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HERAUSGEBER Neurowissenschaftliche Gesellschaft e.V. (NWG), Kontakt: Meino Alexandra Gibson, Max-Delbrück-Centrum für Molekulare Medizin, Robert-Rössle-Straße 10, 13092 Berlin, Tel.: +49 (0)30 9406 3336, gibson@mdc-berlin.de, www.nwg-info.de

CHEFREDAKTEURIN Chefredakteurin Petra Wahle, AG Entwicklungsneurobiologie, Fakultät für Biologie & Biotechnologie, Ruhr-Universität, ND 6/72, 44780 Bochum, Tel.: 0234-32-24367

REDAKTION Susanne Hannig, Max-Delbrück-Centrum für Molekulare Medizin, Robert-Rössle-Str. 10, 13092 Berlin (Germany), Tel.: +49 (0)30 9406 3336, susanne.hannig@mdc-berlin.de

JOURNAL MANAGER Torsten Krüger, De Gruyter, Genthiner Straße 13, 10785 Berlin, Germany. Tel.: +49 (0)30 260 05-173, Fax: +49 (0)30 260 05-250, E-Mail: Neuroforum.Editorial@degruyter.com

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COVER ILLUSTRATION The cover shows two male crickets fighting (photographed by Jan Rillich). As in other animals, they must decide when it would be more opportune to fight on, or turn and flee. Paul Stevenson and Jan Rillich from Leipzig University found that crickets implement the decision by differentially modulating the behavioural threshold to flee with different neurotransmitters (OA - octopamine, DA dopamine, NO nitric oxide, 5HT serotonin), released in response to potentially rewarding experiences (e.g. resource possession), and aversive-experiences (e.g. opponents aggressive actions during a fight).

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Inhalt

Editorial

Wechsel des Chefredakteurs und Umstellung auf Englisch

https://doi.org/10.1515/nf-2018-0035

In der ersten Hälfte des Jahres 2018 waren Petra Wahle und Heiko Luhmann gemeinsam als Chefredakteur/in von Neuroforum tätig. Mitte 2018 haben wir den Wechsel zu Petra Wahle voll umgesetzt. Wir danken Heiko Luhmann an dieser Stelle herzlich für viele Jahre erfolgreicher Arbeit für die NWG und Neuroforum. Unter Heikos Leitung wurde der Wechsel zum Verlag De Gruyter vollzogen.

Was bleibt beim Alten? Wir werden weiterhin fünf eingeladene Übersichtsartikel pro Ausgabe publizieren. Wir bitten daher um Vorschläge für Autoren und Themen, sie sind stets willkommen. Ebenso hoffen wir, weiterhin eine Ausgabe pro Jahr als Spezialheft zu einem Thema zu publizieren. Für die Ausgabe 03/2019 haben sich Marco Prinz, Freiburg, und Josef Priller, Berlin, als Ko-Editoren mit dem Thema Neuroinflammation zur Verfügung gestellt.

Was gibt es Neues? Es gibt vor allem eine wichtige Neuerung und – so hoffen wir – Arbeitserleichterung für unsere Autoren und unsere Gutachter. Wir haben im Vorstand der NWG über eine Umstellung der Artikel ausschließlich auf Englisch diskutiert und in einer Abstimmung uns einstimmig dafür ausgesprochen. Ab dieser Ausgabe werden daher auch die im Heft gedruckten Artikel auf Englisch erscheinen, in identischer Form wie online in e-Neuroforum. Sie erhalten auch nur noch ein- und dieselbe DOI. Wir erhoffen uns eine verbesserte Zitierbarkeit der Artikel, aber auch die Möglichkeit, deutsche Kollegen im Ausland, englischsprachige Kollegen, die an deutschen Forschungseinrichtungen arbeiten oder in Deutschland ausgebildet wurden bzw. längere Zeit geforscht haben, als Autoren gewinnen zu können. Für das kooperative Mitwirken bei der Umstellung bedanken wir uns hiermit bei den Verantwortlichen im De Gruyter-Verlag.

Alle Artikel werden von zwei Gutachtern begutachtet, in den meisten Fällen dem Editorial Board angehörend. In Einzelfällen werden wir zukünftig weitere Kollegen um Gutachten bitten, um eine größtmögliche Fachnähe zu gewähren. Wir möchten hier bereits schon den Mitgliedern des Editorial Boards und den externen Gutachtern für ihre konstruktive Mitarbeit danken. Wir hoffen, dass Sie/Ihr auch weiterhin bereit sind/seid, Artikel für Neuroforum zu begutachten – dann aber nur noch eine, nämlich englische Version, und dies vermutlich hin und wieder auch mal „on (very) short notice“. Dank dafür!

Auf der Neuroforum-Website von De Gruyter können Sie EToc alerts anfordern, um über neu publizierte Artikel aktuell informiert zu werden. Des Weiteren gibt es seit Mitte 2018 einen Twitter-Account (*@NeuroforumNWG*), der von unserer Kollegin in der Redaktion, Susanne Hannig, bestückt wird. An Susanne und an Meino Gibson geht ein herzlicher Dank. Eure Ideen und Euer Engagement sind besonders viel wert.

Nach wie vor können Begleitmaterialien zu den Artikeln, wie Videos und Bilder mit hoher Auflösung, kostenfrei über die Neuroforum-Website veröffentlicht werden. Dort stehen auch alle Ausgaben von Neuroforum als PDF zur Verfügung, beginnend ab dem Jahr 1995. Ausgewählte Artikel werden kostenfrei im Open Access publiziert.

Wir hoffen, dass Sie die NWG auf diesem Weg unterstützen werden.

Mit freundlichen Grüßen

Petra Wahle
Editor in Chief

Eckhard Friauf
Präsident

Review Article

Paul A. Stevenson* and Jan Rillich

Fight or flee? Lessons from insects on aggression

https://doi.org/10.1515/nf-2017-0040

Abstract: Aggression between members of the same species serves to secure resources, but the costs can quickly outweigh benefits. Hence, for aggression to be evolutionarily adaptive, animals must decide when best to flee, rather than fight. How its done, is arguably best understood in crickets. These insects implement the decision by simply modulating the behavioural threshold to flee. This threshold is raised by potentially rewarding experiences (e. g. resource possession), via the amine octopamine, so that the animal is less prone to flee and persists longer in fighting. Conversely, the threshold is lowered by nitric oxide, released in response to aversive stimuli (e. g. the opponent's agonistic signals), thus increasing the tendency to flee. A cricket then flees, when the sum of its opponent's actions exceeds the threshold. Subsequently, serotonin keeps the threshold low, so that losers remain submissive; possibly by inhibiting dopamine, which is necessary for recovery of aggression in losers.

Keywords: serotonin, octopamine, nitric oxide, social behaviour, decision making

Introduction

Darwin (1859) recognised that the struggle for existence was most severe between individuals of the same species – after all they compete for the same niches, foods and sexual partners. Although intra-specific aggression can ensure survival, it's a dangerous game, and the costs of injury can quickly exceed the potential gains. Hence, for aggression to be evolutionarily adaptive, all animals must know when it would be more opportune to fight or to flee. But how? Behavioural game theory (Maynard-Smith and Price, 1973; Hardy and Briffa, 2013) posits that the ritualised fighting strategies common in animals and even indigenous peoples, with impressive threats preceding blows, have evolved as a low-risk means to assess win chances. Win chances largely depend on physical attributes such as strength and weaponry (teeth, claws, horns), but also on an individual's aggressive motivation, or tendency to invest energy in fighting. Aggressive motivation, in turn, is largely experience dependent. It is promoted by the presence of resources, which can differ in value for each contestant, and fuel the weaker to prevail, for example, in defence of offspring (Maynard-Smith and Parker, 1976; Hsu et al., 2006). Winners also tend to become more aggressive and win subsequent interactions, whereas losers become submissive, even towards unfamiliar opponents (the loser effect). Defeat is also often coupled with depression-like symptoms in animals and humans that can become severe, particularly after repeated defeats (de Boer et al., 2016) and can even shorten lifespan (Razzoli et al., 2018). But what are the proximate mechanisms underlying experience-dependent changes in aggressive motivation and in the assessment of costs, benefits and win chances? How, exactly, do animals decide when to fight or flee?

The answers of course lie in the brain. Aggression is influenced by numerous neurotransmitters, modulators and hormones and the drugs that affect them (Trainor et al., 2017). These signalling systems, with widespread innervation patterns and multiple, functionally unique receptors as mediators are highly complex (Carhart-Harris and Nutt, 2017), and it has thus proven elusive to decipher their natural, behavioural functions in aggression (Oliver, 2015).

Here, we summarise how experiences control the decision to fight or flee via the action of neurotransmitters in insects, primarily adult male crickets (*Gryllus bimaculatus*). But first, why crickets? In addition to having a comparatively simpler nervous system, their spectacular fighting behaviour is highly stereotyped, and hence easily quantified (Figure 1). Even so, as in mammals, aggression in crickets is promoted by physical activity, winning, the presence of resources, and is suppressed by defeat, particularly multiple defeats, with potentially lifelong consequences (Stevenson and Rillich, 2017). Furthermore, our work illustrates that crickets can make seemingly complex social decisions without conscious reasoning, and this is arguably their greatest experimental advantage. Work on

***Corresponding author: Paul A. Stevenson,** University of Leipzig, Faculty of Life Sciences, Institute for Biology, Talstrasse 33, 04103 Leipzig, Germany, E-Mail: stevenson@rz.uni-leipzig.de
Jan Rillich, University of Leipzig, Faculty of Life Sciences, Institute for Biology, Talstrasse 33, 04103 Leipzig, Germany

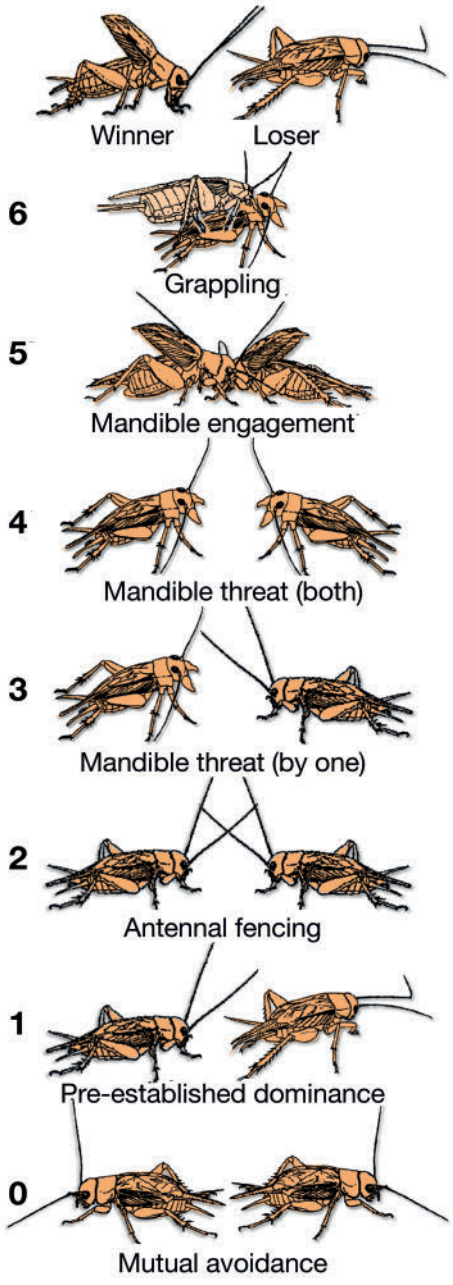

Figure 1 Levels of escalating aggression in crickets. Fights can conclude at any level, when one opponent retreats, but they usually escalate to level 5 and last several seconds. Losers exhibit reduced aggression for about 3 h after defeat, whereas winners become hyper-aggressive. Modified from Stevenson et al., 2000.

insects, also point to some remarkable similarities in the mechanism underlying aggression in insects, rodents and man (Thomas et al., 2015; Stevenson and Rillich, 2017), that will be mentioned here. Our main aim, however, is to point out novel insights into how crickets make the actual decision to fight or flee, which is less well understood in other model animals.

Controlling the decision to fight – the role of octopamine (OA)

In his pioneering work on crickets, Franz Huber (1955) found that elements of aggressive behaviour can be elicited by electrical stimulation of the brain. The natural aggression-releasing stimulus, however, is antennal contact between male crickets during fencing behaviour, and comprises both mechanical and olfactory components (Sakura and Aonuma, 2013; Rillich and Stevenson, 2015). Male-male contact leads to release of the amine octopamine (OA) in crickets (Adamo et al., 1995; Figure 2) and to direct excitation of OA neurones by pheromone sensitive receptors in *Drosophila* (Andrews et al., 2014). Much like the related amines noradrenaline (NA) and adrenaline (AD) in vertebrates, OA acts in insects as a stress hormone, released to cope with high energy demand and to support fight or flight responses (Verlinden et al., 2010). Whereas a consistent relationship between NA/AD and mammalian aggression has yet to be established (Nelson, 2006), pharmacological and genetic manipulations show that OA increases aggression in crickets (Stevenson et al., 2005) and fruit flies (Hoyer et al., 2008; Zhou et al., 2008). However, pharmacological depletion revealed that neither OA, nor any other amine, is necessary to actually initiate aggression (Stevenson et al., 2000). Furthermore, although simply lashing a male cricket's antennae with the cut antennae of another male is sufficient to elicit an aggressive response (rival song production, mandible spreading, cf. Figure 1), this is not altered by aminergic drugs (Rillich and Stevenson, 2015). After antennal stimulation, however, the crickets escalate higher, and persist longer in actual fights and this effect is dependent on OA. This is just one example illustrating that OA mediates the aggression-promoting effects of a variety of experiences (Figure 3).

A less insect-specific effect is that of physical exertion, a naturally reinforcing and rewarding activity in rodents (Herrera et al., 2016) that also enhances aggression in man (Wood and Stanton, 2012). In crickets, flying induces OA release (Adamo et al., 1995) and a subsequent transient increase in aggression (Hofmann and Stevenson, 2000), that is blocked by OA-receptor antagonists and mimicked by the OA agonist chlordimeform (CDM; Stevenson et al., 2005). Although the pesticide CDM binds almost irreversibly to OA receptors, the crickets are not protected from losing a contest. Hence, the decision to flee must be controlled independent of OA.

Winning increases aggression in numerous animals (Hsu et al., 2006). In rodents, this winner effect is mediated by androgens (Oliviera et al., 2011) and dopamine

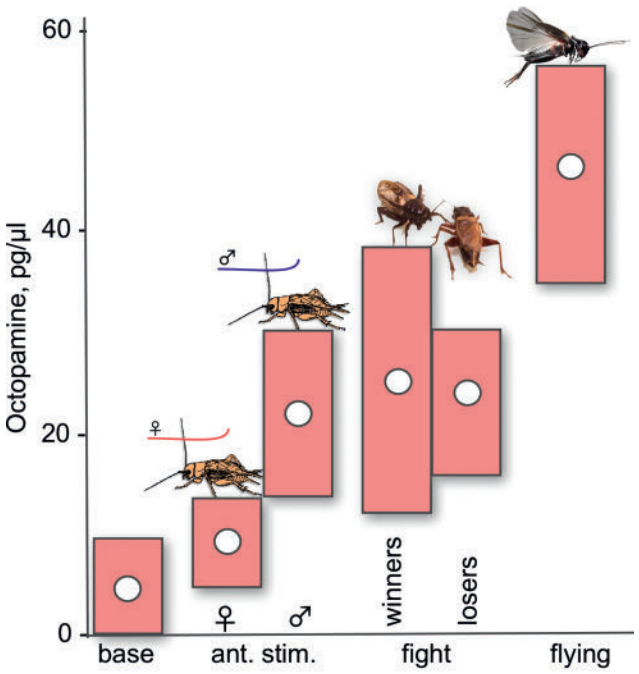

Figure 2 Haemolymph levels of octopamine in male crickets (µg/µl medians and interquartile ranges) at rest (base) and following antennal stimulation with either a male or female antenna (ant. stim. ♂, blue stroke, ♀, red stroke), after fighting in winners and losers, and after flying. Adapted from Adamo et al., 1995.

(DA, Becker and Marler, 2015), but in crickets by OA (Rillich and Stevenson, 2011). Physical fighting in crickets increases OA levels (Adamo et al., 1995; Figure 2) and interrupting fights before their conclusion revealed that the physical exertion of fighting alone can establish a winner effect (Rillich and Stevenson, 2011). Surprisingly though, crickets also show a winner effect after only observing an opponent retreat, without physical exertion. This is reminiscent of the case in humans, where testosterone levels rise after watching a previous victory in sports (Carre and Putnam, 2010).

Possession of a resource, such as territory, enhances aggression in rodents, but the cause is little understood (Fuxjager et al., 2010). In crickets, burrows are valuable resources that protect from predators, attract females, and are vigorously defended (Rodriguez-Munoz et al., 2008). In the laboratory, crickets given a shelter to occupy, show a transient increase in aggression, that is dependent on OA (Rillich et al., 2011). Since shelter residency, or watching an opponent retreat, requires little energy and is hardly stressful, OA is not acting here simply as a stress hormone. It seems rather to function as a central neuromodulator to mediate the aggression-promoting effects of experiences that are potentially rewarding, or at least not aversive. OA conveys reward signals in appetitive learning para-

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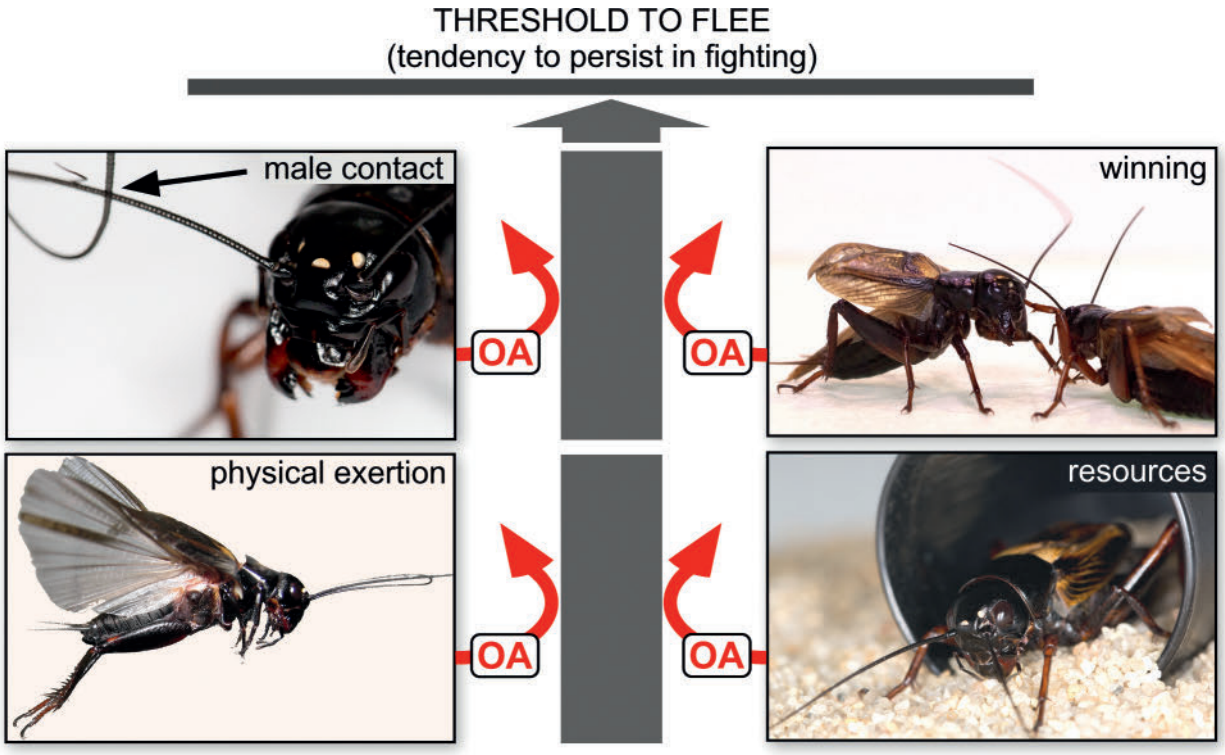

Figure 3 Schema to illustrate that the experiences in crickets of male contact, physical exertion (flying), winning and resource possession (burrow residency) each lead to the release of octopamine (OA), which then acts as a neuromodulator to promote aggression by raising the threshold to flee. The cricket thus becomes less likely to flee in response to the agonistic actions of an opponent (see Figure 4) and as a result tends to persist longer in fighting. Modified from Stevenson and Rillich, 2017.

digms in crickets (Mizunami and Matsumoto, 2017). Furthermore, neurones identified as important for aggression in *Drosophila* (Zhou et al., 2008), appear to be of the same type that signal sucrose reward in honeybee olfactory learning (Hammer, 1993). However, as the experiments with antennal stimulation illustrate, OA does not increase the tendency to actually initiate aggression. As discussed below, OA appears rather to promote aggression by raising the threshold to flee, which in effect increases the propensity to persist longer in fighting (Figure 3). In this respect, OA can be considered to represent the motivational component of aggression in insects.

Controlling the decision to flee – the role of nitric oxide (NO)

Very little is known about how animals make the decision to flee from an opponent in an aggressive interaction (see, however, Certel et al., 2010 on novel insights into how *Drosophila* implements the decision to court or fight a conspecific, and Evans et al., 2018 concerning a synaptic threshold mechanism for the decision to escape from harmful stimuli in rodents).

Behavioural theories agree that an animal's decision to flee is based on its assessment of offensive, agonistic signals exchanged during fighting, but it is debated whose signals are assessed: the signaller's own, the opponent's, or both (Arnott and Elwood, 2009). The secret in crickets was revealed by imposing handicaps to impair agonistic signalling (Rillich et al., 2007). We first noted that crickets still fight, without significant change in win chances, with either fully disabled mandibles or blackened eyes. Surprisingly though, blinded crickets practically always (98 %) beat opponents with disabled mandibles. This, seemingly odd finding, conforms fully with the Cumulative Assessment Hypothesis of Payne (1998). This posits that individuals evaluate only their opponent's actions in a contest, and flee when the accumulated sum exceeds a critical threshold. Accordingly, in our experiment, the blinded cricket persists longer and eventually wins since it perceives no visual threats and greatly reduced physical impact from an opponent with disabled mandibles. The latter by contrast, experiences the full brunt of the blinded opponent's actions, and hence flees earlier.

Later experiments revealed that the NO signalling pathway plays a leading role in opponent assessment and controlling when to flee (Stevenson and Rillich, 2015; Figure 4). As in mammals (Bedrosian and Nelson, 2014), NO appears to dampen aggression in crickets. When this system is pharmacologically activated, crickets rarely escalate to physical fights (cf. Figure 1), and they last only half as long (2–6 s). By contrast, when blocked, crickets fight for up to a minute or more (Stevenson and Rillich, 2015). Handicapping revealed that NO does not reduce aggressive motivation. For example, blinded crickets treated with a NO-donor fight opponents with lamed mandibles with unchanged ferocity and persistence, but they now win less than 50 % of fights instead of nearly always in controls. Conversely, instead of nearly always losing against blinded opponents, crickets with disabled mandibles won half the fights when treated with a NO synthesis inhibitor. These compensatory effects of nitridergic drugs indicate that NO mediates the impact of the opponent's agonistic signals. This was verified by testing how a potentially aversive stimulus, not normally experienced during fighting, affects subsequent contest behaviour. Whereas light wind stimulation of the abdominal cerci had no effect on its own, when preceded by male antennal stimulation, the wind stimulus induced normally aggressive crickets to behave like losers, and retreat on contacting another male without fighting. However, if they received a NO synthesis blocker, the antennal/wind stimulus regime no longer induced loser behaviour (Rillich and Stevenson, 2017). Thus, male contact sets the behavioural context during which a cricket begins to evaluate external stimuli as aversive. These external stimuli then promote behaviour via the action of NO.

If true, that crickets add up their opponents' actions and flee when the accumulated sum exceeds some critical level, then winners must also have a memory of the sum of their opponents' actions. Indeed, winners that receive aversive (wind) stimuli just after winning, subsequently behave like losers on confronting a fresh opponent (Stevenson and Rillich, 2015). Again, this effect is not evident

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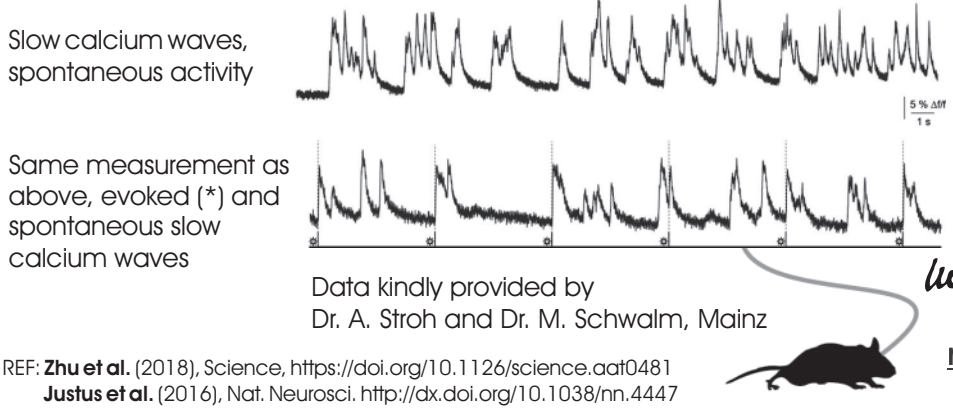

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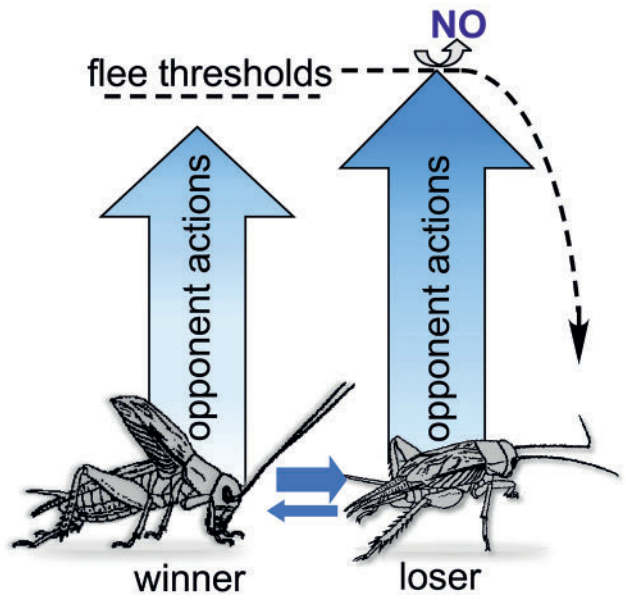

Figure 4 Schema depicting current understanding of how crickets decide when to flee. Each cricket enters into a fight with a set threshold to flee (dashed line), that is determined by previous experience (Figure 3) and can thus be different for each individual, and possibly even higher in the prospective loser, as in this figure. During fighting, the contestants exchange agonistic signals (solid blue arrows), which can vary in frequency and intensity between individuals (as indicated by arrow thickness). Crickets evaluate their opponent's actions as aversive stimuli, and flee the moment when the accumulated sum experienced during a contest (vertical arrows) exceeds a critical amount, which corresponds to the threshold to flee. Aversive stimuli experienced in an aggressive context induce the release of nitric oxide (NO), which acts as a neuromodulator to promote retreat, by lowering the threshold to flee. Losers thus appear to be submissive, since they retreat in response to even the slightest contact with an aggressive male. Details in Stevenson and Rillich 2015; Rillich and Stevenson, 2018.

when NO synthesis is blocked, or when the aversive stimuli are given 1 min or more after winning. Thus, winners need to accumulate only a few more aversive stimuli within a brief susceptible period to recruit NO and become subordinate. We speculate that winners of other species including our own, may be similarly susceptible to post-conflict depression, particularly in the absence of a rewarding experience normally associated with victory.

Social defeat and the loser effect

After fleeing, loser crickets remain submissive for some 3 h and retreat on contacting another male, even if unfamiliar (Stevenson and Rillich, 2013). Such loser effects are common in invertebrates and vertebrates including humans, but the underlying physiological mechanisms remain unclear for most animals (Hsu et al., 2006; Oliveira et al., 2009). In crickets, NO seems to be necessary for both initiating retreat and establishing loser depression. Inhibiting NO signalling prolongs the loser effect, whereas activators induce early recovery (Iwasaki et al., 2007; Stevenson and Rillich, 2015). Recovery from the loser effect also occurs immediately after flying, or burrow residency, and both these effects depend on OA (Hofmann and Stevenson, 2000; Stevenson et al., 2005; Rillich et al., 2011). However, although the OA agonist CDM induces early recovery, natural recovery is not affected by blocking OA receptors. Contrasting this, dopamine (DA), which appears to have no effect on the aggression exhibited by socially naive crickets, is both sufficient and necessary for natural recovery of aggression after defeat (Rillich and Stevenson, 2014).

Since OA is not necessary for initiating aggression, or recovery from defeat, it is unlikely that it promotes aggression by increasing the propensity to fight *per se*. The most parsimonious explanation is that OA raises the threshold to flee, in response to an opponent's agonistic signalling efforts, so that the animal in effect persists longer at fighting the opponent. Supporting this, losers respond to male antennal stimulation with the mandible threat display equally well as socially naive crickets (Rillich and Stevenson, 2015) and will attack another loser, if this loser retreats on sight, before contact (Rillich et al., 2007; Stevenson and Rillich, 2013). Thus, losers remain potentially aggressive, and only appear to be non-aggressive because they have a low threshold to flee, and accordingly retreat immediately when they contact an aggressive male.

Serotonin and aggression – insects are not so different

Serotonin (5-hydroxytryptamine, 5HT) is an evolutionarily ancient and well conserved neurotransmitter that is considered to function as the primary orchestrator of aggressive behaviour in invertebrates and vertebrates including humans (de Boer et al., 2015). While the mechanism is highly complex, 5HT in vertebrates is thought mainly to dampen aggression, e. g. by promoting withdrawal via 5HT1A and or 5HT1B receptors in the dorsal Raphe nucleus (Olivier, 2015). In invertebrates, however, 5HT is generally attributed with the reverse effect: 5HT, its precursor 5-hydroxytryptophan, 5HT1A agonists and genetic activation of specific 5HT neurones are reported to increase aggression and win chances, while reducing the tendency to flee

in crustaceans (Kravitz, 2000), fruit flies (Johnson et al., 2009; Alekseyenko et al., 2014) and stalk-eyed flies (Bubak et al., 2014).

The precise role of 5HT during normal fighting behaviour in socially naive crickets is uncertain (Dyakonova and Kruschinsky, 2013; Stevenson and Rillich, 2017). So far, we have failed to find a clear effect of serotonergic drugs on normal fighting behaviour of socially naive crickets (Stevenson et al., 2000; Rillich and Stevenson, 2015, 2017). Losers, however, are severely affected (Rillich and Stevenson, 2018). For example, blocking 5HT2-like receptors inhibits the acquisition of submissiveness in losers, while blocking re-uptake of endogenous 5HT with fluoxetine prohibits recovery from social defeat. This indicates that 5HT is released specifically after defeat to maintain the low threshold to flee that typifies loser behaviour. In *Drosophila*, 5HT was recently found to modulate stress-induced behavioural depression (Ries et al., 2017), but it is not known to influence post defeat depression in these insects. In rodents, however, submissive behaviour after defeat is reduced by 5HT2A antagonists injected into the amygdala (Clinard et al., 2015) and there is recent evidence for a similar aggression-suppressing effect of 5HT in crayfish after defeat (Bacque-Cazenave et al., 2017). It thus appears, that 5HT2-like receptors are involved in maintaining submissive behavior after social defeat in mammals, insects and possibly crustaceans. In crickets, work in progress suggests that this action of 5HT depends on prior release of NO, and could be implemented by inhibiting DA-mediated recovery of aggression after defeat (Figure 5).

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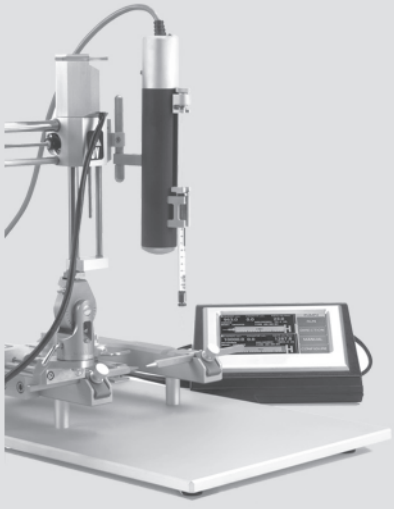

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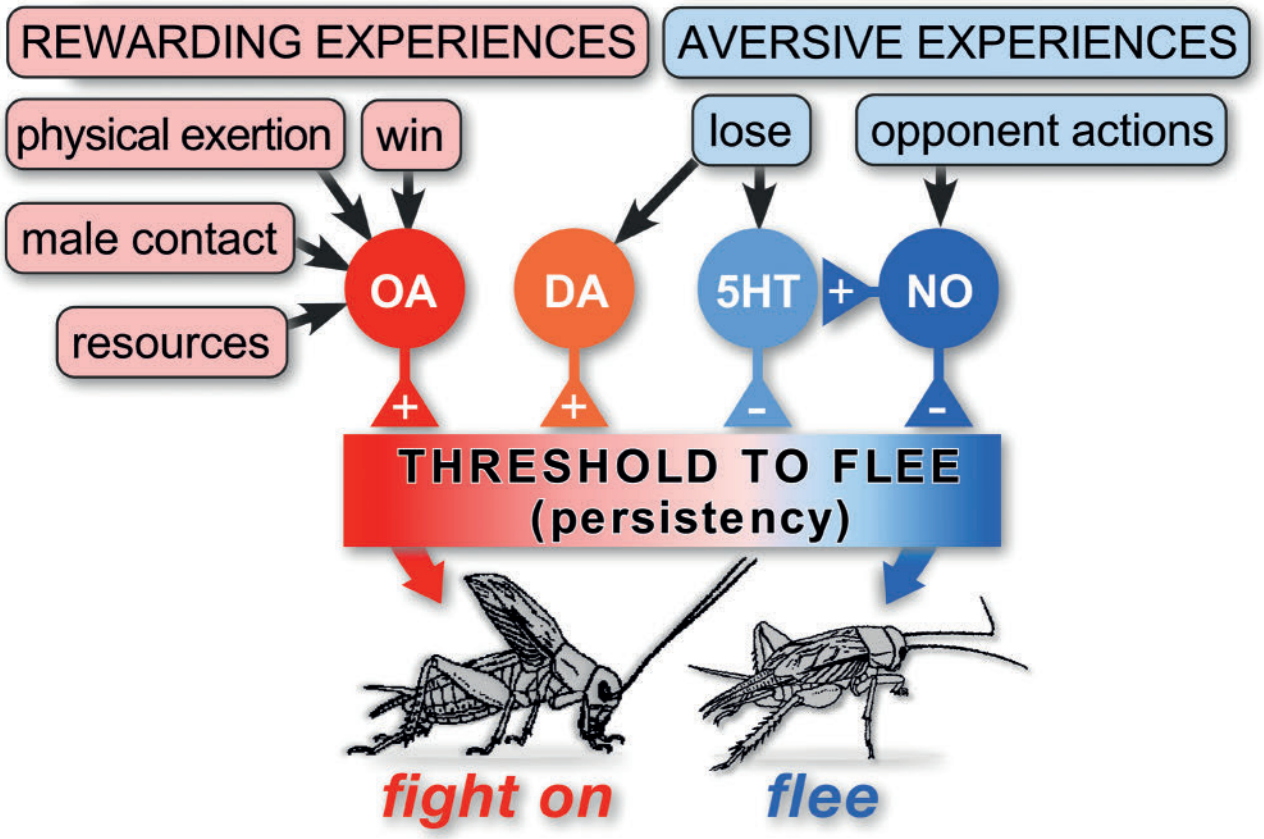

Figure 5 Hypothetical schema of the neurochemical control of aggression in crickets that best fits current data. Potentially rewarding, or at least non-aversive experiences promote fighting via the action of octopamine (OA, +), which raises the threshold to flee so that the animal tends to persist longer in fighting. Aversive experiences accumulated during fighting (e. g. opponent actions) promote retreat by lowering the threshold to flee *via* nitric oxide (NO, –). After defeat, serotonin acts via $5HT_2$-type receptors to maintain submissiveness (loser effect) by keeping the threshold to flee low (5HT, –) and thus preventing recovery of aggression in losers. The natural recovery of aggression after defeat requires dopamine, which acts by raising the threshold to flee (DA, +). Reproduced from Rillich and Stevenson, 2018.

Aggression and "personality" in crickets?

In mammals and man, social defeat, and particularly repeated intermittent defeat (chronic social defeat), is widely recognised as a major stressor that induces depression-like symptoms with long lasting general behavioural consequences (de Boer et al., 2016). Individuals of invertebrate species also show consistent behavioural differences (animal "personality"), that are thought to be both a cause and a consequence of variations in contest behaviour (Briffa et al., 2015). In crickets, winners are significantly more proactive than losers as a result of previous aggressive experience (Rose et al., 2017a, 2017b). In particular, chronic social defeat dramatically increases the duration of the loser effect, and has potentially lifelong effects on the expression of diverse behaviours. We suspect that 5HT is involved. For example, 5HT2 receptor antagonism increases resilience to multiple defeat, whereas blocking 5HT uptake increases the susceptibility to chronic defeat stress (Rillich and Stevenson, 2018).

Conclusions and outlook

Work on crickets has revealed that animals can implement the seemingly complex social decision of when best to fight or flee, quite simply, by exploiting the powers of neuromodulation. By using OA and NO to differentially modulate the threshold to flee, our model (Figures 4 and 5) satisfies the basic requirements of setting the propensity to persist in fighting, in balance with the perceived value of a disputed resource, previous agonistic experience, and the aggressive potential of the opponent as disclosed during combat. This is achievable without need of conscious reasoning, which is at least food for thought on

how more complex brains, such as our own, make similar judgements. Particularly so in view of some notable similarities in the neurochemical control of aggression in insects and mammals, such as 5HT's part in maintaining submissiveness after defeat (Rillich and Stevenson, 2018). Furthermore, the key roles revealed for OA and NO in controlling the decision to fight or flee in crickets, may also spark new thought on how the corresponding amines NA and AD and NO function in mammalian aggression which is far from clear. In crickets, though, we know practically nothing about the involved neurones. However, by exploiting genetic techniques, neurones that contain biogenic amines and influence aggression have been identified in fruit flies, and progress continues here on how they function naturally in aggressive behaviour. Now that these techniques are becoming available for crickets (Watanabe et al., 2018), it can be expected that similar advances will be made in this model system.

Dedicated to Franz Huber, whose advice I (PAS) still recall: "*don't forget the behaviour Paul – don't forget the behaviour!*"

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Bionotes

Dr. Jan Rillich
Universität Leipzig,
Fakultät fürLebenswissenschaften,
Institut für Biologie,
Talstr. 33, 04103 Leipzig,
Deutschland
Tel Tel.: +49 341 9736988
E-Mail: rillichj@gmail.com

Dr. Jan Rillich is currently a DFG research fellow at the University of Leipzig, where his research with Paul Stevenson focuses on the neuronal mechanisms of aggression in crickets. He studied Biology at the University of Leipzig and obtained his doctorate there in 2006. He has worked as a post doctorate researcher in the laboratories of Jochen Pflüger FU-Berlin and Amir Ayali, Tel Aviv, Israel.

Prof. Dr. Paul A. Stevenson
Universität Leipzig,
Fakultät fürLebenswissenschaften,
Institut für Biologie,
Talstr. 33, 04103 Leipzig,
Deutschland
Tel +49 341 973 6879
E-Mail: stevenson@rz.uni-leipzig.de

Prof. Dr. Paul A. Stevenson obtained a Bachelor in Zoology from the University of Nottingham, England followed by a Master in Biology at the University of Konstanz, Germany, where he also obtained his Doctorate in 1988 under Wolfram Kutsch. He has worked as Assistant Professor in Jochen Pflüger's lab in Berlin, and Klaus Schildberger's lab in Leipzig, where he was appointed to Associate Professor (*ausserplanmässig*) in 2009. His research focuses on the neuronal basis of locomotion and social behaviour in insects and how this is controlled by biogenic amines.

Review Article

Patrick O. Kanold*

The first cortical circuits: Subplate neurons lead the way and shape cortical organization

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Abstract: The cerebral cortex is essential for our sensory experiences and conscious thought. Its neural connections, in particular sensory areas of the cerebral cortex, are shaped and sculpted by our early sensory experiences. Onset of these first sensory experiences of the world mark an important developmental event, enabling our worldy interactions to shape the makeup of our cerebral cortex. These long-lasting effects of early sensory experience are particularly striking in human communication, since early exposure to the mother's language is required to detect all nuances in the underlying sounds. Early interactions with the world are mediated by a key set of neurons, subplate neurons, which remain part of the developing cerebral cortex until most of them disappear at later stages of development. They play a crucial role in the developing mammalian brain. Here I review the circuitry and functional roles of cortical subplate neurons, focusing on their purpose in the development of primary sensory cortices.

Introduction

Our sensory experience is crucial to brain function, and whatever we experience early in life can end up shaping perception in adulthood. This effect of early experience is especially striking in the auditory system, which is essential for human communication. Early experience with language sculpts the auditory system such that sounds specific to certain languages can be detected. One crucial question is: at which age and in which part of the brain do sensory experiences elicit circuit changes to enable the perception of specific sounds? Studies of maternal voice suggest that prenatal experience plays a role in development of the auditory system. Since newborns already show a preference for maternal voice (DeCasper and Fifer, 1980; Mehler et al., 1988; Voegtline et al., 2013) the relevant processes are likely active from early stages in development. This review highlights organization of the fetal cortex and examines structures and circuits that underlie the development of sensory processing functions, in particular the processing of sound information.

***Corresponding author: Patrick O. Kanold,** Department of Biology, Institute for Systems Research, University of Maryland, College Park, Maryland 20742, USA, E-mail: pkanold@umd.edu

Prenatal sensory development

A large fraction of human cortical development occurs in the womb (Fig. 1A), even though the womb does attenuate sensory activation. While somatosensation (the sense of touch) can be active in utero, visual stimuli do not penetrate the womb and thus the retina will not easily be activated. By contrast, it has been well observed that human fetuses can respond to sounds before birth. In prenatal humans, auropalpebral reflexes (blink of the eye to loud sounds) emerge in the 20th gestational week (Birnholz and Benacerraf, 1983) (Fig. 1B), indicating that the inner ear is transducing sounds and that at least brainstem circuits involved in reflexive responses are functioning. However, because sounds are attenuated by the uterus, auditory thresholds are higher at these early developmental ages than after birth (Werner, 2007). Similar developmental progressions occur in other mammals, although some commonly used animal species (e. g. rodents and ferrets) are altricial, being born in a very immature state with closed eyes and ears. Thus, many developmental events occurring in utero in humans occur ex utero in these species and are thus readily studied (Fig. 1B). However, because eyes and ears are initially closed in these animals there also exists a period in which sensory transduction can occur, but where sensory inputs are attenuated.

The ability of the human fetus to respond to sounds raises the question of what stimuli impinge on the developing auditory system and what are the functional consequences of such stimulation. Both external sounds and maternal heartbeats can elicit fetal magnetoencephalographic (MEG) responses (Blum et al., 1985; Wakai et al., 1996; Eswaran et al., 2000; Lengle et al., 2001; Schleussner et al., 2001; Schneider et al., 2001; Zappasodi et al., 2001;

Figure 1

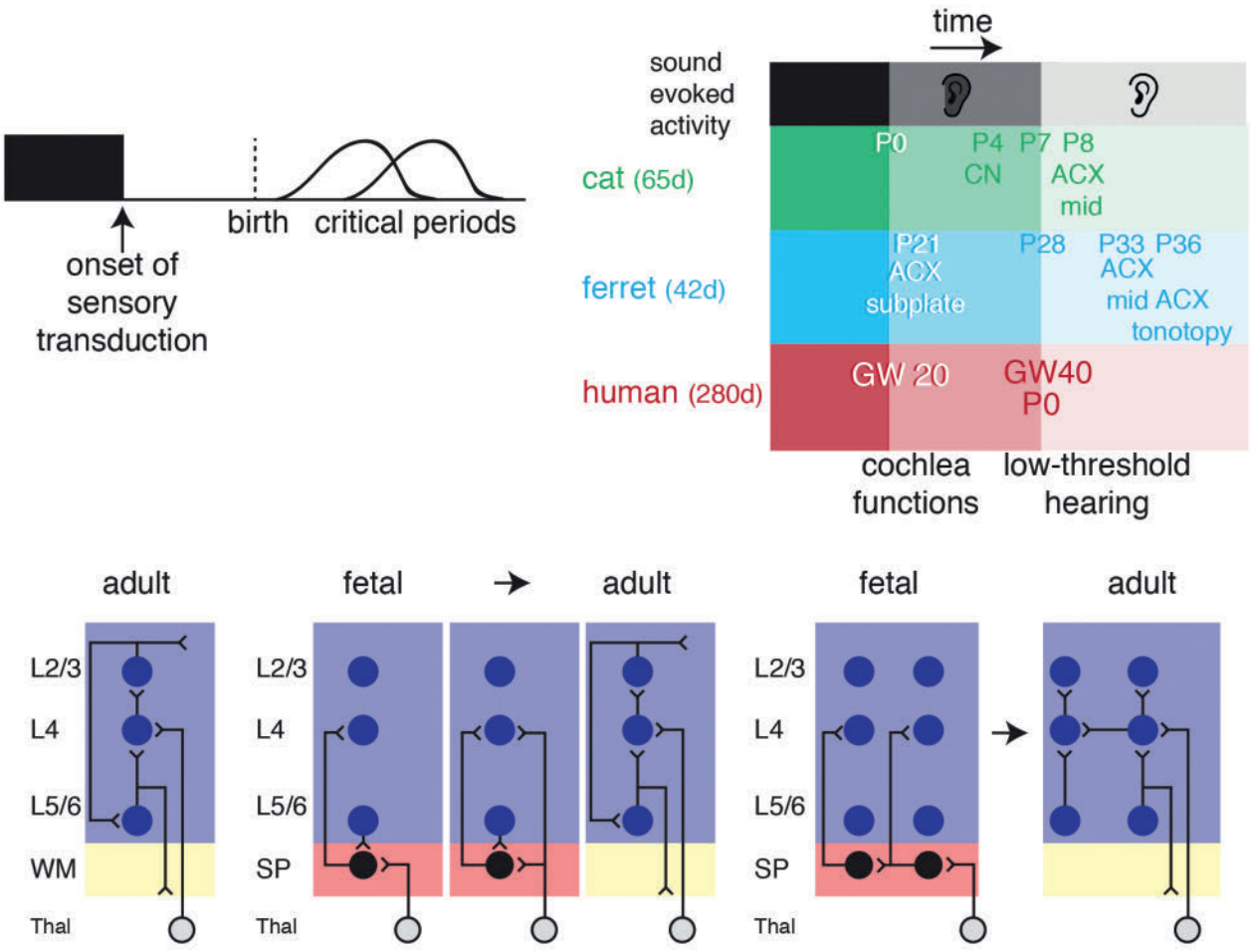

Figure 1: Changing circuits in the developing sensory cortex
A: Schematic of sensory development in humans. Sensory transduction can occur before birth. Critical periods, during which sensory experience can cause persistent alterations in sensory development have been identified postnatally. B: Schematic diagram of auditory development in three species. Gestation period indicated in brackets. Shading indicates amount of sensory information present. Black: Sensory transduction is absent. Dark gray: Sensory transduction is present but sound is attenuated by closed ears or the womb. Light gray: Sounds are not attenuated. P: postnatal day; GW: gestational week. ACX=Auditory cortex. C: Circuitry of adult sensory neocortex. WM=white matter; Thal=thalamus. D: Changing circuitry of developing sensory neocortex. E: Intra-SPN connection could precede and seed intra-L4 connections. CN=Cochlear nucleus.

Eswaran et al., 2002; Draganova et al., 2005; Porcaro et al., 2006). Even though auditory experience in a human fetus is attenuated by the womb, the preference for maternal voice in newborns (DeCasper and Fifer, 1980; Mehler et al., 1988; Voegtline et al., 2013) suggests that sounds can activate the human auditory system in utero, and that these sounds are processed in a complex manner supporting recognition of the mothers' voice.

While some motor responses seem reflexive, the selectivity of newborn infants for maternal voices is strong evidence to suggest that higher order processes are functioning. Since complex auditory processing is thought to occur in the auditory cortex (Nelken, 2004), early sensory experience might already act there. The mammalian cerebral cortex is a complex neural structure characterized by high interconnectivity and required for processing and consciously acting on sensory information. It is well known that sensory experience can shape connection from the thalamus to the cerebral cortex as well as the connections within the cerebral cortex. For example, depriving developing animals of sensory information in early life prevents maturation of connections from the thalamus to the cortex

and alters the pattern and function of intracortical connections (Sanes and Bao, 2009; Erzurumlu and Gaspar, 2012; Espinosa and Stryker, 2012).

Structural differences between the developing and adult cerebral cortex

When and where does sensory experience first interact with and shape the cerebral cortex? The adult cerebral cortex is a laminated structure with 6 layers. In sensory cortical areas, sensory information from the thalamus predominantly innervates the middle (granular) cortical layer (L4). From this input layer, information flows to the more superficial layers (L2/3) and to the deeper layers (L5/6) (Fig. 1C). Neurons from L2/3 and L5/6 project to intracortical or subcortical structures, respectively. In addition, neurons within each layer are also highly interconnected via intralaminar connections.

The developing cerebral cortex shares basic laminar topology with the adult cerebral cortex, however the cortical layers form gradually over development in an inside-out manner (in a structure termed *cortical plate*), hence the deepest layers develop first. One important difference is that the developing cortex contains additional neurons located in the area where white matter will appear (Fig. 1D). These are called subplate neurons (SPNs); they comprise the earliest generated and maturing population of neurons in the mammalian neocortex (Krmpotic-Nemanic et al., 1979; Kostovic and Rakic, 1980; Kanold and Luhmann, 2010). In human auditory cortex, SPN neurons are distinguishable at 12–13.5 weeks (Krmpotic-Nemanic et al., 1979). During development, a large fraction of SPNs disappear, while some SPNs are thought to remain as a subpopulation of deep cortical neurons, layer 6b (L6b) (Kanold and Luhmann, 2010; Marx et al., 2015; Hoerder-Suabedissen et al., 2018). The functional role of L6b neurons in adults is not well understood, but because L6b neurons are modulated by neuropeptides, such as hypocretin, they might play a role in controlling wakefulness (Bayer et al., 2004; Case and Broberger, 2017; Case et al., 2017). It is possible that a fraction of SPNs serve a similar role in development.

SPNs are diverse, which might indicate different functional roles for the different SPN classes. SPNs can be classified into subpopulations based on their dendritic architecture or gene expression profiles (Kanold and Luhmann, 2010). Molecular analysis of SPNs in rodents and humans has revealed a panoply of subplate-specific markers, such as Connective Tissue Growth Factor (CTGF), Complexin3 (Cplx3), Nurr1 etc., suggesting the existence of molecularly-defined SPN populations (Hoerder-Suabedissen et al., 2009; Belgard et al., 2011; Hoerder-Suabedissen and Molnar, 2013; Bakken et al., 2016; Viswanathan et al., 2012, 2017; Lein et al., 2017). Furthermore, molecular profiling has enabled the study of subplate evolution, which has already identified subpopulations that are conserved across species, e. g., from birds to mammals, and other populations that seem to be specific to mammalian neocortex (Montiel et al., 2011; Wang et al., 2011; Molnar et al., 2014). Therefore, the study of how SPN neurons differ across species might hold clues to the evolution of the human neocortex, because SPNs seem to be overrepresented in species with more complex cortical organization (Kostovic and Rakic, 1990; Kanold and Luhmann, 2010). Unfortunately, associations between molecular markers, morphological, and functional SPN types remain unclear.

Subplate neurons provide an early relay of thalamic information and represent an early integrative hub

Important clues to the functional role of SPNs are given by the source of their synaptic inputs as well as by their outputs. From the earliest studies of SPNs it was clear that they were present in primary sensory cortices at times when thalamic axons entered the white matter. From these observations, it was hypothesized that SPNs serve as a transient target and waiting compartment (Kostovic and Rakic, 1990; Ghosh and Shatz, 1992b; Hevner, 2000; Kostovic and Judas, 2002). Physiological brain slice studies confirmed that SPNs in all primary sensory areas received excitatory thalamic inputs (Friauf et al., 1990; Higashi et al., 2002; Zhao et al., 2009) (Fig. 1D).

SPNs can have complex dendritic trees, suggesting that they receive an extensive set of synaptic inputs (Hanganu et al., 2002; Zhao et al., 2009; Kanold and Luhmann, 2010; Liao and Lee, 2012). As mentioned above, SPNs receive thalamic inputs. However, at later developmental ages they also receive excitatory and inhibitory inputs from the developing cortical plate, in particular from the future thalamocortical recipient layer L4 and the deeper layers L5/6, as well as from within the subplate (Viswanathan et al., 2012; Meng et al., 2014) (Fig. 1D).

Thus, SPNs integrate ascending information with intrinsic cortical activity.

Having identified their main inputs, the next clue to SPN function was provided by identifying their synaptic targets. Brain slice experiments in rodents showed that SPNs innervate L4 before thalamic axons activate L4 (Zhao et al., 2009; Deng et al., 2017) (Fig. 1D). This SPN to L4 projection is excitatory and targets both excitatory and inhibitory L4 neurons. Thus, SPN activity can change the balance of activity in L4.

Taken together, these identified circuits indicate that early thalamic activity is relayed to the future thalamic input layer, L4, via an obligatory relay in the subplate. This relay action can be observed in young brain slices. Subplate responds to thalamic afferents with short latency, while L4 responses have longer latency (Friauf and Shatz, 1991; Barkat et al., 2011). This circuit topology highlights the essential role of SPNs in relaying early thalamic inputs to L4 (Fig. 1D), enabling SPNs to influence the developing cortical architecture. Computational analysis has shown that SPNs can induce activity correlations between thalamic terminals and their future targets in L4 and thereby promote strengthening of thalamus-L4 synapses by forming a "teacher circuit" (Kanold and Shatz, 2006; Kanold, 2009; Butts and Kanold, 2010). This instructive role of SPNs might also generalize and apply to intracortical circuits. For example, SPNs connect to each other, and thus their activity might cause correlated activity in spatially distinct populations of L4 neurons. Such correlations might contribute to formation of spatially patterned connections within L4 (Fig. 1E).

Besides projecting to L4 and other targets in the developing cortical plate, SPNs have also been shown to connect to subcortical structures such as the thalamus (McConnell et al., 1989, 1994; Viswanathan et al., 2017; Hoerder-Suabedissen et al., 2018). As a result, SPNs sit at the nexus between immature ascending and descending thalamocortical and corticothalamic pathways.

Subplate neurons are the first cortical neurons to exhibit sensory responses and nascent topographic organization

Given that SPNs in sensory cortices receive thalamic inputs, it follows that peripheral sensory stimulation might activate them, because peripheral receptors can function before onset of thalamic transmission to L4. The opening of eyes and ears in altricial animals, such as mice, roughly coincides with the onset of thalamic transmission to L4 (Barkat et al., 2011). Although it has commonly been assumed that before this time point no sensory activation of cortex is present, direct and indirect evidence suggest otherwise. Peripheral receptors, like retinal photoreceptors or cochlear hair cells, can function at earlier ages, and thus sensory evoked activity could be present along ascending sensory pathways. Recordings in ferrets and mice, born with closed eyes and ears, showed that cells in the visual pathway can respond to visual stimuli before eye opening (Krug et al., 2001; Akerman et al., 2002; Tian and Copenhagen, 2003; Akerman et al., 2004; Chen et al., 2009). Recent electrophysiological studies of the ferret auditory system indicated that the auditory cortex can respond to sound ~10 days before ear opening (Wess et al., 2017) (Fig. 1B). In these immature animals, sound-evoked local field potentials (LFPs) were present in both the future thalamocortical recipient layer, L4, as well as in subplate. Oscillatory LFP activity in response to whisker stimulation is also present in the subplate of the somatosensory cortex in neonatal rodents (Yang et al., 2009). Since LFPs reflect bulk electrical activity, these signals contain both neuronal spiking activity as well as synaptically-evoked potentials. To identify which population of neurons underlies this early activity, laminar recordings of single-unit activity (i. e. extracellular recorded spikes that can be assigned to a single neuron) were performed. These recordings revealed that the earliest responses originated from SPNs, and that responses in L4 emerged at later ages (Wess et al., 2017) (Fig. 2A). Furthermore, at ages during which responses were present in both subplate and L4, SPNs responded at shorter latencies, indicating that sound information reached L4 via SPNs; this is consistent with the SPN to L4 projections at early ages (Fig. 1D, 2B). These experiments indicate that sensory information is present in the cerebral cortex at much earlier ages than previously assumed and that the earliest active neurons are located in the subplate and not in L4. These results show that at least in the auditory system it is likely that sensory information is present in the sensory cortex shortly after the sensory end organs are capable of sensory transduction.

One hallmark of sensory cortices is their topographic organization: stimulus features, such as sound frequency, are mapped out on populations of neurons such that neighboring populations respond to similar features – with the overall stimulus preference varying smoothly across the cortex. The existence of early sound-evoked activity raised the question of whether early responses also showed topographic organization. LFP recordings

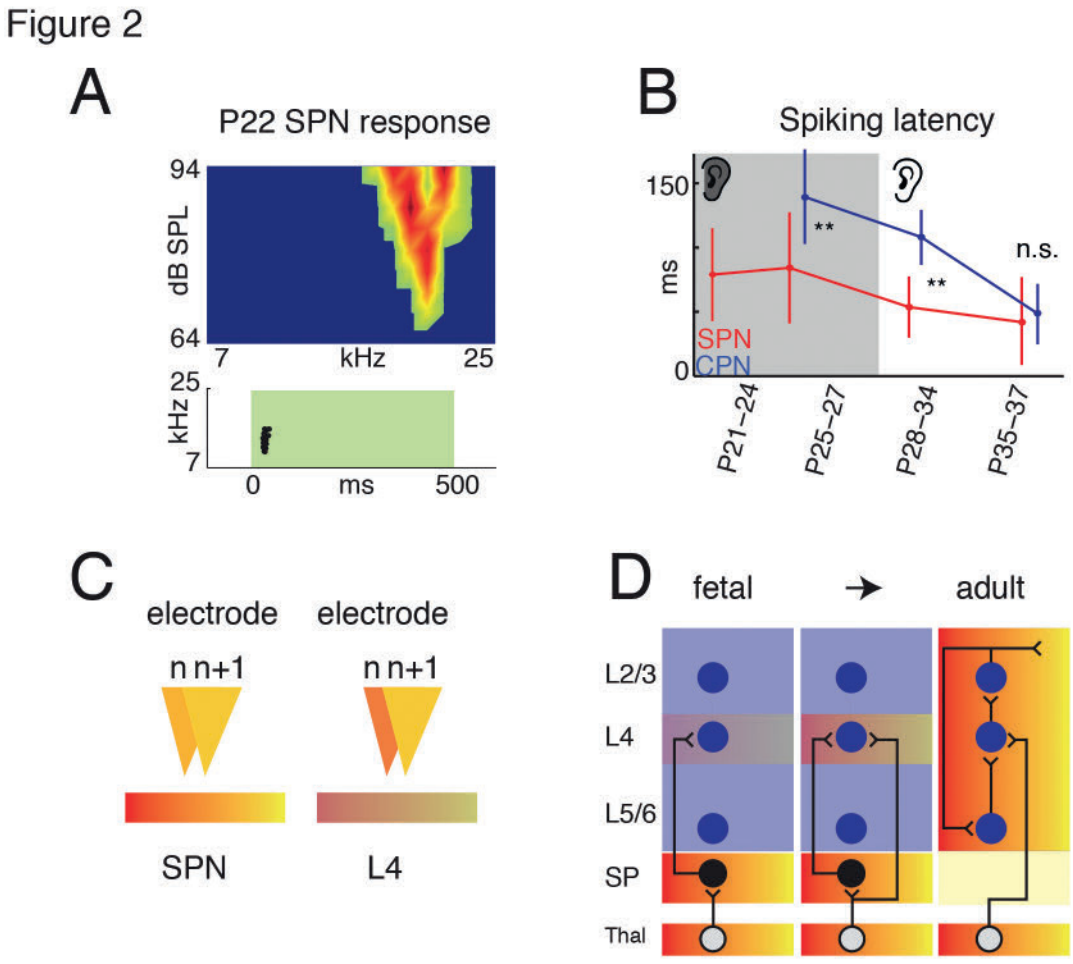

Figure 2: Early auditory responses in subplate
A: Example of a sound-responsive SPN. Shown are spiking rates (color) in response to tones of particular loudness. Note that this neuron is selectively responding to mid-frequency tones. Adapted from Wess et al. 2017. B: Latency of sound-evoked activity is shorter in SPN than in mid cortical plate neurons (CPN). Adapted from Wess et al. 2017. C: Cartoon illustrating the difference in frequency selectivity of LFP activity on neighboring electrodes. Colors represent different sound frequencies (Red: low tone frequency Yellow:high tone frequency). A higher local tuning similarity is present in subplate than L4. D: Hypothesized sequential development of tonotopy in cortical columns. Subplate is topographically organized at early ages. SP inputs to L4 establish frequency selectivity and promote the establishment of thalamic axon connections of the same frequency band to L4. Thus, L4 neurons will start to show an orderly progression of frequency preferences across columns.

using multi-electrode arrays demonstrated that neighboring electrodes in the subplate showed similar frequency preference, while neighboring electrodes in L4 showed less similarity (Fig. 2C). In addition, stimulus preference similarities were larger for closer electrodes, indicating that subplate might contain topographic maps of stimulus preference. These findings suggest that the topographic organization of the sensory cortex might be sketched out within the subplate (Wess et al., 2017) and transferred to L4 via the "teacher-circuit" (Fig. 2D).

Subplate damage and dysfunction are implicated in neuro-developmental disorders

Because SPNs are the earliest cortical neurons to mature, they are also the first to be susceptible to injury. Furthermore, researchers have suggested that SPN dysfunction plays a role in multiple neurodevelopmental disorders such as autism spectrum disorders (ASDs), cerebral palsy, and schizophrenia. To directly investigate the consequences of early SPN damage, SPN lesion studies have been performed in animal models. Such studies used ex-

citotoxic lesions via focal injections of kainic acid (Ghosh et al., 1990; Ghosh and Shatz, 1992a, 1993, 1994; Lein et al., 1999; Kanold et al., 2003; Kanold and Shatz, 2006) or targeted immuno-ablations (Kanold et al., 2003; Kanold and Shatz, 2006; Tolner et al., 2012) to remove SPNs in early development. Lesioning in very early development, at time points before thalamic axons have reached L4, showed that SPNs are required for normal ingrowth of thalamic axons to their target in L4 (Ghosh et al., 1990). Lesioning at a slightly older age, when thalamic axons have entered L4 but before these connections had matured, prevented the anatomical patterning and functional maturation of thalamocortical connections (Ghosh and Shatz, 1992a, 1993, 1994; Kanold et al., 2003; Tolner et al., 2012) as well as intracortical inhibition (Kanold and Shatz, 2006). Taken together, these animal studies showed that loss of SPNs prevents essential steps of cortical development from taking place, and that these neurons play a key role in promoting normal cortical development. Moreover, the multitude of lesioning effects across development suggests that SPNs play critical roles throughout.

Additional evidence for a role of SPNs in neurodevelopmental disorders arose from studies showing that hypoxic insults to the developing human fetus can result in damage to the subplate region (Kostovic et al., 1989; McQuillen and Ferriero, 2005). Further animal studies conclusively showed that neonatal hypoxic-ischemic injuries can cause loss of SPNs (McQuillen et al., 2003; Mikhailova et al., 2017), alter their morphology (McClendon et al., 2017), and lead to altered excitatory and inhibitory cortical circuits impinging on SPNs (Sheikh et al., 2018).

SPNs have also been implicated in autism spectrum disorders. Histological studies on human postmortem tissue from autism patients shows an altered boundary between L6 and white matter (Avino and Hutsler, 2010) as well altered neural cell number and patchy subplate gene expression changes (Courchesne et al., 2011; Stoner et al., 2014). Furthermore, exposure to valproate acid (VPA) during pregnancy results in enhanced risk of autism in humans and rodents (Roullet et al., 2013; Nicolini and Fahnestock, 2018) and rodent studies have shown that such neonatal exposure alters circuits to developing SPNs (Nagode et al., 2017).

Collectively, these studies show that SPNs are a common target in multiple animal models of neurodevelopmental disorders. Since SPNs influence the development of cortical neurons, altered subplate circuits likely give rise to altered cortical circuits and cortical function. It is possible that SPNs are also disrupted in other conditions. Further studies of SPNs in a variety of conditions are needed. The recent availability of molecular markers should enable these studies.

Subplate neuron activity can be modulated: potential effects of maternal exposure to drugs and pharmaceuticals

Excitatory and inhibitory inputs are not the only inputs to SPNs. Histological and brain slice studies have shown that SPNs are targeted by many neuromodulatory systems that can function in the developing brain. For example, SPNs can be modulated by acetylcholine (ACh) or serotonin (Hanganu and Luhmann, 2004; Dupont et al., 2006; Hanganu et al., 2009; Liao and Lee, 2011, 2014). Furthermore, SPNs label for a variety of other neuropeptides such as substance P, neuropeptide Y (NPY) etc. (Chun and Shatz, 1989; Antonini and Shatz, 1990; Kanold and Luhmann, 2010). In addition, SPNs that persist as L6b neurons are modulated by neuropeptides (Bayer et al., 2004; Case and Broberger, 2017; Case et al., 2017) suggesting that these neuropeptides might also influence SPNs at earlier ages. Therefore, fetal exposure to agonists or modulators of these signaling systems – such as maternal consumption of alcohol or drugs of abuse – might alter activity of SPNs directly via acting on SPN receptors. It has been noted that fetal drug exposure could lead to altered development of cortical circuits (Thompson et al., 2009). Altered SPN activity and function could underlie some of these developmental effects. Similarly, maternal stress or inflammation (Estes and McAllister, 2016) can potentially alter SPN function. However, to date none of these possibilities have been explored.

Open questions

SPNs are known to constitute a key neuronal population in early development, but many questions remain. In sensory systems, these neurons provide an early sketch of future cortical organization. However, the role of SPNs in other cortical regions has not been investigated. Many advances have been made in understanding SPN circuits and function, but most of these studies have been performed in rodents. Given that SPNs are more numerous in species with more complex brains, e. g. in humans, studies in other species are needed. Finally, SPNs are in a prime

position to be modulated by a variety of substances that cross the placenta, but evidence of such effects on SPN activity is lacking.

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Bionotes

Patrick O. Kanold,

Department of Biology
University of Maryland
1116 Biosciences Res. Bldg.
College Park, MD 20742 USA
Phone: +1 (301) 405.5741
E-mail: pkanold@umd.edu

Patrick Kanold is a Professor at the University of Maryland, College Park. He obtained his Dipl.-Ing. in Electrical Engineering at the Technische Universität Berlin 1994; his Ph.D. in Biomedical Engineering from the Johns Hopkins University in Baltimore, USA. From 2000–2006 he was a postdoctoral fellow and Instructor at the Department of Neurobiology at Harvard Medical School in Boston, USA. Since 2007 he is at the University of Maryland College Park, USA.

Review Article

Daniela Brunert and Markus Rothermel*

Neuromodulation of early sensory processing in the olfactory system

Neuromodulation der frühen sensorischen Verarbeitung im olfaktorischen System

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Abstract: At any given moment, we are continuously presented with information that is received from multiple sensory organs. Thus, our brain simultaneously processes enormous amounts of data in order to render an understanding of our environment. Adjustment of sensory processing is therefore important for tuning perception in a context-dependent fashion, i. e. to facilitate adequate behavioral responses by promoting the efficient sensory processing of relevant stimuli, while suppressing unimportant signals. The basic mechanisms that underlie the modulation of sensory information remain largely unknown, especially when considering early sensory circuits. Importantly, an ability to selectively manipulate these processes would offer great advantages for both basic and translational biomedical research. Here, we highlight the vertebrate olfactory bulb as a model system for early sensory processing and its utility in demonstrating the complexity of neuromodulatory actions.

Zusammenfassung: In jedem Moment sind wir von einer Vielzahl von Informationen umgeben, die gleichzeitig von mehreren Sinnen empfangen werden. Eine enorme Menge an Daten muss daher in unserem Gehirn gleichzeitig verarbeitet werden, um unsere Umwelt richtig zu verstehen. Eine Anpassung der sensorischen Verarbeitung ist wichtig, um unsere Wahrnehmung kontextabhängig optimieren zu können, d. h. um adäquate Verhaltensreaktionen zu ermöglichen, muss eine effiziente sensorische Verarbeitung relevanter Stimuli gefördert und unwichtige Signale unterdrückt werden. Die zugrundeliegenden Mechanismen der sensorischen Informationsmodulation sind, insbesondere in frühen sensorischen Schaltkreisen, weitgehend unbekannt. Die Fähigkeit, diese Prozesse selektiv manipulieren zu können, wäre sowohl für die Grundlagenforschung als auch die translationale biomedizinische Forschung von großem Vorteil. Hier betrachten wir das olfaktorische System der Vertebraten als Modellsystem für die Untersuchung früher sensorische Verarbeitung und demonstrieren die Komplexität neuromodulatorischer Vorgänge anhand dieses Systems.

***Corresponding author: Markus Rothermel,** Dept. Chemosensation – AG Neuromodulation, RWTH Aachen University, 52074 Aachen, Germany, m.rothermel@sensorik.rwth-aachen.de
Daniela Brunert, Dept. Chemosensation – AG Neuromodulation, RWTH Aachen University, 52074 Aachen, Germany, D.Brunert@sensorik.rwth-aachen.de

Introduction

Animals, including humans, live in an ever changing environment. In order to brave environmental changes, all organisms take up and process sensory information. However, it is becoming more and more apparent that sensory information is modulated in a situation-dependent fashion. There are many examples known, which demonstrate how our brain actively "tunes" sensory information. Most readers have probably already experienced some of these examples personally, e. g. the famous "cocktail-party effect" (McLachlan and Wilson, 2010) whereby despite strong background noise one can still listen to one's conversation partner or that things smell much stronger and more appetizing when we are hungry (Soria-Gomez et al., 2014). Disorders in sensory sensitivity adjustment can lead to mild symptoms such as over-reactiveness to certain stimuli (e. g. loud noise), whereas disorders in sensory filtering can cause severe conditions such as autism spectrum or attention deficit disorders. It is estimated that 1 out of 160 children worldwide suffers from a condition falling into the autism spectrum (www.who.int). Therefore, elucidating the mechanisms by which sensory information is modulated is one of the most important and challenging questions in modern neuroscience. The means by which these modulations are performed, we will

refer to as "neuromodulation", a concept we would like to discuss, and maybe redefine, within this article. In doing so, we will focus entirely on the olfactory system of vertebrates, illustrating the complexity of neuromodulation, and highlight the use of the olfactory system as a promising model in neuromodulation research.

Neuromodulation

Neuromodulation is a very ambiguous term. In medicine, neuromodulation is defined as a "field of science, medicine and bioengineering that encompasses implantable and non-implantable technologies, electrical or chemical, for the purpose of improving quality of life and functioning of humans" (Definition of the International Neuromodulation Society; www.neuromodulation.com). In neuroscience research, however, neuromodulation was, and in part still is, used to separate slower and more diffuse forms of neuronal communication from fast synaptic transmissions (see Bucher and Marder, 2013). Early on, it has been recognized that this definition might not be sufficient to comprise all forms of neuromodulation, rather defining it as "the alteration of cellular or synaptic properties by a neuron or a substance released by neurons"(Katz, 1999). We feel that this definition might still be too limited in scope as it excludes a vast amount of substances (not released by neurons) that can strongly modulate neuronal processing. Therefore, we prefer to use the term neuromodulation here for anything that alters neurons or neuronal processing, independent of the alterant's origin. This definition includes modulatory influences from endocrine sources, processes that are vital for the response of an animal to changes in its internal state.

Neuromodulation of early sensory processing

It is known that all neuronal circuits are subject to modulatory influence (e. g. Jacob and Nienborg, 2018). This modulation is most easily detected in sensory systems, where perception of a stimulus changes depending on factors such as mood or attention. As such, neuromodulation can be found across all sensory modalities (Reynolds and Chelazzi, 2004; Zelano and Sobel, 2005; Ferezou et al., 2006). Since neuromodulation occurs at all levels of processing (see e. g. Hurley and Hall, 2011), it is not always clear where the modulation of sensory information exactly happens; especially if only behavior is used as a measurable output. Additional levels of complexity arise from the multiplicity of potential neuromodulators that are present in every circuit and from the understanding that neuromodulation can be mediated not only by sources outside, but also within a given brain area; a concept termed extrinsic vs. intrinsic neuromodulation (see Lizbinski and Dacks, 2017). This plethora of modulating influences is the reason why in any system, it is hard to form a cohesive theory of neuromodulatory action ranging from the sensory uptake to the behavioral outcome.

In recent years new techniques including imaging and optogenetics (as later discussed in more detail) have been developed, significantly increasing our knowledge on neuromodulatory processes. Many studies using these techniques have so far focused on modulations in higher brain centers (Fu et al., 2014; Jacob and Nienborg, 2018). Neuromodulation of early sensory processing, however, might be of critical value for a general understanding of neuromodulatory processes in health and disease. This is because not only are modulations at early stages likely to affect all subsequent processing steps, but also because early sensory levels might be more accessible to pharmacological intervention compared to centers embedded deep inside the brain. As such, due to its accessibility and relative simplicity, we would like to introduce the olfactory bulb as an ideal model system to study neuromodulation of early sensory processing.

The olfactory bulb as model for neuromodulatory research

The sense of smell, though under-appreciated in human, is of critical importance to most animals (Sarafoleanu et al., 2009). Humans, who mostly navigate the world through vision, also rely heavily on olfaction (McGann, 2017). For example, there is strong evidence that humans use olfaction for food preference. Furthermore, olfaction exhibits pronounced subconscious effects, whereupon it has been shown to influence mood (Zald and Pardo, 1997) or mate choice (Thornhill et al., 2003).

The olfactory system, which from an evolutionary perspective is probably the oldest of all senses, displays some unique features compared to other sensory systems. For example, the olfactory cortex comprises only three layers and sensory information relayed to the olfactory cortex does not have to pass through the thalamus. This direct input of olfactory information to brain areas involved in mood and emotion (i. e. the amydgala, discussed below)

suggests a close relationship between olfactory and affective information processing (Soudry et al., 2011). However are also many similarities between olfaction and the other sensory systems. Information is taken up and relayed to higher brain centers after being heavily processed. Like in other sensory systems, this transformation from primary to a secondary representation is often "expansive", meaning that the number of principal neurons increases from lower to higher processing centers, typically leading to a sparse stimulus representation in downstream networks (Babadi and Sompolinsky, 2014).

Several recent technical developments have revolutionized neuroscientific and neuromodulatory research, most notably optogenetics, the control of neuronal activity and cell signaling by light, (see Spangler and Bruchas, 2017) as well as optophysiology, the optical recording of cell activity using different probes, e. g. for calcium (Chen et al., 2013), dopamine (Patriarchi et al., 2018) glutamate (Marvin et al., 2013; Marvin et al., 2018) or acetylcholine (Jing et al., 2018). These optical probes enable the monitoring of large neuronal populations simultanesously. In basic research settings, these techniques are usually combined with modern genetics and/or modified viruses to provide unparalleled specificity in targeting and manipulating cell populations of interest.

The olfactory bulb, due to its size and location in mice (see Figure 1) offers the possibility to apply these new techniques easily in living animals (Spors et al., 2012; Wachowiak et al., 2013). It is especially well-suited for studying early neuromodulatory processes in particular, since, in contrast to other sensory systems, early stations of sensory information processing are easily accessible. Moreover, the relative simplicity of this system, coupled to knowledge of its connectivity, should allow for easier formation of a holistic picture of neuromodulation. Also, for mice, the model animal of choice in many aspects of neuroscience, due to its susceptibility for genetic manipulation, olfaction is one of the most important senses. Taken together, these features render the mouse olfactory bulb a very appealing model system for the study of early sensory neuromodulation.

Neuroanatomy of the vertebrate olfactory bulb

The olfactory bulb is the first central processing station of olfactory information. Odorants are detected inside the nasal cavity by olfactory sensory neurons (OSN), primary sensory neurons that express a single type of olfactory receptor out of a repertoire of approximately 1200 receptors in mice (~ 350 in humans) (Glusman et al., 2001; Nei et al., 2008). Olfactory receptor neurons project an unbranched axon to the olfactory bulb. The cellular composition and synaptic buildup of the olfactory bulb is very well established (for review see Wachowiak and Shipley, 2006). Briefly, it consists of several layers harboring different cell types that together shape olfactory information (Figure 1). The outermost layer is the olfactory nerve layer. Axons of sensory neurons expressing the same type of olfactory receptor are sorted within this layer and enter the olfactory bulb. The functional unit, into which sensory neurons expressing the same olfactory receptor converge to form synapses with interneurons, as well as olfactory bulb output neurons is called a "glomerulus". The layer in which these glomeruli reside is the glomerular layer. Here, also some major types of interneurons can be found, most notably GABAergic periglomerular cells (PG), dopaminergic and GABAergic superficial short axon cells (SA), as well as glutamatergic external tufted cells (ET). The output neurons of the bulb are tufted and mitral cells (MTC) that reside in the external plexiform and the adjacent mitral cell layer, respectively. The granule cell layer, located below the mitral cell layer, is comprised of granule cells (GC), a major source of inhibition in the olfactory bulb.

Different forms of neuromodulatory sources for the olfactory bulb

Neuromodulatory cues can originate either from within a particular brain structure that is being modulated ("intrinsic neuromodulation") or from a remote area ("extrinsic neuromodulation", (see Lizbinski and Dacks, 2017). Intrinsic neuromodulatory processes within the olfactory bulb (OB) are extensive. They are present in all OB layers and examples range from a mechanism called presynaptic inhibition of olfactory sensory neurons, (most likely mediating a form of gain control; see Wachowiak and Shipley, 2006) to tonic inhibition of granule cells by other interneurons (Pressler and Strowbridge, 2006). Here, we will only discuss extrinsic influences in more detail and do so for the vertebrate olfactory bulb. In addition to modulatory sources from higher brain centers (centrifugal projections from neuromodulatory centers and cortical backprojections, something that can be summarized as "top-down" inputs) we will also discuss peptidergic and hormonal neuromodulation from sources outside the OB.

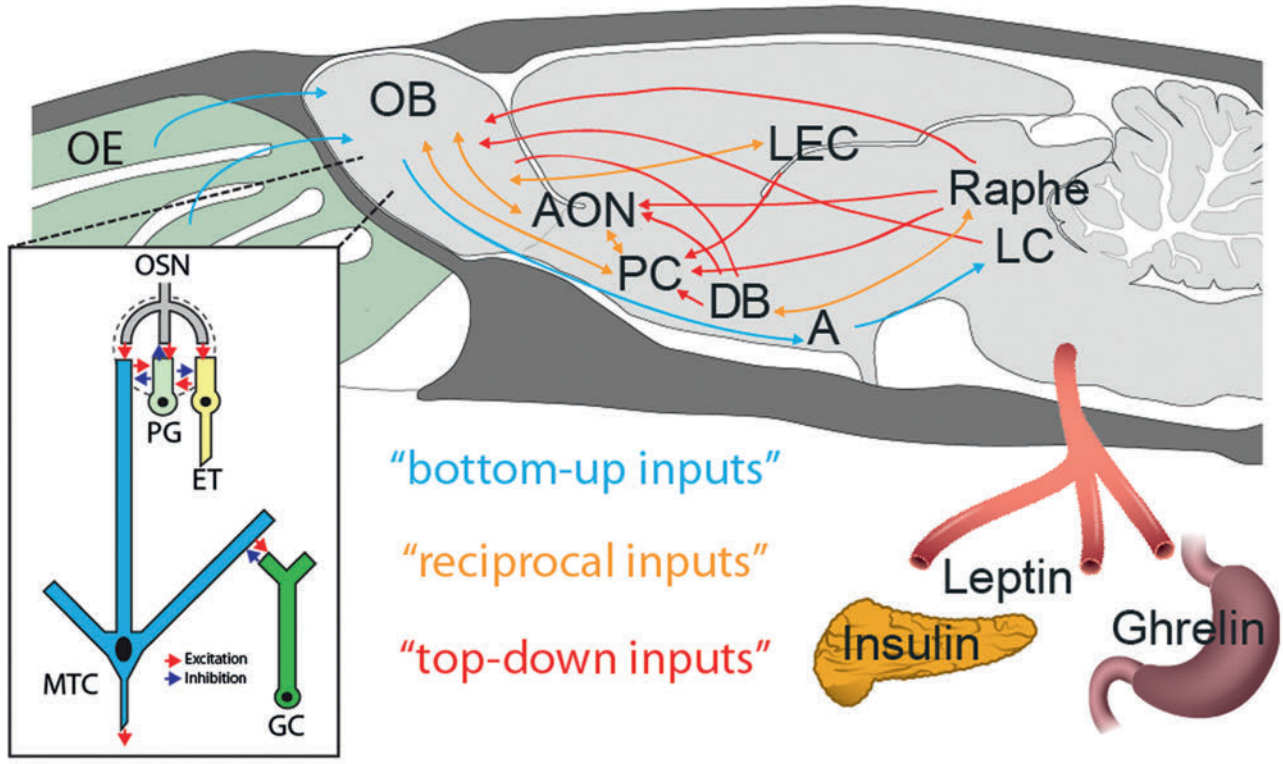

Figure 1: Diagram summarizing the neuromodulatory sources discussed in this review.
Olfactory sensory neurons (OSNs) located in the olfactory epithelium (OE) project axons into the olfactory bulb (OB). OSN axons synapse with projection neurons (mitral and tufted cells, MTC) and with interneurons (periglomerular, PG and external tufted, ET). MTC also make connections with granule cells (GCs) and PGs (simplified scheme). Brain regions receiving bottom-up information are marked with blue arrows, regions reciprocally-connected with orange arrows, and top-down inputs are marked with red arrows. AON, anterior olfactory nucleus; PC, piriform cortex; DB, diagonal band of broca; A, amygdala; LEC, lateral entorhinal cortex, LC, locus coeruleus. Courtesy of A.C. Puche, modified from (Aungst et al., 2003) and "The Rat Nervous System" 2nd Edition.

"Neuromodulatory" projections

The term "neuromodulatory brain centers" is used to describe relatively small pools of neurons which signal through neurotransmitters that are classically referred to as "neuromodulators". These centers include the locus coeruleus for noradrenergic projections, the *raphe nuclei*, for serotonergic projections, the band of broca for cholinergic projections and the ventral tegmental area for dopaminergic projections (Kandel, 2013). Each of these centers innervate a large variety of different brain structures that themselves are highly interconnected, thereby complicating the effort to understand effects of each of these modulatory centers on a particular circuit. Though several studies have attempted to assign discrete functions to each of the neurotransmitters, e.g. acetylcholine for mediating attentional processes (Parikh and Sarter, 2008; D'Souza and Vijayaraghavan, 2014), serotonin for influencing mood (Salomon and Cowan, 2013) and noradrenalin for controlling alertness (Waterhouse and Navarra, 2018), it has become apparent that their functions are far more complex and a complete understanding requires considering interactions between the neuromodulatory brain centers (e.g. cholinergic innervation of *raphe nuclei*, Kalen and Wiklund, 1989).

The olfactory bulb receives centrifugal projections from three different neuromodulatory centers: the locus coeruleus (LC), the horizontal band of broca (HDB) and the *raphe nuclei*.

Noradrenergic innervation of the OB by LC neurons is quite heavy (McLean et al., 1989). Behavioral studies have shown diverse functions for noradrenalin in the OB, ranging from lowered odor detection thresholds to odor learning and memory effects (see Linster and Escanilla, 2018). Recent physiological studies using imaging and electrophysiological recordings from OB neurons (Eckmeier and Shea, 2014; Manella et al., 2017) were able to shed light on the role of noradrenalin in signal-to-noise regulation, influencing OB input, modulating mitral cell spontaneous activity and increasing both the number and amplitude of sensory evoked responses.

One of the major influencers of neuromodulatory structures is the amygdala (which itself, however, does not belong to the classical neuromodulatory centers) (Price and Amaral, 1981; Retson and Van Bockstaele, 2013). The amygdala is a critical structure for emotional learning, valence coding and stress (Root et al., 2014; Gore et al., 2015; Maren, 2016). A recent study indicated amygdala connections to the LC as one major circuit by which the amygdala can shape early sensory processing (Fast and McGann, 2017). The amygdala must rely on indirect modulation pathways since, despite the direct input it receives from the OB (Haberly and Price, 1977; Schneider and Scott, 1983), no back projections to the OB have been reported.

The OB also receives serotonergic innervation from a large number of neurons of the median and dorsal *raphe nuclei* (McLean and Shipley, 1987; Steinfeld et al., 2015). However, despite this knowledge, its effects on olfactory perception are far from clear. One reason might be the recently-reported dual transmitter release of serotonin and glutamate from *raphe nuclei* derived fibers (Liu et al., 2014). Moreover, serotonergic fibers innervate broad areas of olfactory cortex like e. g. the piriform cortex (Lottem et al., 2016). Recent physiological studies have reported several cellular effects: serotonin was shown to increase baseline as well as odorant-evoked responses in periglomerular and superficial short axon cells (Brunert et al., 2016) and to modulate mitral cell activity in a heterogeneous fashion (Hardy et al., 2005; Brunert et al., 2016; Kapoor et al., 2016) (Figure 2).

Cholinergic modulation in the OB has been implicated in enhanced odor coding by OB output neurons, and in improved odor discrimination ability (Doty et al., 1999; Cleland et al., 2002; Mandairon et al., 2006; Chaudhury et al., 2009; Devore and Linster, 2012; Li and Cleland, 2013; Chan et al., 2017). Studies that used electrical basal forebrain stimulation to investigate modulation effects at the level of the OB (Kunze et al., 1991, 1992; Zhan et al., 2013; Bendahmane et al., 2016), were unable to discriminate between modulation effects caused by cholinergic and GABAergic neurons (which themselves project to the OB). A study using optogenetic activation of cholinergic neurons in basal forebrain reported inhibition of spontaneous activity and preferential suppression of weak sensory responses in MTCs, sharpening their odorant response spectra (Ma and Luo, 2012). However, the neural pathways underlying this modulation remain unclear because basal forebrain cholinergic neurons target olfactory cortical areas, which themselves strongly modulate OB circuitry (Woolf et al., 1984; Carlsen et al., 1985; Linster et al., 1999; Zimmer et al., 1999; Boyd et al., 2012; Markopoulos et al., 2012; Otazu et al., 2015). By contrast, optogenetically activating cholinergic axons directly in the OB, was shown to add an excitatory bias to MTCs: the enhancement of MTC odorant responses occurred independent of the strength or even polarity of the odorant-evoked response (Rothermel et al., 2014) (Figure2). The observation that a direct stimulation of cholinergic OB inputs modulates OB activity distinctly from that of non-selectively activating cholinergic HDB neurons is consistent with the idea that indirect pathways from HDB to the OB may differentially contribute to cholinergic modulation of early sensory processing. For example, cholinergic axons in both piriform cortex and anterior olfactory nucleus can be observed after viral expression in HDB, and both of these secondary cortical areas can, in turn, modulate OB processing. This example demonstrates that results from neuromodulatory experiments, even when using similar techniques, must be interpreted carefully.

Cortical top-down modulation

Cortical top-down areas primarily release glutamate instead of classical neuromodulators, but can be equally as complex. Similar to classical neuromodulatory inputs, most brain areas receive cortical top-down inputs from multiple sources. In general, cortical areas receiving bottom-up neural signals from primary sensory areas mostly also return top-down cortical input to these areas. The olfactory bulb receives cortical top-down inputs from at least 3 different sources (Matsutani and Yamamoto, 2008): the lateral entorhinal cortex (LEC), the anterior olfactory nucleus (AON) and the piriform cortex (PC).

The lateral entorhinal cortex receives (Igarashi et al., 2012) and transfers olfactory information from the olfactory bulb to the hippocampus (Steward and Scoville, 1976). It is involved in olfactory discrimination learning and the integration of olfactory information (Staubli et al., 1984; Chapuis et al., 2013). Recently, two spatially segregated types of feedforward (to hippocampus) and feedback neurons, which send direct connections either to piriform cortex or the OB, have been identified in the LEC (Leitner et al., 2016).

The AON sends a majority of cortical top-down projections to the olfactory bulb (Carson, 1984; Shipley and Adamek, 1984) and has been implicated in a range of different functions, including serving as the first site of integrated odor percept formation, reconstructing olfactory memory traces (Haberly, 2001), social interaction (Wacker et al., 2011; Oettl et al., 2016), controlling food intake (Soria-Gomez et al., 2014), episodic odor memory (Aqra-

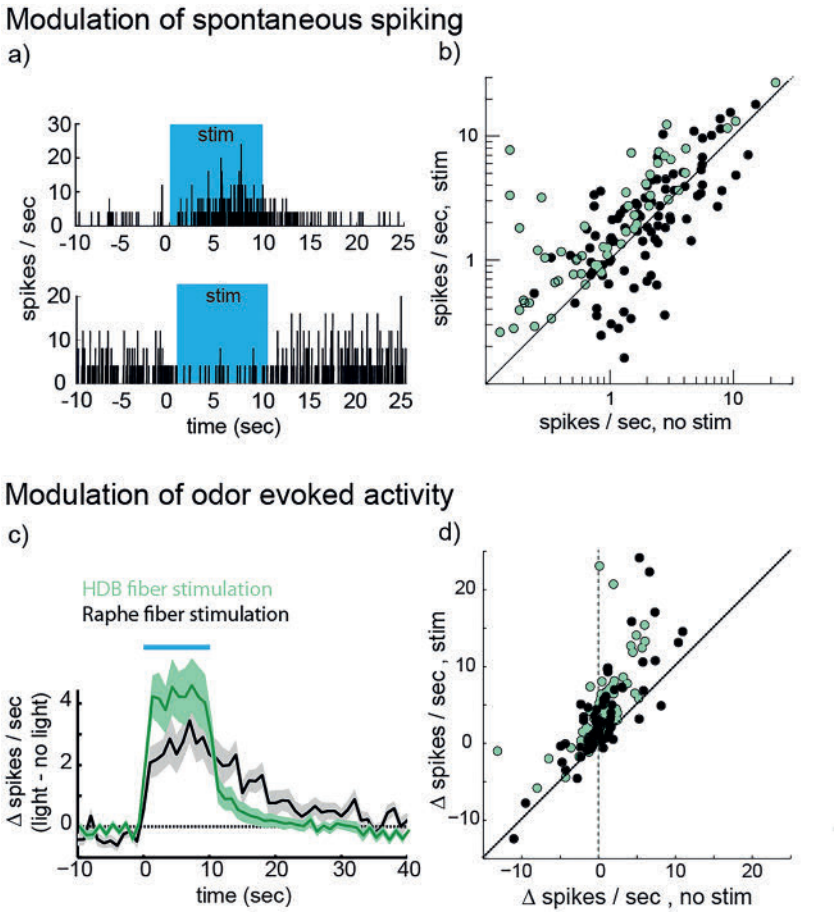

Figure 2: Diagram comparing the effects of cholinergic and serotonergic modulation on OB output activity in anesthetized mice. a) Exemplary rate histograms of two presumptive mitral/tufted cells (MTC) illustrating the effects of optically stimulating *raphe nuclei*-derived fibers in the OB on spontaneous activity (measured in the absence of inhalation). Note the qualitatively different effects in these two units. b) Plot of spontaneous firing rate of individual units before (no stim) and during (stim) optical stimulation of serotonergic (black circles) or cholinergic fibers (green circles) in the OB. c) Time course of effects of optical serotonergic (black trace) or cholinergic (green trace) fiber stimulation on odorant-evoked spike rate, averaged across all units. d) Plot of odorant-evoked changes in MTC spiking (Δ spikes/sniff) in the absence of (no stim) and during (stim) optogenetic stimulation of serotonergic (black circles) or cholinergic (green circles) afferents to the OB. Serotonergic and cholinergic fiber stimulation was performed in separate experiments. Effects on OB output neuron activity 1) are depending on the neuromodulatory center being activated, 2) display relatively fast on and offset kinetics that are center specific, and 3) can vary with sensory input (spontaneous compared to odor-evoked activity). In summary, these data support the idea that different neuromodulatory systems can modulate OB processing in distinct ways, even working in concert or independent of sensory inputs, in order to modulate sensory processing in a context-dependent fashion. For detailed material and methods please see (Rothermel et al., 2014; Brunert et al., 2016).

bawi and Kim, 2018) and integrating activity within and between the two OBs (Schoenfeld and Macrides, 1984; Lei et al., 2006; Kikuta et al., 2010; Esquivelzeta Rabell et al., 2017; Grobman et al., 2018). To date, very few studies have investigated the influence of centrifugal AON projections on OB circuit function; one study demonstrated that optogenetically activating these inputs, depolarizes as well as disynaptically inhibits MTCs, thereby enabling precisely timed spikes in a population of MTCs and shaping of OB output (Markopoulos et al., 2012). By selectively expressing the calcium-sensitive protein GCaMP in AON projection neurons, another study imaged fluorescence signals from AON axon terminals in the OB (Rothermel and Wachowiak, 2014). Using two-photon imaging, different odorants were shown to activate different subsets of centrifugal AON axons, pointing to a surprising richness in the representation of odor information by cortical feedback to the OB. Furthermore, this study revealed insights into the complexity and interplay between different top-down systems: activating classical neuromodulatory centers (the basal forebrain in this case) drove AON inputs to the OB independent of odorant stimulation. These results

demonstrate that top-down centers can also serve as a descending relay for other systems, as previously discussed for the amygdala-locus coeruleus circuit.

The piriform cortex is the primary location where the percept of "odor objects" is thought to be formed (Gottfried, 2010; Wilson and Sullivan, 2011). Piriform inputs to the OB seem to mainly activate granule cells (Price and Powell, 1970; Pinching and Powell, 1972; Davis et al., 1978; Davis and Macrides, 1981; Boyd et al., 2012), which in turn inhibit OB output neurons (Balu et al., 2007; Strowbridge, 2009; Boyd et al., 2012). More recently, top-down projections from piriform cortex in the OB were visualized (Boyd et al., 2015; Otazu et al., 2015), demonstrating that an inactivation of piriform cortex decorrelates mitral, but not tufted cells odor responses (Otazu et al., 2015). These studies did not observe that different odorants activated different subsets of top-down fibers (as demonstrated for the AON), but rather found a general relay of odor information back to the OB, highlighting the unique role of the AON in sensory information processing.

Hormonal and Peptidergic Neuromodulation

Neuromodulation in the OB can also occur via molecules other than classical neurotransmitters (see Table 1). These substances can be subdivided into hormones (signaling molecules of different chemical structure that are secreted in the body and transported via the bloodstream) and neuropeptides (small protein-like molecules released by neurons to communicate with each other). The nomenclature used can be confusing as many of these signaling molecules can act both systemically as hormones, as well as locally in the brain as neurotransmitters (see McClard and Arenkiel, 2018). Therefore, the functional context in which they are discussed, is important.

Hormones, with receptors expressed in the OB, have different sources within the body, e. g. insulin, which is released by pancreatic beta cells in response to feeding state in a glucose-dependent manner (Henquin, 2011), or ghrelin, which is an appetite-stimulating hormone produced primarily by the stomach (Kojima et al., 1999). Importantly, certain blood molecules can more easily pass into the OB compared to other brain areas, since the blood-brain barrier at the OB is more permeable (Ueno et al., 1996). Additionally, density of the capillary network in the glomerular layer is one of the highest reported for the entire brain (Lecoq et al., 2009). Furthermore, there are specialized transport systems for specific hormones (e. g. insulin) that increase the local concentration within the OB (Banks et al., 1999). Thus far, the functions of OB-active hormones have been linked to the metabolic regulation of food intake (see Palouzier-Paulignan et al., 2012). The olfactory system is known for its major contribution to the hedonic evaluation of food (affecting food choice and consumption) and it seems reasonable that olfaction would be modulated according to foraging needs. To date, olfactory-modulating substances including ghrelin, which acts as an orexigenic molecule (i. e. stimulating food uptake), insulin and leptin, which act as anorexigenic molecules (i. e. inhibiting food uptake), and adiponectin, which can regulate insulin sensitivity have been identified. Thoroughly investigated in this respect is insulin, which causes an increase in firing frequency in OB mitral cells and an inhibition of spike adaptation (Fadool et al., 2000). As a substrate, the voltage-activated K+ channel Kv1.3 has been identified which, when phosphorylated by insulin, causes a change in mitral cell excitability.

The number of neuropeptides with modulatory function in the OB is large, however most of them are generated locally within the OB: e. g. pituitary adenylate cyclase-activating polypeptide (PACAP, Irwin et al., 2015) or the circadian rhythm-mediating vasoactive intestinal polypeptide (VIP, Miller et al., 2014). Some neuropeptides like substance P or enkephalins have been observed both locally, as well as in axonal fibers within the OB (Halasz and Shepherd, 1983) and their resulting effects within the OB can not be clearly assigned to either extrinsic or intrinsic sources. Furthermore, neuropeptide-secreting fibers from multiple brain centers project to the OB. One example includes calcitonin gene-related peptide (CGRP)-containing fibers from the trigeminal ganglion, which potentially reduce the activity of OB interneurons, thus mediating an interaction between trigeminal and odorant sensations (Genovese et al., 2016). Another prominent example is oxytocin, which is important for social recognition, and has been shown to induce maternal behavior in female rats when infused into the OB (Yu et al., 1996). Oxytocin release in the forebrain originates from neurons in the paraventricular nucleus of the hypothalamus. It has been recently reported that same-sex social recognition in mice is dependent on oxytocin. In this study oxytocin was shown to activate AON cells projecting to the OB, thereby modulating mitral cell firing (Oettl et al., 2016). However, cells positive for oxytocin receptor can also be found in deeper layers of the OB (see http://www.gensat.org/imagenavigator.jsp?imageID=31777), thereby also potentially enabling direct modulation effects.

Table 1: Extrinsic neuromodulation of the OB.
List of the more prominent examples of extrinsic neuromodulators in the olfactory bulb with their point of origin and their cellular effects within the olfactory bulb. Note that this list is not exhaustive. For many of the listed modulators so far just the receptor presence within the OB has been demonstrated while the modulatory outcome is still unknown.

Neuromodulator	Primary Source	Effect on OB circuit	Publications
Classical Neuromodulatory Projections			
Acetylcholine	Horizontal dorsal Band of Broca (HDB)	Modulation of various cells types	(D'Souza and Vijayaraghavan, 2014)
Noradrenalin	Locus coeruleus (LC)	Increase in signal-to-noise ratio	(Linster and Escanilla, 2018)
Serotonin	Dorsal and Median *raphe nuclei* (RN)	Modulation of various cell types	(Lizbinski and Dacks, 2017)
Cortical Feedback Projections			
Glutamate	Piriform cortex	Activation of granule cells, thereby decorrelation of mitral cell output	(Boyd et al., 2012) (Otazu et al., 2015)
Glutamate	Anterior olfactory nucleus	Monosynaptic activation and disynaptic inhibition of MCs enabling precise spike timing	(Markopoulos et al., 2012)
Glutamate	Entorhinal cortex	Unknown	--
Hormones			
Ghrelin	Stomach	Unknown	--
Insulin	Pancreas	Increase in mitral cell firing frequency	(Fadool et al., 2000)
Leptin	Adipose tissue	Unknown	--
Adiponectin	Adipose tissue	Regulation of insulin receptor expression	(Miranda-Martinez et al., 2017)
Neuropeptides			
Oxytocin	Paraventricular nucleus (PVN) of the hypothalamus	Unknown	--
Orexins	Lateral hypothalamus	Unknown	--
Calcitonin gene-related peptide (CGRP)	Trigeminal ganglion	Reduces the activity of OB interneurons to mediate interaction between trigeminal and olfactory sensations	(Genovese et al., 2016)
Relaxin-3	Nucleus incertus	Unknown	--

Research potential of the olfactory system for sensory neuromodulation

Research on neuromodulation in the olfactory bulb is still in its beginning stages. This is probably due to the fact that the olfactory system has received less attention than other sensory systems, which are considered more significant to humans. Therefore, and especially in combination with new tools in the fields of optogenetics and optophysiology, research on the olfactory bulb as a model system for neuromodulation of early sensory processing, has much untapped potential.

One example is the modulation of sensory processing by attention. While cholinergic neuromodulation has been classically associated with attentional processes, recent data indicate that activity of noncholinergic HDB neurons (GABAergic or glutamatergic) is more strongly correlated with attention, whereas cholinergic neuron activity is correlated with reward and punishment, as well as outcome expectations (Hangya et al., 2015). To further complicate things, even a neurotransmitter co-transmission of HDB neurons has been recently reported (Case et al., 2017). In contrast to deep brain areas, more exposed structures like the olfactory bulb enable simple activity visualization in top-down fibers using optophysiological probes (Rothermel and Wachowiak, 2014). Therefore, they have enormous potential to solve long outstanding questions in the field, e. g. what task(s) engage(s) which top-down system(s).

Another example is the ability to visualize responses of single cells of the OB over an extended time period. Work on early sensory processing in other systems often requires deep brain electrophysiology. However, following individual cells over an extended time period is challenging using this technique. By using high resolution two-photon imaging in the olfactory bulb, cells of interest can be unambiguously identified between recording sessions, and therefore modulatory influences like experience can be investigated on a single cell level (Kato et al., 2012).

In addition, the olfactory system has received much attention recently in the field of artificial intelligence and machine learning. Despite its simplicity, or maybe because of it, olfactory system-based artificial neural networks perform much faster and better at classifying objects in a noisy environment than commonly used visual system-based artificial neural networks (see Srinivasan et al., 2018). This further highlights the need to achieve a deeper understanding of sensory processing in the olfactory system.

Summary

Neuromodulatory processes in sensory systems are of critical importance, enabling all organisms to survive in an ever changing environment. This review provides a short overview on the best understood neuromodulatory systems, using the olfactory bulb as a model system for early sensory processing. It is intended to highlight the complexity of the topic as well as to emphasize the need for further research. Broadening the general definition of neuromodulation enables the inclusion of more modulatory factors, which are of vital importance. We believe that substantial progress in the field of neuromodulation can only be achieved if different fields of expertise (e. g. hormonal and neuronal; different sensory systems) work in close collaboration. In conclusion, we envision an open and interdisciplinary field of neuromodulation, which includes fields and topics ranging from basic to clinical research.

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Bionotes

Daniela Brunert
Dept. Chemosensation – AG Neuromodulation
RWTH Aachen University
52074 Aachen
Germany,
D.Brunert@sensorik.rwth-aachen.de

Daniela Brunert studied biology at the Ruhr University in Bochum and received her Ph.D. from the International Graduate School at the RUB working on neuromodulation in the mouse olfactory epithelium. She received postdoctoral training at the University of Florida under the supervision of Barry Ache, where she received a Feodor Lynen Fellowship and the University of Utah under the supervision of Matt Wachowiak where she was awarded the Young Investigator Award of the Association for Chemoreception Sciences for her work on serotonergic modulation of the olfactory bulb. After working briefly in the lab of Thomas Pap at the WWU Münster she joined the lab of Markus Rothermel at the RWTH Aachen.

Markus Rothermel
Dept. Chemosensation – AG Neuromodulation
RWTH Aachen University
52074 Aachen
Germany,
m.rothermel@sensorik.rwth-aachen.de

Markus Rothermel studied biology at the Ruhr University Bochum. His doctoral thesis with Hanns Hatt at the Department of Cellphysiology focused on “trigeminal perception” and was funded by scholarships from the research training group GRK 736, the Wilhelm and Günther Esser-Foundation and the Ruhr-University Research School. For his postdoctoral time he joined the laboratory of Matt Wachowiak (Boston University and the University of Utah, USA) focusing on information processing in the rodent olfactory system, a project for which he was awarded a DFG research fellowship. In October 2014, he returned to Germany in order to establish an Emmy Noether research group funded by the German Research Foundation at the RWTH Aachen University. His main interests are a systematic investigation of sensory filtering processes in health and disease.

Review Article

Barbara Gisevius*, Sarah Hirschberg*, Aiden Haghikia*

Impact of Diet and the Gut Microbiome on Neurodegeneration and Regeneration in Neurological Disorders

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Abstract: Recent advances in the field of neurodegenerative disorders point to a possible association between diet, gut microbiota composition and disease incidence. Hence, the so-called *gut-brain axis*, or more precisely the *gut-microbiome-brain axis*, has gained increasing attention. There are several ways in which gut content can impact the central nervous system, i. e. either I) directly via bacterial components and dietary metabolites that are systematically available, II) by intermediates, such as circulating immune cells or III) via direct neuronal connections, i. e. the vagus nerve.

New technologies for the identification of bacteria, like next generation sequencing, are enabling a higher resolution understanding of microbiota composition. Therefore, it is now possible to elucidate direct interactions between the gut microbiome, the metabolome, and the gut-associated immune system. In addition to these interactions and of equal importance are the interdependencies of gut metabolites with cells of the central nervous system. In this review, we discuss how the gut microbiome can promote neuronal regeneration or degeneration, depending on health status and diet, and how its modulation may be exploited for novel therapeutic applications.

Zusammenfassung: Aktuelle Forschungsergebnisse im Bereich neurodegenerativer Erkrankungen deuten vermehrt darauf hin, dass die Ernährung und damit assoziiert die Zusammensetzung des Darm-Mikrobioms einen entscheidenden Einfluss auf die Entstehung und den Verlauf verschiedenster Krankheiten haben. Die sogenannte Darm-Hirn Achse, oder präziser die Darm-Mikrobiom-Hirn Achse hat dadurch deutlich an Aufmerksamkeit gewonnen. Dabei kann der Darm das zentrale Nervensystem auf unterschiedliche Weisen beeinflussen, I) direkt durch bakterielle Bestandteile und Metaboliten von Bakterien, II) durch Manipulation der im Körper zirkulierenden Immunzellen, oder III) durch direkten Kontakt, z. B. über den N. vagus.

Fortschritte auf dem Gebiet der Molekularbiologie, wie das *Next Generation Sequencing* ermöglichen aufgrund ihres hohen Auflösungsvermögens die genaue Identifikation von Bakterien und die Kompositionen ganzer Mikrobiome. Dadurch ist es möglich, die Interaktionen zwischen dem intestinalen Mikrobiom, dem Metabolom und dem Darm- assoziierten Immunsystem detailliert zu erforschen.

In dieser Arbeit diskutieren wir den Einfluss des Mikrobioms, der Ernährung und den damit verbundenen Gesundheitszustand auf die Neuroregeneration. Der Fokus liegt dabei auf der Möglichkeit, wie dieses Wissen in Zukunft für therapeutische Zwecke genutzt werden kann.

Introduction
The gut and its microbiome

Colonization of the human gut by various bacterial species occurs initially during or shortly after birth. Already the method of birth, i. e. by caesarean section or naturally, is the key factor for the abundance (Toscano et al., 2017) and amount of gut bacteria (Huurre et al., 2008). In addition to the vaginal passage (Dominguez-Bello et al., 2010), another factor known to contribute to the origin of gut microbiota, is breast-feeding (Backhed et al., 2015). Also, the possibility of colonization in utero is currently being examined (Willyard, 2018), which is supported by the presence of bacterial DNA in the placenta (Aagaard et al., 2014).

***Corresponding author: Barbara Gisevius**, Department of Neurology, Ruhr-University Bochum, St. Josef-Hospital Bochum, Germany, E-Mail: barbara.gisevius@rub.de
Sarah Hirschberg, Department of Neurology, Ruhr-University Bochum, St. Josef-Hospital Bochum, Germany, E-Mail: sarah.hirschberg@rub.de
Aiden Haghikia, MD, Department of Neurology, Ruhr-University Bochum, St. Josef-Hospital Bochum, Gudrunstr. 56, 44791 Bochum, Germany, tel: +49-234-509-2411, fax: +49-234-509-2414, E-Mail: aiden.haghikia@rub.de

In humans, the colon is the organ containing the highest number of microbial species (Sender et al., 2016). The majority of these microbes are members of three bacterial *phyla*, referred to as enterotypes, namely *Firmicutes*, *Bacteroidetes*, and *Actinobacteria* (Tap et al., 2009). Due to the enormous number and diversity of these gut-dwelling bacterial species, the human organism is capable of digesting several food-derived nutrients by taking advantage of bacterially-derived enzymes. *Bacteroides thetaiotamicro,* for example, produces a variety of enzymes that can degrade a range of carbohydrates (Xu et al., 2003). This symbiotic relationship that enables a broad range of nutritive sources has figured largely in human evolution. Perhaps the most prominent example involves mitochondria, bacteria that lost their cellular autonomy and became endosymbiotically-derived organelles (Stilling et al., 2014, Archibald, 2015, Raina et al., 2018).

The primary metabolites and end products of bacterial fermentation include short chain fatty acids (SCFA) (Salminen et al., 1998), micronutrients such as vitamins (Fresia Fernandez, 1987), and secondary bile acids (Ajouz et al., 2014). These microbial products diffuse passively, or are actively transported across gastrointestinal tract endothelia, where they become available for downstream organs via blood circulation (Conlon and Bird, 2014). However, this route is not only used by essentially beneficial metabolites, but also by potentially harmful products of pathogenic bacteria or *pathobionts*. However, during a state of healthy homeostasis, or *eubiosis,* these potentially harmful metabolites are less relevant, since non-pathogenic bacteria outnumber, and thus suppress the growth of pathogenic species (Kamada et al., 2012).

In addition to the influence of host genetics (Bonder et al., 2016), use of antibiotics (Dethlefsen et al., 2008), or immune defense (Wang et al., 2015), the contribution of diet is known to be a key regulator of microbial composition (Ley et al., 2008). Diet begins shaping development of the gut microbiome immediately following birth. For example, components of breast milk (as opposed to formula milk) already affect bacterial gut composition in newborns (Harmsen et al., 2000). During the first three years of life, this composition of bacterial communities evolves towards those found in adults. Furthermore, the composition of fecal microbiota differs between human populations of different origins, highlighting the influence of additional selective pressures, such as dietary habits, hygiene, and general lifestyle, i. e. exercise and smoking. Additionally, gut bacterial diversity increases, in a population-independent manner, during adolescence (Yatsunenko et al., 2012).

The effect of dietary change on the microbiome, as an important environmental factor, depends on the duration of change. Short-term alterations in dietary behavior can influence microbial composition without a large effect on the enterotypes. By contrast, sustained and long-lasting changes to diet are able to affect enterotype states (Wu et al., 2011).

In general, a typical human diet consists of three major components, i. e. carbohydrates, proteins, and fat, which also serve as different substrates for our gut bacteria. In the Western diet these substrates upon reaching the colon, mainly consist of dietary fibers, which comprise non-starch polysaccharides. Additional substrates found here include simple sugars, oligosaccharides, starch, proteins, and lipids (Conlon and Bird, 2014). Importantly, consuming a high amount of dietary fiber is beneficial for health, as it has been shown repeatedly to reduce risk of coronary heart disease (Liu et al., 1999) and diabetes (Montonen et al., 2003). Furthermore, organic acids, the resulting end products of carbohydrate catabolism, serve as additional energy sources for resident bacteria. It is also here where SCFA, in particular, exert a vast number of effects, especially by acting on the immune system once they have been absorbed by the gut epithelium (Conlon and Bird, 2014). However, the direct effects of SCFA on the central nervous system (CNS), need to be better understood.

Dysbiosis and disease

Symbiosis between the commensal microbiome and the innate and adaptive immune system has provided crucial developmental advantages in eukaryote evolution. Hence, it is not surprising, that a dysbalance of the microbiome composition, also denoted as *dysbiosis*, exerts detrimental effects on human health and immunity (Levy et al., 2017). A dysbiosis of the gut microbiome can be caused by internal or external factors, such as sleep deprivation, stress, use of antibiotics, or dietary components (Dethlefsen et al., 2008, Bailey et al., 2011, Devkota et al., 2012) and an increasing number of chronic disorders are associated with an altered microbial composition. For instance, high salt intake exacerbates disease activity in several – mainly autoimmune – diseases, mediated by an increase in pro-inflammatory immune cell subsets (Jorg et al., 2016).

The commensal microbiome essentially participates in regulating the immune tolerance (Weiner et al., 2011). As such, regulatory immune components such as regulatory T cells (Treg) are crucial for development of a sufficient immune tolerance, especially towards enteric microbiota

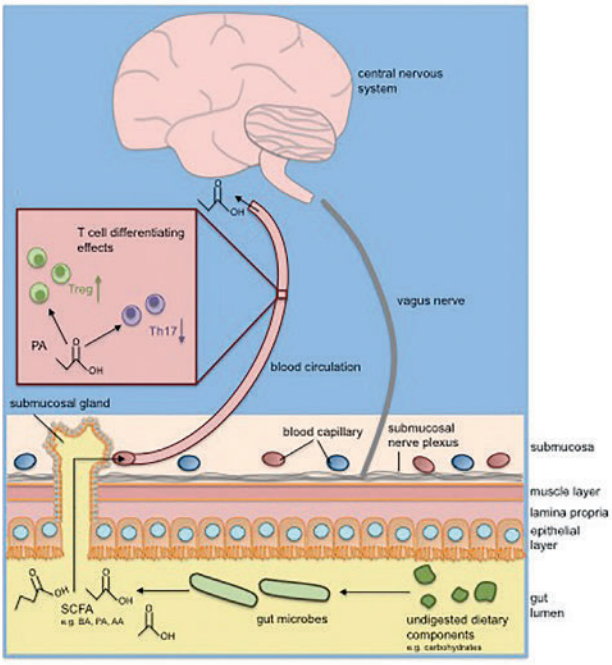

Fig. 1: Microbiome metabolites differentially affect the immune and the central nervous system Short chain fatty acids (SCFA) are metabolites, originating from the fermentation of fiber-rich diet by the commensal gut bacteria. SCFA serve as an energy source for gut epithelia, but also pass from the gut lumen into blood circulation and interact with immune cells within the lamina propria cells of the submucosal nerve plexus. The impact of short chain fatty acids within the CNS is indirect in the case of a shifted immune cell balance towards Treg. Especially in diseases with a disrupted blood-brain-barrier, such as MS, changes in CNS-resident immune cells can directly affect the CNS. BA, butyric acid, PA, propionic acid, AA, acetic acid.

(Sakaguchi et al., 2008). Pathobionts occur at low abundances in healthy individuals, but tend to expand in the diseased organism, as is the case for inflammatory bowel disease (IBD). IBD is characterized by chronic inflammation of the gastrointestinal tract (de Souza and Fiocchi, 2016), leading to a compositional shift in the commensal microbiome (Frank et al., 2007, Lupp et al., 2007, Butto et al., 2015).

Besides gastrointestinal and autoimmune diseases, a dysbiotic state is currently discussed in neurodegenerative disorders. An important microbiome-related metabolic pathway – the kynurenine pathway – for example, was shown to be associated with several neurodegenerative and neuroinflammatory diseases, and depression (Lombardi et al., 2018). For decades, the focus in chronic diseases, such as autoimmune and neurodegenerative diseases has been on the association with a genetic predisposition. However, more recently the direct impact of environmental factors like the microbiome composition has gained attention (Chen et al., 2016b). The microbiome involvement is further supported by animal studies, showing an attenuation or even the complete absence of neurologic disease, once the animals were kept under bacteria-free conditions (Wu et al., 2010, Berer et al., 2011). Human migration studies have demonstrated that multiple sclerosis (MS) incidence increases in subjects who move from low risk countries to countries with higher MS prevalence, usually countries far north of the equator (Gale and Martyn, 1995). This notion initially led to the *theory of latitude*, i. e. reduced sun exposure being the major risk factor, not considering dietary habits. How certain components of the diet may have an impact on neuroinflammation and –degeneration was recently shown for fatty acids, especially the differential roles of short versus long chain fatty acids (SCFA, LCFA). We could show, that administration of LCFA in the experimental model of MS worsened disease course via polarization towards T-helper (Th) 1 and Th17 cells, whereas the SCFA propionic acid diminished clinical symptoms due to an increase of intestine-derived Treg (Haghikia et al., 2015).

Additionally, the observed conversion to a rather anti-inflammatory environment by propionic acid treatment is accompanied with a decrease in demyelination and less axonal loss, which we observed during disease course in mice by Luxol Fast Blue and Bielschowsky silver staining (Haghikia et al., 2015). The question, if these neuroprotective effects are only mediated by reduced inflammation or via a local action of propionic acid on CNS cells, remains unanswered. A recent study has shown that Treg are able to directly increase neuronal remyelination and oligodendrocyte differentiation, thereby affecting remyelination processes (Dombrowski et al., 2017). In addition, anti-inflammatory cytokines like interleukin-10 are capable to trigger neuroregeneration (Chen et al., 2016a). There is cumulative evidence for the neuroprotective capacity of (mainly regulatory) immune-mediated processes, nevertheless, various findings point to a direct neuroprotective effect by commensal metabolic components. However, these components can also exert damaging effects on neurons, especially in high concentrations. In animal models investigating autism-like diseases, administration of high dose propionic acid (e. g. 500 mg/kg body weight), provoked autism-like behavior (Macfabe, 2012, Choi et al., 2018). This corresponds with findings within the disease propionic-acidemia, which is characterized by a reduced activity of the propionyl-CoA carboxylase, leading to an impaired metabolism of propionic acid, accompanied with propionic acid accumulation. This observed autism-like behavior is supposed to be triggered by an increased in-

hibitory GABA-ergic neurotransmission (Morland et al., 2018).

Apart from secondary neurodegeneration as a result of inflammation, in patients with Parkinson's disease, a dysbiosed microbiota has been observed, that is characterized by a reduced abundance of *Prevotellaceae*. Furthermore, changes in Parkinson's patients' microbiome also correlate with disease progression (Minato et al., 2017): the relative abundance of *Enterobacteriaceae* is associated with motor dysfunction (Scheperjans et al., 2015). Additionally, psychiatric diseases such as depression and autism spectrum disorders (ASD) have also been linked to alterations of the gut microbiome (Kang et al., 2013, Jiang et al., 2015). By high-throughput pyrosequencing of bacterial genomic DNA extracted from fecal samples of patients with major depressive disorder, an increase in the levels of *Bacterioidetes*, *Proteobacteria*, and *Actinobacteria* was found, while the level of *Firmicutes* was decreased in comparison to healthy controls. Furthermore, the severity of depressive symptoms is inversely correlated with a reduction of *Faecalibacterium*. ASD have also been linked to a less diverse gut microbiome and to alterations in different bacterial genera, namely reduced abundances of *Prevotella*, *Coprococcus*, and unclassified *Veillonellaceae* (Kang et al., 2013), as well as to gastrointestinal disruption that correlates with disease severity (Adams et al., 2011). Therefore, the effect of microbiota transfer therapy has been investigated in a clinical trial. After a 2-week antibiotic treatment followed by bowel cleanse and a subsequent performance of fecal microbiota transplantation, patients displayed a reduction of gastrointestinal symptoms, accompanied by a significant improvement in behavioral ASD symptoms (Kang et al., 2017). Although this example promises hope for fighting other diseases that have been associated with an altered microbiome, it also needs to be assessed carefully. Since most of the microbiome sequencing studies lack a temporal and causal relationship between microbial alterations and disease initiation, the use of probiotics and fecal transplant therapies is still a matter of debate. It is not yet understood, if depleting disease-associated pathogens, by probiotics or fecal transplants, will have any positive effect on these diseases (Khoruts and Sadowsky, 2016).

In contrast to the aforementioned correlations between an altered gut microbiome and neurologic diseases, a healthy diet is associated with lower risk of first clinical diagnosis of central nervous system demyelination; a healthy diet defined as rich in vegetables, legumes, fish, poultry, and eggs (Black et al., 2018).

Interactions between gut and the brain

The term *gut-brain axis* has emerged from observing the direct effects of gut metabolites on the CNS and accordingly, the interaction between the gut and the enteric nervous system is well worked out. Classically, the interaction has long been understood as a "ONE WAY" process concerning the regulation of gastrointestinal functions by the brain. The sympathetic and parasympathetic nervous system modulates gut function, e. g. motility or secretion of several components into the gut lumen (Rhee et al., 2009). However, the impact is reciprocal, and this facet has only recently gained attention (Mayer et al., 2014). Besides the beneficial effects of gut-derived SCFA on the CNS via the immune system, other bacterial products have long been known to directly manipulate neurons. Botulinum and tetanus neurotoxins are bacterial toxins, which directly exert severe damage in neurons. Botulinum toxin blocks synaptic vesicle fusion and the release of neurotransmitters (Rossetto et al., 2014), whereas tetanus toxin is internalized into signaling endosomes and retrogradely transported to the neuronal soma, where it blocks neurotransmission (Calvo et al., 2012, Yang and Chiu, 2017). The effects of the many bacterial metabolites on neurons remain to be explored, yet scarce evidence suggests that some could affect CNS neurons up to the level of the dopaminergic reward system (Diaz Heijtz et al., 2011).

These recent findings on the direct effects of gut metabolites on the CNS have initiated a paradigm shift also in drug development programs targeting (De Vadder et al., 2014, Stilling et al., 2016, Hoyles et al., 2018) Parkinson's, Alzheimer's and MS diseases (Berer et al., 2011, Hill et al., 2014, Sampson et al., 2016). The molecular mechanisms by which SCFA are able to directly influence cellular processes have also been analyzed in cancer research (Augenlicht et al., 2002, Matthews et al., 2012). These mechanisms are mediated either by receptor activation or by epigenetic modulation. SCFA activate the orphan G-protein coupled receptors (GPR) 41 and 43, also known as free fatty acid receptor (FFAR) 2 and 3 (Brown et al., 2003) among other effects, modulating the induction of immune regulatory mechanisms such as Treg differentiation (Smith et al., 2013). Due to their small molecular size, SCFA have also been shown to directly inhibit epigenetic modifiers like the histone deacetylases (HDAC) of class I and II (Candido et al., 1978, Davie, 2003, Harrison and Dexter, 2013). For instance, the key players active in maintaining homeostasis of lysine acetylation are histone acetyltransferases (HATs) and HDACs. HATs catalyze the transfer of an acetyl-group

from acetyl-CoA onto lysine residues of histone proteins. This process leads to a relaxation of nuclear chromatin structure. By contrast, HDACs remove acetyl groups from lysine residues, causing chromatin condensation. Changing the conformation of the chromatin framework either increases (relaxation) or decreases (condensation) transcriptional processes (Chuang et al., 2009). HDAC inhibitors promote chromatin relaxation and thus translational activation. Since acetylation is not exclusively limited to chromatin but also in various proteins as post-translational modifications, HDAC inhibitors may exert varying effects on cellular processes. These effects include modulation of protein expression and function, mitochondrial behavior, intracellular transport, and metabolic processes (Kazantsev and Thompson, 2008). Protein post-translational modifications are discussed as important drivers of neurodegenerative diseases, since they could serve as a link for the gap between environmental factors and genetic disease susceptibility. An imbalance of HAT and HDAC activity is considered to favor neurodegenerative conditions (Chuang et al., 2009). Assuming that SCFA manipulate neurons by HDAC inhibition, our daily diet may have a greater impact on the development of, not just autoimmune diseases, but also neurodegenerative disorders. Beneficial effects of chromatin remodeling have already been shown in an Alzheimer's disease model, using the HDAC inhibitor sodium 4-phenylbutyrate (Ricobaraza et al., 2009). Although there is sparse evidence that SCFA induce direct neuroregenerative effects, an altered HDAC activity has already been proven to participate in processes including neuronal damage. For instance, nuclear export of HDAC1 induces axonal damage that leads to to neuronal death (Kim et al., 2010). Hence SCFA, like known HDAC I and II inhibitors, may prove to have therapeutic potential.

Potentially indirect neuroprotective effects of SCFA include the secretion of anti-inflammatory cytokines such as interleukin-10 from Tregs, and interleukin-4 from Th2 cells. These cytokines have been shown to protect damaged neurons and synapse formation after brain injury (Siffrin et al., 2010, Chen et al., 2016a, Vogelaar et al., 2018).

The presence and composition of our commensal microbiome not only participates in normal gastrointestinal function, but may also influence development of the brain, its function and the occurrence of its diseases. This is important, not only considering maintenance of a healthy diet in order to promote proper brain functioning, but most importantly for expecting mothers, who by maintaining a balanced diet can encourage a child's normal brain development during pregnancy. It was demonstrated in mice that a maternal diet high in fat negatively impacts the offspring's social behavior, caused by a reduction of oxytocin-immunoreactive neurons and a reduction of long term potentiation in dopaminergic neurons within the ventral tegmental area (Buffington et al., 2016). By contrast, a diet containing omega-3 polyunsaturated fatty acids has beneficial impacts on neurodevelopment by influencing the hypothalamic-pituitary-adrenal (HPA) axis. Since the HPA axis mainly determines stress reactivity, these metabolic components prevent depressive-like behaviors due to better stress resistance (Pusceddu et al., 2015). Hence microbiome manipulation, either by diet or by specific prebiotics, may open new therapeutic avenues for treating various systemic diseases including neurodegeneration.

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Bionotes

Barbara Gisevius
MD, Department of Neurology
Ruhr-University Bochum
St. Josef-Hospital Bochum
Gudrunstr. 56
44791 Bochum
Germany
tel: +49-234-509-2411
fax: +49-234-509-2414
E-Mail: barbara.gisevius@rub.de

2010–2013: Bachelor of Science in Biology, Faculty of Biology and Biotechnology, Cell Morphology and Molecular Neurobiology, Ruhr-University Bochum, Germany
2013–2015: Master of Science in Biology with focus on neurobiology, Faculty of Medicine, Neuroimmunology, Ruhr-University Bochum, Germany
since 2015: PhD study in Biology with focus on the direct effects of gut metabolites (i. e. short chain fatty acids) on neurons in the context of Multiple Sclerosis, Faculty of Medicine, Neuroimmunology, Ruhr-University Bochum, Germany

Aiden Haghikia
MD, Department of Neurology
Ruhr-University Bochum
St. Josef-Hospital Bochum
Gudrunstr. 56
44791 Bochum
Germany
tel: +49-234-509-2411
fax: +49-234-509-2414
E-Mail: aiden.haghikia@rub.de

Aiden Haghikia hat sein Medizinstudium an der Ruhr-Universität Bochum abgeschlossen, wo er im Rahmen des neurowissenschaftlichen Graduierten Kolleg am Lehrstuhl für Neuroanatomie (Prof. Rolf Dermietzel) seine Promotionsarbeit zur funktionellen Charakterisierung von astrozytären Gap Junctions durchführte. Nach seiner Facharztausbildung in der Neurologischen Klinik der Ruhr-Universität Bochum im St. Josef-Hospital (Leitung Prof. Gold) arbeitete er als Postdoc im Labor von Prof. Lars Fugger an der University of Oxford (Neuroimmunogenetik). Er hält eine Universitätsprofessur für Translationale Neuroimmunologie inne und ist seit 2017 leitender Oberarzt der Neurologischen Klinik, Leiter der MS-Ambulanz/neuroimmunologischen Forschung in Bochum.

Sarah Hirschberg
MD, Department of Neurology
Ruhr-University Bochum
St. Josef-Hospital Bochum
Gudrunstr. 56
44791 Bochum
Germany
tel: +49-234-509-2411
fax: +49-234-509-2414
E-Mail: sarah.hirschberg@rub.de

2010–2013: Bachelor of Science in Biology, Faculty of Biology and Biotechnology, Developmental Neurobiology, Ruhr-University Bochum, Germany
2013–2015: Master of Science in Biology with focus on neurobiology, Faculty of Medicine, Neuroimmunology, Ruhr-University Bochum, Germany
since 2015: PhD study in Biology with focus on neuroregeneration and neurodegeneration in Multiple Sclerosis, Faculty of Medicine, Neuroimmunology, Ruhr-University Bochum, Germany

Review Article

Maren Engelhardt*, Nora Jamann and Winnie Wefelmeyer*

Small domain, large consequences: the axon initial segment as a key player in neuronal excitability

Kleine Domäne, große Konsequenzen: die Bedeutung des Axoninitialsegments für neuronale Erregbarkeit

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Abstract: The axon initial segment (AIS) is a crucial axonal domain for neuronal function – it allows neurons to generate action potentials, maintain their polarity or modulate their own excitability, thereby adapting to sudden and more long-term changes in network state. Although the AIS has been a well-described structure in neurons with work dating back to the 1960s, its fundamental role in neuronal function has only really been appreciated in the last decade. It is therefore no surprise that the AIS now also emerges as a hub for the onset of various pathophysiological conditions. In this review, we will focus on AIS development, function, and plasticity in the context of neuronal network activity and will highlight recent results that indicate a role for the AIS in the regulation and fine-tuning of input-output relations in single neurons.

1 Introduction

Our classical understanding of CNS neurons highlights the role of the somatodendritic domain for integration of synaptic inputs and the dynamic adaption of neurons to changes in network state, particularly via plasticity at dendritic spines. The axonal domain of a neuron however, is seen as a rather static output device with little to no retained plasticity after the developmental period of neuronal networks. This classic "textbook" view is changing. A growing body of evidence suggests that electrogenic microdomains in the axon play an important role for the fine-tuning of neuronal excitability. A particular focus in this context is placed on the axon initial segment (AIS), the axonal domain responsible for action potential (AP) initiation (Fig. 1; for review see e. g. (Bender and Trussell, 2012; Kole and Stuart, 2012). Over the past decade, a number of studies have highlighted the fact that the AIS undergoes periods of structural plasticity during development, and is a hub for rapid and more long-term changes in both structure and function, directly influencing a neuron's output and therefore its role within functional networks (for review see e. g. (Jamann et al., 2017; Wefelmeyer et al., 2016). Parameters emerging as influential for AIS plasticity are e. g. (i) its location on the axon (proximal or distal to the soma), (ii) its length, and (iii) its molecular architecture, all of which have been shown to adapt dynamically to changes in network state. Some of these examples will be discussed in this review.

A very recent "rediscovery" was that axons can emerge from a dendrite and that this has substantial effects on a neuron's firing properties. Incidentally, it was no other than the pioneering neuroscientist Santiago Ramón y Cajal who was the first to notice that axons do not always emerge directly from the soma (Cajal, 1937). He alluded to the fact that "*currents flowing into the axon do not pass through the soma except when the latter is between the dendritic and the axonal apparatus*" (Cajal, 1897). Indeed, axon location is quite diverse and hence, the location of the AIS is equally heterogeneous and often cell type specific (Fig. 1A;

***Corresponding authors: Maren Engelhardt,** Institute of Neuroanatomy, Medical Faculty Mannheim, Heidelberg University, Germany, maren.engelhardt@medma.uni-heidelberg.de
Winnie Wefelmeyer, Centre for Developmental Neurobiology, King's College London, London, UK, winnie.wefelmeyer@kcl.ac.uk
Nora Jamann, Institute of Neuroanatomy, Medical Faculty Mannheim, Heidelberg University, Germany, nora.jamann@medma.uni-heidelberg.de

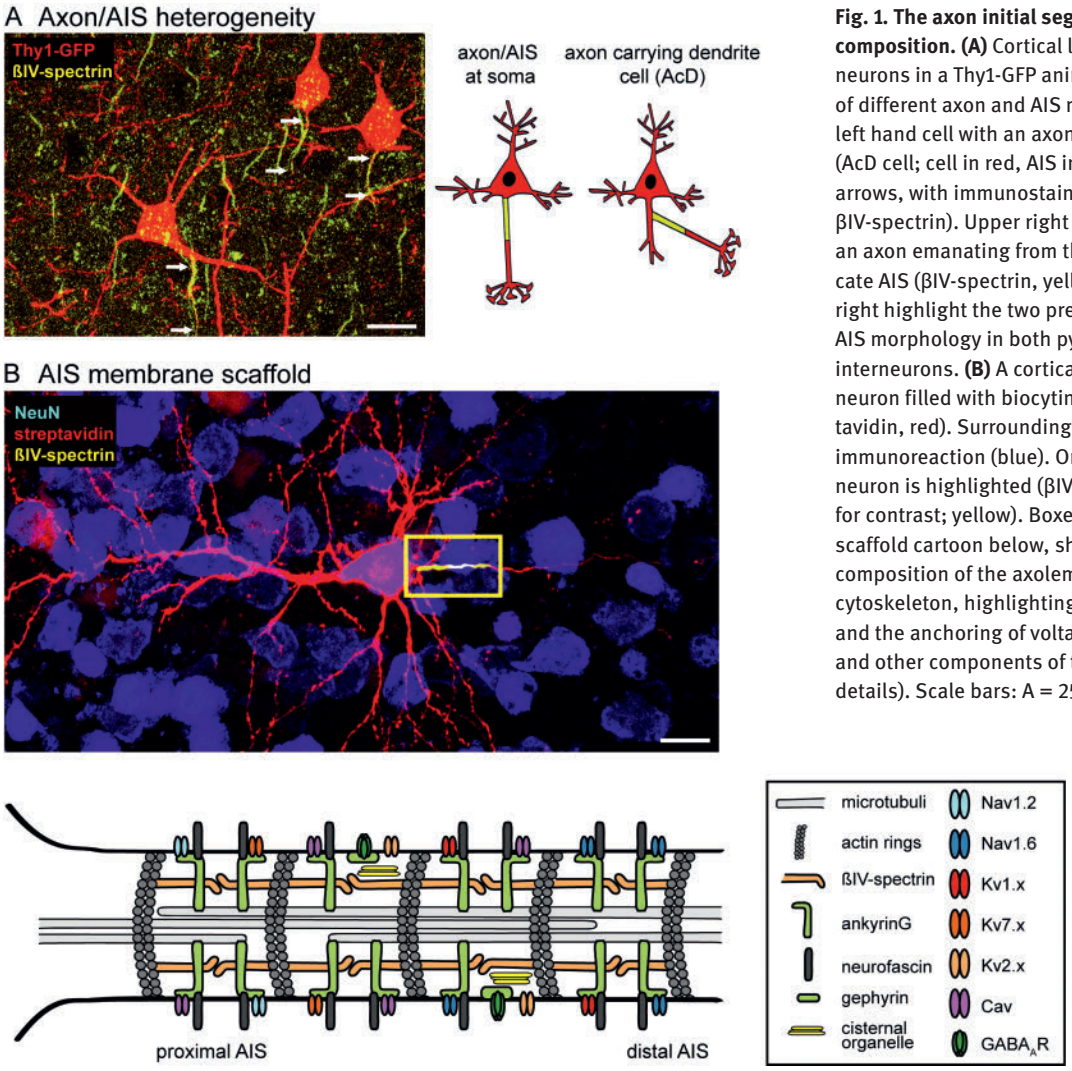

Fig. 1. The axon initial segment and its molecular composition. (A) Cortical layer II/III pyramidal neurons in a Thy1-GFP animal with examples of different axon and AIS morphologies: lower left hand cell with an axon carrying dendrite (AcD cell; cell in red, AIS in yellow indicated by arrows, with immunostaining against AIS marker βIV-spectrin). Upper right hand cells both have an axon emanating from the soma, arrows indicate AIS (βIV-spectrin, yellow). Cartoons on the right highlight the two prevalent forms of axon/AIS morphology in both pyramidal cells and interneurons. **(B)** A cortical layer II/III pyramidal neuron filled with biocytin (developed with streptavidin, red). Surrounding cells visible by NeuN immunoreaction (blue). Only the AIS of the filled neuron is highlighted (βIV-spectrin enhanced for contrast; yellow). Boxed region is depicted in scaffold cartoon below, showing the molecular composition of the axolemma and submembrane cytoskeleton, highlighting protein interactions and the anchoring of voltage-gated ion channels and other components of the AIS (see text for details). Scale bars: A = 25 µm, B = 20 µm

(Ernst et al., 2018; Hamada et al., 2016; Hausser et al., 1995; Herde et al., 2013; Hoefflin et al., 2017; Martina et al., 2000; Meza et al., 2018; Peters, 1968; Thome et al., 2014; Triarhou, 2014)). These axon and AIS phenotypes can have significant impact on the excitability and firing properties of neurons (Gulledge and Bravo, 2016; reviewed in Kole and Brette, 2018). A common denominator in these many different cell populations however is the axonal scaffold and surrounding niche that characterize the AIS.

2 Molecular architecture

The AIS of most CNS neurons is located at the unmyelinated proximal axon. It constitutes a specialized axonal microdomain distinguished from the remaining axon by several structural features specific to it and to the nodal region of nodes of Ranvier, which essentially recapitulate the AIS architecture with slight modifications (Rasband, 2010). In general, the AIS comprises a special cytoskeletal scaffold with numerous binding partners linking it to the extracellular matrix and to the inside of the axon, thus creating a highly stable compartment (Fig. 1B).

Early electron microscopy studies identified several ultrastructural features that distinguish the proximal axon,

then termed 'initial segment', from its other parts and components of the somatodendritic domain: (i) a dense granular undercoating of the axolemma, (ii) an almost complete lack of ribosomes, and (iii) fascicles of microtubules, which can vary in density and number (Palay et al., 1968; Peters, 1968; Peters et al., 1968). Recent development of super-resolution nanoscopy has dramatically improved our understanding of AIS structural features. For example, studies using dissociated hippocampal neurons *in vitro* have indicated that a periodic, ~190 nm spaced submembrane lattice of the AIS consists of longitudinal, head-to-head ßIV-spectrin molecules connecting to actin rings (D'Este et al., 2015; Leterrier et al., 2017b; Leterrier et al., 2015; Zhong et al., 2014).

The major scaffolding protein of the AIS, however, is ankyrin-G (ankG; Fig. 1B). Encoded by the *ANK3* gene, ankG is known to exist as three alternatively spliced isoforms with molecular weights 480 kDa, 270 kDa and 190 kDa, respectively (Jenkins et al., 2015). It is essential for assembly and maintenance of the AIS (Hedstrom et al., 2008; Jenkins and Bennett, 2001; Leterrier et al., 2017a; Sobotzik et al., 2009; Zhou et al., 1998) and comprises a modular protein with a membrane-binding domain, a spectrin-binding domain, a serine-rich tail, as well as carboxy-rich domains (Bennett and Lorenzo, 2013). AnkG mediates linkage between axonal surface and central regions by anchoring membrane-associated surface proteins, such as voltage-gated ion channels (see chapter on AIS function for details) plus the cell adhesion molecules neurofascin 186 kDa (NF-186) and NrCAM, to axonal microtubules via interactions between microtubule-associated proteins and ankG's carboxyterminal side (Kuijpers et al., 2016; Leterrier et al., 2011). Functionally, this highly organized architecture renders axons very stable, protecting them against cytoskeletal damage. The 480 kDa ankG isoform also plays an important role in stabilizing somatodendritic GABAergic synapses by interaction with the $GABA_A$ receptor-associated protein (GABARAP; (Tseng et al., 2015)).

While ribosomes and other molecules of translational machinery are notably absent from the axon hillock and AIS, stacks of smooth endoplasmic reticulum, termed cisternal organelle (CO), have been described (Benedeczky et al., 1994; Somogyi et al., 1983b). Interestingly, the CO and its molecular components such as the actin-binding protein synaptopodin, and Ca^{2+}-store-associated receptors (e. g. RyR, IP3R or SERCA; (Anton-Fernandez et al., 2015; Sanchez-Ponce et al., 2011)) have a structural and potentially functional correlate in the spine apparatus of dendrites, which orchestrates spine turnover and contributes to homeostatic plasticity (Deller et al., 2007; Vlachos et al., 2013; Vlachos et al., 2009). A similar contribution to structural plasticity and cellular excitability has been proposed for the CO in the AIS (Jedlicka et al., 2008; Schluter et al., 2017; Segal, 2018). Considering that AP initiation is modulated by fast Ca^{2+} influx (Bender and Trussell, 2009), strategic placement of the CO in many cortical neurons points towards a significant contribution of this Ca^{2+}-store to neuronal function. The fact that it dynamically adapts to changes in network state strengthens this hypothesis (Schluter et al., 2017).

The AIS also provides a substrate for cell contacts outside of its axolemma. Axo-axonic GABAergic interneurons (also called Chandelier cells), establish exclusive synapses with the AIS of principal neurons (reviewed in (Inan and Anderson, 2014)). First described in the 1970s (Jones, 1975; Szentagothai and Arbib, 1974), these synapses are present in numerous cortical areas and species (Somogyi, 1977; Somogyi et al., 1982; Somogyi et al., 1983a). At the AIS, the synaptic contacts locate preferentially near the CO at the axolemma (Benedeczky et al., 1994; King et al., 2014; Somogyi et al., 1983b). Intriguingly, Chandelier cells have been proposed to act as circuit switches (Woodruff and Yuste, 2008), yet whether they excite or inhibit postsynaptic pyramidal neurons is still a matter of debate and likely depends on network state (Woodruff et al., 2010; Woodruff et al., 2011). During development, they can undergo significant remodeling of their axon terminals (Fish et al., 2013; Steinecke et al., 2017; Taniguchi et al., 2013), temporally coinciding with maturation of the AIS (Pan-Vazquez et al., 2018); Jamann & Engelhardt, unpublished).

Another major function of the AIS is to contribute towards establishment of both a passive cellular diffusion barrier as well as a filter for vesicular transport, thereby sorting somatodendritic from axonal cargoes and consequently contributing to the maintenance of neuronal polarity (reviewed in (Leterrier and Dargent, 2014; Nirschl et al., 2017)). Early studies using amphibians and rodents suggest that, due to the high concentration of membrane proteins clustered at the AIS, it might serve as a "barrier" that could uphold neuronal polarity (Dotti and Simons, 1990; Matsumoto and Rosenbluth, 1985). Indeed, maintenance of neuronal polarity was shown to be severely impacted when the master regulator ankG is absent from the AIS, resulting in neurons mislocalizing dendritic and axonal cargoes both *in vitro* (Hedstrom et al., 2008) and *in vivo* (Sobotzik et al., 2009). Due to the strong immobilization of transmembrane channels by cell-adhesion molecules (CAMs) and ankG, and because membrane protein diffusion is limited at the AIS (Boiko et al., 2007; Brachet et al., 2010; Nakada et al., 2003; Winckler et al., 1999), a 'picket fence'

model was proposed (Nakada et al., 2003). This model describes the AIS diffusion barrier as composed of mostly immobile 'pickets' (transmembrane channels, receptors, CAMs), while the submembrane scaffold functions as a 'fence' (Fig. 1). One proposed model speculates that much like the postsynaptic density, ankG-anchored transmembrane proteins may not actually serve as physical filters, but rather to limit diffusion of proteins due to the density of the scaffold itself (Leterrier, 2018).

While the mechanism of intracellular trafficking at the AIS remains controversial, it is generally accepted that both the diffusion of soluble macromolecules as well as vesicular transport are dependent on AIS-associated gatekeepers (Bentley and Banker, 2016; Song et al., 2009), which may operate independent of the ankG scaffold (Farias et al., 2015; Jenkins et al., 2015). Typically, vesicles containing axonal cargoes are preferentially sorted before entering the axon with no visible reduction in velocity at the AIS (Jenkins et al., 2015; Liu et al., 2018; Petersen et al., 2014). This is not the case for somatodendritic cargoes. By contrast, they are excluded from entering the axon or in case of unintended entry, are reversed within the AIS (Burack et al., 2000; Petersen et al., 2014; Watanabe et al., 2012), thus highlighting a potential specific sorting process at the AIS (for review see (Leterrier, 2018; Nirschl et al., 2017)).

3 AIS function

As outlined above, the AIS is the site of action potential (AP) initiation and thus critically important for neuronal network function. Despite an early appreciation that the AIS is the likely site of AP initiation (Coombs et al., 1957), a thorough understanding of why this might be so did not surface until much later. Since Hodgkin and Huxley's groundbreaking studies (Hodgkin and Huxley, 1952a, b, c; Hodgkin and Katz, 1949a, b, c), we know that APs are critically dependent on Na^+ flux. In fact, the density, distribution, and different subtypes of Na^+ channels are mainly responsible for rendering the AIS as the neuronal site with the lowest threshold for AP initiation. Multiple Na^+ channel subunits have been reported at the AIS whereby the exact composition depends on the studied cell type (Boiko et al., 2003; Lorincz and Nusser, 2008). However, Nav1.6 appears to be the major Na^+ channel subunit at the AIS of most neurons (Hu et al., 2009; Lorincz and Nusser, 2008, 2010) and is thus the main player responsible for AP initiation. Nav1.6 channels activate at lower thresholds, more rapidly, and demonstrate less inactivation than Nav1.2 channel subunits (Colbert and Pan, 2002; Hu et al., 2009; Rush et al., 2005; Schmidt-Hieber and Bischofberger, 2010; Zhou et al., 2004; Katz et al., 2018.) They often localize distally towards the AIS end (Hu et al., 2009; Lorincz and Nusser, 2008; Van Wart et al., 2007), which is advantageous for AP initiation due to increased isolation from the capacitive load of the somatodendritic domain (Baranauskas et al., 2013; Eyal et al., 2014); reviewed in Kole and Brette, 2018). By contrast, Nav1.2 channels have been reported to localize at the proximal AIS and soma in mature pyramidal neurons of the prefrontal cortex. This specific location likely makes these channels responsible for backpropagation of APs into the somatodendritic domain, rather than participation in AP generation (Fig. 2A; (Hu et al., 2009; Yin et al., 2017)).

An often-debated topic involves the relative density of functional Na^+ channels at the AIS compared to the somatodendritic domain. Immunohistochemistry and EM studies consistently demonstrate that the concentration of Na^+ channels is highest at the AIS (Fig. 1; (Kole et al., 2008; Lorincz and Nusser, 2008)). However, immunostaining cannot reveal whether labelled proteins are actually functional. Furthermore, cell-attached and outside-out channel recordings reported a uniform density of Na^+ channels between the soma and proximal axon (Colbert and Johnston, 1996; Colbert and Pan, 2002). A potential explanation for this discrepancy came from Kole et al., who demonstrated that the strong link of Na^+ channels to the underlying cytoskeleton at the AIS can reduce the estimated channel density obtained in patch-clamp experiments (Kole et al., 2008). Using voltage-clamp and Na^+ imaging experiments, they suggested that Na^+ channel density is up to 50 times higher in the AIS than in the somatodendritic domain (Kole et al., 2008). However, using outside-out patches, Hu et al. estimated a 19-fold enrichment of Na^+ channels at the AIS (Hu et al., 2009) and Fleidervish et al. measured only a 3-fold difference, utilizing Na^+-imaging (Fleidervish et al., 2010). Interestingly, all of these studies were performed in layer V pyramidal neurons, hence a fundamental difference in cell type is unlikely to explain the discrepancies.

While general consensus has yet to be reached regarding the quantity of Na^+ channels along the AIS, important insight regarding AIS function has been generated by focusing on K^+ channels (Fig. 2B). Repolarization of the AP is mainly achieved by Kv3, Kv4 and Ca^{2+}-activated BK channels (for review see (Bean, 2007)). Of note, none of these channel subtypes are reported to localize specifically to the AIS, suggesting that precise localization is not crucial for their effect on AP shape. Instead, AIS-localized

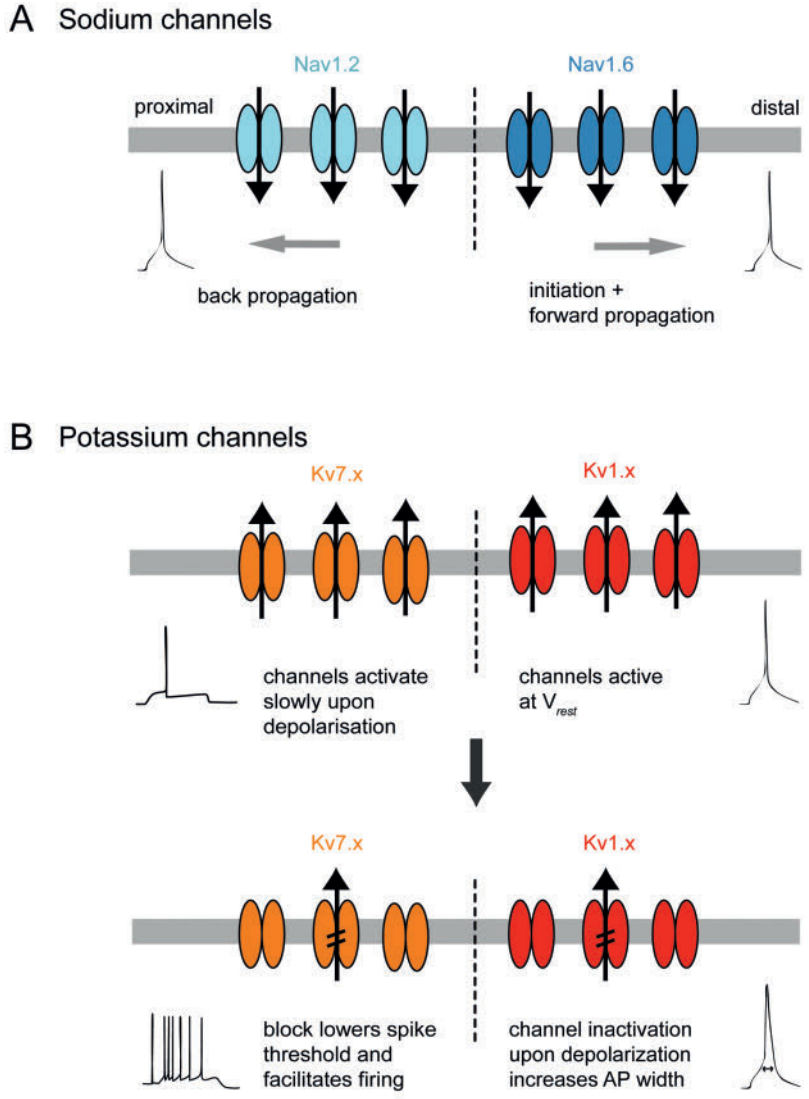

Fig. 2. Ion channels at the AIS and their function in regulating action potentials. (A) The main Na^+ channel subtype responsible for AP initiation is Nav1.6, which is located at the distal end of the AIS. In some cell types, Nav1.2 is expressed proximally and thus influences backpropagation of APs into the somatodendritic domain. (**B**) The main K^+ channel subtypes located at the AIS are Kv7 and Kv1 channels. Kv7 channels slowly activate with subthreshold depolarizations and can thus restrict repetitive firing. Kv1 channels are active at resting membrane potential and inactivate with subthreshold depolarizations, leading to an increase in AP duration. This in turn may increase neurotransmitter release. Other channels localized to the AIS include Cavs as well as neuromodulatory receptors, however, their precise role and location remain elusive. The potential functional relevance of these channels is discussed in the text.

K^+ channels, in particular Kv1 and Kv7 channels, appear to regulate neuronal activity in a more subtle manner.

In layer V pyramidal neurons, Kv1 channels are enriched at the AIS and serve to control action potential waveform (Kole et al., 2007; Lorincz and Nusser, 2008; Shu et al., 2007). These K^+ channels are active at rest and inactivate with slow, subthreshold depolarization. Once inactivated, the AP width increases, leading to increased vesicle release from presynaptic terminals (Fig. 2B; (Kole et al., 2007; Shu et al., 2007)). Kv1 channels at the AIS thus play a role beyond all-or-none AP initiation, in addition to contributing to repolarization of the AP.

Kv7.2 and Kv7.3 channels localize throughout the neuron, but are enriched at the AIS by binding to ankG (Fig. 1; (Pan et al., 2006)). They activate slowly with subthreshold depolarization and are responsible for mediating the M-current (for review see (Brown and Passmore, 2009)). At the AIS, they control AP threshold and reduce neuronal excitability (Fig. 2B; Shah et al. 2008). They also stabilize the resting membrane potential, thereby contributing to maintenance of Nav channel availability by preventing their subthreshold, depolarization-induced inactivation (Battefeld et al., 2014). They can thus both increase AP conduction as well as restrict neuronal excitability, demonstrating the complex role K^+ channels play in AP generation.

Whether and, if so, what type of Ca^{2+} channels localize within the AIS is still a field of active research and appears to depend on neuronal cell type. For example, T- and R-type Ca^{2+} channels are enriched at the AIS in dorsal cochlear nucleus interneurons as well as in pyramidal and

Purkinje cells, where they can influence AP generation and timing, particularly during complex spikes (Bender and Trussell, 2009). By contrast, Layer V pyramidal neurons of the prefrontal cortex exhibit an accumulation of P/Q and N-type Ca^{2+} channels at the AIS. These channels appear to increase neuronal excitability as well as contribute to AP repolarization through activation of BK Ca^{2+}-activated K^+ channels (Yu et al., 2010). Finally, AP generation can also be modulated by metabotropic receptors at the AIS, for example via 5HT1A and D3 receptors (Bender et al., 2010; Cotel et al., 2013; Yang et al., 2016; Yin et al., 2017).

4 AIS plasticity

AIS plasticity can be subdivided into two categories: developmental plasticity and plasticity elicited by changes in network state in mature neurons (Fig. 3). In cell type-specific manners, the first emergence of AIS in developing neurons can be detected as early as E9.5 in mouse motoneurons (Le Bras et al., 2014) and E14.5 in mouse cortical neurons and Cajal-Retzius cells (Gutzmann et al., 2014). In higher mammalian NPY-positive interneurons (*Sus scrofa*), the first AIS appear around E70 and exhibit both a length increase and proximal shift until P30 (Ernst et al., 2018). Structurally, the AIS matures during periods of activity-dependent plasticity in sensory systems of mice (Fig. 3A; (Gutzmann et al., 2014; Schluter et al., 2017)) and of chicken (Kuba and Ohmori, 2009; Kuba et al., 2010), a feature so far not observed in non-sensory cortices (Gutzmann et al., 2014). Furthermore, reduction of AIS length during postnatal development has also been observed in nonhuman primate prefrontal cortex (Cruz et al., 2009; Fish et al., 2013).

The first evidence that AIS structure is dynamic and can be modulated by manipulating neuronal activity came from two hallmark papers in 2010 (Fig. 3B-C; (Grubb and Burrone, 2010; Kuba et al., 2010). Grubb and Burrone demonstrated that augmenting neuronal activity *in vitro*, either by using an increased K^+ concentration in the extracellular medium or by optogenetic stimulation of individual pyramidal cells in hippocampal neurons leads to distal relocation of the entire AIS. This plasticity was accompanied by reduction in intrinsic excitability, suggesting that it serves a homeostatic purpose of attempting to reduce neuronal activity back to more normal levels. Kuba et al. demonstrated that reducing neuronal activity by removing sensory input can also impact the AIS. After removal of cochlea in the chick *in vivo*, AIS length increased in nucleus magnocellularis neurons. Immunostaining indicated that this also increased distribution of Na^+ channels at the AIS, which can explain the observed increase in excitability.

Taken together, these results suggest that this second form of AIS plasticity equally serves a homeostatic purpose, namely to increase excitability after a loss of presynaptic input. In a follow-up study using the chick auditory system, Kuba et al. showed that AIS elongation was accompanied by a change in expression of K^+ channels: Kv1 channel expression decreased, whereas Kv7 channel density increased (Kuba et al., 2015). Since Kv7 channels have much slower activation kinetics compared to Kv1, this further serves to increase neuronal activity by reducing the shunting conductance during AP initiation. This finding is intriguing because it links structural and intrinsic plasticity and suggests that this might also occur in other models of AIS plasticity, especially given the tight link between structure and function in this domain. Grubb and Burrone observed no changes in AIS Na^+ channel distribution in their original study, yet whether K^+ channel expression might have changed remains unclear. However, in a follow-up study using organotypic hippocampal slices, Wefelmeyer et al. demonstrated that the shift in AIS location is not reciprocated by the axo-axonic synapses formed by Chandelier cells onto the AIS of principal neurons (Wefelmeyer et al., 2015). This creates a mismatch between the position of the AIS and its synapses, and likely contributes to the homeostatic decrease in excitability by increasing the amount of GABAergic synapses located between the soma and the site of AP initiation.

Both a shift in AIS position (Chand et al., 2015; Evans et al., 2015; Hamada and Kole, 2015; Hatch et al., 2017; Lezmy et al., 2017; Wefelmeyer et al., 2015), as well as a change in AIS length (Baalman et al., 2013; Engelhardt et al., 2018; Kaphzan et al., 2011; Kuba et al., 2015; Vascak et al., 2017) have since been observed repeatedly *in vitro* and *in vivo* including in disease models (Fig. 3D). It remains an open debate whether AIS-specific alterations are causal to, or simply correlate with disease phenotypes. As can be expected, mutations in the various isoforms of voltage-gated ion channels clustered at the AIS have been linked to numerous forms of epilepsy (reviewed in (Child and Benarroch, 2014; Wimmer et al., 2010). Similarly, conditions that result in changes of network state such as Angelman syndrome (Fig. 3D; (Kaphzan et al., 2011)), Alzheimer's disease (Hatch et al., 2017), or demyelination pathologies (Hamada and Kole, 2015) can lead to structural AIS modifications with functional implications for neuronal firing properties. Likewise, misguided axonal vesicle sorting observed in neurodegenerative diseases has been associated

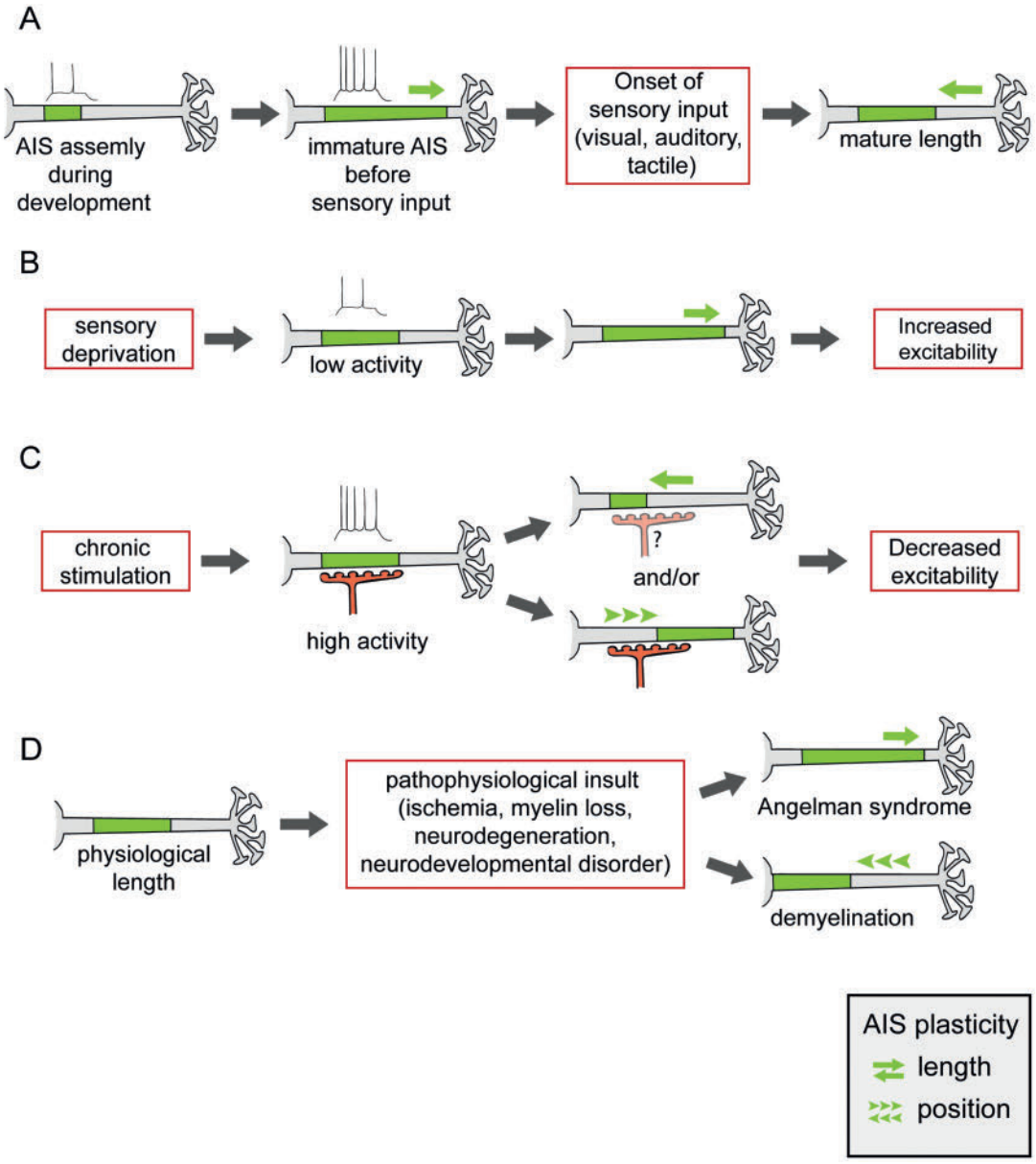

Fig. 3. AIS plasticity. (A) During development of sensory systems, AIS of cortical pyramidal neurons gradually increase in length until the onset of synaptic drive (e. g. eye opening, active whisking), which then results in significant length reduction. This process is activity-dependent. **(B)** Sensory deprivation *in vivo* reduces synaptic drive and leads to AIS elongation and increased cellular excitability. **(C)** Chronic stimulation *in vitro* with increased synaptic drive results in both AIS shortening and a distal shift. During the latter, axo-axonic synapses remain in place, therefore further reducing cellular excitability. **(D)** AIS remodeling under various pathophysiological conditions can result in both length and position changes. See text for details. AIS in this cartoon are not scaled to actual cell size but rather exaggerated for visualization purposes.

with the AIS (Zempel et al., 2017). However, at this point, the most plausible role of AIS in human disease is linked to mutations in *ANK3*. Several genome-wide association studies have shown *ANK3* to be associated with neurodevelopmental disorders including bipolar disorder, schizophrenia, and autism spectrum disorders (Iqbal et al., 2013; Schizophrenia Psychiatric Genome-Wide Association Study, 2011; Zhu et al., 2017).

While most of the above-mentioned studies have shown AIS plasticity after long-term manipulation, shorter-term plasticity has also been observed. Two recent studies demonstrating AIS plasticity after brief manipulations intriguingly both involve the M-current mediated by Kv7 channels, either only seconds after acetylcholine release or after an hour of cholinergic stimulation (Lezmy et al., 2017; Martinello et al., 2015). Evans et al. observed an AIS

shortening *in vitro* after only three hours of treatment in hippocampal neurons (Evans et al., 2015). This observation might pertain to a precursor of the distal AIS shift seen after using the same stimulation protocol for two days (Evans et al., 2013; Grubb and Burrone, 2010), since both types of plasticity are mediated by L-type Ca^{2+} channels and calcineurin.

5 Outlook

Clearly, various forms of AIS plasticity exist and depend on cell type, experimental conditions and time-scales observed. It is important to note, however, that the vast majority of these plasticity mechanisms appear to be homeostatic in nature. We therefore propose that the AIS is a key hub for neuronal network homeostasis. At present, numerous questions remain unanswered. For example, which precise biophysical properties underlie AP initiation? Which mechanism(s) drive(s) AIS plasticity? How is the rigid AIS scaffold organized when the domain undergoes length changes or relocates along the axon? How does AIS plasticity contribute to network function? How do mutations in *ANK3* contribute to the etiology of neurodevelopmental disorders? Fortunately, the wealth of new research that has emerged in recent years has sparked a great deal of interest in the field and we can look forward to further boosts in understanding the axon initial segment in the near future.

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Bionotes

Maren Engelhardt
Institute of Neuroanatomy
Medical Faculty Mannheim
Heidelberg University
Ludolf-Krehl-Str. 13–17
68167 Mannheim
Germany
maren.engelhardt@medma.uni-heidelberg.de

Maren Engelhardt studied Biology at Ruhr-University Bochum and received her PhD in Neuroscience from the Dept of Neurobiology at Regensburg University in 2005. After a postdoc at the University of California in Los Angeles (UCLA) from 2005–2010, she joined the Institute of Neuroanatomy at the Medical Faculty Mannheim of Heidelberg University as a group leader in late 2010. Since 2016, she is also the acting head of Microscopic Anatomy and Histopathology in Mannheim.

Nora Jamann
Institute of Neuroanatomy
Medical Faculty Mannheim
Heidelberg University
Ludolf-Krehl-Str. 13–17
68167 Mannheim
Germany
nora.jamann@medma.uni-heidelberg.de

Nora Jamann studied Medicine at the Medical Faculty Mannheim of Heidelberg University and joined the Institute of Neuroanatomy in 2014 for her experimental medical thesis. She has spent time abroad for lab rotations and as part of her medical education at the Universidad Andrés Bello in Santiago, Chile and the Centre Hospitalier Universitaire de Butare in Rwanda, Africa.

Winnie Wefelmeyer
Centre for Developmental Neurobiology
King's College London
New Hunt's House
Guy's Hospital Campus
London
SE1 1UL
UK
winnie.wefelmeyer@kcl.ac.uk

Winnie Wefelmeyer studied Bioinformatics at the Free University Berlin, then joined the Wellcome Trust program in Neuroscience at the University of Oxford, where she obtained her DPhil at the Department of Pharmacology in 2011. Since then, she has been a Postdoc at the Centre for Developmental Neurobiology at King's College London in the UK. She recently received a Daniel Turnberg Travel Fellowship to spend time in Israel and foster collaborations.

Forschungsförderung

Christine R. Rose*

DFG-Research Unit 2795: "Synapses under Stress: Early events induced by metabolic failure at glutamatergic synapses"

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The brain is one of the major energy consumers of the human body. Most of the ATP is used by the Na^+/K^+-ATPase (NKA; Fig. 1) which sets the Na^+ and K^+ gradients across the plasma membrane and compensates for changes in intra- and extracellular Na^+ and K^+ concentrations occurring upon activation of voltage- and ligand-gated channels (Sweadner 1989). The inwardly-directed Na^+ gradient generated by the NKA also provides the energy for a plethora of secondary active transporters, e. g. the sodium/calcium exchanger (NCX) and various transporters that terminate synaptic transmission via efficient re-uptake of neurotransmitters (Rose and Chatton 2016; Somjen 2002) (Fig. 1). Other ATP-consuming ion transporters, such as the plasma membrane Ca^{2+}-ATPase, are vital for intracellular Ca^{2+} homeostasis (Harris et al. 2012). The vacuolar-type H^+-ATPase (v-ATPase) creates the proton gradient necessary for neurotransmitter accumulation in presynaptic vesicles (Cotter et al. 2015) (Fig. 1).

Despite their considerable energy consumption, neurons themselves do not contain significant energy stores, but depend on close metabolic interactions with astrocytes (Allaman et al. 2011; Rose and Chatton 2016). Astrocytes furthermore shape excitatory synaptic transmission by controlling extracellular ion concentrations and by taking up glutamate (Rose et al. 2018; Verkhratsky and Nedergaard 2018) (Fig. 1); again processes directly or indirectly linked to activation of NKA and ATP consumption. Finally, astrocytes can release neuroactive substances, among them D-serine, feeding back onto surrounding neurons (Henneberger et al. 2010) and are involved in neurovascular coupling (Petzold and Murthy 2011). The term "tripartite" synapse highlights the strong functional interplay between neurons and astrocytes and emphasizes the fact that understanding synaptic function and dysfunction requires knowledge about pre- and postsynaptic neurons, as well as the surrounding glia (Allen and Eroglu 2017).

Conditions under which the brain's energy demands exceed its availability, referred to as metabolic stress, give rise to rapid functional changes. An extreme form of metabolic stress is caused by brain ischemia, which can result in tissue damage and severe neurological deficits and which represents one of the leading causes of disability and death in our ageing population. The main mechanisms of delayed cell death, including the so-called "excitotoxic" action of the transmitter glutamate, are well described. In contrast, there are significant gaps in our understanding of the early changes in neuronal and glial function during reduced energy availability. As these synaptic changes are among the earliest and most "upstream" events in the ischemic cascade, a better understanding of what causes metabolic stress in synapses during ischemia is translationally relevant.

The Research Unit (*RU*) "*Synapses under stress: Early events induced by metabolic failure at glutamatergic synapses*" will close this gap and will combine molecular biology, biochemistry, imaging, electrophysiology and optogenetic approaches together with mathematical simulations to unravel the dependence of synaptic function on cellular metabolism. The main scientific goals of the *RU* are to gain inclusive knowledge about the energy dependence of glutamatergic synapses of the mouse forebrain and to reveal the exact sequence of early events induced by transient moderate energy depletion. Analysing the main cellular compartments (pre- and postsynaptic elements, perisynaptic astrocyte processes) and the extracellular space will provide a novel integrated view of synaptic function and involved neuron-glia interactions, and enable the deciphering of existing feed-back and feed-forward loops between the different compartments. Investigating the reversibility of the induced effects will enable to gain better insight into the processes within the

***Corresponding author: Christine R. Rose,** Heinrich Heine Universität Düsseldorf

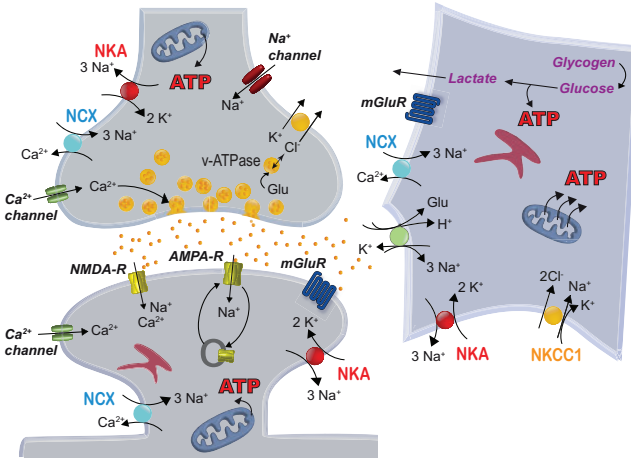

Figure 1: Ion fluxes and ATP-consuming processes at tripartite glutamatergic synapses (summarized from Harris et al., 2012 and Rose & Chatton, 2016).

ischemic penumbra and to understand the factors driving cells towards irreversible demise after an ischemic stroke.

The RU will start its work at the beginning of 2019. In its first funding period, it will receive about 2 million € over three years. The RU is led by Christine R. Rose at the Heinrich Heine University Düsseldorf together with her deputy Christoph Fahlke at the Forschungszentrum Jülich. Further members are Christian Henneberger (Rheinische Friedrich-Wilhelms University Bonn), Gabor Petzold (German Center for Neurodegenerative Diseases and University Bonn), Jürgen Klingauf (Westfälische-Wilhelms University Münster), Andreas Reiner (Ruhr University Bochum) and Nadine Erlenhardt (Heinrich Heine University Düsseldorf). Moreover, Michel J.A.M. van Putten and Stephan A. van Gils, two Mercator Fellows from the University of Twente (The Netherlands) are members of the consortium.

The following main questions will be addressed:

- What are the immediate effects of acute metabolic stress on ion homeostasis?
- What are the consequences of metabolic stress for astroglial function and neuron-glia interaction?
- What are the consequences of metabolic stress on presynaptic function and glutamate release?
- How do postsynaptic properties and ion signaling change in response to metabolic stress?

More specifically, the *RU* will analyse acute changes in ion concentrations, transmitter homeostasis, as well as the function and the subcellular distribution of ligand- and voltage-gated ion channels which control electrical and chemical signaling. The consortium will study the major cellular components of glutamatergic synapses, i. e. pre- and postsynaptic neuronal compartments as well as perisynaptic astrocytes. All groups will focus on glutamatergic synapses of the mouse cortex as a joint model system and use a common protocol for induction of transient chemical ischemia. Adaptive and pathological processes will be addressed at the molecular, cellular and systems' level, employing experimental systems of increasing complexity that range from primary cell culture to acute and organotypic tissue slices to *in vivo* models of ischemic stroke. Experimental data generated will be used to develop a mathematical model. This should make it possible to simulate the processes taking place at the synapses "in silico", i. e. on the computer, providing a novel, concerted view on early functional changes of synapses under stress.

Altogether, the research programme will lead to a thorough understanding of immediate responses of the tripartite synapse to transient energy shortage, of their functional consequences, as well as of the potential reversibility of the induced effects. This will generate a new, integrative understanding of basic pathomechanisms of metabolic failure, which is urgently needed to develop better therapeutic strategies to combat stroke-induced brain damage.

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Appendix

German Summary: DFG-Forschungsgruppe (FOR) 2795: Synapsen unter Stress: akute Veränderungen durch mangelnde Energiezufuhr an glutamatergen Synapsen

Das Gehirn des menschlichen Körpers hat einen im Vergleich zu anderen Organen sehr hohen Energieverbrauch. Wenn sein Bedarf die Menge an bereitstehender Energie überschreitet, führt dies zu raschen Veränderungen in seiner Funktion. Eine besonders dramatische Form des Energiemangels tritt bei einem ischämischen Insult auf. Dieser kann zu Gewebsuntergang und schwerwiegenden neurologischen Ausfällen führen und stellt eine der häufigsten Ursachen für Behinderungen und Tod in unserer alternden Gesellschaft dar. Die Gründe für den in Folge eines Schlaganfalls beobachteten verzögerten Zelltod sind recht gut verstanden, darunter die sog. exzitotoxische Wirkung des synaptischen Botenstoffs Glutamat. Die frühen Prozesse, die durch eine mangelnde Energieversorgung an Synapsen hervorgerufen werden, sind hingegen noch weitgehend unbekannt. Ein besseres Verständnis ihrer Ursachen und Auswirkungen ist jedoch geboten, da sie die ersten Ereignisse der ischämischen Kaskade darstellen.

Die Forschungsgruppe (FOR) 2795 „*Synapsen unter Stress: akute Veränderungen durch mangelnde Energiezufuhr an glutamatergen Synapsen*“ wird diese Fragen adressieren und die frühen zellulären Antworten nach Unterbrechung der Energieversorgung an Synapsen des Großhirns der Maus in den Blick nehmen. Dabei wird eine Kombination von Molekularbiologie, Biochemie, Elektrophysiologie, Imaging und Optogenetik zur Anwendung kommen, die durch mathematische Simulationen ergänzt werden. Die FOR 2795 wird sich insbesondere auf Änderungen in Ionenkonzentrationen, in der Transmitterhomöostase, sowie in der Funktion und subzellulären Verteilung von Ionenkanälen fokussieren. Wesentlich hierbei ist die Einbeziehung sowohl von neuronalen Kompartimenten (Prä- und Postsynapse) als auch von Gliazellen (Astrozyten) in die funktionelle Betrachtung, welche eine neue Sichtweise auf Schädigungsmechanismen eröffnen wird. Die einzelnen Teilprojekte der FOR werden eine gemeinsame Strategie für die Induktion von metabolischem Stress anwenden, jedoch unterschiedlich komplexe Systeme bearbeiten. Letztere reichen von Zellkulturen über Gewebeschnitte bis hin zu *in vivo*-Systemen und einer computergestützten Modellierung. Die FOR 2795 wird somit die molekularen und zellulären Prozesse an Synapsen, die in direkter Abhängigkeit vom zellulären Energiestatus stehen, entschlüsseln. Des Weiteren wird sie Mechanismen identifizieren, die für akute Störungen der synaptischen Funktion sowie für Zellschädigungen nach Zusammenbruch der Energieversorgung verantwortlich sind. Sie wird damit ein neues, ganzheitliches Verständnis grundlegender Pathomechanismen generieren, welches dringend für die Entwicklung besserer therapeutischer Strategien zur Behandlung von Schlaganfall-induzierten Hirnschädigungen benötigt wird.

Bionotes

Prof. Dr. rer. nat. Christine R. Rose:
Institute of Neurobiology
Heinrich Heine University Duesseldorf
Building 26.02.00, Room 35
Universitaetsstrasse 1
40225 Duesseldorf, Germany
Tel: ++49 (0)211 8113416

1990: Diploma in Biology, University of Konstanz. 1993: Dissertation (Dr. rer. nat.), University of Kaiserslautern. 1994–1997: Postdoc at the Dept Neurology, Yale School of Medicine, New Haven, CT, USA. 1998-1999: Postdoc at the Dept of Physiology, Saarland University, Homburg. 2000–2003: Postdoc at the Dept of Physiology, TU and LMU Munich. 2002: Professional dissertation (Habilitation) in Physiology, LMU Munich. 2003–2005: Heisenberg-Stipend of the DFG, Dept of Physiology LMU Munich. Since 2005: Full Professor and Head of the Institute of Neurobiology at the Heinrich Heine University Duesseldorf.

Forschungsförderung

Beate Krickel und Albert Newen*

DFG-Graduiertenkolleg 2185 “Situierte Kognition”

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Werden kognitive Prozesse allein durch neuronale Aktivität bestimmt oder können auch unser Körper, Werkzeuge, unsere physische Umgebung oder das soziale Umfeld wesentliche Elemente von Kognition sein? Dieser Frage widmet sich das im Juni 2017 gestartete interdisziplinäre Graduiertenkolleg „Situierte Kognition“ an der Ruhr-Universität Bochum und der Universität Osnabrück. Unter der Leitung von Prof. Dr. Albert Newen (Sprecher, Philosophie, Ruhr-Universität Bochum) und Prof. Dr. Achim Stephan (Stellv. Sprecher, Kognitionswissenschaft, Universität Osnabrück) sind insgesamt 12 Projektleiterinnen und Projektleiter beider Universitäten aus Philosophie, Psychologie und Neurowissenschaft an dem Graduiertenkolleg beteiligt. Für die interdisziplinäre Forschung und die Ausbildung der insgesamt 12 Doktorandinnen und Doktoranden hat das Kolleg 3 Millionen Euro für zunächst viereinhalb Jahre von der Deutschen Forschungsgemeinschaft zur Verfügung gestellt bekommen.

Die Haupthypothese des Kollegs ist es, dass traditionelle Modelle des menschlichen Geistes defizitär sind und mit neuesten empirischen Erkenntnissen der Kognitions- und Neurowissenschaft nicht kompatibel sind. Eines dieser traditionellen Modelle, das seit Beginn der Kognitionswissenschaften grundlegend ist, wird oft als ‚Sandwich-Modell der Kognition‘ bezeichnet. Es geht von drei Kernmerkmalen von Kognition aus: Erstens ist Kognition von Wahrnehmung und Handlung klar getrennt. Sie liegt als ‚Belag‘ zwischen den beiden Sandwichhälften, wobei die eine die Wahrnehmung symbolisiert und die andere Handlungen. Kognition ist demgemäß ein abgegrenzter (modularer), rein interner, neuronaler Prozess, welcher Wahrnehmungen in Handlungen umwandelt. Zweitens werden diese Umwandlungen wesentlich durch die regelbasierte Kombination, Strukturierung und Verarbeitung von mentalen Repräsentationen realisiert. Drittens haben einige Kognitionswissenschaftler lange angenommen, dass die relevanten Regeln sprachähnlich sind (in einer „Sprache der Gedanken“ vorliegen), d. h. nach syntaktischen Regeln kombinierbar sind, satzähnliche Strukturen generieren und nach logischen Prinzipien organisiert sind.

Diese Grundannahmen werden durch neueste empirische Erkenntnisse in Frage gestellt, die nahelegen, dass der Körper und die physische und soziale Umwelt eine wichtigere Rolle in kognitiven Prozessen spielen als bisher angenommen. Wahrnehmung wird nicht mehr als ein rein passiver Prozess verstanden, der von Kognition vollständig getrennt ist, sondern als ein Prozess, der bereits kognitive Elemente in Form von Erwartungen enthält. Zudem zeigt sich, dass unser Gedächtnis oft über Auslagerung (‚Externalisierung‘) des zu Erinnernden auf physische Gegenstände, Werkzeuge, Körperteile oder –bewegungen (‚Embodiment‘) funktioniert. Die zugrundeliegenden ‚Regeln‘, die durch biologische, psychologische und soziale Mechanismen realisiert sind, erweisen sich zunehmend als probabilistisch, kontextabhängig und flexibel. Des Weiteren scheinen für die Modellierung dieser Phänomene symbolische Repräsentationen überflüssig zu sein.

Um ein adäquates neues Modell des Geistes zu entwickeln, sollen die neuen empirischen Erkenntnisse auf philosophisch-kritische Weise überprüft und weitere empirische Studien zur Prüfung des Sandwich-Modells durchgeführt werden. Dabei stehen folgende Kernfragen im Fokus des Kollegs:

1) Können extrakraniale Elemente selbst Teil von Kognition sein oder dienen diese lediglich als Inputs zu rein neuronalen kognitiven Prozessen?
2) Besteht Kognition notwendigerweise in der Verarbeitung mentaler Repräsentationen oder können (zumindest basale) kognitive Prozesse als repräsentationslos verstanden werden?
3) Ist die klare Trennung von Wahrnehmung (Input), Kognition (Verarbeitung), und Verhalten (Output) mit den empirischen Befunden vereinbar und wie können wir kognitive Verarbeitung neu verstehen?

***Korrespondenzautor: Albert Newen,** Institut für Philosophie II, Ruhr-Universität Bochum, Institut fur Philosophie, Universitätstr. 150, 44780 Bochum, Nordrhein-Westfalen, Germany, albert.newen@rub.de
Dr. Beate Krickel, Institut für Philosophie II, Ruhr-Universität Bochum, Institut fur Philosophie, Universitätstr. 150, 44801 Bochum, Nordrhein-Westfalen, Germany, beate.krickel@ruhr-uni-bochum.de

Diese Fragen werden in insgesamt 13 Teilprojekten des Kollegs mit vier verschiedenen Schwerpunkten untersucht:

a) *Situierte Wahrnehmung und Handlung*: Drei Teilprojekte untersuchen die Rolle von Handlungen für die Wahrnehmung. Eine Kernthese dabei ist, dass Wahrnehmung kein passiver Inputgenerator ist, sondern ein aktiver Prozess der wesentlich von der Umwelt und den Handlungsmöglichkeiten des Akteurs bestimmt wird. Diese Perspektive wird philosophisch weiter ausgearbeitet und in empirischen Studien untersucht. Zum Beispiel wird am Tiermodell (Tauben) untersucht, ob Stimuluseigenschaften und Handlungsvorbereitung von denselben Neuronen im Gehirn verarbeitet werden. Andere Studien werden durchgeführt, bei denen Versuchspersonen ein Gürtel angelegt wird, der durch kleine vibrierende Motoren an der nördlichen Seite diesen einen neuen Orientierungssinn verleiht. Wie wird diese Vibrationssensorik in Raumkognition transferiert? In jedem Fall scheint die Handlungskomponente hier eine zentrale Rolle zu spielen.

b) *Situierte Affektivität:* In zwei Teilprojekten wird die Rolle des Körpers für die Verarbeitung von Emotionen, deren Erkennen, Erinnern und Regulieren untersucht. Im Vordergrund stehen dabei die biopsychologische Untersuchung der Rolle von Hormonen und die philosophische Auswertung der Rolle von körperbasierter Emotionsverarbeitung bei der moralischen Bewertung von Handlungen und Situationen.

c) *Situiertes Soziales Verstehen*: In zwei Teilprojekten wird die Rolle des sozialen Kontexts für die Entwicklung des sozialen Verstehens bei Kindern untersucht. Eine philosophisch-theoretische Auswertung sogenannter *false belief tasks* soll zeigen, wie sich pragmatische Prozesse auf die kognitive Entwicklung einer *theory of mind* auswirken. Zudem soll mithilfe von *visual cliff* Experimenten untersucht werden, welche Rolle der soziale Kontext für das Explorations- und Entscheidungsverhalten von Kindern hat.

d) *Situiertes Sprachverstehen und linguistische Bedeutung*: In drei Teilprojekten wird theoretisch und empirisch die Rolle des Körpers und der Sinnesmodalitäten für Sprachverstehen und Spracherwerb untersucht. Es soll analysiert werden, welche Rolle Gestik und andere Körperbewegungen für Sprachproduktion und das Verstehen von Metaphern spielen. In den empirischen Projekten wird untersucht, in welchem Maße Sprachverstehen und -erwerb von der Aktivierung sensomotorischer Hirnareale abhängen. Die Untersuchung von Erwerb und Verstehen von abstrakten Begriffen wird dabei einen Fokus bilden.

Die theoretischen Implikationen der vier Themenblöcke werden in zwei theoretischen Meta-Projekten zusammengefasst, die somit die Antworten auf die drei Kernfragen bündeln.

Für eine gelungene theoretische Reflexion der empirischen und theoretischen Erkenntnisse aus den Teilprojekten ist eine enge Zusammenarbeit, eine fundierte interdisziplinäre Ausbildung und methodische Offenheit essentiell. Dies wird durch das Ausbildungsprogramm des Kollegs gewährleistet—durch halbjährliche interne Workshops, jährliche Konferenzen, eine Summerschool, ein individuell angepasstes Fortbildungs- und Seminarprogramm, den Austausch mit international renommierten Gastwissenschaftlerinnen und Gastwissenschaftlern, und internationale Forschungskooperationen. Mittlerweile sind bereits über 25 Veröffentlichungen entstanden, davon mindestens 9 von DoktorandInnen und Postdocs. Zudem wurde unter Mitwirkung vieler Mitglieder des Kollegs eine Überblicksedition bei Oxford University Press veröffentlicht, die das gegenwärtige Forschungsfeld zur situierten Kognition repräsentativ darstellt (Newen, A., de Bruin, L. & Gallagher, S. (2018). *The Oxford Handbook of 4E Cognition*. Oxford: Oxford UP).

Website des Graduiertenkollegs: www.situated-cognition.com

Bionotes

Prof. Dr. Albert Newen
Institut für Philosophie II, Ruhr-Universität Bochum Institut fur Philosophie, Universitätstr. 150, 44780 Bochum, Nordrhein-Westfalen, Germany
E-Mail: **albert.newen@rub.de**
Phone: +49-234- 32-22139
Fax: +49-234- 32-14963

Prof. Dr. Albert Newen ist seit 2007 Professor für Philosophie des Geistes an der Ruhr-Universität Bochum—eine der führenden Forschungsuniversitäten in Deutschland. Er ist Sprecher des Graduiertenkollegs „Situated Cognition“, seit 2011 Direktor des interdisziplinären *Center for Mind, Brain, and Cognitive Evolution* und seit 2018 Präsident der Deutschen Gesellschaft für Kognitionswissenschaft. Es war Gastwissenschaftler und -professor an Universitäten, wie Oxford, Stanford und Urbana-Champagne. In seiner interdisziplinären Forschung kombiniert er philosophische Theoriebildung intensiv mit Forschungsergebnissen aus der Psychologie, Psychiatrie und Neurowissenschaft. Seine Arbeit wurde durch mehrere Preise ausgezeichnet, wie z. B. den Doktorandenpreis der Universität Bielefeld, den Bennigsen-Foerder Preis des Staates Nordrhein-Westfalen und den Preis für „Philosophie in der Psychiatrie“ verliehen durch die Deutsche Gesellschaft für Psychiatrie (DGPPN). Zu seinen Veröffentlichungen zählen mehr als 100 Artikel in peer-review Zeitschriften und 15 deutsch- und englischsprachige Bücher.

Dr. Beate Krickel
Institut für Philosophie II, Ruhr-Universität Bochum Institut fur Philosophie, Universitätstr. 150, 44801 Bochum, Nordrhein-Westfalen, Germany
E-Mail: **beate.krickel@ruhr-uni-bochum.de**

Dr. Beate Krickel ist wissenschaftliche Mitarbeiterin am Philosophischen Institut II der Ruhr-Universität Bochum und akademische Koordinatorin des Graduiertenkollegs „Situated Cognition.“ Sie hat Cognitive Science und Philosophie in Osnabrück und Münster studiert, bevor sie ihre Doktorarbeit zum Begriff des biologischen Mechanismus an der Humboldt Universität zu Berlin verfasst hat. Ihre Forschungsgebiete liegen im Bereich der Philosophie der Kognition und des Geistes und der Wissenschaftstheorie.

Forschungsförderung

Anna-Sophia Buschhoff, Igor Barg, Julia Siekmann, Peer Wulff*, Christine Selhuber-Unkel*

DFG-Graduiertenkolleg 2154 „Materials for Brain: Dünnschichtbasierte Funktionsmaterialien für die minimal-invasive Therapie von Erkrankungen des Gehirns“

Christian-Albrechts-Universität zu Kiel

https://doi.org/10.1515/nf-2018-0019

In der modernen Medizin gewinnen technologische Therapieansätze zunehmend an Bedeutung. Dies gilt in besonderem Maße für Erkrankungen des Nervensystems, von denen einige heute bereits sehr wirksam mit Hilfe von Neuroimplantaten behandelt werden können. Eine wahre Erfolgsgeschichte ist beispielsweise das Cochlea-Implantat (CI): Ein elektronischer Innenohrersatz, welcher weltweit zum Einsatz kommt und stark hörgeschädigten Menschen die Möglichkeit gibt, wieder an der auditiven Welt teilzunehmen. Auch die Tiefenhirnstimulation und Brain-Computer-Interfaces (BCI) haben in den letzten Jahren mit eindrucksvollen Erfolgen Aufsehen erregt.

Weniger im Fokus der öffentlichen Aufmerksamkeit, aber mit hohem therapeutischen Potential, sind nichtelektrische Implantate z. B. zur kontrollierten Medikamentenfreisetzung. In der Langzeittherapie komplexer neurologischer Erkrankungen werden die Patienten derzeit oft langfristig und in hohen systemischen Dosen Arzneistoffen ausgesetzt, z. B. zur Verhinderung eines epileptischen Anfalls. Allerdings ist das Gehirn als eigentliches Zielgebiet der Wirkstoffe durch die Blut-Hirn-Schranke abgeschirmt, so dass die Wirkstoffkonzentration im Gehirn häufig nur einen Bruchteil der peripheren Blutkonzentration erreicht. Es ist daher erstrebenswert Materialsysteme zu erforschen, die eine lokalisierte Medikamententherapie direkt im Gehirn erlauben. Damit könnte die nötige Wirkstoffkonzentration im Zielgebiet erreicht, in der Peripherie jedoch gesenkt werden, so dass bei gesteigerter Wirkeffizienz weniger systemische Nebenwirkungen entstehen. Das Einbringen von derartigen Systemen bietet sich insbesondere dann an, wenn z. B. im Rahmen invasiver Diagnostik bereits ein Zugang besteht.

Eine Herausforderung für die Realisierung derartiger lokaler Behandlungsstrategien im Gehirn sind die besonderen Anforderungen an die dafür verwendeten Materialien. Sie müssen biokompatibel, belastbar und hochflexibel sein, um sich an die Gegebenheiten im Gehirn anpassen zu können. Bei Medikamenten-basierten Ansätzen müssen die Materialien außerdem sowohl als Wirkstoffdepot agieren können, als auch in der Lage sein, Substanzen kontrolliert und in besonderen Fällen auf externe Reize hin abzugeben. Um adäquate Funktionsmaterialien für solche Implantate zu entwickeln, ist eine enge Vernetzung von materialwissenschaftlicher und medizinischer Forschung unabdingbar. An dieser interdisziplinären Schnittstelle setzt das im April 2017 an der Christian-Albrechts-Universität zu Kiel gestartete Graduiertenkolleg „Materials for Brain“ an, das von der Technischen Fakultät und der Medizinischen Fakultät getragen wird. Rund 20 Wissenschaftlerinnen und Wissenschaftler aus Medizin und Materialwissenschaft forschen gemeinsam an der Frage, wie mithilfe von Biomaterialien Erkrankungen wie Epilepsie, Hirntumore und Gefäßaneurysmen effizienter behandelt werden können. Dafür werden sie von der DFG mit 4,1 Millionen Euro gefördert.

Das wissenschaftliche Programm des Graduiertenkollegs behandelt die Erforschung neuartiger Biomaterialien im Kontext ihrer biologischen Funktion. Beispielsweise werden wenige Mikrometer dicke metallische Dünnschichten, die sich in Form von hochkomplexen dreidimensionalen Strukturen erzeugen lassen, auf ihre

***Korrespondenzautor: Prof. Dr. Christine Selhuber-Unkel,** GRK 2154 „Materials for Brain“, Institut für Materialwissenschaft, Christian-Albrechts-Universität zu Kiel, Kaiserstr. 2, 24143 Kiel, E-Mail: grk2154@tf.uni-kiel.de
Peer Wulff, GRK 2154 „Materials for Brain“, Institut für Materialwissenschaft, Christian-Albrechts-Universität zu Kiel, Kaiserstr. 2, 24143 Kiel, E-Mail: grk2154@tf.uni-kiel.de

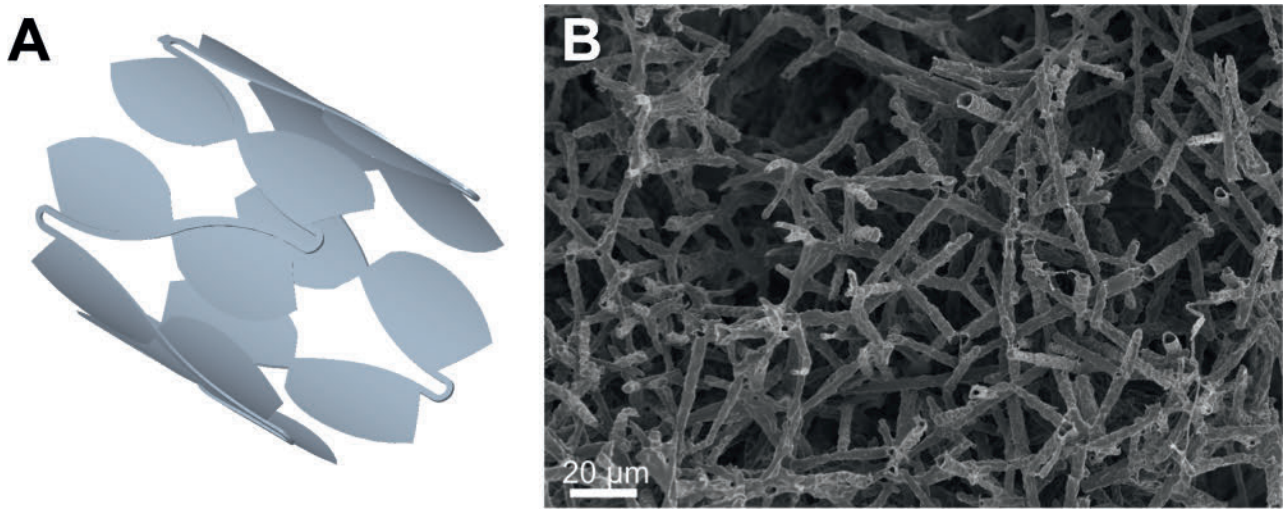


Abb. 1: Strukturierte Materialien, die im GRK 2154 eingesetzt werden. (A) Struktur eines dünnschichtbasierten Flow-Diverter Stents. (B) Rasterelektronenmikroskopische Aufnahme eines hochporösen Netzwerks aus Poly(L-lactid-co-caprolacton).

Funktion als Flow-diverter Stents untersucht (Abb. 1A). Diese Flow-diverter Stents sollen zur minimalinvasiven endovaskulären Behandlung von Gehirngefäßaneurysmen eingesetzt werden, da sie den Bluteinstrom in das Aneurysma minimieren und sich das Aneurysma infolgedessen langfristig verschließt. Des Weiteren werden hochporöse, polymerbeschichtete Materialien als Wirkstoffreservoirs erforscht (Abb. 1B), die eine gesteuerte Freisetzungskinetik von Wirkstoffen bewirken und sich somit insbesondere für die Therapie von Hirntumoren oder Epilepsie anbieten. Die funktionellen Eigenschaften der Materialien sowie deren Interaktionen mit dem lebenden Gewebe werden sowohl *in vitro* in Zellkulturbedingungen als auch *in vivo* mittels krankheitsrelevanter Modellorganismen getestet. Diagnostische Methoden wie MRT, EEG, aber auch histologische Untersuchungen und Verhaltensbeobachtung sollen einerseits Aufschluss über den Einfluss der Implantate auf Struktur und Funktion des gesunden Gehirns geben und andererseits die therapeutische Effizienz der neuen Material-basierten Ansätze aus loten.

Ein wichtiges Kernziel des Graduiertenkollegs ist die Ausbildung von hochqualifiziertem wissenschaftlichen Nachwuchs an der Schnittstelle zwischen Ingenieurswissenschaften und Medizin. Daher ist das Qualifizierungsprogramm des Graduiertenkollegs auf Interdisziplinarität und Internationalität ausgerichtet: Die Promovierenden werden durch je ein Mitglied der Technischen und der Medizinischen Fakultät betreut, sie führen interdisziplinäre Laborrotationen durch und nehmen an fächerübergreifenden Peer-Coaching-Programmen teil. Zusätzlich ist ein mehrmonatiger Forschungsaufenthalt im Ausland ein wesentlicher Baustein der Graduiertenausbildung, der den internationalen Charakter des Graduiertenkollegs prägt.

Das Graduiertenkolleg „Materials for Brain“ fördert daher die intensive interdisziplinäre Promovierendenausbildung auf einem Zukunftsgebiet der Medizin und Materialwissenschaft. Durch sein wissenschaftliches Programm erarbeitet das Graduiertenkolleg materialbasierte Strategien zur minimalinvasiven und nebenwirkungsarmen Therapie von Erkrankungen des Gehirns und hofft so, die Lebensbedingungen von Patienten mit komplexen Erkrankungen des zentralen Nervensystems zu verbessern.

Homepage: www.grk2154.uni-kiel.de

Korrespondenzadresse

GRK 2154 „Materials for Brain“
Institut für Materialwissenschaft
Christian-Albrechts-Universität zu Kiel
Kaiserstr. 2
24143 Kiel
E-Mail: grk2154@tf.uni-kiel.de
Tel.: +49 431 880 6198

Prof. Dr. Christine Selhuber-Unkel

Christine Selhuber-Unkel hat in Heidelberg und Uppsala Physik studiert und in Heidelberg im Bereich der Biophysik promoviert. Nach ihrer Postdoc-Zeit am Niels Bohr Institut in Kopenhagen wechselte sie an die Christian-Albrechts-Universität zu Kiel. Seit 2010 ist sie Professorin für Biokompatible Nanomaterialien am dortigen Institut für Materialwissenschaft und seit 2017 Sprecherin des Graduiertenkollegs 2154. Ihr Interesse gilt der Wechselwirkung von Zellen mit Biomaterialien und deren biophysikalischen Mechanismen.

Peer Wulff

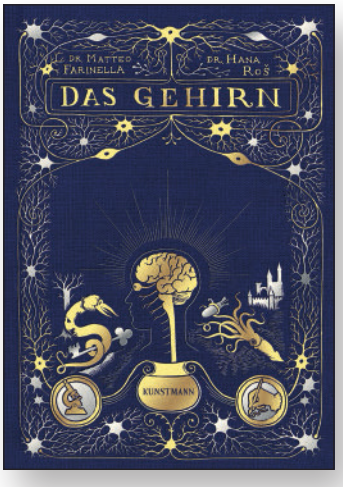
Peer Wulff hat in Hamburg Medizin und Molekulare Neurobiologie studiert und ist nach Assistenzarztzeit in der Neurologie und wissenschaftlicher Postdoc-Zeit in Heidelberg 2006 an die Universität Aberdeen gewechselt, wo er zuletzt den Bereich Translational Neuroscience geleitet hat. Seit 2012 ist er Professor für Neurophysiologie an der Christian-Albrechts-Universität zu Kiel. Sein Interesse gilt den Zusammenhängen zwischen neuronalen Schaltkreisen und Verhalten unter physiologischen und pathophysiologischen Bedingungen.

Rezension

Hana Roš, Matteo Farinella: *Das Gehirn*

Besprochen von **Eckhard Friauf**, Biology Animal Physiology,
TU Kaiserslautern, Germany, E-Mail: eckhard.friauf@bio.uni-kl.de

https://doi.org/10.1515/nf-2018-0028



Rezension zu „DAS GEHIRN“

Wissenschaftliche Inhalte einem interessierten Laienpublikum spannend und verständlich darzustellen erfordert ein gehöriges Maß an Kreativität und Originalität. Mit dem dieses Jahr im Münchner Verlag Antje Kunstmann erschienenen Buch „Das Gehirn“ ist seit kurzem ein solches Werk auf dem Markt, dem dies hervorragend gelungen ist. Bereits 2013 erschien die englische Originalausgabe unter dem vielsagenden Titel „Neurocomic“. Sehr anschaulich – in des Wortes doppelter Bedeutung – führen die promovierten Autoren Matteo Farinella und Hana Roš in fünf Kapiteln durch neurowissenschaftliche Hauptareale. Von Prolog und Epilog gerahmt werden die faktenreichen und zugleich fantastisch fiktiven Kapitel Morphologie, Pharmakologie, Elektrophysiologie, Plastizität und Synchronizität angegangen. Auf der phantasievollen Tour in die Tiefen und Höhen unseres Denkorgans kommen die Neurogrößen Santiago Ramón y Cajal, Camillo Golgi, Charles Scott Sherrington, Bernard Katz, Alan Hodgkin, Andrew Huxley, Luigi Galvani, Eric Kandel, Iwan Pawlow und Hans Berger in über 250 Schwarzweiß-Cartoons zu Wort. Fast wie Popstars treten die zehn Herren auf. En passant lernt der auf gewundenen Pfaden Reisende – Fachfrau und Fachmann wird es nicht überraschen – einen Riesenkalmar, die Meeresschnecke Aplysia und einen konditionierten Hund kennen. Mich hat die abenteuerliche Reise durch die verschlungenen Neuronenwälder von Neuroland mehrfach an Alice im Wunderland erinnert, sie war wundervoll und wundersam zugleich. Und der illustrative Stil hat mich immer wieder bezaubert. Das märchenhafte Werk ist flott aufgebaut sowie federleicht umgesetzt, zudem künstlerisch anspruchsvoll und ansprechend gestaltet. Allein das Betrachten und Betasten des spektakulären Einbandes (Kunstmann, nomen est omen) ist ein schönes multimodales Sinneserlebnis mit ‚Immer-wieder-Aktions-Potential‘. Am Ende der Graphic Novel wird mit der Kurzbetrachtung des Dualismus-Problems auch eine philosophische Komponente eingebaut. Wegen der Vereinfachung der Thematiken verstecken sich im 126-seitigen Buch auch ein paar kleinere sachliche Fehler, die der Detailteufel zu verantworten hat. Diese sind wohlwollend entschuldbar, sie zu suchen und zu finden – um dann bei der Entdeckung zu schmunzeln – erhöht den großen Spaß an der vergnüglichen Entdeckungsreise. Viel Vergnügen!

Hana Roš, Matteo Farinella
Das Gehirn
Kunstmann-Verlag, 136 Seiten
Euro 20,00 € (D)
sofort lieferbar
erschienen im September 2018
Übersetzt von Ulrike Becker
ISBN 978-3-95614-264-2

Nachrichten

Eckhard Friauf*

Die Otto-Loewi-Medaille der NWG

https://doi.org/10.1515/nf-2019-0002

Im Rahmen der 25-Jahresfeier der Gesellschaft im Juli 2018 wurde erstmals die Otto-Loewi-Medaille der NWG vergeben. Die Medaille ist mit einem Preisgeld von 10,000 € versehen. Erster Preisträger ist Helmut Kettenmann, der für seine herausragenden Arbeiten und seine Einsatzbereitschaft geehrt wurde. Die Laudatio hielt Frank Kirchhoff (siehe hierzu „Verleihung der Otto-Loewi-Medaille an Prof. Dr. rer. nat. Helmut Kettenmann“, Neuroforum 03/18, S. 228 ff.).

Otto Loewi ist durch seine Entdeckungen zur chemischen Übertragung von Nervenimpulsen besonders bekannt geworden, für die er zusammen mit Henry Dale 1936 den Nobelpreis für Physiologie oder Medizin erhielt (‚för deras upptäckter rörande kemiskt överföring av nerverkan‘). Loewi wurde 1873 in Frankfurt in eine jüdische Familie geboren. An der Universität Straßburg studierte er Medizin und erhielt 1896 seinen Doktortitel. Kurz darauf beschloss er, einer wissenschaftlichen Karriere nachzugehen und wurde Assistent und 1900 Privatdozent an der Universität Marburg. Dort arbeitete er zunächst am Metabolismus von Zellen und konnte zeigen, dass Tiere aus Abfallprodukten von Proteinen, nämlich Aminosäuren, wieder neue Proteine herstellen können (Über Eiweißsynthese im Thierkörper, 1902). Danach war Loewi einige Monate Gastforscher in London und lernte dort Henry Dale kennen. 1904 erhielt er eine außerordentliche Professur in Marburg, 1905 zog es ihn nach Wien. Die Universität Graz stellte ihn 1906 ein, als letzten Juden bis Ende des Zweiten Weltkriegs, und übergab ihm 1909 den Lehrstuhl für Pharmakologie. 1921 führte Loewi in Graz frappierend einfache und bahnbrechende Experimente an zwei isolierten Froschherzen durch, in denen er die Existenz und Wirkung eines chemischen Botenstoffes, des Vagusstoffes Acetylcholin, nachweisen konnte. Loewi selbst beschrieb dieses Ereignis 1953 wie folgt: „In the night of Easter Sunday, 1921, I awoke, turned on the light, and jotted down a few notes on a tiny slip of paper. Then, I fell asleep again. It occurred to me at six o’clock in the morning that during the night I had written down something most important, but

I was unable to decipher the scrawl. That Sunday was the most desperate day in my whole scientific life. During the next night, however, I awoke again, at three o’clock, and I remembered what it was. This time I did not take any risk; I got up immediately, went to the laboratory, made the experiment on the frog’s heart, described above, and at five o’clock the chemical transmission of the nervous impulse was conclusively proved. Careful consideration in daytime would undoubtedly have rejected the kind of experiment I performed, because it would have seemed most unlikely that if a nervous impulse released a transmitting agent, it would do so not just in sufficient quantity to influence the effector organ, in my case the heart, but indeed in such an excess that it could partly escape into the fluid which filled the heart, and could therefore be detected. Yet the whole nocturnal concept of the experiment was based on this eventuality, and the result proved to be positive, contrary to expectation.“ Bis 1938 war er Tausenden von Studierenden menschliches Vorbild und geschätzter Lehrer. Im gleichen Jahr nahmen ihn die Nazis in Schutzhaft. Es gelang Loewi, über Belgien und England 1940 in die USA zu kommen und in New York eine Forschungsprofessur zu erhalten. 1961 starb er dort 88-jährig, begraben ist er in Woods Hole.

Bei der Entscheidung des NWG-Vorstands, die Medaille nach Otto Loewi zu benennen, gab es mehrere starke Argumente: seine Experimentierfreude sowie seine

***Corresponding author: Eckhard Friauf**, Biology, Animal Physiology, TU Kaiserslautern, Germany, E-Mail: eckhard.friauf@bio.uni-kl.de

herausragenden Pionierarbeiten an der Synapse, die Nervenzellen untereinander und mit Muskelzellen verknüpft und kooperieren lässt. Ferner die Synapse als symbolisch verbindendes Element für alle Teile der Neurowissenschaftlichen Gesellschaft. Schließlich haben aber auch Loewis bewegtes internationales Leben und sein Weltbürgertum – er hatte drei Staatsbürgerschaften – überzeugt. Die Idee der NWG ist, die Medaille im Abstand von 3–5 Jahren zu vergeben. Vorschläge aus dem Mitgliederkreis der NWG sind immer willkommen.

Weiterführende Artikel

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Kirchhoff, F. (2018). Jugend forscht – Sonderpreis der Neurowissenschaftlichen Gesellschaft. Neuroforum *24*, 227–235, doi:10.1515/nf-2018-0009

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Zimmermann, H. (1998). In Stockholm geehrt und von den Nazis verjagt – Otto Loewi, Entdecker des „Vagusstoff“ und Pionier der chemischen synaptischen Transmission. Neuroforum *4* 283–284. https://www.leopoldina.org/fileadmin/redaktion/Mitglieder/CV_Loewi_Otto_D.pdf

Nachrichten

https://doi.org/10.1515/nf-2019-0001

Forschungspreise der Neurowissenschaftlichen Gesellschaft 2019

Auch für 2019 hatte die NWG wieder zwei Wissenschaftspreise ausgelobt: den Schilling Forschungspreis der Neurowissenschaftlichen Gesellschaft 2019 und den Thermo Fisher Scientific Technologiepreis 2019. Beide Preise honorieren herausragende Leistungen auf einem Gebiet der Hirnforschung, wobei der Schilling-Preis eher die gesamt Forschungsleistung würdigt, während der Thermo Fisher Preis vor allem neue methodische und technologische Forschungsansätze auszeichnet. Beide Preise sollen junge Wissenschaftler/innen bis zu einem Alter von 35 Jahren unterstützen. Der/die Bewerber/in sollte in einem deutschen Labor arbeiten oder als Deutsche/r im Ausland tätig sein. Die Bewerbung kann entweder direkt oder durch Vorschlag erfolgen. Eine Mitgliedschaft in der Neurowissenschaftlichen Gesellschaft ist nicht Voraussetzung. Die Preisverleihung erfolgt auf der Göttinger Tagung der Neurowissenschaftlichen Gesellschaft vom 20. – 23. März 2019, die Preisträger wurden zu einem Hauptvortrag dort eingeladen.

Thermo Fisher Scientific Technologiepreis

Der mit 2.500 Euro dotierte Thermo Fisher Scientific Technologiepreis der Neurowissenschaftlichen Gesellschaft 2019 geht an Jonas Wietek, Arbeitsgruppe Experimentelle Biophysik an der Humboldt-Universität zu Berlin. Der Preis wird von der Firma Thermo Fisher Scientific finanziert und ist ein persönlicher Preis.

Jonas Wietek hat die ersten Licht-aktivierten Anionen-leitenden Kanalrhodopsine (ACRs) konstruiert und damit das neue Feld der photoaktivierbaren inhibitorischen Ionenkanäle initiiert. In seiner Forschung nutzt er molekularbiologische und elektrophysiologische Methoden um ACRs mit vielfältigen biophysikalischen Eigenschaften zu erschaffen, und damit geeignete Werkzeuge zur neuronalen Inhibition bereitzustellen.

Die Entwicklung und Entdeckung neuartiger ACRs hat bereits heute eine substantielle Bedeutung für die Neurowissenschaften und die Optogenetik erlangt, da die Verwendung von ACRs zur neuronalen Inhibition effizient und in allen Modellorganismen anwendbar ist. Somit ist es bereits heute möglich, Hirnareale, Netzwerke von Nervenzellen oder auch einzelne Neuronen mit hoher Präzision zu deaktivieren und somit die Funktionsweise neuronaler Strukturen detailliert zu untersuchen.

Jonas Wietek gewann den TSF Technologie-Preis 2019

Jonas Wietek hat seit August 2018 eine Postdoc-Stelle in der Arbeitsgruppe Experimentelle Biophysik an der Humboldt-Universität zu Berlin inne, wo er auch seine Masterarbeit und seine Promotion abgeschlossen hatte.

Schilling Forschungspreis

Der Schilling Forschungspreis der Neurowissenschaftlichen Gesellschaft 2019 wird von der Hermann und Lilly Schilling-Stiftung gestiftet und ist mit 20.000 Euro dotiert. Er wird an Friederike Zunke vom Biochemischen Institut der Christian-Albrechts-Universität zu Kiel verliehen.

Die Parkinson Erkrankung ist eine neurodegenerative Erkrankung, die durch den progressiven Verlust von Nervenzellen charakterisiert ist. Dieses Absterben der Neurone wird durch die Akkumulation des synaptischen Proteins α-Synuclein hervorgerufen, dessen Aggregationsmechanismen lange unklar waren.

Friederike Zunke erhält den Schilling Forschungspreis der Neurowissenschaftlichen Gesellschaft 2019 für ihren Beitrag zu einem besseren Verständnis der molekularen Ursachen der Parkinsonerkrankung. Dabei fokussiert sich ihre Arbeit insbesondere auf die Bildung der pathologischen und zelltoxischen α-Synuclein Aggregate. So konnte sie die fatalen Auswirkungen von lysosomalen Dysfunktionen und die damit verbundene Akkumulation von lysosomalen Lipiden auf die Aggregation des neurotoxischen α-Synucleins zeigen. Dieses bessere Verständnis der molekularen Krankheitsursachen ist essentiell für die Weiterentwicklung von Therapiemöglichkeiten in der Parkinson Erkrankung, die bisher unzureichend sind, da sie ein

weiteres Voranschreiten der Krankheit nicht verhindern können.

Infolgedessen sind die Arbeiten von Friederike Zunke maßgeblich an der Etablierung von Therapeutika beteiligt, die zu einer Verminderung von lysosomalen Lipiden und somit zur Reduktion von pathologischen α-Synuclein Aggregationen führen.

Friederike Zunke promovierte in der Biochemie der Christian-Albrechts-Universität zu Kiel und verbrachte währenddessen einen Forschungsaufenthalt an der Harvard Medical School/Massachusetts General Hospital. Für ihren Postdoc ging sie an das Neurologische Institut der Northwestern University in Chicago, bevor sie als Arbeitsgruppenleiterin wieder zurück ans Biochemische Institut die Universität Kiel kehrte.

Friederike Zunke ist die Schilling-Forschungspreisträgerin 2019

Die Auswahl der Preis wird durch ein Preiskomitee bestehend aus dem Vorstand der NWG und den Sektionssprechern getroffen.

Programmübersicht Göttinger Jahrestagung der NWG 2019

Wednesday, March 20, 2019

12:00 – 13:00 Plenary Lecture, *Opening Lecture*
Ann McKee (Boston, USA): **Chronic traumatic encephalopathy (CTE): an update including the problem with football (soccer)**

13:00 – 14:30 Postersession I

14:30 – 16:30 Symposia I (S1-S6)

S1 Common principles of spatial and temporal sensory processing, Chairs: Jan Clemens (Göttingen), Carlotta Martelli (Konstanz), Marion Silies (Mainz)

- **Berthold Hedwig** (Cambridge, UK): **Unraveling a delay-line and coincidence detector circuit for auditory pattern recognition**
- **Carlotta Martelli** (Konstanz): **Adaptive responses and population dynamics in the olfactory system of Drosophila**
- **Karin Nordstrom** (Adelaide, Australia): **Hoverfly vision in naturalistic surrounds**
- **Barani Raman** (Saint Louis, USA): **A computational logic for olfaction**
- **Katja Sporar** (Göttingen): **Cellular and circuit mechanisms that separate luminance and contrast sensitivity in peripheral visual processing**
- **Alexander S. Chockley** (Köln): **Subgroups of femoral chordotonal organ neurons differentially affect leg movements and coordination in Drosophila melanogaster**

S2 Optogenetics – tool development and application in neuroscience, Chair: Alexander Gottschalk (Frankfurt/M.)

- **Benjamin R. Rost** (Berlin): **Optogenetic tools for neuroscience beyond the classical application of microbial rhodopsins**
- **Soojin Ryu** (Mainz): **Optogenetic manipulation of the stress response in larval zebrafish**
- **Ofer Yizhar** (Rehovot, Israel): **Optogenetic dissection of prefrontal circuits for cognitive control**
- **Alexander Dieter** (Göttingen): **Improved spectral resolution of optogenetic vs electric stimulation of the auditory nerve**
- **Silvia Rodriguez-Rozada** (Hamburg): **Interrogation of neuronal circuit function using customized optogenetic actuators and silencers**

S3 Keeping neurons alive – erythropoietin, its variants and its receptors, Chairs: Nina Hahn (Göttingen), Ralf Heinrich (Göttingen)

- **Christel Bonnas** (Göttingen): **EV-3, an endogenous human erythropoietin isoform with distinct functional relevance**
- **Daniela Ostrowski** (Kirksville, USA): **How erythropoietin mediates its neuroprotective effects**
- **Edith Marianne Schneider Gasser** (Zürich, Switzerland): **Erythropoietin signaling in mouse angio-oligo-neurogenesis**
- **Pardes Habib** (Aachen): **Erythropoietin regulates anti-apoptotic TMBIM family members after ischemic stroke**

- **Nina Hahn** (Göttingen): **Epo-induced neuroprotection: crucial role for orthologues of the orphan cytokine receptor CRLF3**

S4 Neurological autoimmunity: the role of pathogenic autoantibodies against neuron and glia proteins, Chairs: Christian P. Moritz (Saint Etienne/Lyon, France), Claudia Sommer (Würzburg)

- **Dominik Jäger** (Lübeck): **Development of autoantibody test systems against neural proteins**
- **Edgar Meinl** (Martinsried): **Autoantibodies against myelin oligodendrocytes glycoprotein (MOG)**
- **Claudia Sommer** (Würzburg): **Autoantibodies in peripheral neuropathies**
- **Brigitte Theresia Wildemann** (Heidelberg): **The clinical spectrum and diagnosis of AQP4-IgG-associated and MOG-IgG-associated disorders**
- **Yara Nasser** (Saint Etienne, France): **Anti-FGFR3 antibody: a biomarker of sensory neuronopathies or an active player of neuron degeneration?**

S5 Serotonin and its developmental role in shaping brain plasticity and neuropsychological phenotypes, Chairs: Natalia Alenina (Berlin), Francesca Calabrese (Milan, Italy), Piotr Popik (Krakow, Poland)

- **Natalia Alenina** (Berlin): **Serotonin and development: the role of the peripheral serotonergic system**
- **Judith Homberg** (Nijmegen, Netherlands): **Increased maternal extracellular serotonin levels beneficially influences offspring's anxiety- and anhedonia-like behaviour**
- **Agnieszka Nikiforuk** (Kraków, Poland): **High and low serotonin: implications for neuropsychiatric disorders**
- **Sophie Scotto-Lomassese** (Paris, France): **Role of serotonin in maternal behavior**
- **Franziska E. Müller** (Hannover): **The impact of serotonergic signaling in astrocytes**

S6 Novel insights into the regulation of hypothalamic neurocircuits and functions, Chairs: Henning Fenselau (Köln), Sophie Steculorum (Köln)

- **Cristina García Cáceres** (Garching): **UCP2 in astrocytes regulates the activation of NPY neurons to control feeding behavior**
- **Rüdiger Klein** (Martinsried): **Central amygdala circuits controlling appetitive behavior**
- **Alexey Ponomarenko** (Düsseldorf): **Temporal separation of neuronal ensembles in hypothalamus regulates innate behaviors**
- **Jan Siemens** (Berlin): **t.b.a.**
- **Tim Gruber** (Garching): **Remodeling of the hypothalamic vasculature upon hypercaloric feeding depends on astroglial HIF1α and VEGF**
- **Hanna Elin van den Munkhof** (Köln): **Applying unsupervised machine learning to study the lateral hypothalamic circuitry underlying motivated behaviour in freely moving mice**

16:30 – 18:00 Postersession II

19:00 – 20:00 Plenary Lecture, *Zülch Lecture*
Giulio Tononi (Madison, USA): **Consciousness: from theory to practice**

Thursday, March 21, 2019

9:00 – 10:00 Awarding Plenary Lectures
Schilling Award Lecture
Friederike Zunke (Kiel): **Molecular disease mechanisms and therapeutic approaches in Parkinson's disease**
TFS Technology Award Lecture
Jonas Wietek (Berlin): **Encounters in anion channelrhodopsin research – a personal perspective on the development of inhibitory optogenetic tools**

10:00 – 11:30 Postersession III

11:30 – 13:30 Symposia II (S7-S12)

S7 Short-term adaptation in early auditory processing: from synaptic depression to focal perception, Chairs: Andrea Lingner (Martinsried), Michael Pecka (Martinsried)

- **Andrea Lingner** (Martinsried): **Time course of stimulus-history dependent adaptation of auditory spatial perception**
- **Israel Nelken** (Jerusalem, Israel): **Cortical mechanisms underlying stimulus-specific adaptation and deviance detection**
- **Henrique von Gersdorff** (Portland, USA): **Building fast and resilient inhibitory synapses with Ca2+ nanodomains and microdomains**
- **Matthew A. Xu-Friedman** (Buffalo, USA): **Regulation of auditory nerve synaptic function by activity**
- **Elisa G. Krächan** (Kaiserslautern): **Novel form of synaptic plasticity: rebound effect at MNTB-LSO inputs**
- **Jörg Encke** (Garching): **Adaptation to stimulus statistics enhances the separability between interaural level differences on a population basis.**

S8 From astrocytes to behaviors: searching the cellular and molecular roots of emotion dysfunctions, Chairs: Barbara Di Benedetto (Regensburg), Inga Neumann (Regensburg)

- **Oliver J. Bosch** (Regensburg): **Partner loss impairs brain oxytocin signalling: physiological and emotional consequences in monogamous prairie voles**
- **Barbara Di Benedetto** (Regensburg): **Astrocytic EphrinA impacts the distribution of synaptic AMPA receptors in health and depression**
- **Giovanni Marsicano** (Bordeaux, France): **CB1 receptor signaling in the brain: the where matters**
- **Christine R. Rose** (Düsseldorf): **Astrocyte regulation of neuronal excitability**
- **Celia Roman** (Regensburg): **Antidepressant drugs require astrocytes to prime an early synaptic pruning and remodelling in the prefrontal cortex**
- **Carl Meinung** (Regensburg): **Oxytocin rapidly affects astrocytic morphology via a Sp1-Gem axis**

S9 Resolving the cognitive function of prefrontal circuits: from neurons to behavior, Chairs: Ilka Diester (Freiburg), Ileana Hanganu-Opatz (Hamburg)

- **Sarah Rachel Heilbronner** (Minneapolis, USA): **Connectivity reveals prefrontal cortical circuit homologies between rodents and primates**
- **Christoph Kellendonk** (New York, USA): **Thalamo-prefrontal interactions in working memory**
- **Thilo Womelsdorf** (Nashville, USA): **Prefrontal cortex circuits as a hub for flexible learning and attentional filtering of goal-irrelevant information**
- **Marie Carlén** (Stockholm, Sweden): **Quantitative whole brain mapping of the monosynaptic input to four different cell types in the mouse medial prefrontal cortex**
- **Mattia Chini (Hamburg): Microglia inhibition rescues developmental hypofrontality in a mouse model of cognitive impairment**
- **Abhilash Dwarakanath** (Tübingen): **Low frequency oscillatory bursts in the macaque prefrontal cortex predict spontaneous transitions in the content of consciousness**

S10 Brain-machine-interface in paralysis, Chair: Niels Birbaumer (Tübingen)

- **Ramos-Murguialday, Ander** (Tübingen): **t.b.a.**
- **Gabriel Curio** (Berlin): **Non-invasive single-trial EEG detection of evoked human neocortical population spikes**
- **Eilon Vaadia** (Jerusalem, Israel): **Volitional Control of spatiotemporal patterns of neuronal synchrony via brain-machine interface**
- **John Donoghue** (Geneva, Switzerland): **Potential challenges for implantable brain computer interfaces**
- **Daniel G. Schmidt** (Ulm): **Executive eye movement impairment in presymptomatic amyotrophic lateral sclerosis mutation carriers**

S11 The 4Rs in animal-based neuroscience research: Refinement, Reduction, Replacement, Responsibility, Chairs: Roman Stilling (Münster), Stefan Treue (Göttingen)

- **Ulrich Dirnagl** (Berlin): **Navigating ethics and evidence in preclinical neuroscience research**
- **Michael Heide** (Dresden): **Brain organoids as ideal replacements of animal models in neuroscience? – Chances and limitations of a brain in a dish**
- **Malcolm R. Macleod** (Edinburgh, UK): **The Reproducibility Opportunity**
- **Stefan Treue** (Göttingen): **Responsibility includes communication and transparency about animal research**

S12 Breaking News I, Chair: Marc Spehr (Aachen)

- **Felix Clotten** (Köln): **Descending control of two coupled locomotor systems**
- **Andreea Constantinescu** (Wien, Austria): **Multiplexing motor functions and impulsive traits is molecularly dissociated by subthalamic metabotropic glutamate receptor 4**
- **Jennifer Heck** (Magdeburg): **C-terminal splicing of presynaptic calcium channels contributes to the variability of neurotransmitter release**
- **Madhura Ketkar** (Mainz): **A luminance-sensitive cell type in Drosophila facilitates visual contrast computation**
- **Özge Demet Özcete** (Göttingen): **Sound encoding at individual inner hair cell synapses**
- **Aarti Sehdev** (Konstanz): **Olfactory object recognition based on fine-scale stimulus timing in Drosophila**
- **Ahmed Shaaban** (Göttingen): **Dissecting key mechanisms of gut-to-brain signalling**
- **Sonja Sivcev** (Praha, Czech Republic): **Testosterone derivatives increase sensitivity of P2X receptors to ATP and antagonize the effect of ivermectin on deactivation**
- **Thede Witschel** (Tübingen): **Finite element simulations of active electroception**

- **Sebastian Mauricio Molina-Obando** (Göttingen): **A combination of GABA- and glutamate-gated chloride channels mediates ON selectivity in the Drosophila visual system**

14:30 – 16:30 Symposia III (S13-S18)

S13 Breaking News II, Chair: Marc Spehr (Aachen)

- **Margarita Anisimova** (Hamburg): **Optogenetic spike-timing-dependent plasticity (oSTDP)**
- **Marcel Brosch** (Magdeburg): **A flexible and transparent electrode array for closed-loop optogenetic stimulation**
- **Oana Constantin** (Hamburg): **Manipulation of intracellular cAMP and membrane potential using light activated adenylyl cyclases and CNG channels**
- **Sofia Elizarova** (Göttingen): **Nanosensor-based Imaging of Presynaptic Dopamine Release**
- **Raziye Karapinar** (Bochum): **Design of an ultra-fast switching mouse melanopsin variant with a narrow action spectrum**
- **Golan Karvat** (Freiburg): **Real-time neurofeedback in freely behaving rats: training a network to study a network**
- **Mauro Pulin** (Hamburg): **Chemogenetic silencing: synaptic mechanisms and long-term effects at Schaffer collateral synapses**
- **Meike Marie Rogalla** (Bremen): **Hearing colors: evaluation of frequency representation in optogenetic midbrain implants**
- **Michael Schweigmann** (Homburg): **Exploring cortical brain networks with flexible LCP microelectrode arrays in parallel to two-photon imaging of anaesthetized and awake mice**
- **Yixin Tong** (Freiburg i.Br.): **Optogenetic stimulation of VTA dopaminergic neurons in a rodent model of depression**

S14 Adaptivity and inhomogeneity in neuronal networks – two sides of the same coin?, Chairs: Ulrich Egert (Freiburg), Stefan Rotter (Freiburg)

- **Júlia V Gallinaro** (Freiburg): **Cell assembly formation and non-random connectivity in networks subject to homeostatic structural plasticity**
- **Anna Levina** (Tübingen): **Self-organization of neuronal dynamics by plasticity and adaptation**
- **Samora Okujeni** (Freiburg): **Self-organized mesoscale inhomogeneity promotes rich activity dynamics**
- **Christos Galanis** (Freiburg): **Dopamine blocks homeostatic excitatory synaptic plasticity in immature dentate granule cells of entorhino-hippocampal tissue cultures**

S15 The brain oxytocin system – its complex impact on autism, social behavior, and stress, Chairs: Benjamin Jurek (Regensburg), Adam Steven Smith (Lawrence, USA)

- **Marta Busnelli** (Milano, Italy): **Oxytocin: its signaling of action and receptor signalling in the brain**
- **Benjamin Jurek** (Regensburg): **The brain oxytocin system and its complex impact on stress and anxiety**
- **Martin Schulte-Rüther** (Aachen): **Social reinforcement learning and its neural modulation by oxytocin in autism spectrum disorder**
- **Adam Steven Smith** (Lawrence, USA): **Oxytocin and social contact reduce anxiety**
- **Magdalena Meyer** (Regensburg): **Oxytocin alters the morphology of hypothalamic neurons via the transcription factor myocyte enhancer factor 2A (MEF-2A)**
- **Dominik Fiedler** (Münster): **Brain-Derived Neurotrophic Factor modulates synaptic properties of ovBNST neurons via TrkB receptors**

S16 Mitochondrial dysfunction in neurodegeneration, Chairs: Ira Milosevic (Göttingen), Nuno Raimundo (Göttingen)

- **Thomas Langer** (Köln): **Proteolytic control of mitochondrial dynamics and neurodegeneration**
- **Elena Rugarli** (Köln): **CLUH is a post-transcriptional regulator of mitochondrial function**
- **Nektarios Tarernarakis** (Heraklion, Greece): **Mitochondrial turnover and homeostasis in ageing and neurodegeneration**
- **Patrik Verstreken** (Leuven, Belgium): **The origin of sleep defects in Parkinson disease**
- **Sindhuja Gowrisankaran** (Göttingen): **Rabconnectin-3a regulates vesicle acidification at the neuronal synapse**
- **King Faisal Yambire** (Göttingen): **Lysosomal and mitochondrial crosstalk: a case for neurodegeneration in LSDs?**

S17 Dissection of a central brain circuit: structure, plasticity and functions of the drosophila mushroom body, Chairs: André Fiala (Göttingen), Bertram Gerber (Magdeburg)

- **Yoshinori Aso** (Ashburn, USA): **Mechanisms to diversify learning rules in parallel memory circuits**
- **Stephan Sigrist** (Berlin): **Mechanisms underlying age-induced memory impairment in relation to mushroom body function**
- **Lisa Scheunemann** (Paris, France): **Serotonergic Modulation of Memory Circuits**
- **Barbara Webb** (Edinburgh, UK): **Modelling the mechanisms of learning in the mushroom body**
- **Nino Mancini (Magdeburg): Function of the anterior paired lateral (APL) neuron in associative olfactory learning in larval Drosophila**
- **Radostina Lyutova** (Würzburg): **Reward signaling in a recurrent circuit of dopaminergic neurons and Kenyon cells in the Drosophila larva**

S18 From normal brain development to pathology: what role does the environment play?, Chairs: Cristiana Cruceanu (München), Simone Mayer (Tübingen)

- **Claudia Buss** (Berlin): **Maternal inflammation during pregnancy and fetal brain development**
- **Cristiana Cruceanu** (München): **Stress hormones during pregnancy and fetal brain development: what we can learn from perinatal tissues and in vitro models**
- **Simone Mayer** (Tübingen): **Early active intercellular signaling networks in the developing human brain**
- **Freda Diane Miller** (Toronto, Canada): **Stem cells and growth factors: building and repairing the murine forebrain**
- **Paola Brivio** (Milano, Italy): **Alteration of serotoninergic system alters neuroplastic mechanisms from postnatal development until adulthood.**
- **Rebecca Winter** (Dresden): **Prevention of schizophrenia deficits via non-invasive adolescent frontal cortex stimulation in rats**

16:30 – 18:00 Postersession IV

19:00 – 20:00 Plenary Lecture, *Hertie Foundation Lecture*
Onur Güntürkün (Bochum): **Cognition without a cortex**

Friday, March 22, 2019

9:00 – 10:00 Plenary Lecture, *Norbert Elsner Lecture*
Nachum Ulanovsky (Rehovot, Israel) **Neural codes for natural navigation in the hippocampal formation of bats**

10:00 – 11:30 Postersession V

11:30 – 13:30 Symposia IV (S19-S24)

S19 From clinical symptoms to motoneuron pathobiology: most recent insights into amyotrophic lateral sclerosis (ALS), Chairs: Jochen Weishaupt (Ulm), Albert C. Ludolph (Ulm)

- **Karin Danzer** (Ulm): **TDP-43 aggregation – implications for ALS**
- **Dorothee Dormann** (Planegg-Martinsried): **Molecular mechanisms of ALS – from nuclear transport defects to protein aggregation**
- **Jochen H. Weishaupt** (Ulm): **From ALS genes to pathogenic principles and targets for individualized therapies**
- **Albert C. Ludolph** (Ulm): **t.b.a.**
- **Alexander Nikolaevich Trofimov** (Maastricht, Netherlands): **Neuroinflammation in a mouse model of amyotrophic lateral sclerosis with FUS gene mutation and effects of standard and new therapies**
- **Diane Penndorf** (Jena): **Replicative reprogramming in the context of physiological CNS aging and age-related neurodegeneration**

S20 Subcortico-cortical loops and their role in sensory processing and perception, Chairs: Livia de Hoz (Berlin), Julio Hechavarria (Frankfurt/M.)

- **Laura Busse** (Planegg-Martinsried): **Visual processing of feedforward and feedback signals in mouse dLGN**
- **Livia de Hoz** (Berlin): **Auditory midbrain coding of temporally sparse statistics**
- **Max F. K. Happel** (Magdeburg): **Recurrent corticothalamic feedback in auditory cortex mediating salient auditory perception**
- **Julio Hechavarria** (Frankfurt/M.): **Understanding the auditory hierarchy: modifications to auditory processing on the way to the cortex**
- **Francisco Garcia-Rosales** (Frankfurt/M.): **Cortical oscillations aid the representation of natural vocalization streams at multiple timescales**
- **Kim Chi Le** (Aachen): **Dual-color imaging for isolating olfactory bulb output streams in mice**

S21 Behavioral decisions based on multimodal information, Chairs: Basil el Jundi (Würzburg), Martin Strube-Bloss (Würzburg)

- **Marie Dacke** (Lund, Sweden): **As the craw flies and the beetle rolls: straight-line orientation from behaviour to neurons**
- **Markus Knaden** (Jena): **Desert ant navigation by olfactory and visual cues**
- **Simon Sponberg** (Atlanta, USA): **Timing, multimodal integration, and coordination in the neural control of agile flight in low light**
- **Matthias Wittlinger** (Freiburg): **Multimodal odometry in navigating Cataglyphis desert ants**
- **Robin Grob** (Würzburg): **Compass systems during ant learning walks: the role of celestial cues for initial compass calibration in cataglyphis ants**
- **Arne Gollin** (Bielefeld): **Estimating body pitch from distributed proprioception: On the role of afferent number and distribution**

S22 The neuronal basis of tinnitus, Chair: Birgit Mazurek (Berlin), Holger Schulze (Erlangen)

- **Birgit Mazurek** (Berlin): **Tinnitus and comorbidities**
- **Arnaud Jean Norena** (Marseille, France): **The pathophysiology of tinnitus**
- **Holger Schulze** (Erlangen): **The fine-tuned brain: better hearing in tinnitus patients due to stochastic resonance?**
- **Pim Van Dijk** (Groningen, Netherlands): **Characteristics of auditory processing associated with tinnitus**
- **Elouise Alexandra Koops** (Groningen, Netherlands): **Cortical tonotopic maps in tinnitus and hearing loss**

S23 Early information selection for robust vision, Chair: Matthias Bethge (Tübingen)

- **Katrin Franke** (Tübingen): **Chromatic processing in the mouse retina**
- **Ziad M. Hafed** (Tübingen): **A vision for orienting in primate superior colliculus**
- **Matthias Bethge** (Tübingen): **t.b.a.**
- **Li Zhaoping** (Tübingen): **Visual selection**

S24 Form follows function? Rules and consequences of structural synaptic plasticity, Chairs: Tobias Rose (Martinsried), J. Simon Wiegert (Hamburg)

- **Anthony Holtmaat** (Geneva, Switzerland): **Synaptic mechanisms for plasticity in the somatosensory cortex**
- **Tara Keck** (London, UK): **Structural dynamics following sensory deprivation in mouse visual cortex**
- **Simon Wiegert** (Hamburg): **The sequence of plasticity inducing events sets the lifetime of hippocampal synapses**
- **Panayiota Poirazi** (Heraklion, Greece): **Memory linking through synapse clustering in active dendrites**
- **Brenna C Fearey** (Hamburg): **Mapping action potential back propagation using SynTagMA**

14:30 – 16:30: Symposia V (S25-S30)

S25 Go with the flow? Processing of sensory flows across modalities, Chairs: Aristides Arrenberg (Tübingen), Jan Benda (Tübingen), Annette Denzinger (Tübingen), Hanspeter Mallot (Tübingen)

- **Karen Carleton** (College Park, USA): **Optimal visual sensitivities: what the cichlid eye needs to tell the cichlid brain**
- **Eric Scott Fortune** (Newark, USA): **Close-loop control of active-sensing movements**
- **Michaela Warnecke** (Baltimore, USA): **Echo flow patterns influence bat flight behavior and neural activity**
- **Douglas R. Wylie** (Edmonton, Canada): **An eye towards hovering: species differences in the processing of optic flow in birds in relation to flight behavior**
- **Dimokratis Karamanlis** (Göttingen): **Natural stimuli reveal a spectrum of spatial encoding across the output channels of the retina**
- **Kun Wang** (Tübingen): **Binocular processing and receptive fields of motion-sensitive neurons in the zebrafish pretectum and tectum**

S26 Neural mechanisms of social decision-making (SFB 1158), Chairs: Igor Kagan (Göttingen), Arezoo Pooresmaeili (Göttingen)

- **Steve W. C. Chang** (New Haven, USA): **The coordinated interplay between prefrontal areas and amygdala in social gaze dynamics and decision-making**
- **Tobias Kalenscher** (Düsseldorf): **Neural mechanisms of social preferences in rats**
- **Alan G. Sanfey** (Nijmegen, Netherlands): **Reciprocity and punishment: insights from decision neuroscience**
- **Anne Christin Saulin** (Würzburg)**: How multiple motives affect the computation of social decisions in the human brain**

- **Caedyn Lachlan Stinson** (Berlin)**: The role of differential sensory input and attributional biases in social effort perception**

S27 Neurodegenerative diseases: shaping neuronal circuits by membrane trafficking, Chairs: Natalia Kononenko (Köln), Brunhilde Wirth (Köln)

- **Michael Alan Cousin** (Edinburgh, UK): **Loss of functional huntingtin causes activity-dependent presynaptic defects in Huntington's disease**
- **Natalia Kononenko** (Köln): **AP-2 prevents amyloidogenic processing of APP via endocytosis-independent regulation of BACE1 trafficking in neurons**
- **Ira Milosevic** (Göttingen): **Endocytosis and autophagy dysfunction in neurodegeneration**
- **Brunhilde Wirth** (Köln): **Protective modifiers unveiled impaired endocytosis in Spinal Muscular Atrophy and opened new therapeutic options**
- **Ferdi Ridvan Kiral** (Berlin)**: Decreased filopodial dynamics at autophagy-deficient photoreceptor axon terminals lead to ectopic synapse formation and neuronal miswiring**

S28 Modulatory circuits of central pain processing, Chairs: Valery Grinevich (Heidelberg), Alexander Groh (Heidelberg)

- **Alexandre Charlet** (Strasbourg, France): **Oxytocin acts on astrocytes in the central amygdala to promote comfort**
- **Luis Garcia-Larrea** (Lyon, France): **The cortical construction of pain**
- **Valery Grinevich** (Heidelberg): **Somatosensory modulation of oxytocin neurons drives social communication**
- **Alexander Groh** (Heidelberg): **Cortical control of thalamic pain processing**
- **Carla Norwig** (Würzburg): **Expression profile of tight junction proteins in a model of diabetic neuropathy**
- **Livia Asan** (Heidelberg): **The cellular basis of volumetric brain changes during chronic pain – a novel approach to correlate voxel-based morphometry with in vivo microscopy**

S29 Orexin beyond sleep, Chairs: Markus Fendt (Magdeburg), Michael Koch (Bremen)

- **Fernando Berrendero** (Madrid, Spain): **Orexin regulation of fear learning and extinction**
- **Marta Carus-Cadavieco** (Köln): **Hypothalamic network oscillations and regulation of feeding behaviour**
- **Nadine Faesel** (Magdeburg): **Role of orexin deficiency in panic-like anxiety**
- **Julia Sabine Schuller** (Bremen)**: Neurochemical investigation of impulse control in a rat model of binge eating disorder**
- **Archana Durairaja** (Magdeburg)**: Role of orexin in cognitive flexibility**

S30 Inhibitory synapse diversity in health and disease, Chairs: Dilja Krueger-Burg (Göttingen), Theofilos Papadopoulos (Göttingen)

- **Matthias Kneussel** (Hamburg): **Neuronal $GABA_A$ receptor trafficking and turnover underlying synaptic transmission and cognitive function**
- **Dilja Krueger-Burg** (Göttingen): **The cell adhesion molecule IgSF9b regulates inhibitory synapse function in the amygdala anxiety circuitry**
- **Jonas-Frederic Sauer** (Freiburg)**: Altered prefrontal pyramidal-GABAergic interneuron circuit architecture in a genetic mouse model of psychiatric illnesses**
- **Scott Haydn Soderling** (Durham, USA): **Proteo-connectomics to discover novel mechanisms of inhibition in vivo**
- **Martin Zeller** (Tübingen): **Amygdala intercalated neurons form an interconnected and functionally heterogeneous network**

16:30 – 18:00 Postersession VI

19:00 – 20:00 Plenary Lecture, *Schram Lecture*
Volker Haucke (Berlin): **Mechanisms of presynapse function and assembly**

Saturday, March 23, 2019

8:30 – 10:30 Symposia VI (S31-S36)

S31 The tripartite synapse in health and disease, Chairs: Gabor Petzold (Bonn), Christine R. Rose (Düsseldorf)

- **Niklas J. Gerkau** (Düsseldorf): **Sodium loading in metabolically compromised cortex**
- **Christian Henneberger** (Bonn): **Perisynaptic astrocyte structure dynamically shapes hippocampal glutamate signalling**
- **Gabor Petzold** (Bonn): **Role of astroglial calcium changes in Alzheimer's disease and stroke**
- **Verena Untiet** (Copenhagen, Denmark): **Astroglial chloride-homeostasis in health and disease**
- **Zhou Wu** (Bonn): **Unravelling potential mechanisms causing astrocytic death during early epileptogensis**

- **Mico Bozic** (Ljubljana, Slovenia): **Astroglial MHC class II molecules are associated with fusion of larger vesicles**

S32 Hearing system adaptation for diverse lifestyles across the animal kingdom, Chairs: Manuela Nowotny (Frankfurt/M.), Stefan Schöneich (Leipzig)

- **Jan Clemens** (Göttingen): **Acoustic communication in the wild – a shared song feature detector drives male and female responses to song in Drosophila**
- **Manuela Nowotny** (Frankfurt/M.): **Talk to me darling – neuronal adaptations for intraspecific communication in the bushcricket ear**
- **Hannah ter Hofstede** (Hanover, USA): **Auditory adaptations for detecting echolocating predators in moths and katydids**
- **Christine Köppl** (Oldenburg): **Death on silent wings – adaptations for sound localization in the barn owl**
- **Lina Maria Jaime Tobon** (Göttingen): **Understanding sound encoding: correlation of response properties of afferent inner hair cell synapses at near physiological conditions**
- **Ajayrama Kumaraswamy** (Planegg-Martinsried): **Adaptations in an identified honeybee auditory interneuron responsive to waggle dance vibration signals**

S33 Pro-survival versus toxic NMDA receptor signaling and the fight against neurodegenerative disorders, Chairs: Hilmar Bading (Heidelberg)

- **Hilmar Bading** (Heidelberg): **The NMDA receptor paradox: pro-survival versus death signaling**
- **Giles E. Hardingham** (Edinburgh, UK): **Probing the roles of GluN2 C-terminal domain signalling in health and disease**
- **Stuart A. Lipton** (La Jolla, USA): **The novel NMDAR antagonist NitroSynapsin as therapy for hiPSC- and mouse-models of human autism spectrum disorder**
- **Lynn A Raymond** (Vancouver, Canada): **Role for extrasynaptic NMDA receptors in prodromal Huntington disease: mechanisms and therapeutic implications**
- **Liliana Rojas-Charry** (Hamburg): **Specific mutations in presenilin 1 have a differential role on mitochondrial phenotype and function**

S34 The dentate gyrus – from microcircuit function to control of behavior, Chairs: Marlene Bartos (Freiburg)

- **Marlene Bartos** (Freiburg): **In vivo imaging of stable and dynamic memory engrams in the rodent hippocampus**
- **Fritjof Helmchen** (Zürich, Switzerland): **Two-photon imaging of dentate granule cells and CA3 pyramidal cells in mouse hippocampus**
- **Christoph Schmidt-Hieber** (Paris, France): **Probing cellular mechanisms of pattern separation in the dentate gyrus**
- **Heinz Beck** (Bonn): **Mechanisms of sparse coding in the dentate gyrus**
- **Thomas Hainmueller** (Freiburg i. Br.): **Imaging the dentate gyrus circuitry during virtual navigation.**

S35 The presynaptic active zone: converging and diverging mechanisms across species, Chairs: Robert Kittel (Leipzig), Noa Lipstein (Göttingen)

- **Nadine Ehmann** (Leipzig): **Active zone physiology in the context of olfactory information processing in Drosophila**
- **Pascal Kaeser** (Boston, USA): **Dissecting release site architecture for fast neurotransmitters and for neuromodulators**
- **Joshua M. Kaplan** (Boston, USA): **From compost to the clinic: using C. elegans to study psychiatric disorders**
- **Janet Elizabeth Richmond** (Chicago, USA): **Molecular machinery required for synaptic organization and release**
- **Lydia S.B. Maus** (Göttingen): **Resolving the ultrastructural organization of synaptic vesicle pools at hippocampal mossy fiber and schaffer collateral synapses**
- **Martin Baccino-Calace** (Oberengstringen, Switzerland): ***thin*** **promotes presynaptic homeostatic plasticity at the Drosophila neuromuscular junction**

S36 Beyond expression of fear: mechanisms and circuits of the extended amygdale, Chairs: Maren Denise Lange (Münster), Thomas Seidenbecher (Münster))

- **Ki Ann Goosens** (New York, USA): **Mechanisms underlying stress-enhanced fear**
- **Maren Denise Lange** (Münster): **Endocannabinoids impact on responses to predictable and unpredictable threat via CRH neurons**
- **Laura Luyten** (Leuven, Belgium): **Targeting the bed nucleus of the stria terminalis to reduce anxiety in rats and patients**

- **Stephen Maren** (College Station, USA): **The way forward is backward: BNST mediates fear to ambiguous threats**
- **Julia Winter** (Regensburg): **The transcription factor MEF-2A mediates the anxiogenic effect of chronic oxytocin**
- **Roman Kessler** (Marburg): **The watchdog won't stop barking! Top-down control of the amygdala by medial prefrontal cortex in major depression: The role of medication, genetic liability and childhood maltreatment**

10:30 – 12:00 Postersession VII

12:30 – 13:30 Plenary Lecture, *Ernst Florey Lecture*

Antoine Triller (Paris, France) **The synapse: memory in a fluid membrane**

13:30 – 15:00 Postersession VIII

15:00 – 16:00 Plenary Lecture, *Otto Creutzfeldt Lecture*
Kristin Tessmar-Raible (Vienna, Austria) **The brain as a timer: day, season and moon phase coordination in the sea**

Die Online-Registrierung ist noch bis zum **6. März 2019** möglich. Eine Registrierung vor Ort wird ebenfalls angeboten.
www.nwg-goettingen.de/2019

Reisestipendien für Göttinger Tagung 2019 vergeben

Aus den zahlreichen Einsendungen wurden die folgenden Bewerber für ein Stipendium in Höhe von 300 Euro für die Teilnahme an der Göttinger Tagung 2019 (20. – 23. März) ausgewählt:

1. Adzic, Marija (Serbia)
2. Anisimova, Margarita (Germany)
3. Božić, Mićo (Slovenia)
4. Brivio, Paola (Italy)
5. Clotten, Felix (Germany)
6. Daghsni, Marwa (Tunisia)
7. Ebrahimtabar, Forough (Iran)
8. Eckert, Philipp (Germany)
9. Eiffler, Ina (Germany)
10. Fleischmann, Pauline Nikola (Germany)
11. Guedes-Dias, Pedro (USA)
12. Keine, Christian (Germany)
13. Kugler, Christof (Germany)
14. Liedtke, Maik (Germany)
15. Paschen, Enya (Germany)
16. Pentimalli, Tancredi Massimo (Italy)
17. Pina, Eneko (Germany)
18. Rodriguez-Rozada, Silvia (Germany)
19. Sathyanarayanan, Ranganayaki (India)
20. Schlüter, Annabelle (Germany)
21. Schoof, Melanie (Germany)
22. Taylor, Stephanie (Germany)
23. Winter, Julia (Germany)
24. Wu, Zhou (Germany)

Bewerben konnten sich Studenten, Doktoranden und Postdocs, die zum Zeitpunkt der Bewerbung maximal 35 Jahre alt waren und an der Göttinger Tagung mit einem eigenen Beitrag als Erstautor teilnehmen. Als Bewerbungsunterlagen waren ein kurzer Lebenslauf, eine Publikationsliste (falls vorhanden), eine Kopie des Abstracts und ein kurzes Empfehlungsschreiben gefordert.

Einladung zur Mitgliederversammlung auf der 13. Göttinger Tagung der Neurowissenschaftlichen Gesellschaft (20. – 23. März 2019)

Termin: **Donnerstag, 21. März 2019, 13:30 – 14:30 Uhr**
Ort: **Zentrales Hörsaalgebäude, Hörsaal 11**

Vorläufige Tagesordnung:

1. Begrüßung durch den Präsidenten
2. Bestätigung des Protokolls der letzten Mitgliederversammlung
3. Bericht des Schatzmeisters
4. Mitteilungen
5. Bericht zur Göttinger Tagung
6. Wahl des neuen Vorstandes
7. Aktivitäten der Gesellschaft
8. Verschiedenes

Vorschläge für weitere Tagesordnungspunkte reichen Sie bitte **bis spätestens 8. März 2019** bei der Geschäftsstelle ein.

Neurowissenschaftliche Gesellschaft e.V.
Max-Delbrück-Centrum für Molekulare Medizin (MDC)
Robert-Rössle-Str. 10, 13092 Berlin
E-Mail: gibson@mdc-berlin.de

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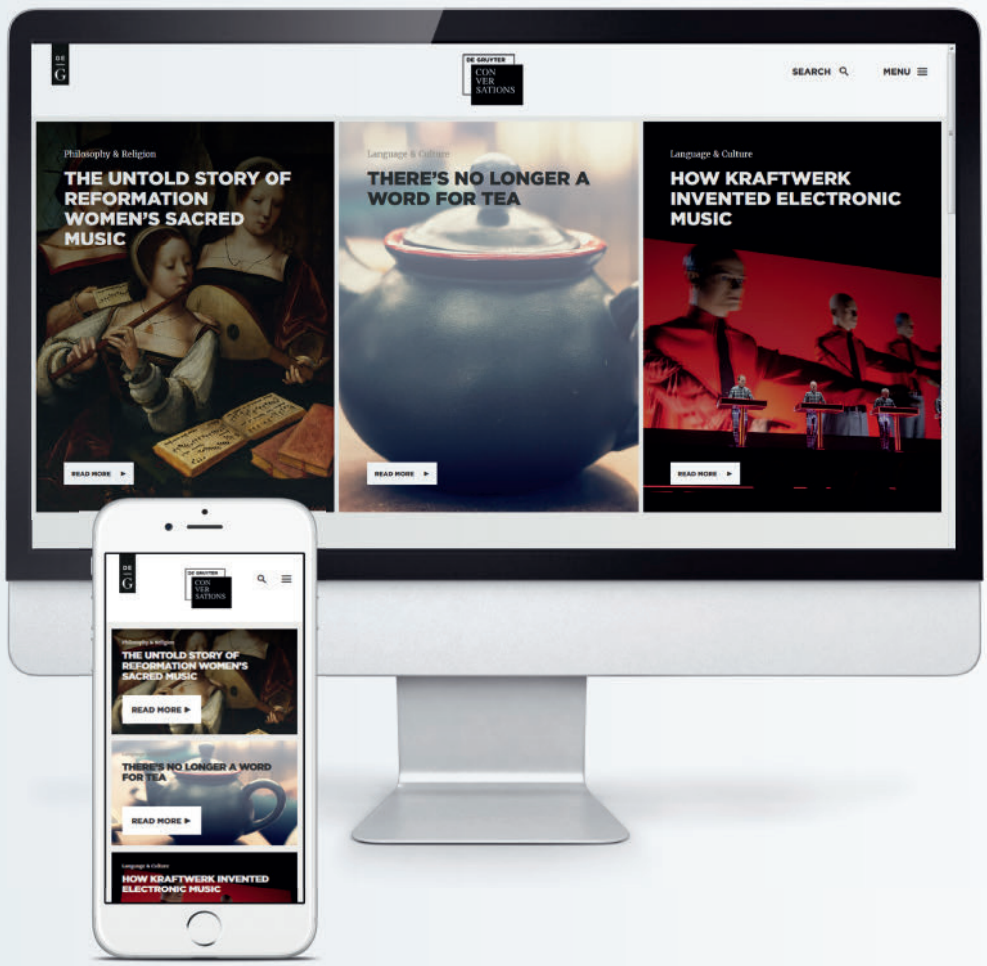

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- ☐ Molekulare Neurobiologie
- ☐ Klinische Neurowisschenschaften
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