomenclature: GluN1, NR1 or NMDAR1?
First reports on NMDAR autoantibodies used the names NR1 or NMDAR1, as they were published before 2009, when a consistent nomenclature for ligand-gated ion channels (incl. NMDAR) was introduced. Later reports on this topic mainly used the old terms NR1 and NMDAR1, while researchers studying the receptor itself adopted the new term GluN1, resulting in nomenclatorial inconsistencies within the scientific literature. Nevertheless, GluN1, NR1, and NMDAR1 all describe the same, obligatory subunit of the NMDAR family and are basically interchangeable. Although NR1 and NMDAR1 are common in the autoantibody literature, we will adopt the IUPHAR recommendation and call the subunit GluN1 and the respective autoantibodies GluN1-AB.

Paraneoplastic syndrome Set of symptoms that is associated with tumours, but not directly caused by the mass effect. In the paraneoplastic syndrome, cell damage is mediated e. g. through humoral responses. If tumour cells express proteins on their surface that are not present in surrounding tissues, these antigens may be recognized as foreign by the immune system, which can trigger generation of autoreactive lymphocytes and autoantibodies like GluN1-AB.

Seroprevalence Indicates how many subjects (typically human) are classified positive for a certain component in their blood serum. In this review, the seroprevalence refers to the percentage of individuals tested positive for GluN1-AB.

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Review Article

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Psychological and neuroscientific advances to understand Internet Use Disorder

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Abstract: Internet Use Disorder (IUD; previously referred to as "Internet addiction") has been considered an emerging public health issue. However, the topic is debated and remains highly controversial. Furthermore, the inclusion of a *Gaming Disorder* diagnosis in ICD-11 by the World Health Organization have rekindled debates on the nature of behavioral addictions. Against this background, the present review aims to provide readers with a summary on the current state of diagnostic approaches, risk factors and neurobiological models of IUD. Moreover, and in this context, the present work will include an outlook on smartphone use disorder (often referred to as "smartphone addiction").

With respect to neurobiological underpinnings of IUD, different approaches including molecular genetics and neuroimaging have been employed. Here we will focus on magnetic resonance imaging (MRI) studies in particular. In doing so, we will outline limitations of the available literature and provide an outlook for future research questions, which aim to integrate IUD with other behavioral and substance-based addictions.

Keywords: Internet addiction, Internet Use Disorder, Smartphone addiction, gaming disorder, magnetic resonance imaging

Zusammenfassung: Internet-Nutzungsstörung (INS; in der jüngeren Vergangenheit zumeist als „Internet-Sucht" benannt) stellt ein viel diskutiertes Thema weltweit dar. Besonders mit der Aufnahme der Diagnose *Gaming Disorder* im ICD-11 der Weltgesundheitsbehörde ist das nächste Level einer oftmals emotional geführten Debatte über die Natur der Verhaltenssüchte erreicht worden. Um den Leser aktuelle Einsichten in den aktuellen Stand der Dinge bezüglich dieses Themenbereiches zu vermitteln, wird in der vorliegenden Übersichtarbeit zunächst zusammengefasst, was über die INS bekannt ist und auch wie sich das Störungsbild entwickelt. Zusätzlich wird versucht, das relativ neue Phänomen der Smartphone-Nutzungsstörung (für viele eher bekannt als „Smartphone-Sucht") in dem großen Themenkomplex der INS zu verorten.

Über diese theoretischen und diagnostischen Aspekte hinausgehend, gibt der vorliegende Artikel eine Übersicht über neurowissenschaftliche Erkenntnisse, die dabei helfen, die INS besser zu charakterisieren. Viele unterschiedliche Methoden der Neurowissenschaften wurden bereits eingesetzt, um die biologischen Grundlagen der INS zu entschlüsseln. Die Magnetresonanztomographie (MRT) stand dabei in der Vergangenheit besonders im Fokus, so dass Befunde aus der MRT-Forschung auch im Fokus dieses Übersichtsartikel stehen werden. Der Artikel endet mit Limitationen der aktuellen empirischen Forschung. Zusätzlich wird ein Ausblick auf die nächsten Schritte in dem lebhaften Forschungsfeld der INS gegeben.

Schlüsselwörter: Internet-Sucht, Internetnutzungsstörung, Smartphone-Sucht, Computerspiel-Sucht, Gaming Disorder, Magnetresonanztomographie

1 Background

The study of "Internet addiction" started scientifically with the landmark publication of Kimberly Young (1996), who described the case of a 43 year old woman being "hooked-up" to the Internet. The case report describes symptoms that strongly overlap with symptom-level criteria for (non-)substance use disorders, which led to significant impairments in daily life. Since then, considerable progress has been achieved, not only regarding the scientific discussion on the nature of "Internet addiction," but also with respect to the increasing digitization

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of societies around the globe. As just one example, fast and low cost broadband Internet connections, as well as mobile Internet access have facilitated nearly instant transfer of huge data packages, thus allowing the streaming of video, massive multi-player online games, as well as voice-to-voice and peer-to-peer video communication. Moreover, the World Wide Web (WWW), arguably the most important Internet application to date, has evolved from a digital platform, where users passively consume content (or write e-mails peer to peer), to an increasingly interactive platform, allowing users to publish and promote their own content (even at the scale of peer to masses). The so-called interactive Web 2.0 paved the way for social media platforms such as Facebook, and in doing so, changed considerably both the world we live in, as well as how we interact with others. The importance and prevalence of social media in our world today, is illustrated, for instance, by 2.3 billion monthly active Facebook users (statista.com, 2019), or the more than one billion WeChat users in 2018 (Montag et al., 2019). These social media platforms not only impact how we communicate with one another, but also how we present ourselves to online platforms, clearly facilitating processes of social comparison that affect an Internet user's self-esteem (Vogel et al., 2014).

Perhaps one of the most important accelerators towards a "digital society' was the introduction of multi-purpose mobile computing devices (smartphones), such as the IPhone in 2007, which rapidly became a huge market success and led to investments of several other companies into development of similar devices. The IPhone may at least be partly responsible for the overwhelming number of 2.71 billion smartphone users around the globe in 2019 (statista.com, 2019). Smartphone users are able to access the Internet and online services from nearly anywhere in the world. This led to major improvements in everyday life, including the possibility to access information from anywhere or to chart a course in an unknown territory. Currently, the global Internet penetration rate is around 56 %; more than half of mankind has access to the Internet (internetworldstats.com, 2019). For a general research timeline at the dawn of the Internet of Things, please see Montag & Diefenbach (2018).

More than twenty years after the initial case report from Young describing "Internet addiction", the very term "Internet addiction" still remains a matter of ongoing debate, both in the public and scientific community alike. In parallel, many researchers prefer the terms *problematic Internet use* or *Internet Use Disorder* (for an overview, see also the edited volume on Internet addiction by Montag & Reuter, 2017a). Further yet, another frequently used term that can be found in the literature is *cyber addiction*. Of note, the term *problematic Internet use* is in itself not optimal, because it can describe either a person in transition from normal Internet usage to potentially pathological use (with specific symptom criteria for a diagnosis still to be defined in this area) or describe the spectrum end. Although this development partly adheres to recent dimensional conceptualization of psychiatric disorder, a unified definition of a symptom-criteria based cut-off for *Internet Use Disorder* (IUD) would improve transparency in the literature on addictive Internet use. Although no consensus on symptoms underlying IUD exists, prominent contributions in the field argue that *preoccupation with the Internet* and *withdrawal symptoms when not being online* might be considered as core symptoms of IUD (Tao et al., 2010). Along with negative repercussions in private and professional areas of a person's life that result from one's own online usage, these symptoms would also mirror core symptoms that have been defined for substance use disorders and other behavioral addictions, e. g. pathological gambling (for details on diagnostic issues see also next section). The term *Internet Use Disorder* has been proposed by Brand et al. (2016) in their I-PACE model, to better understand the aetiogenesis of IUD. Use of the IUD nomenclature (instead of "Internet addiction"), can clearly be seen as a response to inclusion of the term *Internet Gaming Disorder* in section III of DSM-5 issued by the American Psychiatric Association (APA; more on the I-PACE model in section III). Importantly, the term IUD fits with recent developments that recognize a diagnosis called *Gaming Disorder* in the latest version of ICD-11 issued by the World Health Organization (WHO, 2018). Of note, further diagnostic issues with respect to IUD and the related topic "smartphone addiction" are presented in the supplement. For co-morbidities of IUD please see the works by Peterka-Bonetta et al. (2019) and the meta-analysis by Ho et al. (2014).

2 The Case of Gaming Disorder in ICD-11: a controversy

With the inclusion of *Internet Gaming Disorder (IGD)* as an emerging disorder in section III of DSM-5 in 2013, convergent research categories were for the first time published, defining an initial working model for diagnostic criteria of a specific IUD (Petry & O'Brien, 2013). Nine criteria were proposed in detail (preoccupation, withdrawal, development of tolerance, loss of control over gaming, loss of interest in earlier preferred activities/hobbies, lying about gaming, putting relationships at risk because of gaming,

playing video games to overcome anxiety, and continuing game play with the knowledge that it has negative consequences). According to DSM-5, out of these nine criteria, five need to be met to fulfill the diagnosis of an IGD. To better understand IGD and its potentially detrimental effects on mental health, these symptom criteria stimulated a large body of research, both in terms of psychometrics (Pontes & Griffths, 2015) as well as underlying neurobiology (Yao et al., 2017), Covering both, the current scientific literature as well as clinical treatment demand (e. g. are patients actually searching for treatments, are specific treatment options available?), the WHO decided to include Gaming Disorder in the draft of the ICD-11 (final inclusion decision to be reached in May 2019; WHO, 2018).

On the WHO's website, the new diagnostic category *Gaming Disorder* is described as "being characterized by impaired control over gaming, increasing priority given to gaming over other activities to the extent that gaming takes precedence over other interests and daily activities, and continuation or escalation of gaming despite the occurrence of negative consequences." As for other diagnostic categories, a timeframe for the symptoms and functional impairments (usually >12 months; significant impairments in everyday life) need to additionally be fulfilled for the clinical diagnosis. Please see also the new work by Pontes et al. (in press) providing a first self-report questionnaire assessing Gaming Disorder according to the proposed WHO framework.

After inclusion of Gaming Disorder in ICD-11, the gaming industry (among others) complained about the premature nature of this proposal (e. g. nytimes.com, 2018). Although some in the research field share this view, the *International Gaming Response Consortium* led by King (2018) responded in a commentary, that aside from this discussion, ample evidence exists that excessive gaming leads to problems in afflicted persons and a diagnosis (perhaps to be revised in the near future with respect to the aforementioned criteria), will facilitate prevention activities and treatment options for those affected by excessive gaming. Importantly, it must be emphasized that the full diagnostic symptoms for *Gaming Disorder* are only met by a relatively small number of individuals. Although large-scale studies investigating the new criteria by ICD-11 in the population are still missing, applying the criteria from DSM-5 suggests that "only" 0.3–1 % of the general population may be affected (see 1.16 % in Germany by Rehbein et al., 2015). However, prevalence rates may be considerably increased in certain demographic groups (e. g. adolescents).

3 Models to understand Internet Use Disorders

Several frameworks have been put forward to understand the aetiogenesis of IUD. In order to come up with a complex framework and given the brevity of this review, we will only focus on the earlier mentioned I-PACE model drawing in parts on the work of Davis (2001) and Dong & Potenza (2014). The acronym I-PACE stands for Interaction of Person-Affect-Cognition-Executive Variables, all contributing to the development of Internet Use Disorder. Among the P variables, personality traits such as low conscientiousness, low self-directedness and higher impulsivity, might represent a vulnerability factor for the development of excessive Internet usage. Although self-directedness is not explicitly mentioned, it might be included in a revision of the I-PACE model, because it has been shown with cross-cultural research, that low self-directedness is robustly associated with higher IUD

symptomatology across cultures (Sariyska et al., 2014; for a general introduction into personality see Montag & Panksepp, 2017). The chance of developing an IUD is even greater, if together with a person's vulnerable personality traits, a history of psychiatric disorder can be observed. What then follows (outgoing from the P variables) is a process of habit formation, that is accompanied and reinforced by emotional reactions towards Internet cues and one's own experience when using online applications (A), together with the development of cognitive maladaptive thoughts (C), and low executive functioning (E), resulting in high bottom-up brain activity (high "hot activity" of the brain, or strongly wanting to use the Internet), when a person is confronted with his/her relevant online cue, and finally, low top-down regulation (low "cold activity" of the brain – hence, emotional brakes are not working properly). This will be elaborated upon with regards to our current neuroscientific understanding in the next section. Importantly, the I-PACE model lacks a molecular perspective on IUD. Beyond the dominance of MRI studies in the field of neuroscientific IUD works, it will therefore be important to also factor in the molecular underpinnings of IUD. Here, work by Montag et al. (2016) could supplement the I-PACE model.

4 Neurobiological basis: initial findings on the neurobiological basis of Internet Use Disorder

Different research strategies and methodological approaches have been employed to delineate the neurobiological basis of IUD, including molecular genetic (Montag et al., 2012; Montag & Reuter, 2017b) and endocrinological approaches (Bibbey et al., 2015), as well as brain imaging approaches such as electroencephalography (Lee et al., 2014) or magnetic resonance imaging (MRI). In line with the proposed symptomatic overlap between IUD and (non-)substance use disorders, particularly the loss of regulatory control and habitual use despite negative consequences, accumulating evidence from a growing number of MRI-based neuroimaging studies reported brain structural and functional alterations in IUD that partly resemble alterations observed in (non-)substance use disorders (for a detailed overview see also excellent recent reviews by Yao et al., 2017).

Based on a wealth of evidence from animal models and, more recently human neuroimaging research, substance-related addictions have been reconceptualized during the last decade as a chronically relapsing disorder of the brain. This disorder is characterized by dysregulations in the brain's motivational circuitry that manifest in regional- and addiction stage-specific changes in striato-limbic-frontal brain systems. The transition from initially voluntary use, towards habitual and ultimately addictive use is accompanied by neuroplastic maladaptations in these circuits, which mediate exaggerated salience and compulsive-like habitual responses to the drug itself and drug-associated cues. Concomitant dysregulations in the prefrontal cortex, a region engaged in executive functions, are thought to mediate progressive impairments in top-down regulatory control over behavior (Koob & Volkow, 2016). The striatal system lies at the core of this circuitry and contributes to both the acute reinforcing effects of potentially addictive drugs, as well as the transition from voluntary to escalating and ultimately addictive use (Everitt & Robbins, 2016). The complex contributions of the striatum to different facets of the addictive process are reflected in the complex functional organization of this structure. Overall, ventral regions of the striatum play a key role in reward and reinforcement processing, whereas dorsal parts of the striatum strongly contribute to cognitive functions and habit formation (Haber, 2016). In line with emerging perspectives on psychiatric disorders as network-level disorders, accumulating evidence suggests that the core behavioral symptoms of habitual use and loss of behavioral control in substance use disorders are mediated by network level dysregulations in cortico-striatal circuits (Zimmermann et al., 2017). The striatum exhibits strong bi-directional connections with nearly the entire cortex. In line with the specific behavioral characteristics of the striatal subregions, the ventral part has strong connections with the ventral anterior cingulate and orbitofrontal cortex, both of which are engaged in reward processes, whereas the dorsal part exhibits strong connections with prefrontal regions that are engaged in regulatory control (Haber, 2016; Zhao et al., 2019). Overall, the different functions and circuitries of the striatal subregions may mediate different aspects of the addictive process, and together, promote the transition towards habitual-like drug seeking and loss of behavioral control (Robbins et al, 2012; Zhou et al., 2018).

Accumulating evidence from animal models and human neuroimaging studies, suggests that cortico-striatal circuits play a particularly important role in the transition to addiction via associative learning processes. Studies in substance use disorders have provided compelling evidence, that cues repeatedly paired with the drug acquire

their excessive motivational significance via operant and instrumental learning processes, which are mediated by drug-induced dysregulations in the cortico-striatal circuitry (Koob & Volkow, 2016; Everitt & Robbins, 2016). Studies in patients with substance use disorders consistently reported exaggerated striatal reward-related reactivity towards drug-associated cues (Kühn & Gallinat, 2011), possibly at the expense of natural rewards (Zimmermann et al., 2018) along with concomitantly decreased frontal activity during executive control processes. Together, these changes are considered to promote drug seeking and take over as the main motivational drive, without adequate regulatory control over behavior. With respect to behavioral addictions, similar changes have been observed. For instance, a recent review of Internet Gaming Disorder (IGD) literature by Yao et al. (2017) reported that IGD subjects, relative to healthy reference populations, demonstrated "hyperactivation in the anterior and posterior cingulate cortices, caudate, posterior inferior frontal gyrus (IFG) which were mainly associated with studies measuring reward and cold-executive functions; and, (2) hypoactivation in the anterior IFG in relation to hot-executive function, the posterior insula, somatomotor and somatosensory cortices in relation to reward function." (p. 313). Thus IGD-mediated neural alterations partly resemble alterations previously observed in other addictive disorders. In particular, when confronted with IUD-related cues, mounting evidence suggests that IUD patients, on the one hand, respond with an exaggerated response in striatal reward processing areas of the brain. On the other hand, deficits in regulatory executive functions/implicit learning abilities (e. g. Sariyska et al., 2017) may reflect deficits in regulatory control. Covering the available imaging literature, Brand et al. (2014, p. 1) concluded that "findings on reductions in executive control are consistent with other behavioral addictions, such as pathological gambling. They also emphasize the classification of the phenomenon as an addiction, because there are also several similarities with findings in substance dependency."

In addition to reports focusing on functional changes in brain cortico-striatal areas, several studies have documented structural alterations in these systems when investigating individuals with substance-use disorders. Most have compared indices of gray matter integrity, (particularly gray matter volume and density), between individuals with chronic substance use and healthy reference groups and reported a relative decrease in gray matter in the substance using group (e. g. Daumann et al., 2011). Recent quantitative meta-analyses of the available literature confirmed notable gray matter reductions in cortico-striatal regions and to a lesser extent limbic regions, across substance-using populations, including patients with alcohol use disorder (Xiao et al., 2015), stimulant use disorder (Ersche et al., 2013) and chronic cigarette smokers (Sutherland et al., 2016). In line with observations of substance-related addictions, a growing number of studies reported gray matter deficits in excessive Internet users, with a recent meta-analysis confirming that individuals with IGD demonstrate decreased gray matter in frontal regions engaged in executive functions (Yao et al., 2017).

However, due to the cross-sectional nature of most included studies, differences observed between individuals with substance use disorders, or with IGD, and those of healthy controls may reflect adaptations mediating the addictive process, or alterations associated with an increased risk for escalating use that preceded onset of the disorder. In a previous study, we assessed brain structure in early users of amphetamine-type stimulants and demonstrated that decreased gray matter volume in the dorsal striatum, amygdala and prefrontal region predicts escalation of stimulant use during the subsequent two years (Becker at al., 2015). This finding suggests that some of the previously observed differences in gray matter between substance users and healthy controls, indeed represent markers of an increased vulnerability, rather than addiction-associated adaptations. To determine whether the cross-sectionally observed cortico-striatal gray matter decreases in IGD precedes the onset of excessive Internet use, we recently employed a combined cross-sectional longitudinal design in excessive Internet gamers and in gaming naïve controls (Zhou et al., 2019). To specifically determine gray matter changes related to excessive Internet gaming and to the development of addictive use, *massively multiplayer online role playing game (MMORPG)-naïve participants* were randomized to either six weeks of daily MMORPG gaming or to a control group that remained gaming-naïve. Brain structural data and the level of online video gaming addiction were assessed at study inclusion and after six weeks of training. Confirming the findings from previous cross-sectional studies, we observed that excessive gamers (also investigated in this study) presented lower posterior right orbitofrontal gray matter volume relative to the gaming-naïve group at study inclusion. Analysis of the longitudinal data, revealed that online video gaming addiction levels increased in the gaming-naïve subjects (being now in the gaming intervention group) during the six weeks of gaming, while left orbitofrontal volumes decreased (also in the excessive gamer group). This could suggest that reductions of prefrontal gray matter represent a direct con-

sequence of Internet gaming, rather than predisposing alterations.

Although most previous studies of brain structural alterations related to excessive Internet use focused on IGD (or broader Internet addiction; please see problems in diagnostics described in the supplement), some initial studies have begun to explore structural alterations associated with excessive use of social media. A recent study from our research team examined associations between problematic use of the social media/messenger app WeChat and gray matter in Chinese students (Montag et al., 2018b). We observed that higher levels of addictive WeChat use symptoms were associated with lower gray matter volume in the subgenual anterior cingulate, a region critically engaged in behavioral and emotional regulation. Furthermore, more frequent (but not more addictive) use of the app's payment function was associated with lower gray matter volumes of the nucleus accumbens, a core reward processing node in the ventral striatum. Decreased gray matter volumes of the nucleus accumbens have also been associated with longer and more frequent Facebook use (Montag et al., 2017). Taken together, this suggests that partly overlapping gray matter deficits in frontal regions engaged in executive control and in striatal regions engaged in motivational functions might be observable across the addictive use of different Internet channels. This also emphasizes the need to differentiate changes related to excessive and addictive use. Further studies are needed to assess whether these findings can be transferred to the broader area of smartphone use disorder/addiction. Initial evidence from EEG studies confirm that SUD might also be associated with deficits in executive functions (Chen et al., 2016), and also changes in brain cortical areas due to daily finger training that accompanies use of a touch display (Gindrat et al., 2015).

5 Limitations

In the past, discussions have too often wrongly labeled and stigmatized everyday life activities with terms such as "addiction". Among these are examples such as being addicted to excessive book reading or to viewing television (Finn, 1992; Millner, 2012). This problem appeared partly because of using a confirmatory approach that is too narrow in studying behavioral addictions, such as simply testing symptoms from recognized disorders such as alcoholism or gambling disorder and transferring it to a possibly new "addiction area". Applying process models such as the I-PACE by Brand et al. (2016) represents a step towards counteracting use of narrowed views. On the other side, researchers should generally be aware not to pathologize everyday life (Billieux et al., 2015). One such example is a report stressing terms such as "Tango addiction" (Targhetta et al., 2013), which probably used the term addiction too loosely.

Although the study of behavioral addiction is an important and timely endeavor (Potenza et al., 2018), many obstacles must be overcome to better understand the nature of these excessive human behaviors. This task will not be easy, because problematic behaviors more and more meld together (e. g. loot boxes that are now planted in video games). If a game player buys such a loot box, a surprise such as better armor or new life energy is provided. This example shows how gambling elements mix with gaming elements in video games. Finally, we wish to emphasize, that in the present review we did not address therapeutical interventions. In particular, cognitive behavioral therapy has been shown to be successful in treating patients with IUD (King et al., 2011; Winkler et al, 2013). As such, both the treatment of patients and psychodiagnostics will profit in the future from Psychoinformatics (Montag et al., 2015a; 2016; Montag, 2019, Montag & Elhai, in press). Application of computer science methods in IUD research and treatment will help paint a more refined picture of actual online usage, which may be a highly relevant means to reflect on one's own online behavior (Lin et al., 2015; Montag et al., 2015b).

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Bionotes

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Review Article

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Learning to navigate – how desert ants calibrate their compass systems

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Abstract: Navigating through the environment is a challenging task that animals cope with on a daily basis. Many animal species have impressive capabilities to navigate in complex or even harsh environments. *Cataglyphis* desert ants are a famous example. These ants use a remarkable navigational repertoire to find their way home after far-reaching foraging trips. How do naïve ants calibrate their visual navigational systems? The ants perform stereotyped sequences of learning walks before switching from tasks inside the darkness of their nest, to foraging under bright sunlight. Here, naïve ants align nest-directed views using the earth's magnetic field as a compass reference. Neuronal plasticity was mapped in two visual pathways to higher brain centers during this transition. Both their first exposure to light, and the performance of learning walks lead to distinct changes in synaptic circuits along both visual pathways, reflecting calibration and memory formation in the ants' visual compass systems.

Keywords: central complex; learning and memory; mushroom bodies; magnetosensation; plasticity

Introduction

Finding our way around can be a demanding task. No matter whether we aim to reach the correct gate, a restaurant arrangement, or our favorite nightspot, to efficiently navigate, it is essential to know where we are, and where we want to go. Many animal species must find their way back to their nest, migrate to a specific destination (sometimes thousands of kilometers), or make their ways in a featureless open ocean. The mammalian brain has a neuronal positioning system for these tasks. Place cells in the hippocampus form an internal map of space, and grid cells in the entorhinal cortex are arranged in a hexagonal pattern providing an internal coordinate system. This discovery is a major breakthrough in research on the neuronal mechanisms of spatial orientation and was awarded with the Nobel Prize in physiology or medicine in 2014 to John O'Keefe, May-Britt Moser and Edvard Moser.

How do ants, with their relatively tiny brains, cope with navigational challenges? Thermophilic desert ants of the genus *Cataglyphis* are famous experimental models for insect navigation. Like other social insects, *Cataglyphis* ants perform cooperative brood care in a common nest, and therefore, are central-place foragers that leave their nest for far-ranging foraging excursions, needing later to return to their nest entrance, an inconspicuous hole in the ground. In contrast to many ant species that employ trail-pheromones to exploit profitable food sources, *Cataglyphis* ants are solitary foragers, relying heavily on a mostly visual guided navigation (Wehner, 2008). While foraging for dead insects during the hottest time of day to avoid predators and competition, the soil temperature may reach a life-threatening 70°C. In the North African desert, ant *Cataglyphis fortis* foraging trips may exceed 1,500 m, with maximum distances exceeding 350 m away from their nest origin. This is equivalent to several thousand times the ants' own body lengths (Buehlmann et al., 2014; Huber and Knaden, 2015; Knaden and Graham, 2016; Ronacher, 2008). Therefore, under high selection pressure, *Cataglyphis* ants evolved to become expert navigators. Many years of behavioral analyses have revealed remarkable navigational capabilities of the foraging *Cataglyphis* ants (reviewed in Ronacher, 2008; Wehner, 2009; Wehner and Rössler, 2013; Rössler, 2019). Investigations on the early ontogeny of these navigational systems have only recently begun.

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Navigation in *Cataglyphis* ants

Desert ants use a powerful navigational tool termed *path integration* when returning to their nest using the shortest way possible – a straight line – even in featureless or unfamiliar terrains. By integrating directional compass and distance information, the ants obtain a vector which leads them home. This vector points towards the nest entrance, with exact direction and path length. Path integration is especially handy in extreme desert habitats, e. g. for *C. fortis* inhabiting featureless saltpans in North Africa. *Cataglyphis* ants use a celestial compass as their main source of directional information. Both the sun position and associated skylight polarization pattern function as global compass cues, enabling the ants to keep track of all walked angles during their random foraging runs (Wehner, 2008). For distance estimation, the ants utilize a step integrating mechanism and optic flow perception (Pfeffer and Wittlinger, 2016; Wittlinger et al., 2006). Since path integration mechanisms are prone to cumulative error, desert ants also use panoramic sceneries as local guidance cues for homing, whenever available. These local visual cues, however, differ among nest sites and may change over time. The ants must therefore learn them before embarking on their first foraging trips (Fig. 1).

However, a skylight-based compass presents additional challenges. For example, both the position of the sun and the associated sky-polarization pattern change throughout the day. Therefore, the internal skylight compass must compensate for this movement, especially during extended foraging trips, or upon subsequent visits to a profitable food site. This is especially true around solar noon, when the sun's horizontal position (azimuth) changes most rapidly. This problem is even more complex considering that the sun's daily path (solar ephemeris) depends on the season and geographical position. An animal, therefore, cannot inherently predict the solar ephemeris. Hence, a celestial compass must be calibrated before embarking upon far-ranging foraging journeys (Grob et al., 2017; Wehner and Lanfranconi, 1981; Wehner and Müller, 1993).

In the following, we discuss recent progress in understanding how *Cataglyphis* ants initiate their navigational systems as they switch from performing tasks under darkness of the nest, to becoming a forager navigating over long distances under bright sunshine (Fig. 1) (Rössler, 2019). In *Cataglyphis*, this behavioral transition is rather sudden, making these ants ideal experimental models for the underlying neuronal plasticity. The foraging success of naïve ants (novices) depends critically on a calibrated celestial compass, and knowledge of the nest-related panoramic scenery. We therefore focus on a conspicuous, early learning behavior and the related plasticity in visual neuronal circuits of the ants' brains. To understand how ant novices acquire navigational knowledge, it was essential to study their behavior in the context of their natural and ecologically relevant habitat. These studies were combined with quantitative analyses of structural synaptic plasticity in visual circuits of two higher integration centers in the brain.

The choreography of learning walks

Cataglyphis workers undergo an age-related polyethism. The ants spend their first four weeks underground inside a dark nest to perform nest-related tasks. Their first day of adult life starts as young callows with a still pale cuticle and no particular task yet. The ants then proceed into a more or less motionless state to serve the colony as living food-stores (interior I). Subsequently, they perform brood care, nest building, or waste management during the interior II stage (Schmid-Hempel and Schmid-Hempel, 1984) (Fig. 1). After about 4 weeks, the ants leave the dark nest to become foragers. During their first short trips close to the nest entrance, novices never bring back any food items. Instead, the ants perform stereotyped sequences of learning walks by meandering in small loops around the nest entrance (Fleischmann et al., 2016, 2017; Stieb et al., 2012; Wehner et al., 2004). Subsequent learning walks explore different sectors around the nest entrance. With increasing experience, learning-walks increase in distance leading the ants farther away from the nest entrance until they eventually start foraging (Fleischmann et al., 2016, 2017). The ants perform this remarkable behavior for 2–3 days (Fleischmann et al., 2017; Stieb et al., 2012; Wehner et al., 2004). This correlates highly with the time needed to induce structural neuronal changes in high-order sensory integration centers, following first sensory exposure or formation of stable long-term memories after associative learning (Falibene et al., 2015; Hourcade et al., 2010; Schmitt et al., 2016; Scholl et al., 2015; Stieb et al., 2010, 2012).

High-resolution video analyses revealed important details in the choreography of learning walks (Fig. 2). The ants repeatedly stop their forward movement to perform rotational body turns. We identified two distinct types of turns – voltes and pirouettes. During voltes, the ants leave their forward path to walk in a small 360°-circle before moving on in the former path direction (Fleischmann et al., 2017). Interestingly, dung beetles perform 360°-rotations on top of their dung ball to take snapshots of skylight cues for alignment of their celestial compass system (el Jundi

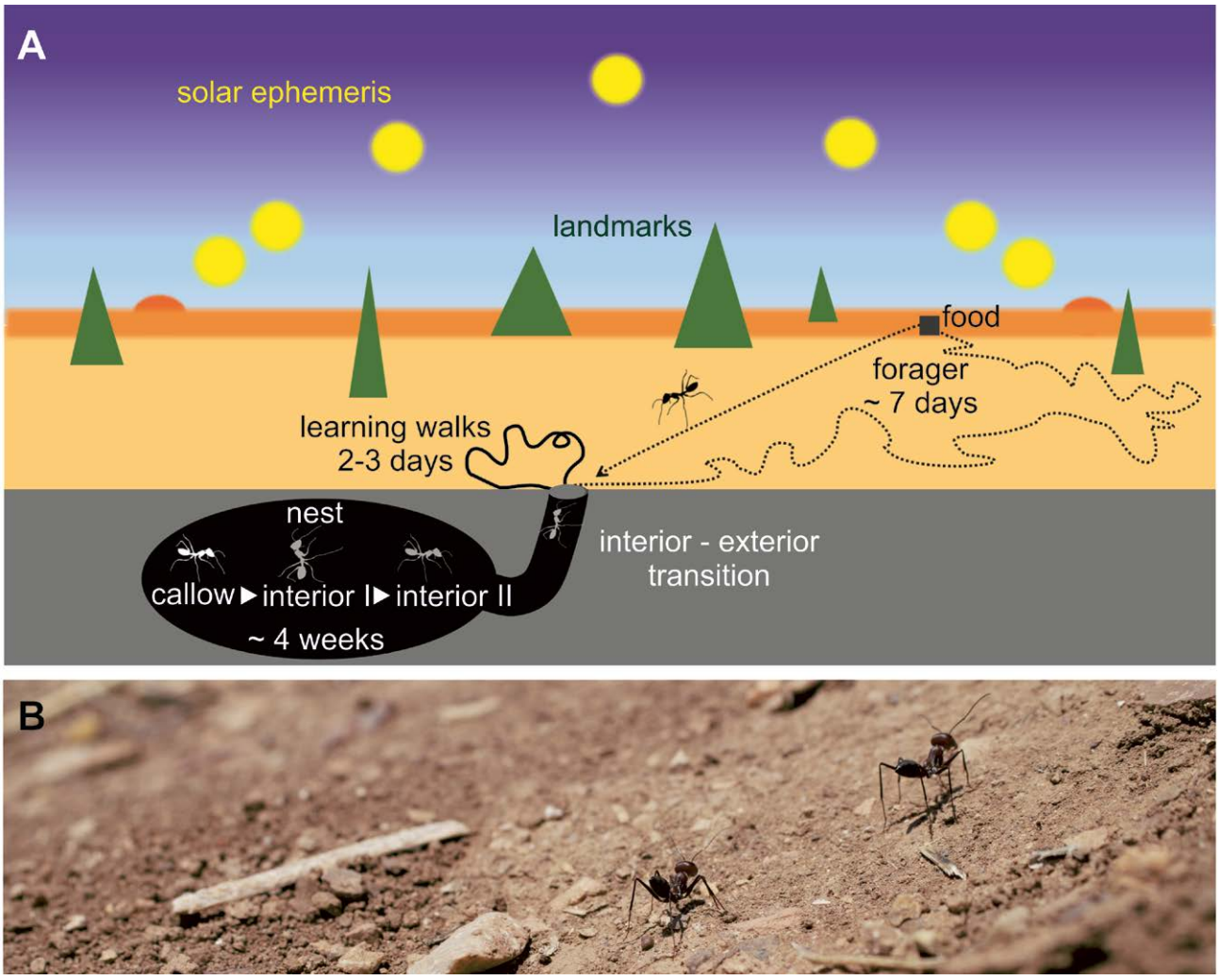

Fig. 1: Individual life history of *Cataglyphis* desert ants. A. The ants spend about 4 weeks under darkness of the nest performing interior tasks as callow, interior I, and interior II. They then move on to perform learning walks close to the nest entrance for 2–3 days. Finally, the ants start foraging, using path integration and guidance by panoramic cues for about 7 days, until they die. The daily course of the sun (solar ephemeris) is depicted as snapshots of different horizontal (azimuthal) positions across the sky, together with visual panorama cues (in green) used for navigation. Further details are in the text. Modified from Rössler (2019). **B.** Two *Cataglyphis nodus* ants set out to forage in their natural habitat in Greece.

et al., 2016). Similarly, desert ants may systematically calibrate their celestial compass system over the day during voltes (Fleischmann et al., 2017). During pirouettes the ants perform tight turns about their own body axes. These pirouettes can be either full (360°) or partial turns (<180°) (Fleischmann et al., 2017; Grob et al., 2017; Wehner et al., 2004). The ants interrupt their rotational movements multiple times making brief stops (>100 ms). Most interestingly, the gaze direction during the longest stops is precisely directed towards the nest entrance. As the ants cannot see their nest entrance from most positions during learning walks, they must use path integration to align their body axes in the direction of the home vector. Comparison of closely related species living in different habitats, revealed that only *Cataglyphis* species living in cluttered habitats with a prominent panoramic scenery perform pirouettes with nest-directed views (*Cataglyphis nodus, Cataglyphis aenescens*: Fleischmann et al., 2017; *Ocymyrmex robustior*: Müller and Wehner, 2010; *Cataglyphis bicolor*: Wehner et al., 2004; for a review see Rössler 2019). *C. fortis* inhabiting featureless salt pans exclusively perform voltes with rare stops that are not nest-directed (Fleischmann et al., 2017). This suggests that the look-back behavior in pirouettes relates to learning the nest-related panoramic scenery. Snapshot memories from different positions around their nest, allow the ants to determine the nest location from within the panoramic scenery (Cartwright and Collett, 1983; Graham et al., 2010; Zeil, 2012). *Cataglyphis* need at

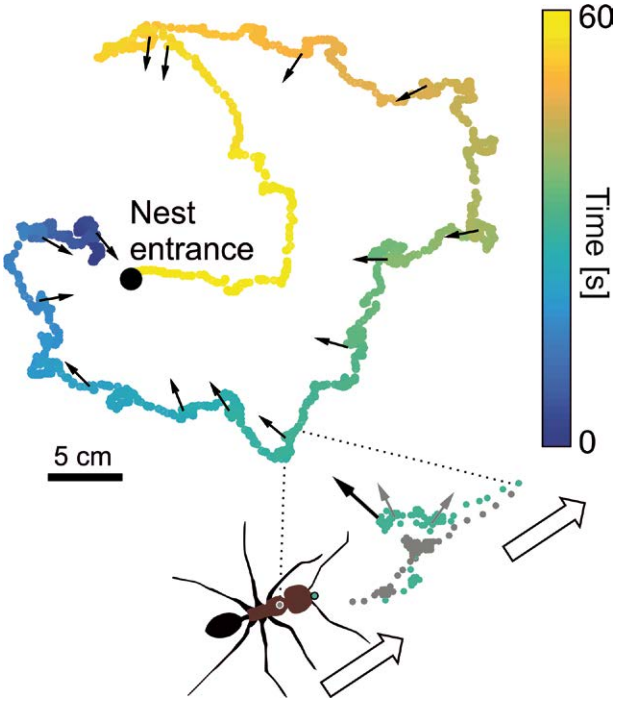

Fig. 2: The choreography of learning walks. During learning walks, desert ants circle around their nest entrance (black dot) in small loops. They repeatedly stop their forward movement to perform pirouettes during which they look back (black arrows) to the nest entrance. Time is color coded. **Inset lower right: Detailed tracking of a pirouette.** During pirouettes, the ants perform a tight turn about their own vertical body axes. The ants stop briefly (> 100 ms) several times while oriented in different directions (arrows). The longest of these stopping phases (black arrow) is precisely directed towards the nest entrance. The tracking positions of the mandibles (green) and the thorax (gray) during a pirouette are indicated. Modified from Fleischmann et al. (2017).

least two days to perform several learning walks in order to use panoramic cues for navigation, as demonstrated in displacement experiments (Fleischmann et al., 2016, 2018b). Furthermore, the ants need enough space during learning walks (at least about 0.5 m distance from the nest entrance), to memorize snapshots from different positions (Fleischmann et al. 2018b). Only after *Cataglyphis* novices had enough time and space to perform learning walks, were they able to use nest-related panoramic cues as a sufficient navigational tool as foragers later on.

The earth's magnetic field is used as initial compass reference

To calibrate their celestial compass and to learn the panoramic scenery surrounding their nest entrance, the ants need an earthbound reference system. Ideally, such a system is both stable over time and accessible during the complete learning walk sequence. Many previous studies have shown that the celestial compass is the main directional information for path integration in foraging ants. Different filter settings to manipulate the skylight above the nest entrance allowed researchers to ask whether naïve ants also use their celestial compass for the alignment of nest-directed views during learning walks. Surprisingly, even with the sun and skylight polarization pattern blocked, novices still performed nest-directed views that clearly did not rely on the celestial compass (Grob et al., 2017).

The question then arose whether these ants might use the earth's magnetic field as a compass cue during learning walks. Results were unambiguous. After disarray of the earth's magnetic field by a flat coil and elimination of the horizontal component of the earth's magnetic field by a Helmholtz coil setup, the ants' views were no longer directed (Fleischmann et al., 2018a). With systematic rotation of the horizontal magnetic field component using Helmholtz coils, the ants gazed towards a fictive nest entrance rotated by the same angle as the magnetic field (Fig. 3; for more details see Fleischmann et al. 2018a). These results clearly demonstrate that the ants use the geomagnetic field as a necessary and sufficient compass cue for path integration during learning walks. This means that compass information is integrated into the path integration system, adding a new compass to *Cataglyphis*' navigational toolkit. The earth's magnetic field not only provides the initial compass system for navigation in novices, it also represents a geostable compass reference, for learning the visual panorama and for calibrating the celestial compass.

Despite increasing behavioral evidence for a role of the geomagnetic field as a cue for orientation or navigation in various animal species, the behaviorally-relevant sensory mechanisms and especially the neuronal processing of geomagnetic information still remains elusive (Lohmann, 2018; Mouritsen 2018; Nordmann et al., 2017). Due to the clear role of the magnetic sense in path integration during learning walks, *Cataglyphis* ants are a highly promising new experimental model for future studies on insect magnetosensation. Here, the geomagnetic compass is the only compass naïve ants rely on during their learning walks, whereas the use of a magnetic sense for directional orientation in other insect species was less apparent or only in combination with other cues (Dreyer et al., 2018; Wajnberg et al., 2010). The short spatial range of learning walks enables high-resolution video analyses of nest-directed views, providing quantifiable behavioral readout

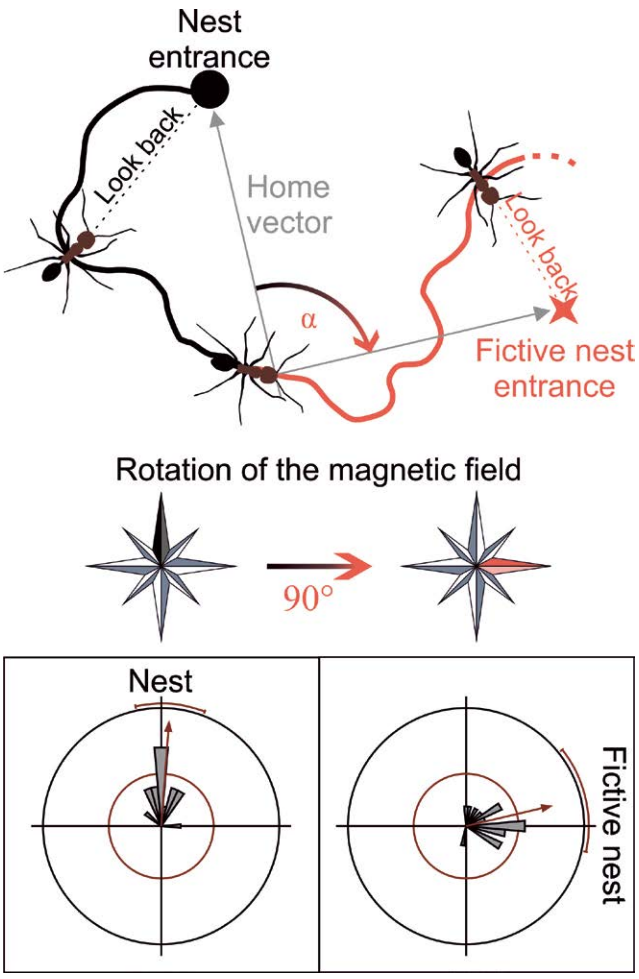

Fig. 3: The earth's magnetic field is a compass cue. Upper: During naïve learning walks *Cataglyphis nodus* relies on the geomagnetic field for directional information during path integration. When a naïve ant leaves its nest to perform a learning walk (black line), it looks back to the nest entrance during pirouettes. However, when the horizontal component of the earth's magnetic field is experimentally rotated using a Helmholtz-coil setup (horizontal rotation angle depicted by the compass), the home vector of the ant is rotated likewise, and the ants look back to a fictive nest entrance during the following pirouette. **Lower:** After rotation of the horizontal component of the magnetic field, mean gaze directions during the longest stopping phases in pirouettes become directed towards a fictive nest entrance rotated by the same angle (90°). Inner circles of the circular plots indicate Rayleigh's critical value (α = 0.05) (further details in Fleischmann et al. 2018a). These results demonstrate that the ants integrate directional information from the earth's magnetic field into their path integration system. Modified from Fleischmann et al. (2018a).

for path integration during navigation. Future experimental manipulations of magnetosensation in freely behaving ants will be combined with studies aiming to understand the sensory mechanisms and neuronal integration of magnetic compass information.

Two visual pathways for navigation

How is visual navigation information processed in the ants' brains? One hypothesis is that the alignment of views during rotational turns serves to acquire visual information, by using the earth's magnetic field as a geostable compass reference. This may serve both the calibration of celestial information and the acquisition of panoramic snapshot memories (Fleischmann et al., 2017, 2018a; Grob et al., 2017). How are global compass cues and local panoramic image information processed in the ant's brain? Earlier behavioral studies had shown that the ants memorize local panoramic information for up to their lifetimes, whereas global skylight compass and path integration information showed a much faster memory decay, which suggests two channels of visual information transfer (Ziegler and Wehner, 1997).

Physiological studies in the locust and bees, together with recent modeling approaches, suggest that the central complex (CX) integrates sky-compass information, whereas mushroom-body (MB) circuits have the capacity for memorizing image information (Ardin et al., 2016; Hoinville and Wehner, 2018; Homberg et al., 2011; Stone et al., 2017; Webb and Wystrach, 2016). The CX and MB visual pathways in *Cataglyphis* were characterized using neuronal tracing combined with immunolabeling of synaptic proteins and ultrastructural investigations, which allowed the characterization of differences in the synaptic architecture of both circuits (Fig. 4) (Grob et al., 2017; Schmitt et al., 2016). The CX pathway starts from a polarization-sensitive upper region of the eye, the dorsal rim area, and proceeds with neuronal projections to the optic ganglia, and via the anterior optic tract, to the anterior optic tubercle, and from there, to the lateral complex and the lower division of the CX. In contrast, the MB pathway is characterized by direct neuronal connection from projection neurons in the medulla via the anterior superior optic tract to the MB calyces.

Interestingly, both visual pathways comprise exceedingly large synaptic complexes at the input to the two integration centers – the CX and the MBs (Schmitt et al., 2016; Stieb et al., 2010) (Fig. 4 insets). The CX pathways in each hemisphere converge on about 100 synaptic complexes in the lateral complex. The large (>5 µm diameter), cup-shaped presynaptic sites contain ~100 active zones with contacts to many profiles of a relatively small number of postsynaptic tangential neurons that relay information to the lower division of the CX central body. These convergent synaptic circuits might guarantee a reliable and precise transmission of binocular sky-compass information (Schmitt et al., 2016). In the MB pathway, projection

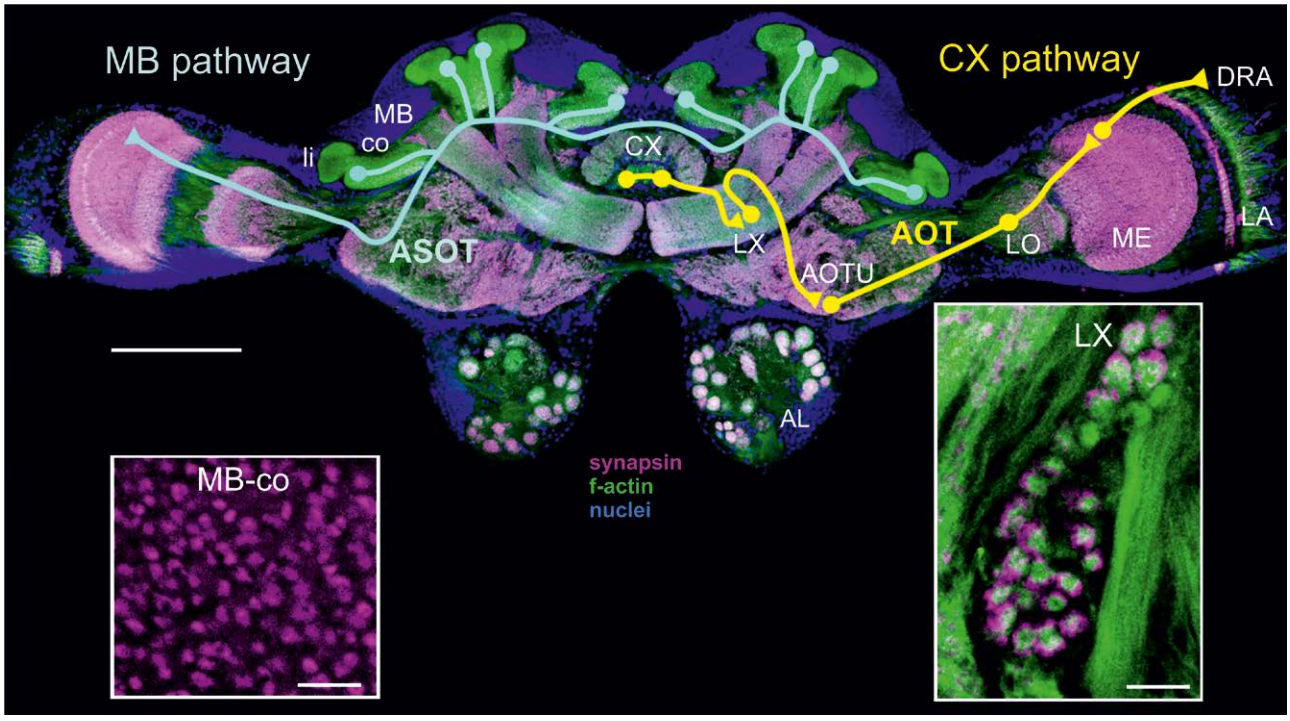

Fig. 4: Two visual pathways for navigation in the *Cataglyphis* brain. The visual pathway to the central complex (CX or sky-compass pathway) is depicted in the right brain hemisphere of a *C. fortis* brain, and the visual pathway to the mushroom bodies (MB pathway) is highlighted in the left hemisphere. The brain is labeled with an antibody to the presynaptic protein synapsin (magenta), staining of f-actin in dendritic and axonal profiles by phalloidin (green), and detection of cell nuclei with Hoechst 3458 (blue). Scale bar = 200 µm. Further abbreviations: AL antennal lobe, AOT anterior optic tract, AOTU anterior optic tubercle, ASOT anterior superior optic tract, co collar, CX central complex, DRA dorsal rim area, LA lamina, li lip, LO lobula, LX lateral complex, ME medulla. The two lower images show high magnifications of large synaptic complexes at the input to the MB calyx collar (MB-co) and the lateral complex (LX). Scale bars = 10µm. The brain image is modified from Stieb et al. (2012). The pathways are combined from results by Schmitt et al. (2016) and Grob et al. (2017). High magnification whole-mount images of synaptic complexes provided by Kornelia Grübel.

neurons from the medulla project directly to the MBs to form many synaptic boutons in visual input regions (collar) of the medial and lateral MB calyces in both brain hemispheres (Fig. 4). Individual boutons contain ~50 active zones with divergent connections to many profiles of dendritic spines from a large number of Kenyon cells, the intrinsic MB neurons (Groh et al., 2012; Stieb et al., 2010). Synaptic boutons in the MB-calyx collar are estimated to number up to 400,000 (Grob et al., 2017).

The different circuit architecture in the CX and MB pathway is suggestive for differences in the type of information processing (Fig. 6). The direct connection of projection neurons from the medulla to a large number of parallel MB synaptic circuits promoting memory formation is suggestive for the potential storage of complex image information (Ardin et al., 2016). By contrast, the CX pathway comprises a high level of pre-processing in the optic neuropils and converges on a relatively small number of synaptic complexes in the lateral complex that relay the information via tangential neurons to the CX. The CX pathway is highly conserved across insect species studied so far, which are as diverse as locusts, bees, ants, butterflies and dung beetles (Heinze, 2014). It was named sky-polarization pathway since light-polarization information is detected by a group of specialized photoreceptors in the dorsal rim area of the eye and mediated to the CX. Physiological studies in locusts, bees, butterflies and dung beetles suggest that skylight-compass information is systematically mapped in both the lower unit of the central body, a major input region of the CX, and the protocerebral bridge, the predominant output region of the CX (Heinze, 2014; Heinze and Homberg, 2007; Homberg et al., 2011) (Fig. 6). Live calcium imaging studies in *Drosophila* show that this results in an internal representation of the insect's heading (Seelig and Jayaraman, 2015). Recent results in bees show that information about speed (processed as optic flow) is transmitted to the noduli of the CX, suggesting that one important function of the CX circuitry (among other functions in spatial orientation), is to compute path-integration information (Stone et al., 2017).

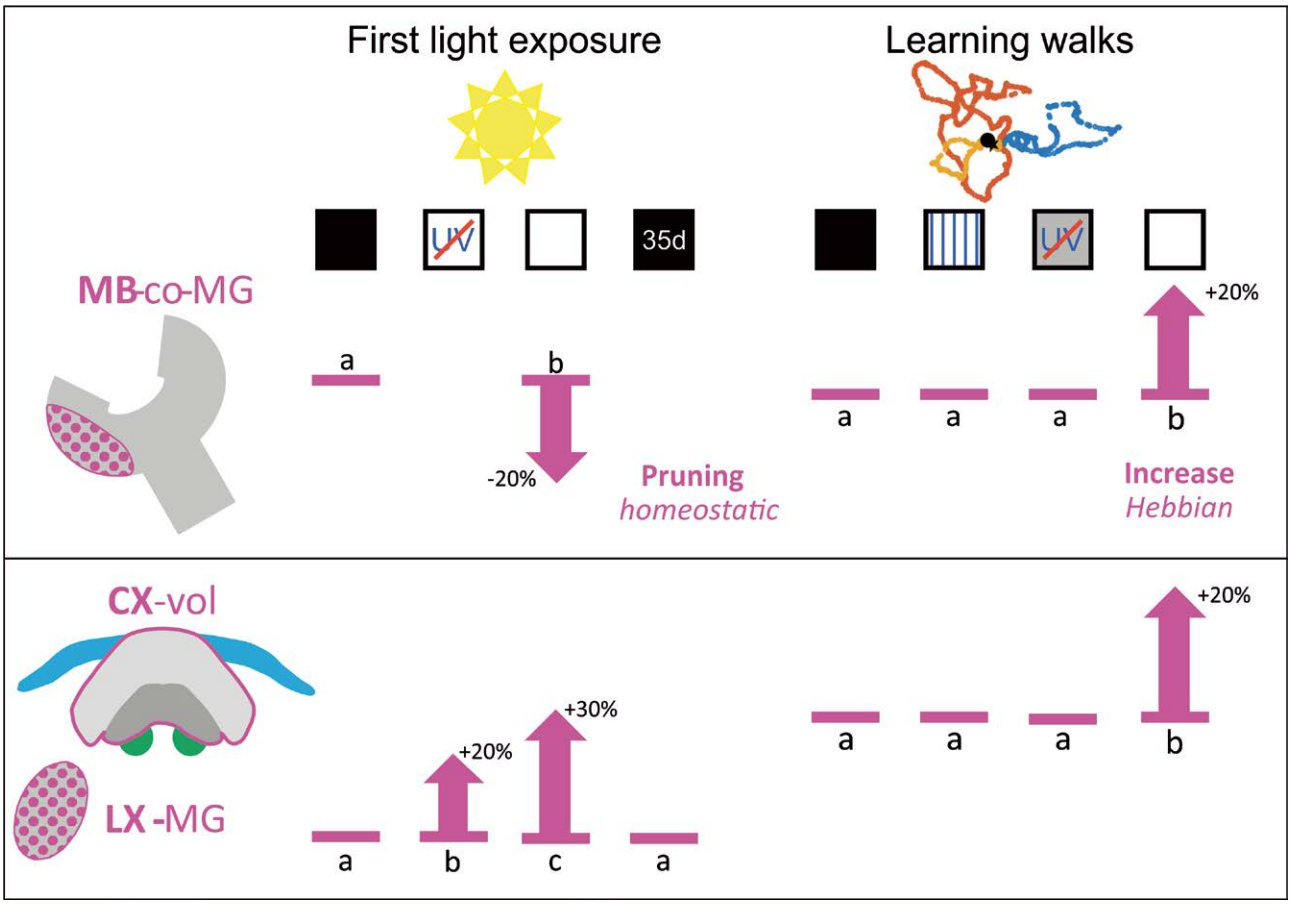

Fig. 5: Neuroplasticity after first light exposure and learning walks. The upper panel summarizes results from quantifications of structural synaptic plasticity in the mushroom body collar (MB-co) after first light exposure and following learning walks.The lower panel shows results on volume changes in the central complex (CX) and numbers of synaptic complexes in the lateral complex (LX). Differences in light conditions are depicted in each case. The percentages represent averages. Statistical significances are indicated by letters (see text for further details on quantitative data). Symbols for first light exposure, from left: same aged without light exposure, UV blocked, full light spectrum, 35 day-old dark reared. Symbols for learning walks, from left: without learning walks (dark), linear polarizer, UV and sun position blocked, full spectrum. Increase or decrease are depicted by arrows including average percentages. Data combined from (Grob et al., 2017; Schmitt et al., 2016; Stieb et al., 2010, 2012).

Microcircuits in the MBs where shown to perform multisensory integration, learning, and associative memory formation (e. g. Menzel, 2014; Owald and Waddell 2015; Gerber et al., 2004). The associative circuits provide a suitable neuronal substrate for storage of multiple visual panoramic snapshots (Ardin et al., 2015). Interestingly, the visual pathway to the MBs is elaborated in insects with enhanced spatial orientation skills and respective visual ecologies as was shown for beetles (Farris and Roberts, 2005), parasitoid and social Hymenoptera (Farris and Schulmeister, 2011), ants (Grob et al., 2017; Groh et al., 2014; Gronenberg, 2001; Yilmaz et al., 2016) and butterflies (Kinoshita et al., 2012). In *Drosophila*, only a small number of visual projections to the MB calyx were found (Vogt et al., 2016).

To recapitulate, analyses of visual neuronal circuits revealed two elaborate pathways in *Cataglyphis* – the CX pathway with the capacity for transferring global sky-compass information, and the MB pathway for transferring and storing local image information. Interestingly, in both visual pathways, the last synaptic relay station (in the lateral complex and mushroom body calyx) is mediated by synaptic complexes comprising large presynaptic boutons that form spheroidal (microglomerular) structures, together with multiple postsynaptic dendritic processes (Fig. 4, insets). The large size of these microglomeruli facilitates quantitative confocal imaging analyses for investigating the role of learning walks in triggering structural synaptic plasticity in both visual circuits.

Learning walks trigger structural synaptic plasticity in the CX and MB pathway

The interior-exterior transition leads to structural synaptic plasticity in both visual pathways. These effects were quantified using 3D reconstruction of confocal microscopy images, volume rendering and semi-automated computer guided quantification (Rössler et al. 2017). The changes can be classified into plasticity after first light exposure and learning related plasticity (Fig. 5).

Plasticity after first light exposure: In the CX pathway, the number of synaptic complexes in the lateral complex significantly increases in foragers compared to interior workers (Schmitt et al., 2016) (Fig. 5). The increase was, on average, 30 % (from an average of 95 to 126 synaptic complexes) following first exposure to light. This effect depended on spectral composition and was reduced to, on average, 20 % (~116) synaptic complexes when the UV part of the spectrum was blocked. UV is important in mediating the sky-polarization pattern in photoreceptors of the dorsal rim area. Conversely, in the MB pathway, first light exposure leads to a significant reduction (on average 20 %) in the density of microglomeruli in the visual MB-calyx collar (for details see Stieb et al., 2010, 2012). In both the CX and MB pathway, the densities of synaptic complexes in age-matched dark reared ants remained unchanged, showing that this plasticity is independent of age and triggered by light. Although plasticity in the CX and MB pathways after first light exposure point in opposite directions, we conclude that they represent homeostatic structural plasticity, adjusting the circuits to drastically changing light conditions. This most likely starts before the onset of learning walks, when the ants briefly exit their nest to perform digging activities during the interior II stage (Fleischmann et al., 2017). The increase in lateral complex synaptic complexes, in contrast to pruning in MB microglomeruli, can be assigned to different functional properties of the input neurons: Whereas the majority of tangential neurons projecting to the CX are GABAergic, projection neurons providing input to the MBs are excitatory (cholinergic) (Schmitt et al., 2016).

Plasticity after learning walks: Skylight manipulations during learning walks revealed that ants expressed a volume increase in the CX (on average 20 %), when novices perceived a naturally changing sky-polarization pattern during three days of learning walks (Fig. 5) (Grob et al., 2017). The volume increase was absent under a linear polarization pattern or blocked UV transmission. This suggests a role of neuronal plasticity in the CX pathway in calibrating the celestial compass system. Our hypothesis is that the geomagnetic compass reference is used for both calibrating path integration input via the sky-compass pathway to the CX, and aligning nest-directed panoramic snapshots transferred to the MBs (Fig.6). It remains unclear, how and whether sky-compass input is linked to the endogenous clock for proper time compensation, which represents another interesting topic for future research.

Visual compartments of the MB calyces showed an increase in density and number (on average 20 %) of microglomeruli after three days of learning walks, but only when novices had perceived a naturally changing sky-polarization pattern (for details see Grob et al., 2017) (Fig. 5). Plasticity was absent when the ants perceived a static polarization pattern or had no UV input. This is very different from the decrease (pruning) of microglomeruli after passive light exposure under natural skylight conditions (Stieb et al., 2010, 2012). Our results from olfactory learning in honeybees and leaf-cutting ants have shown that associative learning and the formation of stable long-term memory, similarly triggered an increase in microglomeruli, but in olfactory subregions of the MB (Falibene et al., 2015; Hourcade et al., 2010). We therefore conclude that the increase of microglomeruli in visual MB after learning walks is suggestive for the formation of visual long-term memory. This suggests that the increase in microglomeruli in visual MB compartments after learning walks, represents learning-related (Hebbian) structural plasticity associated with formation of stable visual long-term memory.

Investigations in other insects, especially *Drosophila*, and modeling work have shown that the CX is also involved in simple landmark learning, spatial memory, landmark orientation and motion control (Fiore et al., 2017; Neuser et al., 2008; Martin et al., 2015; Seelig and Jayaraman, 2015). However results from *Cataglyphis* ants suggest that storage of more complex panoramic scenes requires input to MBs with elaborate numbers of parallel microcircuits that are suitable for visual long-term memory formation. What could be the associative component for nest-directed snapshot memories? The intrinsic association of the nest with nest-directed views (home vector), might alone serve as an internal reward, which was also termed 'genetically encoded anticipatory learning' (Collett and Zeil 2018). Whether and how visual snapshot matches experienced by a homing ant are relayed from the MB output to the CX or to premotor areas, remains another area of future research (Fig. 6). Anatomical data from *Drosophila* suggests potential connections from the MB output via interneurons in the superior protocebrum to the CX, which still needs to be investigated in *Cataglyphis* (Strausfeld and Hirth, 2013) (Fig. 6).

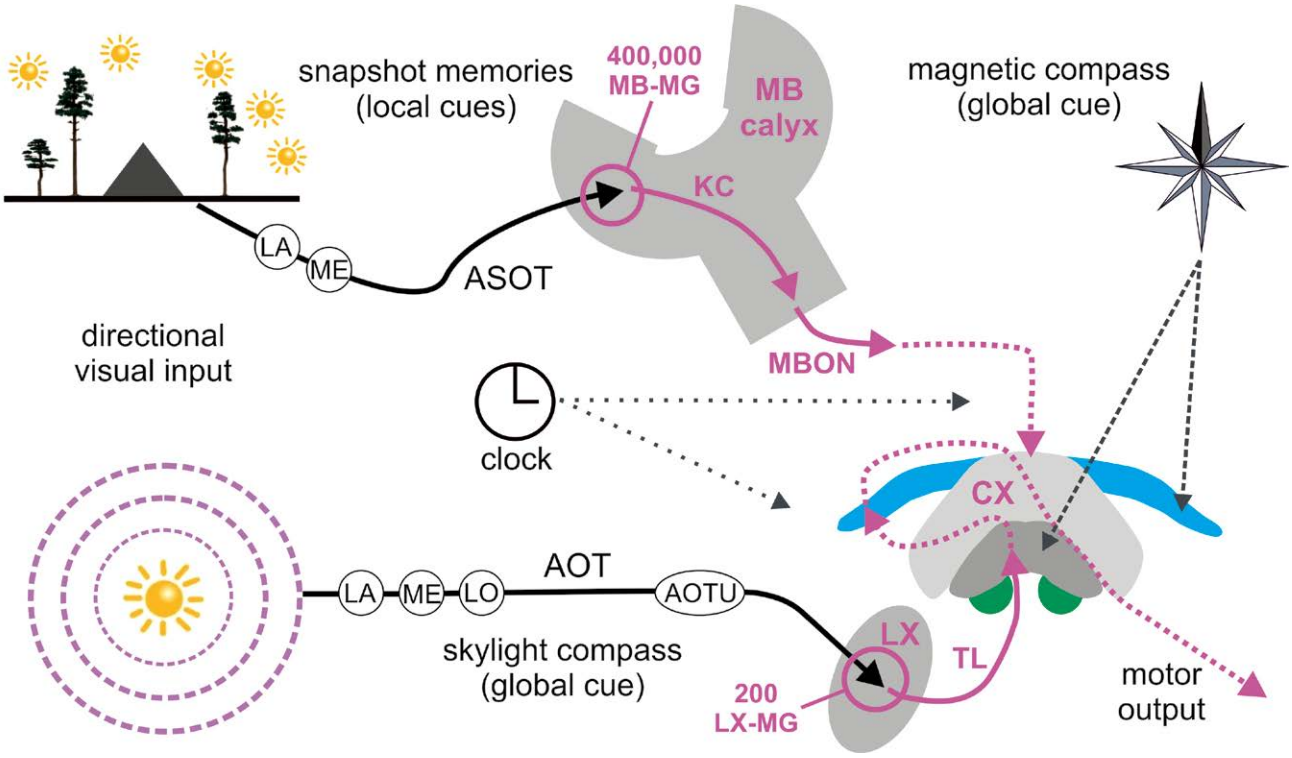

Fig. 6: Model for processing of directional navigational information. The sites of structural synaptic neuroplasticity in visual pathways after first light exposure and following learning walks are labeled in magenta. The left side depicts visual input from the panoramic scenery and skylight-compass cues. Sky-compass information (global cues) is processed via the anterior optic tract (AOT) to the lateral (LX) and central complex (CX), whereas panoramic information (local cues) is processed via the anterior superior optic tract (ASOT) to the mushroom bodies (MB). The input and output connections, together with different numbers of plastic synaptic complexes (microglomeruli, MG) at the input of the MB and LX, are indicated (magenta). The sensory pathways for geomagnetic information, the input of the endogenous clock for time-compensation, a putative connection from the MB output to the CX, and connections to the motor output are still hypothetical and depicted as dashed lines. Further abbreviations: AOTU anterior optic tubercle, KC Kenyon cell, LA lamina, LO lobula, MBON mushroom body output neuron, ME medulla, TL tangential neuron.

Outlook

Learning walks in *Cataglyphis* ants provide an excellent experimental model to study the interaction between behavior, environment, and the brain in the context of navigation. *Cataglyphis* desert ants initiate their visual navigational systems during this early learning phase, by using the geomagnetic field as a geostable compass reference and directional cue for path integration. The learning behavior and the related plasticity in visual pathways opens a wide range of follow-up questions. Where is the magnetosensor located, how does it work, and how is the information integrated with visual information in the path integration circuitry of the CX? Presently, neither the sensor, nor the central pathway for magnetosensation are known. The ants might even use a magnetic compass during underground navigation before leaving the nest. Why do foragers switch from using a magnetic compass during learning walks to using a celestial compass? Experienced foragers, while apparently ignoring the magnetic compass during foraging runs, perform re-learning walks when confronted with new landmarks around their nest, or when they discover new feeding grounds. In both cases, the ants perform rotational body turns resembling those in naïve learning walks. Do foragers switch back to using the geomagnetic field for navigation under these situations? As the multisensory information must be integrated in the ants' brains during learning walks, future studies will investigate how visual and magnetic compass cues converge in the path integration circuits of the CX and become potentially linked with information from the endogenous clock for time compensation. The remarkable neuronal and behavioral plasticity during the interior-exterior transition of *Cataglyphis* ants, is a highly promising experimental model to investigate the behavioral and neuronal mechanisms underlying the ontogeny of an advanced navigational system housed in a comparatively small brain.

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Review Article

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Non Vitae Sed Scholae Discimus? Schooling Fosters Intelligence

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Abstract: Intelligence is important for success in school. But does schooling also impact intelligence? In this review, we present evidence showing that both the amount and the quality of schooling affect intelligence test performance. Besides, differential effects are addressed. The schooling effect is stronger for academic than for non-academic tracks, shows for different types of intelligence and for different age groups, although it might be stronger for younger children. However, obtaining this state of knowledge has been anything but trivial, given that the duration of school attendance is highly confounded with age effects on intelligence, and that different tracks of schooling comprise a selective intake of students. Therefore, this review also presents methodological solutions that have been applied to these problems. Finally, we outline that the schooling effect on intelligence test scores is not an artifact but primarily due to a "real" enhancement of intelligence.

Keywords: Duration of school attendance, effects of schooling, general vs. specific abilities, intellectual development, quality of schooling

Zusammenfassung: Intelligenz ist wichtig für schulischen Erfolg. Fördert Beschulung jedoch auch die Intelligenz? In diesem Übersichtsartikel präsentieren wir Evidenz dafür, dass sowohl die Schulbesuchsdauer als auch die Beschulungsqualität die Leistung in Intelligenztests beeinflussen. Zudem werden differentielle Effekte beleuchtet. Der Beschulungseffekt ist für akademische Ausbildungsgänge ausgeprägter als für nicht-akademische und zeigt sich in verschiedenen Intelligenzfacetten und Altersgruppen, wobei er für jüngere Kinder am stärksten zu sein scheint. Die Beschulungsdauer ist mit Alterseffekten auf die Intelligenz konfundiert, und verschiedene Beschulungszweige bringen das Problem eines selektiven Intakes von Schülern mit sich. Daher stellt der vorliegende Beitrag außerdem Untersuchungs-Designs vor, mit deren Hilfe diese Probleme gelöst werden konnten. Abschließend wird resümiert, dass der Beschulungseffekt kein Artefakt darstellt, sondern die Folge einer „echten" Intelligenzsteigerung ist.

Schlüsselwörter: Schulbesuchsdauer, Effekte der Beschulung, allgemeine vs. spezifische Fähigkeiten, intellektuelle Entwicklung, Qualität der Beschulung

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Introduction

While writing his famous line in one of the *epistulae morales*, Seneca lamented to his friend Lucilius about the lack of practical focus provided by the Roman schools of philosophy. Over the last 25 years, schools, especially in Germany, have faced similar accusations that they do not sufficiently orient on practical issues. One criticism, for example, was that they do not prepare students sufficiently for the world of employment, and that students accumulate inert knowledge in school, which they cannot use in their daily lives. But does schooling really produce only dull knowledge?

At their core, schools are tasked with teaching students certain academic and social skillsets, and supporting each student's personaldevelopment, all of which are prescribed within curricula and intentionally addressed during instruction. However, although not explicitly intended, schooling might go far beyond this. Children and adolescents undergo considerable growth in their intelligence, that is, in their "ability to understand complex ideas, to adapt effectively to the environment, to learn from experience, to engage in various forms of reasoning, to overcome obstacles by taking thought" (Neisser et al., 1996, p. 77). From the beginning, a major focus guiding intelligence research, has been to identify what factors drive a child's intellectual development. Many explanations have been proposed, for example biological maturation,

nutrition, or parental-guided intellectual stimulation (see Rost, 2013, for review). Interestingly, however, intellectual growth becomes especially sharp as children enter school age (e. g., Rindermann, 2011). Therefore, it remains a central question whether intellectual development might also (or even mainly) be due to schooling, especially given that teaching concepts such as "how to understand complex ideas", "how to adapt to the environment", "how to learn from experience", and "how to reason and take thought" are neither direct themes that can be found in school curricula, nor the intended reason behind such instruction.

In this review, we will discuss evidence suggesting that both the amount and the quality of schooling do indeed foster intelligence. Furthermore, we will show that schooling is the main driving factor behind intellectual development in school age children. We will also see that this schooling effect arises not only for school-related cognitive abilities such as general knowledge or verbal abilities, but also for more general and abstract intelligence facets such as reasoning. We will also discuss possible differential effects of schooling according to students' ages and levels of ability. Finally, we will outline that the schooling effect on intelligence is not an artificial improvement of intelligence test performance, but primarily due to "real" intellectual growth.

Duration of School Attendance and Intelligence

For many years, it has been known that there is a considerable association between the duration of school attendance and students' intelligence, ranging from $r \approx .50$ to $r \approx .60$ (Neisser et al., 1996; Rost, 2013). As the experienced empiricist will instantly remark, this association does not, of course, prove the effects of schooling on intelligence. It might well be possible that students who are already more intelligent stay longer in school, or that additional variables, such as parents' socioeconomic status, influence both the duration of school attendance and intellectual development, causing a spurious correlation between them. In his seminal review, however, Stephen J. Ceci discussed some evidence that schooling might indeed influence intellectual development (Ceci, 1991). For example, children's IQs slightly, but reliably, decreased during summer holidays. Similarly, leaving school early was associated with lower intelligence even after controlling for baseline intelligence, socio-economic status, and school performance. Based on these findings, he suggested that every year of school missed might cause a loss of IQ points.

However, rigorous testing of this hypothesis is challenging because duration of school attendance is but one of many other factors impacting intellectual growth. These factors comprise, for example, neuronal maturation and the accumulated amount of intellectual stimulation outside of school. All of these factors are indexed by chronological age and are therefore usually subsumed under the age effect. Unfortunately, the duration of school attendance is also indexed by chronological age: The longer students have attended school, the older they are; the older the students are, in turn, the more developed is their brain, and the more intellectual stimulation they have received outside school, etc. Therefore, the decisive question becomes how one can isolate a possible schooling effect from the age effect. In Excursus 1, we present sophisticated research designs by which this problem could be solved.

Excursus 1: Disentangling the Schooling Effect from the Age Effect

To isolate the schooling effect, some studies have taken advantage of cut-off dates for school enrollment. Within each cohort, there are children whose birthdays are close to the cut-off date. Therefore, some children will be enrolled relatively early (e. g. with 5;10 years), whereas some will be enrolled relatively late (e. g. with 6;10 years). After one year, the first group is at age 6;10, just like the latter group which is enrolling at that time. The first group, however, has already received one year of schooling. Thus, comparing their intelligence test scores provides an estimate for the effect of one year of schooling on intellectual development. However, whether a child is enrolled early or late is not independent from his or her cognitive abilities. Smart children will have a higher chance to enroll early. Thus, the first group might be pre-selected based on higher intelligence, whereas the latter group might be pre-selected based on lower intelligence. Consequently, direct comparisons between both groups might lead to an overestimation of the schooling effect. Therefore, findings from the cut-off design can only be interpreted if both groups have displayed equal intelligence test scores at the time point when the children from the first group were enrolled.

To overcome this problem, the regression discontinuity design was applied (RDD; Cahan & Cohen, 1989) (see Figure 1). In the RDD, students from at least two consecutive grades (e. g. grades 1 and 2) are examined. In the first step, a regression analysis within each grade is con-

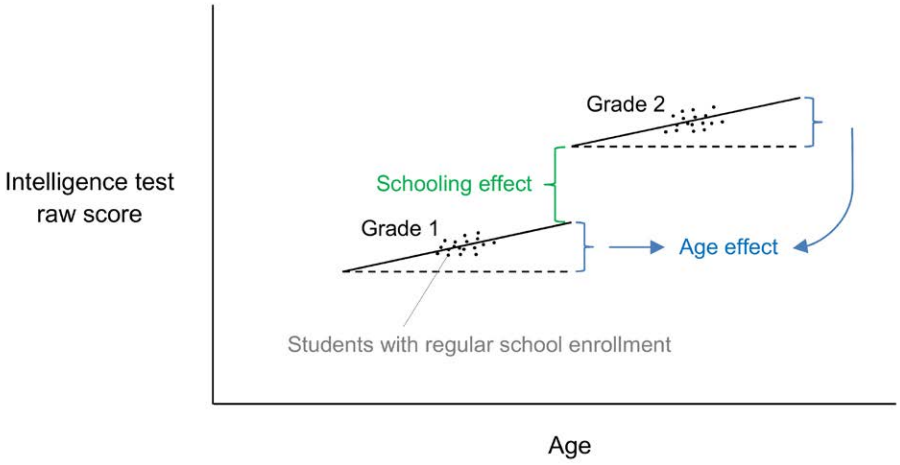

Fig. 1: Rationale of the regression discontinuity design to separate the schooling effect from the age effect on intelligence test scores

ducted. Within grades, the duration of school attendance will be constant, but the students' ages will vary by at least several months up to one year (see above). Therefore, predicting the intelligence test score from age will indicate the age effect on intelligence. Importantly, students who have entered school earlier or later and children whose birthdays fall into a certain range around the cut-off date for school enrollment are excluded from the analyses. In the second step, the intelligence test score of a relatively old student in the lower grade and of a relatively young student in the consecutive grade (having the same age as the old student from the lower grade) are extrapolated (i. e. estimated on the basis of the age effect obtained from the regression analysis based only on the classmates with regular school enrollment). Thus, the chronological ages of both "imaginary" students are the same, but the student from the consecutive grade has received one year more schooling than the student from the lower grade. Therefore, the difference between both students' extrapolated intelligence test scores indicates the schooling effect on intelligence.

Another approach is to examine students of the same cohort with slightly differing ages in intelligence assessments spread across one school year (Cliffordson & Gustafsson, 2008; Rost & Wild, 1995). In this design, some students are the same age, but differ slightly in their duration of school attendance (some are tested early and some are tested late in the school year). Intelligence differences then indicate the schooling effect of the respective time interval. Meanwhile other students differing slightly in their ages are tested at the same time point of the school year. Intelligence differences here would then indicate the effect of the respective age difference. In this way, very fine-grained statements can be made about the effects of, say, one month of schooling or aging on intelligence test performance.

Studies deconvoluting the schooling from the age effect revealed that every year of schooling imparts a considerable effect on intellectual development. Most studies found that one year of schooling causes an increase of about two to four IQ points (e. g., Brinch & Galloway, 2012; Cliffordson & Gustafsson, 2008). However, the magnitude of this effect is variable; prior studies found gains of about six to eight IQ points per year (e. g., Merz et al., 1985; Stelzl et al., 1995). In a review on intellectual growth in childhood and youth, the mean schooling effect was estimated at 5.6 IQ points per year (Rindermann, 2011).

Importantly, this effect is not limited to specific cognitive abilities. One might assume that the schooling effect arises only for school-related cognitive abilities, for example crystallized intelligence (i. e. knowledge and experiences acquired during socialization and, therefore, taught at school). However, studies have found that schooling impacts not only crystallized, but also fluid intelligence (i. e. the ability to reason logically and to solve complex problems without prior knowledge). Most studies find the effect to be roughly comparable across different intellectual abilities (e. g., Cliffordson & Gustafsson, 2008; Merz et al., 1985). For example, in a study with 10-year-olds, gains were 5.9 and 8.6 IQ points (depending on the measure) for verbal abilities and 7.6 IQ points for fluid intelligence (Stelzl et al., 1995). Whereas there are also studies finding larger effects on verbal than on fluid abilities, fluid abilities were still affected to large extent (e. g., Cahan & Cohen, 1989). Thus, the schooling effect is not limited to school-related abilities, but also refers to intellectual abilities not directly related to a curriculum.

Although magnitudes varied somewhat between studies and instruments, the schooling effect was always found to be markedly larger than the age effect. Some studies found the schooling effect to be about twice as large as the age effect (e. g. Cahan & Cohen, 1989). Fur-

thermore, a majority of studies even found the age effect to be close to zero (Cliffordson & Gustafsson, 2008; Rost & Wild, 1995). According to these findings, intellectual growth in school-aged children seems to be mainly or even completely due to schooling. For example, in one study (Merz et al., 1985), the authors compared the estimated effect of one year of schooling with the overall IQ gain in one year, which they obtained from norm tables of the intelligence tests they had administered. For crystallized abilities, the schooling effect made up about 75 % of the overall development. By contrast, for fluid intelligence, 100 % of the overall development was due to schooling. Findings such as these are remarkable, because for a long time it was assumed that fluid intelligence is determined by biological factors and only marginally affected by the environment (Cattell, 1987). However, the schooling effects found on fluid intelligence have falsified this famous hypothesis.

But is the schooling effect the same for all individuals? For example, given the greater plasticity of younger children's brains, one might predict differential effects on IQ depending on students' ages. Indeed, the effect might be larger for younger children than for adolescents, as studies with elementary school children tend to find larger effects than studies with adolescents or young adults. For example, some studies with elementary school children found effects of about six to eight IQ points (Merz et al., 1985; Stelzl et al., 1995), whereas studies focusing on young adults (e. g. 18- or 19-year-olds) found effects of about three to four IQ points (Brinch & Galloway; Cliffordson & Gustafsson, 2008). However, this pattern is not consistent throughout, given that in other studies, the schooling effect was also about four IQ points for elementary children (Rost & Wild, 1995). Ultimately, a general trend remains elusive as long as there is no study comparing children from a range of different grades in the same schools using the same intelligence test. The same is true for other potential moderators, for example students' ability level. Given that the ability gap between individuals with higher intelligence and individuals with lower intelligence becomes larger as individuals develop (Matthew effect; e. g., Rindermann, 2011), one might assume larger schooling effects for smarter students. However, as of yet this has not been investigated. Taken together, it seems likely that there are systematic moderators underlying the variability observed in schooling effect sizes across these relevant investigations. However, to date, relatively little is known about them.

Quality of Schooling and Intelligence

Another focus of intelligence research centers on the impact that the quality of schooling has on intelligence. It might well be that not only the amount of schooling, but also its quality, fosters intellectual development. While this hypothesis has been comparatively less investigated, some results from the above-mentioned studies have already pointed to an effect of schooling quality. For example, it was found that different school tracks (e. g. technology, social science, economics) were differentially related to intelligence (Cliffordson & Gustafsson, 2008). However, this study did not control for possible differences in baseline intelligence across the tracks studied. In another study, baseline intelligence was controlled for, and differential track effects appeared nevertheless: Higher tracks produced larger IQ gains relative to lower tracks (Härnqvist, 1968). A more recent study took advantage of the tracked secondary school system in Germany (Becker et al., 2012). The authors investigated seventh graders from Gymnasiums and three lower-track school types (Sekundarschule, Realschule, Hauptschule) and retested them three years later. To establish comparability between the students from the Gymnasiums and the students from the other school types, they matched the Gymnasium students and the other students on a variety of variables (e. g. baseline intelligence, age, gender, social background, school performance). Subsequently, they inspected intellectual growth progress between both groups until tenth grade. Depending on the matching method employed, intellectual growth of students attending the Gymnasium was 23 to 31 % higher than for students attending the lower tracks. Recently, another investigation (Guill et al., 2017) extended on the Becker et al. study, drawing on a larger, more heterogeneous sample tracked from fifth to ninth grade, and using an additional school type (comprehensive school) for comparison. Although the effect size was somewhat smaller than in the previous study, comparable results were found: Students from Gymnasiums showed greater intellectual growth than students from non-academic tracks. Students from the Gymnasiums also showed somewhat greater growth than students attending the comprehensive school. Howeever, the latter effect was smaller than the first one, which could be expected given that comprehensive schools are at an intermediate academic level between Gymnasiums and non-academic tracks.

Taken together, these studies suggest that not only quantity, but also the quality of schooling impact intelli-

gence. However, it remains an open question on exactly which instructional factors contribute to intellectual development. It might be that curricular content, teacher qualification, and instructional quality (e. g. cognitive activation, individualized support) are decisive factors. Class composition might also play a role, influencing student interactions and instructional quality through the amount of effective teaching time (Guill et al., 2017; Rindermann, 2007). Future studies should direct attention toward identifying specific factors underlying the effect of schooling quality on intelligence.

"Real" Intellectual Growth or Artificial Increase in Test Performance?

As the evidence shows, both quantity and quality of schooling improve intelligence test scores. However, a decisive question is whether this improvement is due to a "real" enhancement of intelligence or whether it is artificial. Some researchers have speculated that schooling fosters specific abilities that simply help the individual complete an intelligence test (Ceci, 1991; Neisser et al., 1996; Van de Vijver & Brouwers, 2009). For instance, schooling might improve students' self-regulation: Schooling might teach students adequate working behavior and working strategies, and students might also become more test-experienced. Higher scores on an intelligence test could therefore be achieved without a "real" enhancement of intelligence. In addition, schooling fosters specific abilities such as reading skills, mathematical skills, or general knowledge (e. g. Bisanz et al., 1995; Cunningham & Carroll, 2011). All of these abilities might be beneficial for successfully completing an intelligence test without a "real" increase in intelligence.

Conversely, there are also studies indicating that schooling impacts more general cognitive abilities that are context-free and not tied to a curriculum, for example conditional reasoning (Artman et al., 2006; Cahan & Artman, 1997; see also Baker et al., 2012). Relatively few studies have examined explicitly which of both hypotheses (artificial versus "real" increase of intelligence test scores) is most consistent with the observed data. Using structural equation modeling with longitudinal data from eleven-year-olds who had been retested at age seventy, Ritchie et al. examined whether development in general intelligence from age eleven to seventy would mediate the effect of years of education on specific cognitive abilities (Ritchie et al., 2015). Three models (full mediation, partial mediation, no mediation) were tested, whereupon the no mediation by general intelligence model best described the observed data. This finding suggests that schooling impacts specific abilities, but not general intelligence. However, the interval between the ages of eleven and seventy is a very long time span. It is possible that during this time, environmental or biological factors might have exerted their influences such that any possible effects of schooling on general intelligence might have dissipated.

Therefore, in one of our own studies (Bergold et al., 2017), we took advantage of the German G8 school reform to investigate the nature of the schooling effect on intelligence test scores at younger ages in two different samples of G8 and G9 students. With the G8 reform, the duration of school attendance had been shortened by one year. However, at the same time both the curriculum contents and the number of lessons were preserved. Therefore, if the impact of schooling on intelligence test scores was completely due to specific, curriculum-dependent abilities, no differences in intelligence test scores between the G8 and G9 students should have emerged because both groups had completed the same curriculum in the same number of lessons. It is worth noting that additional studies have been reported that utilize school reforms as "natural" quasi-experimental treatments (e. g. Brinch & Galloway, 2012). However, changes in those school reforms included *both* the number of years of education as well as modifications to the curricula. Therefore, those studies could not investigate whether the schooling effect is due to fostering of curriculum-dependent skills or due to fostering of more general, curriculum-independent cognitive abilities. Both G8 and G9 students from Sample 1 completed the Berlin Intelligence Structure Test (BIS; Jäger et al., 1997); G8 and G9 students from Sample 2 completed the Intelligence-Structure-Test 2000 R (IST 2000 R; Liepmann et al., 2007). Outlined further in Excursus 2 are details about the principle of intelligence testing with both the BIS and the IST 2000 R given as examples.

Excursus 2: How to Measure Intelligence

An intelligence test is grounded on an established intelligence model that defines and structures cognitive abilities. The items are deduced from the intelligence model, so that their content would represent the cognitive ability to be measured as well as possible. The problems presented in the items are usually clearly defined and the items most often have a multiple-choice format. Depending on the intelligence facet to be measured, items might involve different cognitive operations and contain verbal, numerical, or figural material. For example, tests measuring fluid intelligence will require the test taker to

Example 1: Verbal similarities

Find out the two words which have something in common.
(a) coffee (b) house (c) car (d) hill (e) tea (f) bread

(correct answer: a and e)

Example 2: Number series

The number series presented below follow a certain mathematical rule. Find out the rule and write down the next number.
1 3 5 7 9 ?

(correct answer: 11)

Example 3: Figural analogies

Three pictures are given. There is a relation between the first picture at the left and the second picture at the right side. There is a similar relation between the third picture below and one of the five alternatives (a), (b), (c), (d), and (e). Please find out the alternative for a correct relation.

(correct answer: d)

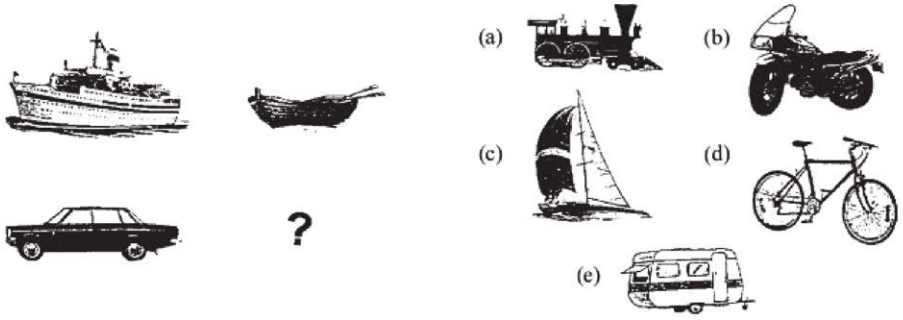

Fig. 2: Examples of (pseudo-)items measuring verbal (Example 1), numerical (Example 2), and figural (Example 3) reasoning ability (reprinted from Intelligence, Vol. 33, Schulze, Beauducel, & Brocke, Semantically meaningful and abstract figural reasoning in the context of fluid and crystallized intelligence, pp. 143–159, 2005, with permission from Elsevier)

solve logical problems illustrated by figural material. By contrast, tests measuring crystallized intelligence might assess the test taker's general knowledge and vocabulary. As another example, the BIS (which we used for Sample 1 in our study) distinguishes between four cognitive operations (operation speed, memory, creativity, and processing capacity) and the three types of cognitive contents (verbal, numerical, and figural). Their integral represents general intelligence. The basic module of the IST 2000 R (which we used for Sample 2) consists exclusively of tasks requiring logical thinking with verbal, numerical, or figural material, indicating verbal, numerical, and figural reasoning ability, respectively. The composite score indicates general reasoning ability which is closely linked to general intelligence. Figure 2 provides some item examples from the IST 2000 R (because of copyright protection, these examples are pseudo-items, reprinted from Schulze et al., 2005).

In both samples, the G9 students outperformed the G8 students in most of the intelligence facets assessed and, consequently, in general intelligence. Further, in a structural equation model (see Figure 3), the path from schooling (G8 vs. G9) to general intelligence was stronger than the paths from schooling to the more specific facets of intelligence. Although there were some limitations of the study, most notably being the missing control for baseline intelligence, the fact that similar results arose from both samples supports the conclusion that schooling causes a "real" enhancement of intelligence and not just an artificial improvement of test scores.

What exactly makes schooling a key factor for intellectual development remains an intriguing and open question. Intensive training programs for teaching children how to accurately reason have shown transfer effects to fluid intelligence (Christoforides et al., 2016; Klauer et al., 2002). In principle, schooling can be seen as a very intensive and protracted version of such a training program. Schooling allows students to experience that their reasoning made in daily life might be wrong. The conflict demonstrated in school between invalid daily life conclusions and valid conclusions might lead to cognitive accommodation (see e. g., Artman et al., 2006; Cahan & Artman, 1997). During their entire school career, students are confronted with cognitively challenging tasks in many different disci-

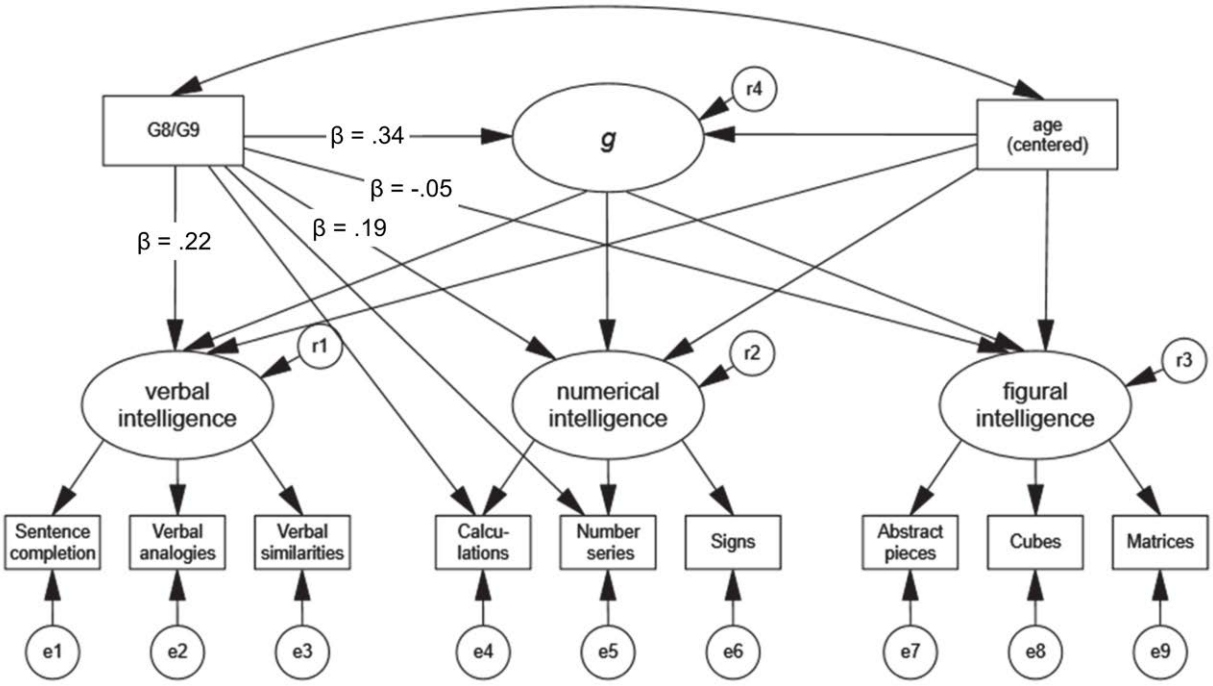

Fig. 3: Structural equation model of the influence of G8/G9 schooling on intellectual abilities (reprinted from Cognitive Development, Vol. 44, Bergold, Wirthwein, Rost, & Steinmayr, What happens if the same curriculum is taught in five instead of six years? A quasi-experimental investigation of the effect of schooling on intelligence, Study B, pp. 98–109, 2017, with permission from Elsevier)

plines, and they spend a great deal of time in elaborated cognitive processes. It is possible that the process of thinking (which is first bound to a concrete context presented in the lessons) separates over the years step by step from the problem context and transfers to more abstract levels, all of which might be underpinned by brain development. Accordingly, neuroscience research has found that mental activities typical for school (e. g. solving calculation tasks) activate neural substrates which are also responsible for reasoning, and that literacy probably changes brain structures (e. g. Baker et al., 2015; Carreiras et al., 2009). Furthermore, as was shown by means of the cut-off design (see Excursus 1), first graders showed a greater increase in activation of the right posterior parietal cortex than kindergarten children of the same age, underscoring their greater improvement in executive functioning (Brod et al., 2017). Therefore, continued instruction might serve as fruitful stimulation of brain development. It seems that through many years of instruction, children "learn to think." In summary, schooling is a very powerful device to foster individuals' intelligence. Thus, it should be in the best interests of a nation's wealth and prosperity to invest as much as possible in high-quality education of children as young as possible.

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Review Article

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Alpha-synuclein as therapeutic target in Parkinson's disease

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Abstract: It took 180 years from James Parkinson's descriptions in "An essay on the shaking palsy" to the discovery of alpha-synuclein as key player in Parkinson's disease (PD). The identification of a PD causing mutation in the gene of alpha-synuclein was followed immediately by detection of its presence in Lewy bodies, inclusions found in the brains of patients. While many open questions remain, findings on how alpha-synuclein pathology emerges, propagates and causes neuronal death provide hope for development of disease-modifying therapeutics beyond the current dopamine replacement therapy. The recent hypothesis of a prion-like transmission of alpha-synuclein pathology raises controversy but also inspired numerous exciting research avenues, partially already translating into novel drug targets. This review summarizes evidence for a critical role of alpha-synuclein in PD pathogenesis followed by a discussion of current promising treatment avenues.

Keywords: synucleinopathy, prion, neurodegeneration, neuroprotection, dopamine

Zusammenfassung: 180 Jahre vergingen zwischen James Parkinson's "An essay on the shaking palsy" und der Entdeckung der zentralen Rolle von alpha-synuclein in der Pathogenese von Parkinson's disease (PD). Der Identifikation einer PD verursachenden Mutation im alpha-synuclein Gen folgte rasch der Nachweis des Proteins in Lewy Körperchen, den charakteristischen Proteineinschlüssen im Gehirn der Patienten. Trotz vieler ungeklärter Fragen, Forschungsergebnisse zur Entstehung, Ausbreitung und Neurotoxizität der alpha-synuclein Pathologie geben Hoffnung auf die Entwicklung einer Krankheits-modifizierenden Therapie, über die Dopaminersatztherapie hinaus. Die Hypothese, dass alpha-synuclein Pathologie sich ähnlich wie ein Prion ausbreitet, wird kontrovers diskutiert, und initiierte viele interessante neue Forschungsansätze und therapeutische Zielstrukturen. Dieser Übersichtsartikel fasst die Evidenz für eine zentrale Rolle von alpha-synuclein in der Pathogenese der PD zusammen, gefolgt von einer Diskussion neuer Therapiestrategien.

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Lack of disease-modifying therapeutics for Parkinson's disease

Parkinson's disease (PD) is the second most common neurodegenerative disorder, affecting more than 1% of the population above 60 years of age. While a growing number of gene mutations define familial PD, the vast majority of cases is sporadic, meaning that the cause of the disease remains elusive for most patients. Neurodegeneration in PD affects diverse neuronal subtypes, including dopamine neurons of the substantia nigra pars compacta (Tretiakoff, 1919). These neurons project to the caudate nucleus and putamen, where loss of dopamine results in cardinal signs of this movement disorder, just as described 200 years ago by James Parkinson, i. e. bradykinesia, rigidity, tremor and gait disturbance (Parkinson, 1817). Of note for therapeutic interventions: dopaminergic neurons have extensively degenerated and striatal dopamine is largely depleted during the first years after diagnosis (Kordower et al., 2013).

There is currently no treatment to stop or halt progressive neurodegeneration in PD. Arvid Carlsson, using the vesicular monoamine transporter inhibitor reserpine in rodents and rabbits, identified a major role of dopamine in brain and the potential of its precursor 3,4-dihydroxyphenylalanine (DOPA) to counteract the "tranquillizing" effects of reserpine in vivo (Carlsson et al., 1957; Carlsson et al., 1958). In 1960 Oleh Hornykiewicz made the landmark discovery of dopamine loss in PD brains (Ehringer and Hornykiewicz, 1960). Only one year later he demonstrated the astounding effect of L-DOPA administration to PD patients. L-DOPA, which crosses the blood brain barrier, offered an immediate and substantial relief from akinesia, which tremendously improved the quality of

life for patients and remains the current gold standard of drug treatment. Unfortunately, long-term treatment elicits uncontrolled involuntary movements, termed dyskinesia. Furthermore the drug does not improve many motor and non-motor symptoms which severely reduce the quality of life, including for example some speech deficits, tremor, cognitive decline, anxiety and sleep dysfunction. Notably, dopamine replacement does not halt progression of the disorder and its symptoms (Schapira et al., 2014). Consequently, the main focus of research in PD is to develop novel treatments that address these shortcomings.

Development of such disease modifying therapeutics requires knowledge on cause and mechanisms of neurodegeneration. Despite intensive research it is still not known why dopaminergic neurons die predominantly in PD. It has been proposed that dopamine and its metabolites represent a toxic burden for neurons making them more vulnerable to additional impacts of environmental toxins such as pesticides (Chesselet, 2003). In fact some toxins are taken up specifically by the dopamine transporter and cause mitochondrial dysfunction and oxidative stress, which may explain mitochondrial deficiency in PD (Schon and Przedborski, 2011). In addition, there is considerable involvement of glial activation around the site of neurodegeneration which could contribute to neuronal susceptibility (Ouchi et al., 2009). Unfortunately, similar to many other neurological diseases, prospective novel therapeutics targeting these mechanisms have so far failed in clinical trials (Schapira et al., 2014). Many reasons have been proposed for such failure, including the inadequacy of animal models, methods and evaluation criteria used in pre-clinical studies, which are often followed by clinical trials with low power to detect neuroprotective effects in patients. Apart from redesigning of preclinical and clinical trials, there is a need for basic research on the therapeutic targets by studying how gene mutations or risk factors initiate or contribute to the cascade of events that causes neurodegeneration.

The rise of alpha-synuclein as key therapeutic target

At present, one protein is heavily targeted for development of novel therapeutics: alpha-synuclein. Its role first emerged with the discovery of a mutation in the gene encoding alpha-synuclein (*SNCA*) in familial PD (Polymeropoulos et al., 1997). Shortly after, alpha-synuclein was found to be a main component of Lewy bodies, a pathological hallmark of sporadic PD first described by Friedrich Lewy (Lewy, 1912; Spillantini et al., 1997). Additionally, elevated expression of alpha-synuclein due to gene multiplications or nucleotide polymorphisms can cause PD or significantly increase the risk to develop the disease (Devine et al., 2011). While the crucial role of alpha-synuclein is thus established, it is still not fully understood how alpha-synuclein pathology connects to neurodegeneration, and why specific neuronal subtypes, such as the dopaminergic neurons of the substantia nigra, are preferentially affected in PD.

Curiously, alpha-synuclein pathology is involved in other neurodegenerative diseases, together frequently referred to as synucleinopathies. In multiple system atrophy, alpha-synuclein aggregation affects mainly oligodendroglia (Papp-Lantos bodies). Lewy bodies are also found in neurocognitive disorders such as Dementia with Lewy bodies (DLB). DLB is commonly distinguished from Parkinson's disease dementia (PDD) based on arbitrary defined earlier onset of cognitive impairment compared to motor symptoms. Both PD and DLB overlap in many clinical features, genetics, neuropathology, and management and are therefore currently regarded as subtypes of an alpha-synuclein-associated disease spectrum (Jellinger and Korczyn, 2018). Simple malfunctions of the protein are unlikely to cause such complex and diverse disease development. But what may trigger heterogeneous yet specific pathology? Is there a causative link between alpha-synuclein aggregation and disease progression, or are Lewy bodies merely by-products of neurodegeneration? Sufficiently answering these most critical questions will facilitate the development of urgently-required disease modifying therapy for synucleinopathies.

The answers may be found in the propensity of alpha-synuclein to associate into more or less toxic protein assemblies. Physiologically, the 140 amino acid protein alpha-synuclein, as indicated by its name, concentrates in nerve terminals and is also found in the nucleus. The protein was suggested to form alpha-helically folded tetramers, probably membrane-bound, but there is also compelling evidence for a monomeric state in mammalian cells (Theillet et al., 2016). The physiological function of alpha-synuclein is poorly understood. It is involved in transmitter release at nerve terminals and appears to be able to remodel membranes (Bendor et al., 2013). Mice lacking the alpha-synuclein gene show only modest differences in transmitter release, which could be somewhat aggravated by additional knockout of the beta- and gamma-synucleins, supporting some functional redundancy (Anwar et al., 2011). However, the detrimental role of the protein in neurodegeneration undoubtedly involves "gain

of toxic function". Probably triggered by factors such as higher expression, disturbance in metabolism, or interaction with other agents (environmental toxins, infections), alpha-synuclein becomes prone to oligomerization and ultimately forms the amyloid fibril with a cross beta-sheet quaternary protein structure which constitutes Lewy bodies. During this process, alpha-synuclein forms multiple kinds of species, or strains, which seem to differ in their capacity to spread out and cause acute cell death (Winner et al., 2011; Luk et al., 2012; Peelaerts et al., 2015). The proportion of nigral neurons bearing Lewy bodies seems stable (about 3,6 %), supporting that the harboring neurons die while new bodies are forming in the remaining neurons (Greffard et al., 2010). Mutations in the gene for alpha-synuclein, described as cause for familial PD, increase alpha-synuclein aggregation or elevate the level of assembly-prone free alpha-synuclein by reducing its ability to associate with membranes (Burre et al., 2015). Thus, it is conceivable that in synucleinopathies different triggers, or pathological alterations in specific cells, shift alpha-synuclein assembly towards the more toxic species which then drive the disease progression.

The prion-like concept applied to alpha-synuclein pathology

The idea of propagation of alpha-synuclein pathology with disease progression is substantiated by the highly influential work of Heiko Braak and colleagues (Braak et al., 2003). By analyzing brains of subjects with clinical diagnosis of PD and nigral Lewy body pathology versus subjects without reference to PD symptoms but Lewy body pathology versus subjects with neither PD symptoms nor Lewy body pathology they were able to conceive a staging procedure based upon the readily recognizable topographical extent of the lesions. Lewy bodies first emerge in the olfactory bulb and brain stem (stage 1–2), followed by the substantia nigra (stage 3, symptomatic PD), the temporal cortex and the neocortex (stage 4–6, cognitive decline). Subsequently alpha-synuclein pathology was even demonstrated in the peripheral and enteric nervous system of PD patients, which could explain why non-motor symptoms such as constipation characterize the prodromal, early phase of PD. Pathology may actually be initiated in the periphery and spread to the central nervous system, because there is evidence for transport across nerves to central neurons. Truncal vagotomy was reported to reduce the risk to develop PD (Svensson et al., 2015; Liu et al., 2017), but others did not arrive at the same conclusion (Tysnes et al., 2015). As such, there is controversy about the "PD starts in the gut" hypothesis, which requires further research. A recent study demonstrated that colonizing the gut of alpha-synuclein overexpressing mice with microbiota of PD-affected patients enhances the behavioral impairments, while antibiotic treatment was protective, supporting a pivotal role of gut bacteria in PD pathogenesis (Sampson et al., 2016).

Support for a prion-like spread came from findings of Lewy bodies in fetal mesencephalic dopaminergic neurons that had been transplanted into the putamen and caudate nucleus of patients with advanced PD (host-to-graft propagation) (Li et al., 2008). Alpha-synuclein strains injected into rodent brain can induce aggregation and pathology that propagates, with specific strains being more toxic and invasive, perhaps explaining diversity in disease progression in patients (Luk et al., 2012; Peelaerts et al., 2015). Together these studies show that alpha-synuclein can adopt alternative conformations which self-assemble into toxic species. Those transfer across cells and recruit further protein, with the result of self-propagation of pathology characteristic for prion diseases (Fig. 1). Regardless of the evidence, this theory is not undisputed, but the toxicity of certain alpha-synuclein assemblies to neurons has been sufficiently demonstrated. If this process indeed starts in the periphery and/or the olfactory bulb, one would expect those neurons to be preferentially exposed to some (unknown) triggering insult, or harbor a specific intrinsic vulnerability. Interestingly, while inoculation of nigral Lewy body-enriched fractions from postmortem PD brains in mice promoted alpha-synuclein pathology and dopaminergic neurodegeneration (Recasens et al., 2014), the same approach using alpha-synuclein-containing Lewy body extracts purified from peripheral postmortem stellate ganglia did not trigger respective pathology (Recasens et al., 2018). For a definite answer on how alpha-synuclein pathology propagates, further research is required to dissect mechanisms underlying the different pathogenic capacity observed in the aforementioned studies, also including alpha-synuclein aggregates from other peripheral regions, and at different disease stages. Several studies aiming to define a biomarker for PD have reported decreased extracellular alpha-synuclein levels; however, others found increased levels (Malek et al., 2014). Recently alpha-synuclein was reported in extracellular vesicles which are released from neurons and other CNS cells and may present a reservoir for biomarkers (Gamez-Valero et al., 2019). Furthermore, development of specific PET-imaging tracers to track different forms of pathological alpha-synuclein in the periphery and CNS in patients could greatly advance the field (Lionnet et al.,

2018). Of note, novel sensitive protein assays for detection of misfolded alpha-synuclein in cerebrospinal fluid of patients have the potential to be effective tools for the early diagnosis of synucleinopathies (Paciotti et al., 2018). Clearly, PD is a complex disease and there may be multiple alternative pathogenic avenues, differing between patients, which ultimately cumulate in significant neuronal death causing symptomatic PD. Alpha-synuclein may be a common denominator along these avenues which makes it very attractive as therapeutic target.

Therapeutic targeting of alpha-synuclein

For preclinical testing there are several cellular (Lazaro et al., 2017) and animal models (Chesselet and Richter, 2011) of alpha-synuclein pathology available. These models are genetically altered to overexpress the human wildtype or a mutated form of alpha-synuclein, or more recently, were injected with exogenous alpha-synuclein (e. g. synthetic fibrils). There is no perfect model that represents all features of PD, but the model selected for a specific drug trial should obviously harbor the pathomechanism which is targeted (e. g. aggregation of alpha-synuclein), and for the in vivo trials provide a set of related pathological and ideally behavioral readouts to measure drug efficacy (Chesselet and Richter, 2011).

Therapeutic interventions directly targeting alpha-synuclein pathology aim to (i) reduce expression, (ii) inhibit aggregation, (iii) prevent spreading and (iv) increase metabolism (Fig. 1). The following chapters describe examples of compounds and strategies in development for each aim.

Reduce expression

Overexpression of wild-type alpha-synuclein by gene multiplication or polymorphisms in the promotor region is capable of causing disease in a dosage dependent manner (triplication causes a more severe and early onset disease than duplication) (Devine et al., 2011). Furthermore, nigral dopaminergic neurons of sporadic PD patients express about 7-fold higher levels of alpha-synuclein mRNA (Grundemann et al., 2008). The cause of alpha-synuclein mRNA and protein accumulation is still elusive for the majority of patients, but the resulting downstream pathology clearly correlates with disease progression. Specific reduction of gene expression can be achieved by using synthetic non-coding small interfering RNAs (siRNA) against the target mRNA, thereby taking advantage of endogenous RNA interference (RNAi). However, efficient delivery of siRNA into neurons *in vivo* remains challenging due to biological barriers, degradation, low transfection and insufficient distribution. Infusion of naked siRNA against alpha-synuclein into the substantia nigra of nonhuman primates reduced the protein level close to the injection site significantly (McCormack et al., 2010). Packaging of siRNA into nanoparticles increases stability, distribution and transfection rate which allows injection into cerebral spinal fluid with widespread protein knock-down in brain evident 5 days after a single application (Helmschrodt et al., 2017). Similarly, antisense oligonucleotides (ASO) against alpha-synuclein mRNA and conjugated with a monoamine uptake inhibitor achieved protein knock-down in brainstem of mice up to three days after 4 consecutive days of intranasal application (Alarcon-Aris et al., 2018). An alternative avenue could be reduction of mRNA expression by discovery of regulating pathways. Recently, agonists of the beta 2 receptor were associated with a reduction of alpha-synuclein gene expression and a lower risk to develop PD (Mittal et al., 2017). The extensive experience with these drugs can facilitate clinical development. Interestingly, iron was shown to upregulate alpha-synuclein expression at the translational level. Iron accumulates in the substantia nigra of PD patients and thereby increases oxidative stress burden to the neurons (Berg et al., 2002). The combination of oxidative stress and alpha-synuclein accumulation is likely to accelerate protein misfolding and its propagation. Therefore, iron chelators, already approved for other diseases, were tested preclinically with positive results and are now moving forward in clinical trials (Martin-Bastida et al., 2017).

Inhibit aggregation

Given the above described alpha-synuclein self-assembly into toxic species, stabilizing the protein in its physiologic non-toxic (monomeric?) form represents a rational target. Small-molecules that cross the blood brain barrier and interact with alpha-synuclein were shown to improve behavioral, neuropathological and biochemical endpoints in preclinical trials (Levin et al., 2014; Wrasidlo et al., 2016; Richter et al., 2017). Such compounds are for example selected out of large drug libraries using high-throughput screening for ability to reduce oligomer formation (Levin et al., 2014). In that case the precise mechanism(s) of action is(are) determined at later stages. Alternatively

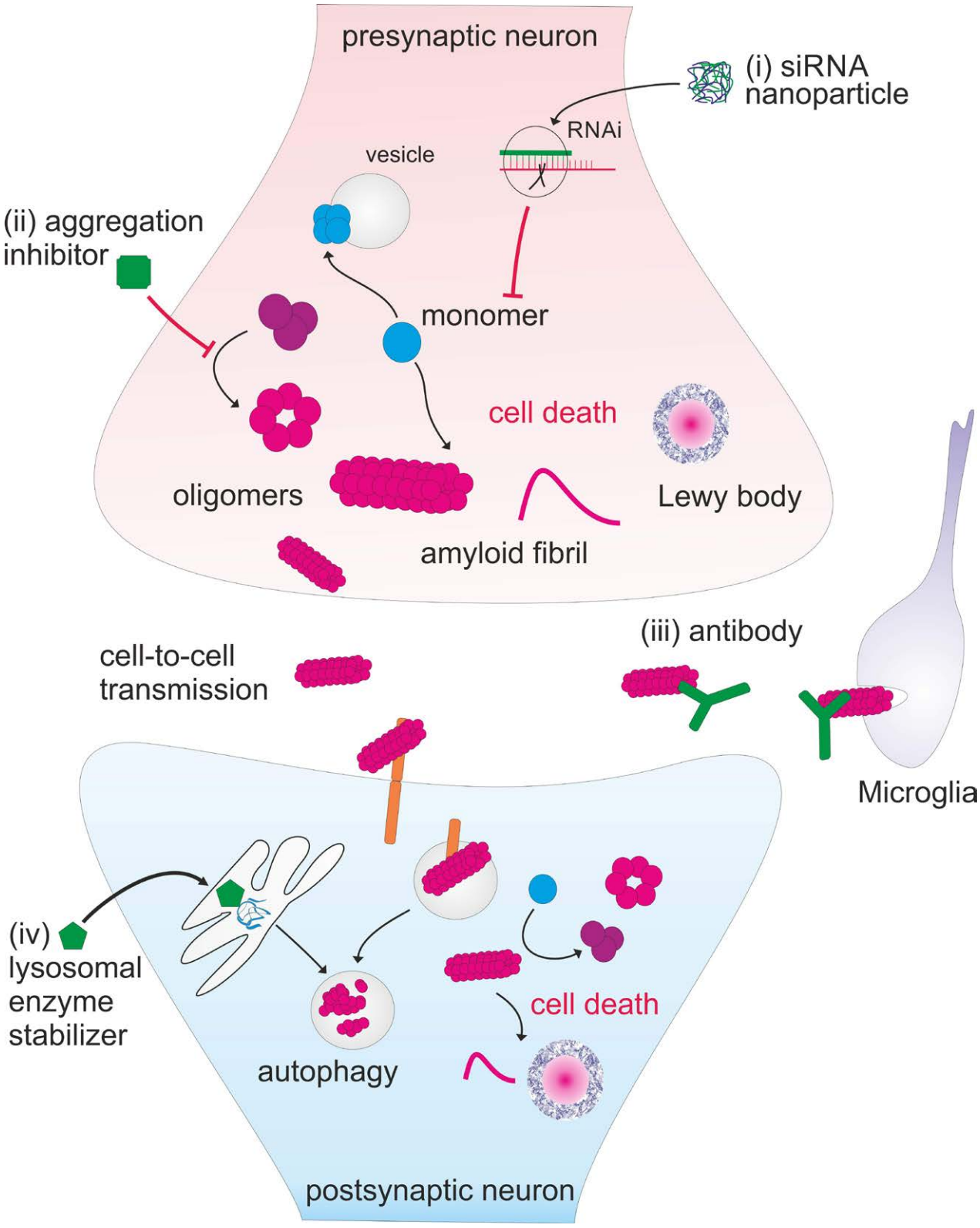

Fig. 1: Therapeutic targeting alpha-synuclein pathology by (i) reducing expression of alpha-synuclein monomers (blue) through RNA silencing (RNAi), (ii) inhibiting the formation of toxic oligomers/strain assembly with small molecules (purple/pink), (iii) prevent spreading of a toxic assemblies through binding to specific antibodies and degradation in microglia, (iv) increase of lysosomal degradation (autophagy pathway) by stabilizing the conformation of specific enzymes from the endoplasmic reticulum to the lysosome (pharmacological chaperoning).

small molecules are chosen based on specific activities, such as shielding of Lys residues with low affinity, thereby interrupting formation of oligomers without interfering with the physiological protein function (Richter et al., 2017). The effects of these drugs *in vitro* and *in vivo* are also highly informative on the mechanism of alpha-synuclein toxicity. For example, one compound was developed de novo by molecular modelling methods targeting a C-terminus domain of alpha-synuclein, which is important for dimerization and membrane penetration. As expected, the compound reduces binding of alpha-synuclein to membranes, which, however, was later shown to represent a physiological and likely protective mechanism, at least in synaptic vesicles. Regardless, the compound is highly effective in reducing protein aggregation and toxicity *in vivo* without overt side effects. The current hypothesis is that it might work by preventing toxic interaction of alpha-synuclein with the plasma membrane and other intracellular organelles, without altering the physiological alpha-synuclein associated with synaptic vesicles (Wrasidlo et al., 2016). These examples show that effects of interference with alpha-synuclein oligomerization are complex and difficult to predict. Therefore these compounds are tested in several different *in vitro* and *in vivo* models to provide a comprehensive picture before moving into clinical trials. It will remain difficult to predict whether targeting the initial process of alpha-synuclein pathology can improve endpoints at the symptomatic stage of PD, where Lewy bodies are widespread and neurons extensively degenerated. Interference with higher order aggregates is usually avoided as it could be deleterious, because increase in the concentration of lower molecular weight assemblies may produce toxic strains.

Prevent spreading

Transfer of misfolded alpha-synuclein and thus propagation of pathology across the brain is targeted via active (alpha-synuclein mimicking peptides) and passive (antibodies against human alpha-synuclein) immunotherapies. Despite numerous challenges, such as achieving blood brain barrier penetration without targeting intracellular alpha-synuclein, avoidance of unspecific inflammatory responses, and the need for repeated applications, there are several candidates currently in clinical trials. Results so far support brain penetration and acceptable safety profiles, however, the recent failure of a similar strategy in a phase 3 trial with Alzheimer´s disease patients cautions to wait for data on clinical endpoints. Knowledge on the exact (disease specific) spectrum of toxic alpha-synuclein species or strains could allow an even more specific antibody to be developed, which is already in progress. Further targets for specific antibodies could be proteins or receptors that specifically facilitate the entry of fibrillary alpha-synuclein into neurons, as recently demonstrated for lymphocyte-activation gene 3 (Mao et al., 2016).

Increase metabolism

Apart from reducing its expression, increasing the metabolism of alpha-synuclein, ideally of its more toxic assemblies, represents another heavily targeted mechanism. Alpha-synuclein degradation pathway involves the lysosome (autophagy). Disturbance of lysosomal function is thought to increase the concentration of aberrant protein assemblies thus contributing to neurodegeneration. Notably, mutations in *GBA1*, the gene for the lysosomal hydrolase acid β-glucosidase, are the most common known genetic risk factor for PD, and the protein is reduced in the substantia nigra of PD patients. Compounds that increase stability and thus activity of this lysosomal protein (Richter et al., 2014; Migdalska-Richards et al., 2017) or generally increase autophagy were successfully tested in preclinical models (extensively reviewed in (Moors et al., 2017)). Among these, Ambroxol, used as expectorant for over 30 years, was surprisingly found to increase the activity of the lysosomal enzyme in a drug screening assay and is now rapidly moving forward in clinical trials.

Summary and outlook

While the current picture of its role in pathogenesis of PD is still incomplete, the high validity of alpha-synuclein as target in PD is beyond doubt. While targeting specific toxic strains is at risk to miss the most relevant species in a patient (or stage of progression), overall downregulation of alpha-synuclein expression will certainly reduce the pathological burden. However, dosage has to be titrated with a potential underappreciated physiological role of the protein in mind. The diversity of the disease likely requires a patient specific combination of strategies in the future. Still, cumulative effects and side effects are difficult to predict. On top of this remains the challenge to measure alpha-synuclein specific pathological endpoints in clinical trials, the hope that the current strategies will not require decades before beneficial effects emerge, and the efforts to diagnose patients early in disease progression prior to overt neuronal loss. Regardless of these caveats,

substantial progress has been made in understanding the disease pathogenesis that hopefully can be translated into disease-modifying therapy for patients in the near future.

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Bionotes

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Franziska Richter graduated 2007 in Veterinary Medicine (Dr. med. vet.) at the FU Berlin working on animal models of Parkinson´s disease. As a postdoc and research faculty in the lab of Marie-Francoise Chesselet, Department of Neurology at UCLA (2007–2012), she performed several preclinical trials in mouse models of alpha-synuclein pathology. In 2012 she joined Prof. Angelika Richter at the Faculty of Veterinary Medicine in Leipzig, extending her field to therapeutic interventions in dystonia. She is currently Professor and Chair of the Department of Pharmacology, Toxicology and Pharmacy at the University of Veterinary Medicine Hannover.

Rezension

Dr. Manuela Macedonia: Beweg Dich! Und Dein Gehirn sagt Danke
Wie wir schlauer werden, besser denken und uns vor Demenzen schützen

besprochen von **Anja Hoffmann**

https://doi.org/10.1515/nf-2019-0004

Nicht nur „Sex sells“, auch Gehirn geht offensichtlich immer. Laut verschiedenen Buchtiteln ist das Gehirn alles: erleuchtet, überfordert, gierig, egoistisch, manipuliert …; es gibt „Das zweite Gehirn“ – den Darm, „Dein Drittes Gehirn“ – in dem Fall das Mikrobiom – die Liste scheint unerschöpflich. Genauso unüberschaubar ist die Gehirn-Ratgeber Literatur: „Power für´s Gehirn“, „Meditation, um das Gehirn zu verändern“, „Fitnessstudio fürs Gehirn“, „Das glückliche Gehirn“ – alles Titel, die heilbringende Methoden versprechen, um die Gehirnleistung zu verbessern. Nun also „Beweg Dich! Und Dein Gehirn sagt Danke. Wie wir schlauer werden, besser denken und uns vor Demenzen schützen“. Was ist davon zu halten?

Die Autorin Manuela Macedonia ist Linguistin und Philologin. Sie hat im Bereich Kognitionspsychologie und Angewandte Linguistik zum Thema „Fremdsprachen lernen und Gedächtnis“ promoviert. Ihre Postdoc-Zeit hat sie am MPI in Leipzig und an der Johannes Kepler Universität in Linz verbracht, wo sie mittlerweile als Senior Scientist arbeitet. Das vorliegende Buch ist nach „Gehirn für Einsteiger“ und „Gehirn für Fortgeschrittene“, die sie beide zusammen mit Professor Stefanie Höhl, Forschungsgruppenleiterin am MPI, veröffentlicht hat, ihr erstes eigenständiges Werk über das Gehirn. Davor hat sie einige Bücher und Spiele zu den Themen „Fremdsprachen“ und „Sprachen lernen“ publiziert.

In sieben Kapiteln unterlegt mit zahlreichen aufgeführten Quellen schildert die Autorin, wie sich Bewegung auf das Gehirn auswirkt. Nach einer Einführung in den Aufbau des Organs geht es rasch zu ihrem zentralen Credo „Ich laufe nicht für meine Figur, ich laufe für mein Gehirn“. Die Grundlagen des Gedächtnisses werden anhand von Hippokampus und Neurogenese beschrieben. Es werden Studien vorgestellt, die den positiven Einfluss von Bewegung auf die Größe des Hippokampus bei „Läuferratten“ zeigen, sowie auf die schulische Leistung von Kindern. Als weitere Grundlage für kognitive Leistungssteigerung werden die Mechanismen Vaskularisierung, Synaptogenese und gesteigerte Ausschüttung von N-Acetylaspartat erläutert. In „Die Kontrollzentrale im Vorderhirn“ geht es um die Themen kognitive Kontrolle, selektive Aufmerksamkeit und Multitasking, sowie den negativen Einfluss von Schlafmangel und den positiven von Bewegung auf diese Prozesse. Das Thema „Essen und Gehirn (und Bewegung)“ nutzt die Autorin zur Einführung in das Belohnungssystem. In den letzten beiden Kapiteln werden schließlich Erkrankungen (ADHS und Depression) sowie Alterungsvorgänge erläutert. Anhand von BDNF, Cortisol sowie der „Fight-or-Flight“-Reaktion wird der Zusammenhang mit Bewegung aufgezeigt sowie die Möglichkeiten, sich selbigen in jedem Alter positiv zu Nutze zu machen.

Das Buch ist in einem lebendigen, persönlichen Stil geschrieben. Ein besonders illustratives Beispiel ist „Die lange Reise einer Buttersemmel ins Belohnungsnetzwerk“. Der Leser erfährt zudem sehr viele Details aus der Lebens- und Familiengeschichte von Frau Macedonia. Das Layout zeichnet sich durch die gelbe Unterlegung von wichtigen Stichworten sowie durch zahlreiche kleine, z. T. Comic-artige Abbildungen aus, die ebenfalls in den Farben Gelb und Schwarz gestaltet sind.

Das Gelb wirkt zwar freundlich und sonnig, aber es führt leider zu einer schlechten Lesbarkeit. Außerdem sind die Zeichnungen, so niedlich sie auch sein mögen, punktuell nicht ganz korrekt oder bieten Informationen, die in dieser Form nicht zielführend sind, wie z. B. die eigenartige Darstellung der Brodman-Areale. Auch im Text hätte ich mir stellenweise ein besseres Lektorat bzw. eine vorige Korrektur durch Fachkollegen gewünscht: Fachbegriffe werden z. T. erst bei der zweiten Nennung erklärt, manchmal gar nicht. Und mitunter ist der Inhalt auch schlichtweg falsch: Weder bildet das Gehirnblut einen eigenen Kreislauf, noch hat sich die Lateralisierung von Hirnfunktionen als falsch erwiesen. Korrelation lässt sich – auch wenn sie große Gruppen betrifft – nicht mit

Kausalität gleichsetzen. Und Demenzen auf Gedächtnisstörungen zu reduzieren, halte ich für fragwürdig – um nur einige Beispiele zu nennen.

Die Kernaussage des Buches „Bewegung ist gut für das Gehirn“ ist unzweifelhaft richtig. Und ich nehme Frau Macedonia ab, dass ihre persönlichen Erfahrungen die Grundlage für dieses Buch bilden. Trotzdem habe ich insgesamt leider den Eindruck gewonnen, dass es der Autorin eher um eine marktwirksame Vermittlung ihres Credos geht, als um eine (populär)wissenschaftliche Diskussion des Themas. Dazu trägt ihre medienwirksame Darstellung im Internet ein Übriges bei: Geschäftstüchtig werden gleich dreitägige Seminare zum Buch angeboten. Ich tue mich daher schwer damit, dieses Buch einer neurowissenschaftlichen Leserschaft zu empfehlen, auch wenn es eine leichte und streckenweise vergnügliche Lektüre war. Wer allerdings einfach eine Motivationshilfe sucht, der mag es zur Hand nehmen.

Dr. Manuela Macedonia
Beweg Dich! Und Dein Gehirn sagt Danke
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Review Article

Uwe Ilg*

Neuroscience for the next generation: Was Schülerlabore für die Neurowissenschaft leisten

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Die Bedeutung erfolgreicher Öffentlichkeitsarbeit nimmt für Universitäten und Forschungseinrichtungen stetig zu. Einerseits trägt eine erfolgreiche Wissenschaftskommunikation dazu bei, dass Wissenschaft zuverlässig in der Gesellschaft verankert ist. Dies betrifft die Bereitstellung der notwendigen finanziellen Mittel als auch die Akzeptanz von Tierversuchen, beide Herausforderungen sind speziell für Neurowissenschaften essentiell. Andererseits ist die Öffentlichkeitsarbeit von großer Bedeutung für die Ansprache des wissenschaftlichen Nachwuchses.

In den Zeiten von *Alternativen Fakten, Fake News, Scientific Misconduct* und *Fake Science* wird es immer wichtiger, dass die Grundlagen der wissenschaftlichen Erkenntnisgewinnung nicht nur Wissenschaftlerinnen und Wissenschaftler vertraut sind, sondern bereits schon in den Gymnasien vermittelt werden. Die stetige Weiterentwicklung der naturwissenschaftlichen Zusammenhänge wird durch das Wechselspiel zwischen Beobachtung, Formulieren einer Hypothese und ihrer experimentellen Überprüfung, getragen. Außerschulische Lernorte, vor allem Schülerlabore, die an Universitäten oder anderen Forschungseinrichtungen angesiedelt sind, bieten eine ausgezeichnete Gelegenheit, Schülerinnen und Schülern diese Zusammenhänge zu vermitteln. Als ein Beispiel soll hier das Schülerlabor Neurowissenschaft der Universität Tübingen vorgestellt werden.

Durch das Exzellenzcluster für Integrative Neurowissenschaften ergab sich Ende 2007 die Möglichkeit, ein Schülerlabor Neurowissenschaften zu etablieren, welches im Schuljahr 2008/09 seinen Betrieb aufnahm. Eine exzellente technische Ausstattung macht es möglich, dass Schülerinnen und Schüler selbstbestimmt in kleinen Gruppen Experimente durchführen, die einerseits Inhalte vom Bildungsstandard der gymnasialen Oberstufe aufgreifen und andererseits Einblicke in aktuelle Forschungsthemen der Neurowissenschaften erlauben. Die Grundlagen der Anatomie des zentralen Nervensystems kann sehr gut an Lammhirnen „erfasst“ und erarbeitet werden (Abbildung 1). Extrazelluläre Ableitungen machen die Aufzeichnung von Aktionspotenzialen individueller Axone bei Schaben auch ohne langwierige Präparation möglich. Im Bildungsplan der Biologie stehen die sich ändernden Leitfähigkeiten der Zellmembran während eines Aktionspotenzials, und im Schülerlabor haben Schülerinnen und Schüler die Möglichkeit, echte Aktionspotenziale zu messen und zu analysieren. Weitere bioelektrische Signale können einerseits von Elektrischen Fischen registriert werden und können mit verhaltensbiologischen Beobachtungen kombiniert werden. Andererseits können am eigenen Körper elektrische Signale in Form der Aufzeichnungen eines EEGs oder eines EMGs durchgeführt werden. Menschliche Wahrnehmungsleistungen werden durch die Ergebnisse von psychophysischen Experimenten charakterisiert. Verhaltensexperimente vermitteln die Grundlagen von Lernvorgängen und die Aufzeichnung von Augenbewegungen lassen Rückschlüsse auf die Verlagerungen der Aufmerksamkeit einer Versuchsperson zu. Schlussendlich können neben biomedizinisch relevanten Aspekten auch theoretische Aspekte der Neurowissenschaft wie die Programmierung eines autonomen Roboters oder die Grundlagen der computergestützten Bildverarbeitung erarbeitet werden. Auch in anderen Schülerlabors werden neurowissenschaftliche Inhalte angeboten. Eine Auswahl findet sich in der Tabelle.

Die Betreuung der Schülergruppen findet vor allem durch Studierende der Biologie, Medizin, Neurobiologie und Psychologie statt, die entweder durch ihre Tätigkeit bereits wichtige Erfahrungen für das gymnasiale Lehramt sammeln oder sich für eine neurobiologische Dissertation orientieren. Für jedes Experiment wurde entsprechendes Lehrmaterial für die studentischen Hilfskräfte erstellt. Begleitend bei der Durchführung der Experimente stehen den Schülerinnen und Schülern Informationen auf der NWG-unterstützten Plattform zur Verfügung (siehe: http://www.dasGehirn.info); die auch schulrelevante Kapitel abbildet (siehe: https://www.dasgehirn.info/entdecken/schule/entdecken-schulrelevantes).

Die Tübinger stellen den Besuchern die Broschüre „*Das Gehirn*“

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Abb. 1: Das Lammhirn als anschauliches Modell für die Anatomie des zentralen Nervensystems. Über die Inspektion der äußeren Anatomie des Gehirns hinaus kann z. B. der Hippocampus präpariert oder der Sehtrakt bis zum seitlichen Kniehöcker verfolgt werden.

(siehe: http://www.neuroschool-tuebingen-schuelerlabor.de/fileadmin/user_upload/Dokumente/lab/Das_Gehirn.pdf) zur Verfügung, eine deutsche Übersetzung der Broschüre „*Brain Facts*“ der Society for Neuroscience (siehe: https://www.brainfacts.org/).

Ein weiteres Betätigungsfeld des Schülerlabors ist die Organisation von jährlichen Lehrerfortbildungen, die von der NWG bundesweit koordiniert werden. Lehrerinnen und Lehrer erhalten einen direkten Kontakt zu Neurowissenschaftler und ihren aktuellen Fragestellungen. So stellt sich zum Beispiel im Jahr 2019 der DFG-geförderte Sonderforschungbereich „Robust Vision“ in der Veranstaltung „Sehen: Menschen, Algorithmen und Maschinen“ vor, eine Möglichkeit für die zunehmend geforderte Öffentlichkeitsarbeit von Forschungsverbünden.

Die bisher beschriebenen Aktionen zielen darauf ab, Schülerinnen und Schüler der gymnasialen Oberstufe zu erreichen und für naturwissenschaftliches Arbeiten zu sensitiveren. Darüber hinaus besteht auch ein Programm für Grundschulen, bei dem sich die Kinder spielerisch die Grundlage der Sinnesphysiologie aneignen. Dieses Programm wird vom Hector-Institut für Empirische Bildungsforschung begleitet und formativ evaluiert. Spezielles Augenmerk wird dabei auf die Entfaltung der Kreativität der Kinder gelegt. Die Vorlesung „Warum sich unsere Sinne täuschen“ der Kinder-Universität an verschiedenen Orten begeistert die kleinen Forscher immer wieder!

Entscheidend für den Erfolg des Schülerlabors in Tübingen ist seine enge Vernetzung mit den neurowissenschaftlichen Instituten (Hertie-Institut für klinische Hirnforschung, Werner Reichardt Centrum für Integrative

Schülerlabore mit speziellen Angeboten zu Neurowissenschaften

Name	Institution	URL	Angebot
X-Lab	Universität Göttingen	http://www.xlab-goettingen.de/	Grundlagen der Erregungsfortleitung an Blutegel, Regenwurm und Heuschrecken
Alfried-Krupp-Schülerlabor	Universität Bochum	http://www.aks.ruhr-uni-bochum.de/index.html.de	Vernetzung Naturwissenschaften mit den Geisteswissenschaften
Goethe Biolab	Universität Frankfurt	http://www.bio.uni-frankfurt.de/42442100/schuelerlabor_goethe_BioLab	Themen zur Neurobiologie und Molekulargenetik
MaxLab	MPI für Neurobiologie, Martinsried	https://www.neuro.mpg.de/maxlab	Lernvermögen von Fruchtfliegen
Natlab	Freie Universität Berlin	https://www.bcp.fu-berlin.de/natlab/index.html	Klassische Konditionierung von Fliegenlarven und Aktionspotenziale von Schaben
Gläsernes Labor	Max-Delbrück-Centrum, Berlin	https://www.mdc-berlin.de/de/glaesernes-labor	Molekularbiologische Ansätze in den Neurowissenschaften
JuLab	Forschungszentrum Jülich	http://www.fz-juelich.de/julab/DE/Home/home_node.html	Humanbiologie am Beispiel von spinalen Reflexen

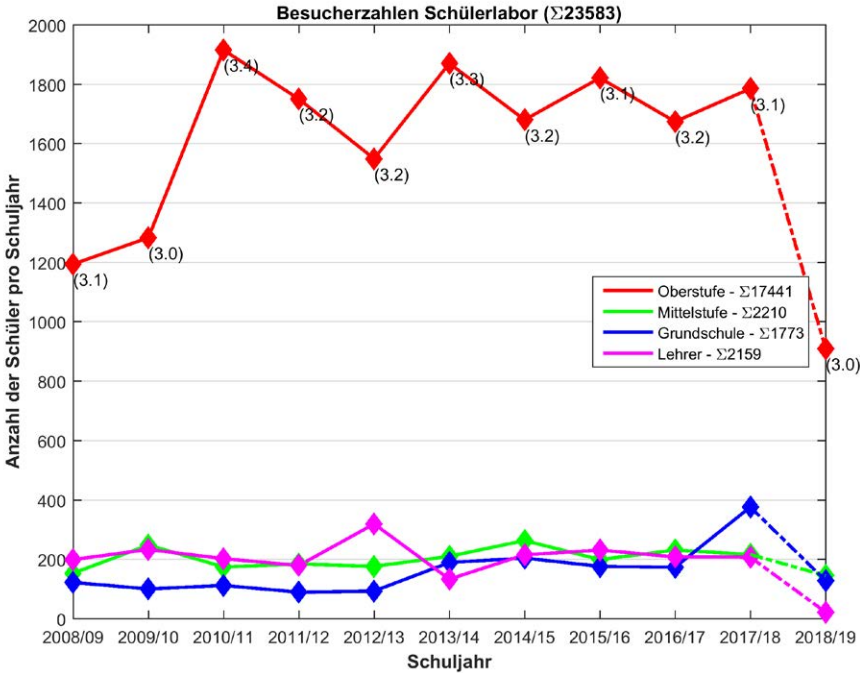

Abb. 2: Besucherzahlen des Schülerlabors (Stand: Februar 2019) getrennt nach Ober- oder Mittelstufe, Grundschulen sowie Lehrerinnen und Lehrer. Die Zahlen in Klammern bei den Besuchen der Oberstufe geben das mittlere Betreuungsverhältnis an (Schülerinnen und Schüler pro studentischer Hilfskraft).

Neurowissenschaften und Max-Planck-Institut für biologische Kybernetik) und der Neurowissenschaftlichen Gesellschaft. Der Organisator des Schülerlabors (Uwe Ilg) ist Neurowissenschaftler am Hertie-Institut für klinische Hirnforschung, leitet dort die Arbeitsgruppe Okulomotorik und ist maßgeblich an der universitären Lehre beteiligt. Die von ihm bearbeiteten Fragestellungen nach den neuronalen Grundlagen von Blick- (Ilg & Thier, 2008) und Handbewegungen (Himmelbach et al., 2013), ihrer Bezugssysteme (Ilg et al., 2004) oder nach den Konsequenzen von Videospielen auf Blickbewegungen (Mack & Ilg, 2014) und Aufmerksamkeitsverlagerungen (Mack et al., 2016) spiegeln sich ganz deutlich in den Experimenten des Schülerlabors. Im Sinne der Nachhaltigkeit ist das Schülerlabor mit einer Fachdidaktik Lehrveranstaltung in die universitäre Ausbildung eingebunden und garantiert so, dass auch zukünftige Lehrerinnen und Lehrer mit den Grundsätzen der naturwissenschaftlichen Erkenntnisgewinnung vertraut sind. Bundesweit betrachtet gibt es sicherlich noch „Luft nach oben“ um junge Menschen mit wissenschaftlichem Arbeiten vertraut zu machen.

Bilanz: Von 2008/09 bis zum Ende des Schuljahrs 2017/18 hatten etwa 23.000 Schülerinnen und Schüler die verschiedenen Veranstaltungen des Schülerlabors besucht (Abbildung 2). – Zumindest von einigen der der früheren Besucher wissen wir, dass sie in der Zwischenzeit ein Studium der Naturwissenschaften oder der Medizin aufgenommen haben.

Durch NWG unterstütze Informationsplattform für Schülerinnen und Schüler:
https://www.dasgehirn.info/
https://www.dasgehirn.info/entdecken/schule/entdecken-schulrelevantes

Lernort Labor: Bundesverband der Schülerlabore
https://www.lernortlabor.de/home.html

Lehrerfortbildungen der NWG
https://nwg-info.de/de/aktivitaeten/lehrerfortbildung

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Forschungsförderung

Barbara Di Benedetto* and Inga D. Neumann*

DFG-Research Training Group (GRK) 2174 „Neurobiology of Emotion Dysfunctions“

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In March 2017 the Research Training Group (Graduiertenkolleg, GRK) GRK 2174 „Neurobiology of Emotion Dysfunctions“ started its work at the University of Regensburg with the recruitment of the first cohort of PhD candidates.

For this innovative and highly competitive GRK, the German Research Council provided funding of almost 4 Mio € for an initial period of 4,5 years. The GRK 2174 involves a core of 10 Principal Investigators and 10 PhD students with additional closely-associated 6 MD students and 8 to 10 PhD students and postdoctoral fellows.

The main focus of this GRK is to investigate neurobiological mechanisms underlying anxiety disorders and major depression. These psychopathologies are associated with severe emotional and social dysfunctions and represent high individual and socio-economic burdens with a lifetime prevalence of about 30 %. Despite intense research efforts over the last 30 years, specific and efficient treatment options for these diseases are still lacking, mostly due to our limited understanding of the extremely complex underlying neurobiological mechanisms. Such complexity often forces researchers to examine relatively narrow neurobiological aspects, with the consequence that research projects frequently lack overarching, interdisciplinary and translational perspectives. These perspectives, however, are essential for the education of graduate students in the increasingly competitive scientific world. Thus, projects need to expand from molecular and cellular levels into more systemic (physiological, neuroendocrine, behavioural) contexts and incorporate translational aspects.

Accordingly, major goals of our graduate qualification programme are to: (i) teach students how to design and perform focused neurobiological projects related to emotion dysfunctions; (ii) build interdisciplinary, national and international networks of clinical and basic scientists who can integrate their scientific questions into multilevel experimental approaches with translational character; and (iii) develop skills for excellent oral and written presentations and scientific management, with both abilities being necessary to pursue a career in neuroscience. Beyond the scientific goals, our GRK, with its high percentage of female supervisors, is committed to recruit and integrate female students into our supportive research networks and mentoring programmes. The active exposure of young scientists to positive female role models should help to prevent career dropouts especially after finishing the PhD training.

To reach these ambitious aims, the GRK 2174 “Neurobiology of Emotion Dysfunction” has combined research efforts from three different Faculties located at the University of Regensburg: the Faculty of Biology and Preclinical Medicine, the Faculty of Medicine and the Faculty of Psychology, Education, and Sport Science. Principal investigators of the GRK were selected based on their previous research achievements in different fields related to the understanding of emotion dysfunctions together with the development of state-of-the-art neurobiological methodologies. Previous experience of several PIs of the GRK in big research consortia that combine the expertise of preclinical and clinical scientists in translational projects have already proven to be successful to investigate complex neurobiological questions. Among them are the BMBF-funded consortium “Novel strategies for the optimized treatment of depression” (OptiMD – Rainer Rupprecht, Caroline Nothdurfter, I. Neumann, B. Di Benedetto) and the research consortium “Neurobiology and Treatment of Adolescent Female Conduct Disorder: The Central Role of Emotion Processing” funded by the EU-FP7-Programme (FemNAT-CD – I. Neumann, Trynke de Jong).

We are certain that an important innovative aspect of our GRK is the implementation of the concept of “tandem supervision”. This model was preferred over the single supervisor to promote the performance of cross-curricular projects and to strongly encourage scientific network-

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Prof. Dr. Inga D. Neumann (Spokesperson GRK), Department of Behavioral and Molecular Neurobiology, University of Regensburg, Universitätsstrasse 31, 93053 Regensburg, Germany, phone: +49 941 9433055, e-mail: inga.neumann@ur.de

ing between the participating PIs and students of the GRK. Whenever possible and scientifically coherent, the "tandem supervisors" have been selected from two different Faculties, with complimentary scientific questions and cutting-edge methodological approaches to offer an interdisciplinary training from different perspectives. This led, for example, to the development of project P1 which combines immunofluorescent-immunohistochemical methods, confocal microscopy and pharmacogenetic manipulations with validated behavioral paradigms to investigate the role of astrocyte-mediated phagocytosis of neuronal synapses in the etiology of depression (P1 – B. Di Benedetto, I. Neumann). Furthermore, this project profits from a cooperation with Maurizio Popoli in Italy. A second project (P2 – Oliver Bosch, Larry Young at the Emory University in USA) aims at examining the interaction of microglia cells and brain neuropeptide systems in the context of partner loss-induced emotion dysfunctions in a monogamous species. Other projects focus on molecular and neuronal underpinnings of social fear learning and extinction. Among them, project P3 investigates the role of the lateral septum in social fear conditioning using an animal model specifically developed to identify alternative neuronal circuits and novel signalling pathways (P3 – I. Neumann, Jens Schwarzbach). Furthermore, high throughput live cell imaging methods and behavioral paradigms have been developed to study protein complexes regulating actin dynamics and class V myosin transport processes involved in vesicular transport mechanisms, mitochondrial dynamics and postsynaptic plasticity underlying emotional fear learning (P4 – Eugen Kerkhoff, Veronica Egger in cooperation with Dori Woods in USA). Additionally, an innovative approach couples deep-sequencing with mass spectrometry to reveal novel epigenetic mechanisms regulating gene expression via non-coding RNAs (e. g. microRNAs and linear non-coding RNAs) at neuronal level, that may control social anxiety-related behaviours (P5 – Gunter Meister, I. Neumann). Project P7 uses similar methods as P1 to investigate the effects of oxytocin on connexin-mediated astrocyte-astrocyte interactions in social anxiety disorders (P7 – I. Neumann, B. Di Benedetto) and profits from a cooperation with Natalie Rouach in Paris. Further specialized biomolecular and biochemical methods such as CRISPR/Cas9 and DREADD technologies have been developed to reveal oxytocin receptor-mediated intracellular signaling pathways and gene expression patterns *in vivo* and in cell culture, which underlie the effects of neuropeptides on anxiety and depression-related behaviour

(P9 – Benjamin Jurek, Christian Wetzel). P10 (Christian Wetzel, Caroline Nothdurfter) aims at identifying molecular pathomechanisms associated with major depression in a human cellular disease model based on patient-derived skin fibroblasts which are reprogrammed into iPSC and differentiated to neural progenitor cells and neurons. The experimental approach reaches from analysis of mitochondrial function to intra- and interneuronal signaling by means of respirometry, live-cell imaging and electrophysiology. To further increase the translational character of the funded projects, the GRK closely cooperates with clinical scientists, who established focused human studies at the Department of Psychiatry and Psychotherapy (Caroline Nothdurfter, Jens Schwarzbach) and at the Institute of Experimental Psychology located in the Faculty of Psychology, Education, and Sport Science (Mark Greenlee). Among these, P6 (Jens Schwarzbach, Mark Greenlee) uses functional Magnetic Resonance Imaging (fMRI) to investigate domain general mechanisms of fear and anxiety in the human brain. Such results are essential to collect and interpret data obtained from patients who suffer from emotion dysfunctions and can be helpful to establish better-suited animal models. A further project which has a highly translational character combines studies in patient-derived cells with the examination of changes in TSPO protein in blood sera to identify potential diagnostic biomarkers (including in vivo MR imaging and spectroscopy) of a stress response in humans (P8 – Caroline Nothdurfter, Christian Wetzel).

With these different approaches and tools, the Research Training Group GRK 2174 "Neurobiology of Emotion Dysfunction" provides PhD students with relevant scientific skills for a future career in neuroscience. To improve management skills, students and associates are additionally involved in the organization of weekly research seminars and journal clubs, annual weekend retreats, symposia and summer schools with nationally and internationally renowned invited speakers. Furthermore, the abovementioned international cooperation partners offer the opportunity for our students to work for few weeks up to three months in the collaborative labs, thereby favouring their integration into international research networks. The networking aspect is further supported by the active participation to international congresses for the presentation of own datasets, helping to improve their oral presentation skills and increase their visibility.

Finally, the GRK 2174, as well as the whole University of Regensburg, is fully dedicated to increase the number of academic female scientists in leadership positions. To reach this goal, our GRK has already organized several activities. We are particularly proud of our first two symposia (in 2017 and 2018) called "Women 4 Science: Work/Life Balance on the Way to the Top" with a unique format, i. e. only female scientists at different career levels (assistant, associate and full professor) were invited to speak about their career steps, focusing on the challenges they had to face when pursuing a scientific career in a still men-dominated working environment and simultaneously combine scientific goals with family duties. The given talks went across a mixture of career and personal relevant steps together with a description of succesfull experiences, but also failures. The informal and warm atmosphere generated by the talks exposed young scientists to different perspectives. After the seminars, all students felt comfortable to discuss about their fears, doubts and expectations with well-renowned scientists, who offered lively and spontaneous mentoring sessions to either single students or small groups.

Overall, the GRK 2174 "Neurobiology of Emotion Dysfunction" offers a multidisciplinary, comprehensive and very intense graduate educational programme with a high emphasis on translational projects which aim to understand the neurobiological underpinnings of emotion dysfunctions and bridge the gap between clinical and basic neurosciences.

Homepage: https://www.uni-regensburg.de/research/grk-emotion/index.html.

Bionotes

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Dr. Barbara Di Benedetto was born in Milan (Italy) and studied Biology at the Universita' degli Studi di Milano. She did her PhD (2008) at the Helmholtzzentrum München (former GSF) on the Neurobiology of anxiety disorders. She worked from 2008 to 2013 as postdoctoral fellow at the Max Planck Institute of Psychiatry in Munich. In 2014, after the birth of her second child, she moved to Regensburg to start her independent group, the "Neuro-Glia Pharmacology lab", in the Department of Psychiatry and Psychotherapy at the University of Regensburg. In 2019 she finished her "Habilitation". Her main scientific interest is on the role of glia-neuron interactions in health and in the etiopathogenesis of anxiety and depressive disorders. Another research interest is about the influence of astrocytes on the development and functions of the blood-brain barrier in health and disease conditions. Since 2017 she is PI in the GRK 2174 Neurobiology of Emotion Dysfunctions.

Prof. Dr. Inga D. Neumann
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e-mail: inga.neumann@ur.de

Prof. Dr. Inga D. Neumann was born in Jena, a city of Thuringia in the former Eastern Germany, and studied biology at the University of Leipzig. She finished her PhD in 1991 and spent 2 years as a postdoctoral fellow in Calgary, Canada, based on a HFSPO stipend. Afterwards, she worked as a senior scientist at the Max-Planck-Institute of Psychiatry in Munich. In 1997, after birth of her second son, she finished her "Habilitation" at the LMU in Munich, and continued as a Heisenberg fellow of the DFG. In 2001 she was appointed as a Full Professor of Physiology/Neurobiology at the University of Regensburg. Her main scientific interests are the neuropeptidergic regulation of anxiety- and depression-related and social behaviours including social preference, aggression and maternal behaviour, as well as of stress responses. Another focus are the molecular and neuronal mechanisms underlying oxytocin effects and its intracerebral release, as well as behavioural and neuroendocrine consequences of chronic psychosocial stress. She is Director of the International Elite Master Programme "Experimental and Clinical Neurosciences" at the University of Regensburg and speaker of the Themenverbund "Aggression and violence in culture and nature" at the University of Regensburg founded in 2010. Since 2017 Director and Spokesperson of the GRK 2174 Neurobiology of Emotion Dysfunctions and Dean of the Faculty of Biology and Preclinical Medicine.

Nachrichten

Claudia Duppé*

Bernstein Conference on Computational Neuroscience 2019

https://doi.org/10.1515/nf-2019-0007

The annual Bernstein Conference is one of the top meetings in the field of computational neuroscience. Having started out as the 'Bernstein Symposium' in 2005, an annual meeting organized for members of the Bernstein Network, it soon turned into a highly reputable international conference on computational neuroscience.

In the many subdisciplines of neuroscience, computational neuroscience is a bridge discipline connecting experimentally and theoretically working researchers. This is reflected very well in the list of this years' invited speakers, all of whom well-established experts in their fields with backgrounds in experimental and/ or theoretical neuroscience. This year's speakers are Eve Marder (USA), Matthias Bethge (Germany), Dora Angelaki (USA), Matthew Botvinick (USA), Claudia Clopath (UK), Nicolas Brunel (USA), Hopi Hoekstra (USA), Gilles Laurent (Germany), Haim Sompolinsky (USA/ Israel), Gašper Tkačik (Austria) and Nachum Ulanovsky (Israel). Their talks will reveal how closely theory and experiment are intertwined on the way to understanding the functionality of the brain.

Susanne Schreiber, organizer of the conference, is pleased that so many acclaimed international researchers have accepted the invitation to Berlin. "I am confident that excellent research in biology benefits from a strong theoretical component. Especially in the days of "big data" and artificial intelligence, the interdisciplinary focus of computational neuroscience is highly relevant for the neurosciences."

Promoting young scientists

In addition to attracting many established international speakers, young scientists are a key concern of the Bernstein Conference as it is the platform for networking on all career levels. One highlight of the Bernstein Conference 2019 will be the presentation of the Brains-for-Brains Award, the Bernstein Network's young researchers' award, which recognizes the special achievements of young scientists who have shown their outstanding potential at a very early career stage – even before starting their doctoral studies. The award will be conferred for the 9th time. Past winners came from Australia, USA, Israel, France, Italy, Canada, the UK and Cuba. Apart from this award, young scientists are also supported with travel grants, which facilitate access to the Bernstein Conference and the attached events for PhD candidates and postdocs to network amongst their peers.

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A platform fostering scientific and public debate

Whether trying to elucidate the neural code for cognition or perception with the help of model organisms, or using machine learning to study such neuroscientific questions – to name but two of the many research topics – computational neuroscience makes a decisive contribution to cutting-edge research, be it in contested fields like artificial intelligence or big data management. The Satellite Workshops preceding the main conference are an ideal platform to discuss topical research questions, novel scientific approaches as well as challenges and controversial issues in computational neuroscience. Apart from fostering the scientific debate within the community of scientists, the Bernstein Conference also reaches out to the general public. The conference program always includes a public evening event, which explicitly addresses a general audience and provides a scientific perspective on current topics and debates.

In 2019, the Bernstein Conference takes place back-to back with the Conference on Cognitive Computational Neuroscience CCN in Berlin, offering two excellent opportunities for international scientific exchange in the field of computational neuroscience in Europe.

Strong network in the background

The Bernstein Network Computational Neuroscience supports science, research and education in computational neuroscience, and disseminates research themes and findings to the public. It is recognized as a non-profit organization. The network started in 2004 with a funding initiative of the Federal Ministry of Education and Research (BMBF) to develop and interconnect research structures in computational neuroscience throughout Germany and to promote the transfer of theoretical insight into clinical and technical applications. With the Bernstein Conference the network organizes the largest annual computational neuroscience conference in Europe.

The interdisciplinary dialog between experimentally and theoretically working scientists is of utmost importance and is fostered at all Bernstein sites. The Bernstein

Network Computational Neuroscience promotes research and teaching in computational neuroscience with a clear commitment to equal opportunities. On a cross-institutional scale, the Bernstein Network offers the **SMART-***START* Joint Training Program in Computational Neuroscience, which specifically prepares young researchers for the interdisciplinary nature of computational neuroscience, embedding them in a strong research network at a very early career stage. Furthermore, the network takes care that the composition of its committees and the selection of speakers for events like the Bernstein Conference is gender balanced.

The Bernstein Network Computational Neuroscience is open to all researchers in the field or related subjects. Members not only benefit from a cooperative and cutting-edge research network in computational neuroscience, they can also rely on the network's central facilities: SimLab Neuroscience, the Bernstein Facility for High Performance Simulation and Data Analytics, facilitates the use of the parallel computing resources at Forschungszentrum Jülich for simulations and databases. G-Node (German Neuroinformatics Node), the Bernstein Facility for Data Technology, connects the Bernstein Network to the International Neuroinformatics Coordinating Facility (INCF). The Bernstein Coordination Site centrally manages and coordinates the network's activities. Their central public relation activities increase the national and international visibility of the network, addressing different scientific and non-scientific audiences.

Sites to visit on the web
www.bernstein-conference.de | #BernsteinConference

Nachrichten

https://doi.org/10.1515/nf-2019-0012

Fortbildungsprogramme der Neurowissenschaftlichen Gesellschaft 2019/2020

Die Mitarbeit der Mitglieder ist gefragt

Es ist wieder Zeit, Vorschläge für die Methodenkurse und die Lehrerfortbildungen der NWG zu sammeln. Diese sind seit Langem eine feste Einrichtung und erfreuen sich großer Beliebtheit. Wir möchten die Mitglieder der NWG auffordern, derartige Kurse, für die die NWG eine finanzielle Unterstützung bereitstellt, im kommenden Jahr anzubieten.

Für die Methodenkurse stellt die NWG 125 € pro teilnehmenden NWG-Mitglied und 62,50 € pro teilnehmenden Nicht-Mitglied bis zu einer maximalen Höhe von 2.500 € pro Kurs zur Verfügung. Die Lehrerfortbildungsveranstaltungen werden mit einem Betrag in Höhe von maximal 250 € pro Veranstaltung unterstützt.

Beide Programme werden mit einem gedruckten Plakat bzw. gedruckten Flyern im Spätsommer des Vorjahres angekündigt. Das Lehrerfortbildungsprogramm erstreckt sich über ein Schuljahr, also von September 2019 bis Juni 2020, das Methodenkursprogramm über das Kalenderjahr 2020.

Einsendeschluss für Angebote ist Montag, der 1. Juli 2019.

Details können bei der Geschäftsstelle der NWG erfragt werden (gibson@mdc-berlin.de).

Weitere Informationen

Methodenkurse 2019: https://nwg-info.de/de/aktivitaeten/kurse_workshops
Lehrerfortbildungen 2018/2019: https://nwg-info.de/de/aktivitaeten/kurse_workshops

Neue NWG-Preise für Studenten: Breaking News' Best Paper Award 2019

Zum ersten Mal wurden auf der Göttinger Tagung der NWG die drei Breaking News' Best Paper Awards 2019 verliehen. Preisträger sind drei Studenten, die einen Kurzvortrag in einer der beiden Breaking News Symposien gehalten haben. Für einen Vortrag in diesen Symposien konnten sich Bachelor, Master und Promotionsstudenten bewerben. Das Programmkomitee wählte aus diesen Bewerbungen 20 Abstracts für die beiden Breaking News Symposien aus. Aus diesen wiederum wählte eine Jury, der auch zwei Vertreter der neu gegründeten Sektion „Junge NWG" angehören, die drei besten Vorträge aus. Kriterien für die Auswahl sind die Aktualität und der Neuheitswert der Ergebnisse und deren eventuelle Bedeutung für zukünftige Forschung sowie die Qualität der Darbietung, sowohl in Bezug auf die Folien der Präsentation als auch auf den Vortragsstil. Das Preisgeld beträgt 500 € für den ersten, 300 € für den zweiten und 200 € für den dritten Platz.

Die Preisträger 2019 sind folgende jungen Wissenschaftler:

1. Preis: Golan Karvat (Optophysiologie, Universität Freiburg)
Real-time neurofeedback in freely behaving rats: training a network to study a network

2. Preis: Sebastian Mauricio Molina-Obando (European Neuroscience Institute, Universität Göttingen)
A combination of GABA- and glutamate-gated chloride channels mediates ON selectivity in the Drosophila visual system

3. Preis: Madhura Ketkar (Institute for Developmental and Neurobiology, Universität Mainz)
A luminance-sensitive cell type in Drosophila facilitates visual contrast computation

Mit diesen neuen Preisen für Studenten möchte die NWG einen weiteren Beitrag zur Verwirklichung eines ihrer Hauptziele, nämlich die Unterstützung des wissenschaftlichen Nachwuchses, beitragen. Dank einer großzügigen zweckgebundenen Geldzuwendung können die Preise auch auf kommenden Tagungen verliehen werden.

Foto: Arvid Leyh

Junge Neurowissenschaftliche Gesellschaft

Kurznotiz
Neu in der NWG: Interessensvertretung für junge NWG-Mitglieder

Auf der Mitgliederversammlung in Göttingen am 20. März 2019 wurde die Gründung einer neuen Sektion für junge NWG-Mitglieder (Studenten, Doktoranden und junge Postdocs bis fünf Jahre nach der Promotion) beschlossen. Sie sieht ihre Aufgabenbereiche vor allem in der Vernetzung von jungen NWG-Mitgliedern und in der Unterstützung junger Mitglieder in ihrem wissenschaftlichen Werdegang durch speziell auf ihre Bedürfnisse zugeschnittene Angebote wie Soft Skill- oder Medientraining.

Die neue Sektion wird sich und ihre Ideen in der nächsten Ausgabe von Neuroforum ausführlicher vorstellen. Vorab sind weitere Informationen unter https://nwg-info.de/de/jnwg zu finden, Fragen und Anregungen können an jNWG@NWG-info.de gerichtet werden.

Die Gründung der neuen Sektion wird eine Mitgliederbefragung zur Sektionszugehörigkeit mit sich bringen, die in naher Zukunft durchgeführt werden wird.

Wahl zum Vorstand der Neurowissenschaftlichen Gesellschaft e.V. für die Amtsperiode 2019 – 2021

Zum Stichtag 31. Januar 2019 wurden 641 Wahlzettel eingesandt. Das entspricht einer Wahlbeteiligung von 28,2 %. Davon waren 595 Wahlzettel gültig, 45 mussten als ungültig gewertet werden, 1 war ohne Absender und ist nicht in das Abstimmungsergebnis eingegangen. Die ordnungsgemäße Durchführung der Wahl wird vom Wahlleiter, Prof. Dr. Michael Synowitz, Kiel, bestätigt.

Präsident	Prof. Dr. Albert Christian Ludolph (Ulm)		
	Ja: 545	Nein: 32	Enthaltung: 18
Vizepräsident	Prof. Dr. Christine R. Rose (Düsseldorf)		
	Ja: 552	Nein: 25	Enthaltung: 18
Generalsekretär	Prof. Dr. Christian Steinhäuser (Bonn)		
	Ja: 564	Nein: 10	Enthaltung: 21
Schatzmeister	Prof. Dr. Ansgar Büschges (Köln)		
	Ja: 570	Nein: 9	Enthaltung: 16

Sektionssprecher

Computational Neuroscience	Dr. Udo Ernst (Bremen) 45 Prof. Dr. Sonja Grün (Jülich)) 93
Entwicklungsneurobiologie/Neurogenetik	Prof. Dr. Petra Wahle (Bochum) 70
Klinische Neurowissenschaften	Prof. Dr. Mathias Bähr (Göttingen) 79 Prof. Dr. Ricarda Diem (Heidelberg) 69
Kognitive Neurowissenschaften	Prof. Dr. Hanspeter A. Mallot (Tübingen) 61 Prof. Dr. Melanie Wilke (Göttingen) 74
Molekulare Neurobiologie	Prof. Dr. Andreas Faissner (Bochum) 87 Prof. Dr. Frank Kirchhoff (Homburg) 108
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Zelluläre Neurowissenschaften	Prof. Dr. Veronica Egger (Regensburg) 92 Prof. Dr. Leda Dimou 57 Prof. Dr. Marc Spehr 48

Der Vorstand der Amtsperiode 2019 – 2021 setzt sich somit wie folgt zusammen:

Präsident
Prof. Dr. Albert Christian Ludolph (Ulm)

Vizepräsident
Prof. Dr. Christine R. Rose (Düsseldorf)

Generalsekretär
Prof. Dr. Christian Steinhäuser (Bonn)

Schatzmeister
Prof. Dr. Ansgar Büschges (Köln)

Sektionssprecher
Computational Neuroscience
Prof. Dr. Sonja Grün (Jülich)

Entwicklungsneurobiologie/Neurogenetik
Prof. Dr. Petra Wahle (Bochum)

Klinische Neurowissenschaften
Prof. Dr. Mathias Bähr (Göttingen)

Kognitive Neurowissenschaften
Prof. Dr. Melanie Wilke (Göttingen)

Molekulare Neurobiologie
Prof. Dr. Frank Kirchhoff (Homburg)

Neuropharmakologie/-toxikologie
Prof. Dr. Angelika Richter (Leipzig)

Systemneurobiologie
Prof. Dr. Benedikt Grothe (Martinsried)

Verhaltensneurowissenschaften
Prof. Dr. Christian Wegener (Würzburg)

Zelluläre Neurowissenschaften
Prof. Dr. Veronica Egger (Regensburg)

Junge NWG
Sophie Seidenbecher (Aarhus; kommissarisch)

Der neue Vorstand trat sein Amt mit dem Ende der Göttinger Tagung der NWG am 23. März 2019 an.

Neueintritte

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

Albi, Angela (Konstanz)
Bartsch, Dr. Julia Constance (Münster)
Birdal, Günes (Köln)
Bohne, Pauline (Bochum)
Bozorg Nia, Dr. Shahrzad (Köln)
Breitenbach, Jürgen (St. Goarshausen)
Bulgur, Deniz (Marburg)
Clavet-Fournier, Valérie (Göttingen)
Dahlmanns, Marc (Erlangen)
De Bruyckere, Dr. Elodie (Köln)
Deneke, Lea Marie (Mainz)
Dietrich, Dr. Susanne (Tübingen)
Dormann, Dr. Dorothee (Planegg-Martinsried)
Dwarakanath, Abhilash (Tübingen)
Eckert, Philipp (Tübingen)
Ehmann, Dr. Nadine (Leipzig)
Elizarova, Anastasia (Nizhny Novgorod, Russia)
Ellenberger, Marek (Marburg)
Elolf, PhD Lauren (West Lafayette, USA)
Fleischmann, Dr. Pauline Nikola (Würzburg)
Franz, Dr. Henriette (Freiburg)
Fröhlich, Dr. Nicole (Tübingen)
Grabot, Dr. Laetitia (Bielefeld)
Gür, Burak (Göttingen)
Haage, Verena (Berlin)
Haghparast, Prof. Abbas (Tehran, Iran)
Haink, Karen Kerstin (Berlin)
Hannah, Ihme (Marburg)
Hassan, Shahzaib (Köln)
Hellwig, Lina (Ulm)
Henning, Lukas (Bonn)
Hojas Garcia-Plaza, Inés (Göttingen)
Idriss, Sherif (Lübeck)
Kalenscher, Dr. Tobias (Düsseldorf)
Karvat, Golan (Freiburg)
Kessler, Roman (Marburg)
Ketkar, Madhura (Göttingen)

Kettler, Dr. Lutz (Freising)
Kizilirmak, Dr. Jasmin (Hildesheim)
Knobloch-Bollmann, Dr. Hanna Sophie (Freiburg)
Knorr, Debbra Yasemin (Göttingen)
Kobylkov, Dmitry (Oldenburg)
Kreutzmann, Judith (Magdeburg)
Kuerschner, Dr. Lars (Bonn)
Le, Kim Chi (Aachen)
Leplow, Prof. Bernd (Halle/Saale)
Liauchuk, Viktoryia (Aachen)
Liedtke, Maik (Rostock)
Linde, Jenice (Aachen)
Lopes Amaro, Diana Ines (Planegg-Martinsried)
Maraslioglu, Ayse (Kaiserslautern)
Marchetta, Philine (Tübingen)
Michael, Maria (Göttingen)
Mushtaq, Zeeshan (Kaiserslautern)
Nasser, Dr. Assef (Tripolis, Lebanon)
Nawrot, Prof. Dr. Martin (Köln)
Neumann, Anne-Marie (Lübeck)
Nicholson, LaShae (Frankfurt am Main)
Nödler, Mareike (Lohfelden)
Nouvian, Dr. Morgane (Konstanz)
Pagella, Sara (Planegg-Martinsried)
Pakan, Dr. Janelle (Magdeburg)
Park, Dr. Hame (Bielefeld)
Peeva, Polina (Berlin)
Pentimalli, Tancredi Massimo (Rom, Italy)
Petersilie, Laura (Düsseldorf)
Philippot, Camille (Bonn)
Plath, Dr. Jenny A. (Kassel)
Pohl, Leonardo (Berlin)
Preissing, Bianca (Bochum)
Pschorr, Dr. Johannes (Biberach an der Riss)
Rogalla, Meike Marie (Oldenburg)
Rojas, Pedro Pablo (Kassel)
Rosenmund, Prof. Dr. Christian (Berlin)
Saber Marouf, Babak (Magdeburg)
Sathish, Dr. Kumar (Bonn)
Saxena, Pankhuri (Göttingen)
Schilling, Tim (Berlin)
Schulze, Jana (Madgeburg)
Sebastian, Malinowski (Aachen)
Segebarth, Dennis (Würzburg)
Sehuanes Tellez, Juan Felipe (Tübingen)
Shcherina, Anna (Nizhny Novgorod, Russia)
Simon, Manuel (München)
Steffen, Dr. Johannes (Magdeburg)
Stöckl, Dr. Anna (Würzburg)
Strasser, Patrik (München)
Straw, Prof. Dr. Andrew David (Freiburg)
Sven, Dannhäuser (Leipzig)
Tavosanis, Prof. Dr. Gaia (Bonn)
Teng, Dr. Zenghui (Düsseldorf)
Thoms, PD Dr. Sven (Göttingen)
Timmermann, Aline (Bonn)
Tomar, Manish (Köln)
Türknetz, Mira (Homburg)
Unger, Felix (München)
Untiet, Dr. Verena (Kobenhavn, Denmark)
Viswanathan, Vivekanandhan (Magdeburg)
Voigt, Matthias (Greifswald)
Völkner, Christin (Rostock)
von Wittgenstein, Dr. Julia (Erlangen)
Voß, Timo-Daniel (Ulm)
Wadle, Simon Lothar (Kaiserslautern)
Weber, Tobias (Kaiserslautern)
Wilke, Justus (Göttingen)
Yurt, Pinar (Göttingen)
Yüzak, Deniz (Göttingen)
Zheng, Dr. Ping (Münster)
Zott, Benedikt (München)

Der Mitgliedsstand zum 28. März 2019 beträgt 2.293 Mitglieder.

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

Prof. Dr. Sonja Grün
Sektionssprecherin „Computational Neuroscience“

Academic Background
1984–1991
Study of Physics at Eberhard-Karls University, Tübingen, Germany
1991–1995
Research Assistant, Weizmann Institute of Science, Rehovot, Israel and Inst. for Neuroinformatics, Ruhr-University Bochum, Germany
1996
Dr. rer. nat. obtained from Faculty of Astronomy and Physics at the Ruhr-University, Bochum, Germany. Supervisors: Prof. A. Aertsen and Prof. C. von der Malsburg
1995–1997
Postdoc (Dept. of Physiology, Hebrew University Jerusalem, Israel; Prof. Abeles)
1998–2002
Senior Fellow (Max-Planck-Institut für Hirnforschung, Frankfurt/M, Germany; Prof. Singer)
2003
Habilitation, Albert-Ludwigs-University Freiburg
2002–2006
Assistant-Professor for Neuroinformatics/Theoretical Neuroscience, Freie University, Berlin, Germany
2006–2011
Unit- und Team-Leader, RIKEN Brain Science Institute, Wako-City, Japan
Since 2011
Professor (full) for Theoretical Systems Neurobiology, RWTH Aachen, Germany
2011–2018
Vice director of Institute of Neuroscience and Medicine (INM-6), Jülich Research Center
Since 2018
Director of Institute of Neuroscience and Medicine (INM-6 and INM-10), Jülich Research Center

Other academic functions
Since 2013 – WP leader Human Brain Project (EU Grants 604102, 720270 and 785907)
2014–2016 – guest profressor at Osaka Univ, Japan
Since 2017 – Member of the steering committee ‘Research Data Management’ of the Jülich Research Center
Since 2017 – Scientific coordinator together with Dr. T. Brochier of International Associated Laboratory (LIA) “Vision for Action” between CNRS Marseille and Research Centre Jülich.
Since 2018 – Faculty of DFG Research Training Group “MultiSenses-MultiScales” RTG 2416

Research Interests
Higher brain functions are attributed to the cortex that is composed of a large number of neurons of highly interconnected neurons. A potential mechanism for neuronal information processing is the coordinated activity of populations of neurons. To approach this level of processing requires to study the spatial and temporal scales of neuronal interaction and the observation of large portions of the network simultaneously. The research group of Sonja Grün focuses on the development of analysis strategies and tools that uncover concerted activity in electrophysiological signals (such as massively parallel spike trains and local field potential recordings). This enables the exploration of the relevance of the observed activity for behavior and cognition. The research goal is to gain an understanding of the spatio-temporal scales at which the cortex operates, and to contribute to uncovering its function. The work includes also the development of open source data analysis software, curation of data with extensive metadata, and the implementation of collaborative, reproducible digital workflows. The validation of network models on experimental data serves to create models that help to to interpret the system dynamics.

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Prof. Dr. med. Mathias Bähr Sektionssprecher „Klinische Neurowissenschaften“

Beruflicher Werdegang
1979–1985
Studium der Humanmedizin an der Universität Tübingen
1985
Approbation als Arzt
1986
Promotion
1986–1987
Zivildienstleistender Arzt von Januar 1986 bis Mai 1987 an der Neurologischen Klinik der Universität Düsseldorf bei Prof. H. J. Freund.
1987–1989
Stipendium der DFG am Max-Planck-Institut für Entwicklungsbiologie (Prof. F. Bonhoeffer) von Mai 1987 bis Juni
1987–1990
Mitglied im Graduiertenkolleg Neurobiologie der Universität Tübingen
1988–1989
Max-Planck-Stipendium an der Washington University St.Louis bei Prof. R.P. Bunge von Oktober 1988 bis März 1989.
1989–1993
Wissenschaftlicher Assistent bei Prof. J. Dichgans an der Neurologischen Klinik der Universität Tübingen
1993
Facharzt für Neurologie und Habilitation über ‚Zelluläre Grundlagen der neuronalen Regeneration im adulten ZNS‘ an der Eberhard-Karls Universität Tübingen
1995
Nachwuchsgruppe Neurobiologie des Ministeriums für Wissenschaft, Forschung und Kunst Baden-Württemberg
1996
Herrmann und Lilly Schilling-Stiftungsprofessur (C3) des Stifterverbandes der Deutschen Wirtschaft
1997/1998
Leitender Oberarzt und Stellvertreter von Prof. Dichgans Koordinator eines EU-Biotech-Forschungsprogrammes
1999
Ruf auf eine C4 Professur für Neurologie der Universitätsklinik Homburg/Saar – abgelehnt 2000
2001
C4 Professur für Neurologie an der Georg-August-Universität Göttingen

Forschungsprojekte
- Präklinische Modelle neurodegenerativer Erkrankungen (Parkinson; Stroke; Multiple Sklerose).
- Entwicklung neuer, translationaler neuroprotektiver Therapieverfahren, medikamentör, mit gentherapeutischen Ansätzen und Stammzell-Transplantation.
- Konzeption und Umsetzung von Investigator Initiated Studies (IITs).
- Aufbau eines Zentrums für Heart&Brain Research.

Auszeichnungen und Ehrenämter
Attempto Preis der Universität Tübingen
Förderpreis des Kuratorium ZNS und der Hannelore-Kohl-Stiftung
Herrmann und Lilly Schilling Stiftungsprofessur
Heinrich Pette-Preis der Deutschen Gesellschaft für Neurologie
Mitglied der Deutschen Nationalakademie der Naturforscher Leopoldina
Fellow of the Royal Academy of Physicians (London)
Präsident der Deutschen Neurowissenschaftlichen Gesellschaft (2007–2009)
Mitglied der Akademie der Wissenschaften zu Göttingen
Mitglied im Lenkungsausschuss des Internetportals ‚dasGehirnInfo.de‘
Mitglied im Vorstand des DZNE-Göttingen

Sprecher des European Neuroscience Institutes (ENI) Göttingen
Sprecher des DFG-Forschungszentrums ‘Center Nanoscale Microscopy and Molecular Physiology of the Brain (CNMPB)

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Homepage department: http://www.neurologie.med.uni-goettingen.de/start/english.html
Homepage lab: http://www.baehrlab.med.uni-goettingen.de/

Prof. Dr. Melanie Wilke Sektionssprecherin „Kognitive Neurowissenschaften“

Beruflicher Werdegang
1997–2001
Studium (M.A.) der Psycholinguistik, Neuropsychologie und Neurobiologie an der Ludwig-Maximilians-Universität, München
2001–2005
Promotion zum Dr. rer. nat. der Neurowissenschaften am Max-Planck-Institut für Biologische Kybernetik
2005–2008
Postdoctoral Fellow am National Institute of Mental Health (NIMH), Bethesda, USA
2008–2011
Postdoctoral Fellow am California Institute of Technology (Caltech), Pasadena, USA
seit 4/2011
Direktorin der Abteilung für Kognitive Neurologie, Universitätsmedizin Göttingen und Projektleiterin der ‘Decision and Awareness Group am Deutschen Primatenzentrum’, Göttingen

Förderpreise und Auszeichnungen
2008
Fellows Award for Excellence in Biomedical Research, National Institutes of Health
2014
Patent: Wilke, M., Kagan, I., Anderson R.A.: Brain repair using electrical microstimulation of healthy nodes. DKT No. 065471-0000038US00/CIT-6260 (filed 07/2013) *(granted 09/2014)*
2011–2022
Hermann und Lilly Schilling-Stiftungsprofessur

Arbeitsgebiete
Mein Themenschwerpunkt liegt auf der Erforschung gesunder und gestörter visueller Wahrnehmungs- und Entscheidungsprozesse. Ein wichtiges Ziel unserer Forschung ist es Brücken zwischen kognitiver Grundlagen- und klinischer Forschung aufzubauen, indem zelluläre Ableitungen, Stimulations- und fMRT-Verfahren systematisch vom Tiermodell auf den Menschen übertragen werden.

Stichworte: Visuelles Bewusstsein, Entscheidungsfindung, Oszillationen, Thalamo-kortikale Interaktionen, räumlicher Neglect

Sonstige berufliche Aktivitäten
seit 2013
Leiterin der Primaten-Plattform und Vorstandsmitglied am Center for Nanoscale Microscopy and Molecular Physiology of the Brain (CNMPB)
seit 2011
Review Editor: Frontiers in Consciousness Research
seit 2015
Associate editor: Neuroscience of Consciousness

Adresse:
Prof. Dr. Melanie Wilke
Kandidatin Sektionssprecherin „Kognitive Neurowissenschaften“
Direktorin Institut für Kognitive Neurologie
Universitätsmedizin Göttingen
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Prof. Dr. Frank Kirchhoff Sektionssprecherin „Molekulare Neurobiologie“

Scientific Education and Employment
since 2009
Full Professor (W3) and Head of the Department of Molecular Physiology,
CIPMM, University of Saarland, Homburg, Germany
2000–2009
Research Group Leader, Max Planck Institute of Experimental Medicine, Göttingen
1997–2008
Lecturer at the Free University of Berlin
1997
Habilitation in Biochemistry, Free University of Berlin
1995–1999
Research Assistant, Cellular Neurosciences, Max Delbrück Center for Molecular Medicine, Berlin
1991–1994
Postdoctoral fellow, Institute of Neurobiology, University of Heidelberg
1986–1990
PhD (Dr. rer. nat.), Institute of Neurobiology, University of Heidelberg
1985
Diploma in Biochemistry, Institute of Neurobiology, University of Heidelberg
1981–1985
Study of Biochemistry, University of Hannover

Honours, Distinctions and Community Services
Since 2018
Senator of the University of Saarland
Since 2016
Member of the Academia Europaea
Since 2016
Coordinator of EU-H2020-MSCA ITN EU-GliaPhD
Since 2015
Editorial board member of NeuroForum
Since 2014
„Visiting Professor“ at the University of Medicine and Pharmacy of Craiova, Craiova, Romania, and of theUniversity of Campinas, Campinas, Brazil
Since 2013
Coordinator of the DFG Priority Programme SPP 1757 “Glial Heterogeneity”
(with Prof. Christine Rose, Düsseldorf)
Since 2013
Member of the International Scientific Advisory Committee (ISAC) Achucarro Basque Center of Neuroscience in Bilbao-Zamudio (Spain)
Since 2010
Editorial board member of Journal of Chemical Neuroanatomy
Since 2009
Editorial board member of GLIA
1987–1989
PhD Fellowship of the Boehringer Ingelheim Fonds
1981–1986
Fellowship of the Studienstiftung des deutschen Volkes

Research Interests
Our research focuses on the molecular and cellular mechanisms of neuron-glia interaction in the central nervous system. We are pursuing the following research questions: How do glial transmitter receptors sense and modulate synaptic transmission? What is the impact for living organisms? How do glial cells respond to acute injuries within the central nervous system?

Adresse:
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e-mail: frank.kirchhoff@uks.eu
homepage: www.kirchhoff-lab.de

Prof. Dr. Veronica Egger Sektionssprecher „Zelluläre Neurowissenschaften“

Werdegang
1996
Diplom in Allgemeiner Physik, TU München
1996–1999
Doktorarbeit am MPI für medizinische Forschung Heidelberg, Abt. Zellphysiologie (B. Sakmann) und Fakultät für Physik der Universität Heidelberg
1999–2000
Postdoc, Zellphysiologie, MPImF Heidelberg (B. Sakmann)
2000–2004
Postdoc (Emmy-Noether), CSHL, New York, USA (Z. Mainen, K. Svoboda)
2001
Schloessmann-Preis “Optical methods in biology” (Max-Planck-Gesellschaft)
2011–2013
Unabhängige Nachwuchsgruppenleiterin (BMBF), Biozentrum, LMU München (B. Grothe)
seit 2013
W2-Professorin, Institut für Zoologie, Fakultät für Biologie und Vorklinische Medizin, Universität Regensburg

Wissenschaftliche Schwerpunkte
Unser Hauptinteresse gilt der zellulären und synaptischen Neurophysiologie im Bulbus olfactorius von Nagern, und dort insbesondere der Rolle der reziproken Synapsen zwischen Mitralzellen und Körnerzellen, sowie auch der Funktion von Interneuronen der Glomerularschicht. Zur Beobachtung einzelner Synapsen kombinieren wir elektrophysiologische Ganzzell-Ableitungen mit hochauflösendem Zwei-Photonen-Ca^{2+}-Imaging und Zwei-Photonen-Uncaging von Transmitter, ergänzt durch Modellierung. Damit konnten wir inzwischen nachweisen, dass die reziproken Synapsen auf Seiten der Körnerzellen wie unabhängige Mini-Neuronen agieren können. Daneben verfolgen wir den systemischen Ansatz, mittels einer semi-intakten Nase-Hirn-Präparation sensorische Verarbeitung *in vitro* zu untersuchen, wobei zunächst die Genese von spontanen Netzwerkoszillationen von Interesse ist.

Adresse:
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Fakultät für Biologie und vorklinische Medizin
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93040 Regensburg
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E-Mail: veronica.egger@ur.de

Ausblick

Prof. Andreas Meisel und Prof. Christian Meisel
Friend or foe? – B cells in stroke

Prof. Seija Lehnardt und Prof. Philipp Henneke
Role of RNA as an activator of immune receptors

Dr. Thomas Blank und Dr. Daniel Erny
The gut-brain axis: Microglia in the spotlight

Prof. Josef Priller und Prof. Marco Prinz
Myeloid hetereogeneity on single cell level

Prof. Dr. Andreas Vlachos
The neuroimmunological synapse: from metaplasticity to brain disease

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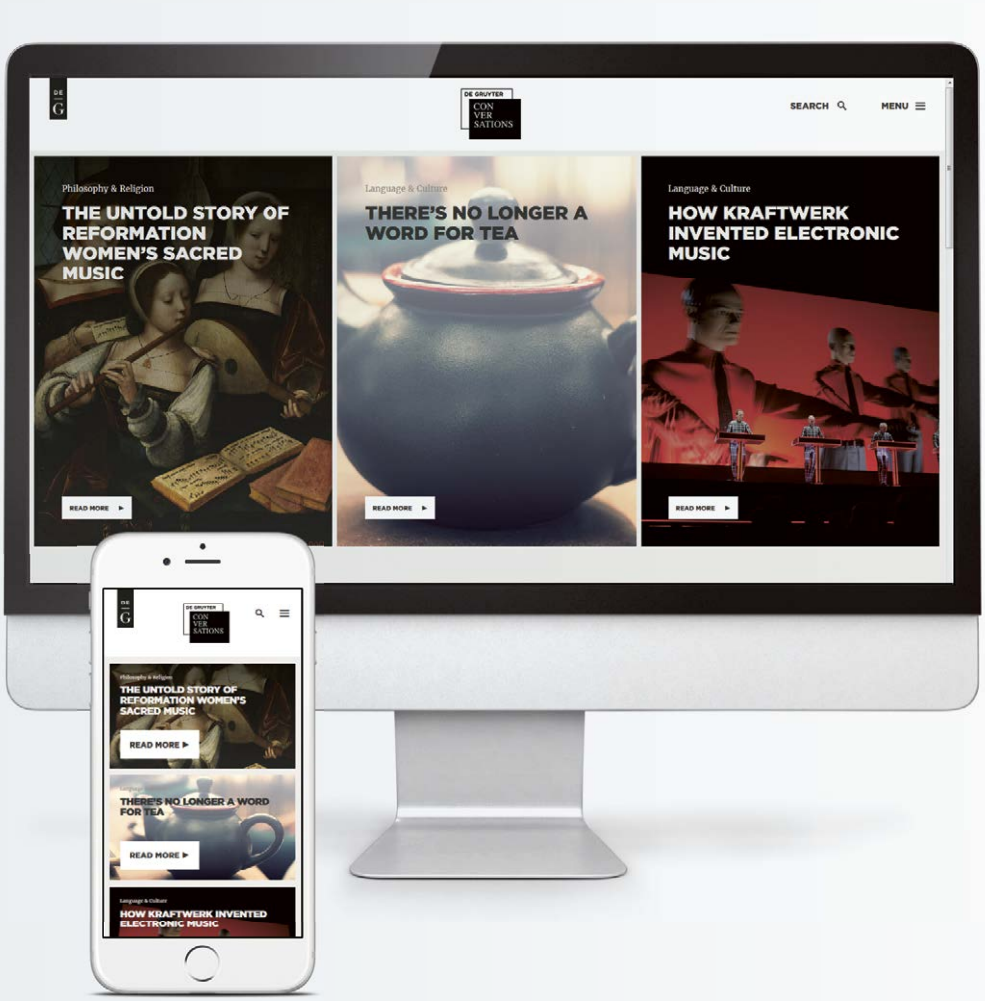

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Ich unterstütze den Antrag auf Beitritt zur Neurowissenschaftlichen Gesellschaft e.V.:

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Neurowissenschaftliche Gesellschaft e.V.
Stefanie Korthals
Max-Delbrück-Centrum für Molekulare Medizin
Zelluläre Neurowissenschaften
Robert-Rössle-Straße 10

13092 Berlin

Ich optiere für folgende 2 Sektionen:
(bitte ankreuzen)

- ☐ Verhaltensneurowissenschaften
- ☐ Zelluläre Neurobiologie
- ☐ Entwicklungsneurobiologie und Neurogenetik
- ☐ Neuropharmakologie und -toxikologie
- ☐ Systemneurobiologie
- ☐ Molekulare Neurobiologie
- ☐ Klinische Neurowisschenschaften
- ☐ Computational Neuroscience
- ☐ Kognitive Neurowissenschaften

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