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INVITED REVIEW

Primary cilia as a novel horizon between neuron and environment

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Abstract
The primary cilium, a hair-like sensory organelle found on most mammalian cells, has gained recent attention within the field of neuroscience. Although neural primary cilia have been known to play a role in embryonic central nervous system patterning, we are just beginning to appreciate their importance in the mature organism. After several decades of investigation and controversy, the neural primary cilium is emerging as an important regulator of neuroplasticity in the healthy adult central nervous system. Further, primary cilia have recently been implicated in disease states such as cancer and epilepsy. Intriguingly, while primary cilia are expressed throughout the central nervous system, their structure, receptors, and signaling pathways vary by anatomical region and neural cell type. These differences likely bear relevance to both their homeostatic and neuropathological functions, although much remains to be uncovered. In this review, we provide a brief historical overview of neural primary cilia and highlight several key advances in the field over the past few decades. We then set forth a proposed research agenda to fill in the gaps in our knowledge regarding how the primary cilium functions and malfunctions in nervous tissue, with the ultimate goal of targeting this sensory structure for neural repair following injury.

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The Primary Cilium: Persisting Relevance in the Adult Central Nervous System (CNS)

While few would still go so far as to disparage primary cilia as inert, vestigial appendages inherited from our single-celled ancestors, the fact remains that these hair-like sensory organelles continue to receive less attention than they deserve. First discovered in protozoans in the late 1600s by the Dutch scientist Antony Van Leeuwenhoek while examining pond water samples under the microscope, cilia and flagella, microtubule-based organelles found in most eukaryotic cells, have been a topic of curiosity and controversy (Haimo and Rosenbaum, 1981; Satir, 1995). Although we now appreciate at least some of the various motor and sensory functions of these organelles, thanks largely to pioneering work by the Czech biologist Jan Purkyne and his student G.G. Valentin, the field of cilia biology is still relatively uncharted (Teich, 1970). We have since discovered that most cells of the human body express primary cilia, which are immotile and sensory in nature, while a handful of specialized cells express the beating, motile variety (Afzelius, 1976; Wheatley et al., 1996). After many years of speculation, poo pooing, and neglect of primary cilia, we are finally beginning to develop tools and approaches to more fully understand their importance to normal cellular physiology as well as their relevance to human disease. Even more recently, we have learned that primary cilia exist and signal throughout the CNS.

The first clue that primary cilia have not become irrelevant to mammalian biology is, of course, the host of problems that arise when primary cilia fail to assemble or signal properly, particularly during development of the organism. Indeed, the wide range of primary ciliopathies, including retinal degeneration, brain and spinal cord malformations, and Bardet-Biedl syndrome, a genetically-related obesity syndrome, has focused the scientific community's attention on the critical role of primary cilia during embryonic development (Gerdes et al., 2009; Lee and Gleeson, 2011). Although it has become widely acknowledged that primary ciliary signaling, for example through Hedgehog-mediated control of cell cycle progression *via* the canonical Wnt pathway, is essential for proper proliferation, differentiation, and migration of cells throughout the developing embryo, much less is known regarding the potential homeostatic, stimulus-triggered, or disease relevant functions of primary cilia once developmental programs have become established (Clement et al., 2009; Wong et al., 2009; Schneider et al., 2010; Gilliam et al., 2012). In particular, investigation of primary cilia within the CNS has increased in recent years, as it has been discovered that they contribute to homeostatic mechanisms and may also be implicated in neuropathological states in the adult organism.

In this review, we provide an overview of several recent technical and conceptual advances in the field of primary cilia biology related to their reparative potential in the CNS. We introduce several newly described non-canonical roles of primary cilia in neuroplasticity, and set forth a proposed research agenda for the study of the role of primary

cilia in damage and repair in the context of neural injury. Novel methods to manipulate primary cilia structure or signaling will likely prove crucial not only to enhance our understanding of their roles in health and disease, but also to provide the foundation for novel therapeutics targeting these organelles.

Research Agenda: to Better Understand Neural Primary Cilia in Health and Disease

Until the past decade, it has been difficult to probe the various functions of primary cilia due to a paucity of refined pharmacological or genetic tools targeting these organelles specifically. However, our understanding of cilia biology has benefited tremendously from new technologies such as transgenic mice conditionally deficient in intraflagellar transport (IFT) genes or Bardet-Biedl syndrome (BBS) genes, as well as virally-delivered DNA/RNA constructs that can downregulate or overexpress the various components of the ciliary protein machinery (Jonassen et al., 2008; Zaghloul and Katsanis, 2009; Boehlke et al., 2010; Kumamoto et al., 2012). Using these approaches, we are beginning to appreciate the many roles that cilia take on far beyond embryonic development and well into adulthood and senescence. With these considerations, we propose the following research agenda.

To better understand normal neural primary cilia physiology and behavior in the adult CNS

While our knowledge of cilia signaling in orchestrating neuronal patterning and other developmental programs during embryogenesis has advanced significantly, the field of cilia biology is still relatively new with regard to mature/adult physiology, especially in the CNS. More basic research aimed at understanding the cilium's role in neuronal excitability, plasticity and behavior, as well as its importance to glial cells, is warranted.

The presence of primary cilia on neurons was first reported in the late 1950s and early 1960s by several scientists working on different model organisms. Duncan and Dahl, each independently studying the rodent nervous system, noted the presence of cilia by ultrastructural analysis of notochord and cerebral cortex, respectively (Duncan, 1957; Dahl, 1963). Meanwhile, developmental geneticist Sydney Brenner and his colleagues also noticed the presence of cilia in the primitive nervous system of the nematode *Caenorhabditis elegans* (Ward et al., 1975). Thus began the search into the structure and functions of neural primary cilia, work that until recently had largely focused on the cilium's role in vertebrate neural tube development in the embryo through Sonic hedgehog signaling (Corbit et al., 2005; Caspary et al., 2007).

As a part of their normal functioning in the mature, intact nervous system, primary cilia contribute to neuroplasticity at the neural stem cell, electrophysiological, and behavioral levels. In both adult neurogenic regions of the brain, the lateral ventricle of the subventricular zone (SVZ) and the subgranular zone (SGZ) of the hippocampal dentate gyrus, neural progenitor cells harbor primary cilia, and so a logical question is whether these cilia contribute to the process of adult neurogenesis. Radial glia-like progenitors in the SGZ depleted of ciliary genes or whose ciliary Hedgehog signaling has become disrupted are unable to proliferate, thus leading to dramatic impairments in adult hippocampal neurogenesis (Han et al., 2008). Similarly, ciliary disruption in radial glia of the SVZ *via* deletion of IFT proteins (important in ciliogenesis and maintained cilia integrity) leads to suppression of neurogenesis in the ventral portion of the SVZ (Tong et al., 2014). Since adult neurogenesis is well acknowledged to provide an additional layer of plasticity to the adult brain above that provided by synaptic dynamics (Kirschen et al., 2017a; Sailor et al., 2017), primary cilia are likely crucial in promoting ongoing cellular reorganization that promotes brain circuit plasticity throughout adulthood.

In the mature neuron at the level of the synapse, primary cilia again demonstrate their role in shaping adult plasticity. Depleting primary cilia in mature dentate granule neurons of the hippocampus not only decreases evoked and spontaneous excitatory postsynaptic currents in these cells and impairs functional glutamatergic synapse formation, but further leads to defects in long term potentiation (LTP) in CA3 pyramidal neurons following high frequency stimulation at the mossy fiber terminal (Kumamoto et al., 2012; Rhee et al., 2016). Such defects likely contribute to hippocampus-specific behavioral deficits in contextual fear conditioning and spatial memory that others and we have observed upon primary cilia depletion (Berbari et al., 2014; Rhee et al., 2016). Still, the electrophysiological and behavioral relevance of primary cilia in other circuits and in other brain regions is yet to be determined. Given that virtually all neurons as well as some glial cells express primary cilia, their roles are likely to be numerous. A summary of known ciliary receptors, signaling pathways, and cellular processes directly related to primary cilia of various neural cell types is shown in **Table 1**.

To characterize the functional ramifications of loss of neuronal primary cilia structural integrity under disease conditions

We still do not know the full scope of neurological diseases to which neuronal cilia may contribute. In addition to determining the neurodegenerative or neuroinflammatory conditions in which cilia are implicated, strategies to target these organelles should be pursued. This could involve, for example, experimentally blocking ciliary disassembly or activating/inactivating of ciliary receptors during neurological insult and tracking functional outcomes both in terms of cellular physiology and behavioral correlates.

With primary cilia so important for proliferation, migration, and patterning/organization of neural cells during normal development, it is natural to wonder whether they participate in similar processes under pathological conditions. Intriguingly, in the corneal epithelial cells of the developing eye, the precise timing of primary cilia assembly is crucial for the coordination of cell localization to form the unique

hexagonal monolayer of cells characteristic of the corneal epithelium (Blitzer et al., 2011). Following the completion of this developmental program, these cilia degenerate, but strikingly, they quickly regenerate following mechanical corneal injury, which disrupts the hexagonal cellular patterning. Could a similar phenomenon occur in the CNS following an insult that disrupts neuronal homeostasis? And by extension, could primary cilia play a central role in coordinating the response to this insult?

To address these questions, others and we have initiated a new line of investigations aimed at understanding primary cilia integrity during and following CNS injury. Firstly, unlike in the corneal epithelium, in the brain, primary cilia are constitutively expressed by neurons of both young and aged animals (with increasing length across the lifespan in certain brain regions) (Guadiana et al., 2016). Secondly, neocortical and hippocampal neuronal primary cilia in the adult brain display a characteristic radial alignment paralleling their cellular polarity, and also exhibit regional heterogeneity in lengths at baseline (Kirschen et al., 2017b) (**Figure 1A**). Upon seizure induction, however, cilia lengths and alignment become disrupted (Parker et al., 2016; Kirschen et al., 2017b). Similarly, cerebral hemispheric ischemia leads to changes in both length and alignment of neuronal cilia (Kirschen et al., 2017b). Intriguingly, the hippocampus and its innervating region the entorhinal cortex exhibit differential responses to brain injury. While a pilocarpine-induced seizure disrupts ciliary positioning in both regions, cilia length is selectively disrupted in the entorhinal cortex but not in the hippocampus.

What these changes signify structurally and molecularly, however, remains to be determined. Given the regional heterogeneity of G protein-coupled receptors and other receptors/effectors along the axoneme (the microtubule-composed cytoskeletal backbone of the cilium) and immediately surrounding area of the cell membrane, we hypothesize that these insults may induce preferential damage at some sites, with relative sparing of others, leading to differential activation or inactivation of downstream pathways involved in mounting an inflammatory or reparative response. Alternatively, changes in cilia length and positioning may represent distal appendage and/or ciliary disassembly, for example *via* Pitchfork (Pifo)-mediated Aurora A (AurA) activation and cilia retraction at the basal body. This could lead to changes in planar cell polarity (PCP) signaling and consequent basal body mis-localization (Sanchez and Dynlacht, 2016). An overview of known and potential physiological/pathophysiological functions of neural primary ciliais depicted in **Figure 1B**.

We also do not know whether these structural changes in cilia following brain injury represent an advantageous reaction that will lead to downstream repair pathways, or rather collateral damage or injury exacerbation. Regardless, it will be important to further characterize the temporal dynamics of ciliary morphological changes over the course of disruptions in CNS homeostasis, as well as to determine their functional consequences. The existing literature on primary cilia signaling in the CNS under physiological conditions is sparse; their role in CNS malfunctioning is even more sparse. Thus, we hope that these preliminary findings will draw more interest in cilia research in the pursuit of both basic neural cilia knowledge as well as their relevance to neuropathology.

Identify and characterize the normal and triggered signaling cascades within neuronal cilia

The aforementioned gap in our knowledge regarding how neural cilia work, from their housekeeping functions to their stimulus-evoked responses, will be important issues to address. Fortunately, given the well-mapped neuronal connectivity and the relatively well understood stimulus-response properties of neural circuits, the basic neuroscience foundation underlying these questions should be feasible to address. Moreover, we can take advantage of strides made in other areas of cilia biology to use as starting points for reference and guidance in the study of neural cilia. For instance, it will be important to determine the molecular makeup of the plasma membrane composing the neuronal cilium as well as the cilioplasm, both in healthy and disease states. Like cilia of other cell types, neuronal cilia throughout the brain cluster G protein-coupled receptors (GCPRs) including adenylyl cyclase III (ACIII) and somatostatin receptor type 3, which when triggered, signal through the second messenger cyclic AMP (cAMP) to regulate various metabolic and secretory functions of the cell (Berbari et al., 2007; Bishop et al., 2007; Ferone et al., 2009) (**Table 1**). Interestingly, primary cilia were hypothesized to sense and regulate calcium homeostasis, as they appeared to act as a unique calcium sequestering compartment (Delling et al., 2013). More recent evidence from the same group suggests, however, that this is not in fact the case (at least in renal cells), as transgenic mice co-expressing a fluorescent cilium marker and a genetically-encoded calcium indicator exhibited no cilia-specific basal or stimulus-evoked changes in calcium flux (Delling et al., 2016).

These recent findings not only highlight that our assumptions regarding cilia biology should be challenged, but also spark questions about how neural cilia may differ from non-neural cilia. Even within the nervous system, how cilia differ by anatomical region under physiological or pathological conditions, as alluded to above, remains to be tested. Looking ahead, we must ask which of the currently available tools will be most ideally suited to address these questions. Several novel technologies that have been successfully employed in other areas of cilia biology should be evaluated for the study of neural cilia. For instance, real-time, fluorescence resonance energy transfer (FRET)-based analysis of cAMP has been used in primary human epithelial cells to monitor cAMP-mediated ciliary dynamics in motile cilia of the airway (Schmid et al., 2006). Likewise, voltage-clamp experiments have been conducted in motile cilia-expressing cells contacting the cerebrospinal fluid, revealing the importance of the ASIC3 channel in monitoring cerebrospinal fluid pH (Jalalvand et al., 2016). Whether such techniques could be

Table 1 Receptor expression and cellular processes of neural primary cilia

Cell type	Known cilia receptors	Downstream effectors, cellular processes	Reference
Glutamatergic hippocampal neuron	ACIII, Sstr3, Arl13b	cAMP, long-term potentiation, glutamatergic synapse maturation	Berbari et al., 2007; Bishop et al., 2007; Kumamoto et al., 2012; Rhee et al., 2016
Glutamatergic cortical neuron, forebrain, & brainstem neurons	ACIII, Sstr3	cAMP, Wnt signaling, telecephalic morphogenesis	Bishop et al., 2007; Willaredt et al., 2008
Olfactory tubercle, nucleus accumbens neurons, hypothalamic neurons	ACIII, Mchr1, 5-HT$_6$, NPY2R	cAMP, energy balance	de Quidt and Emson, 1986; Brailov et al., 2000; Berbari et al., 2008; Loktev and Jackson, 2013
GABAergic cortical interneurons	ACIII, Arl13b	Shh, migration	Baudoin et al., 2012; Higginbotham et al., 2012; Kirschen et al., 2017b
Motor neuron	ACIII, Kif3a	Anterograde axonal transport	Kondo et al., 1994; Ma et al., 2011
Photoreceptor cell	ACIII, Kif3a	RTK signaling, photoreception	Muresan et al., 1999; Abdel-Majid et al., 2002; Christensen et al., 2012
Astrocytes	ACIII	Shh, proliferation, survival	Bishop et al., 2007; Moser et al., 2009, 2014; Yoshimura et al., 2011
Radial glia-like progenitor cells	Kif3a	Shh, Smo, *Stumpy*, proliferation, differentiation	Breunig et al., 2008; Han et al., 2008

ACIII: Adenylyl cyclase III; 5-HT$_6$: serotonin receptor 6; Mchr1: melanin-concentrating hormone receptor 1; NPY2R: neuropeptide Y2 receptor; RTK: receptor tyrosine kinase; Sstr3: somatostatin receptor 3; Shh: sonic hedgehog; Smo: smoothened.

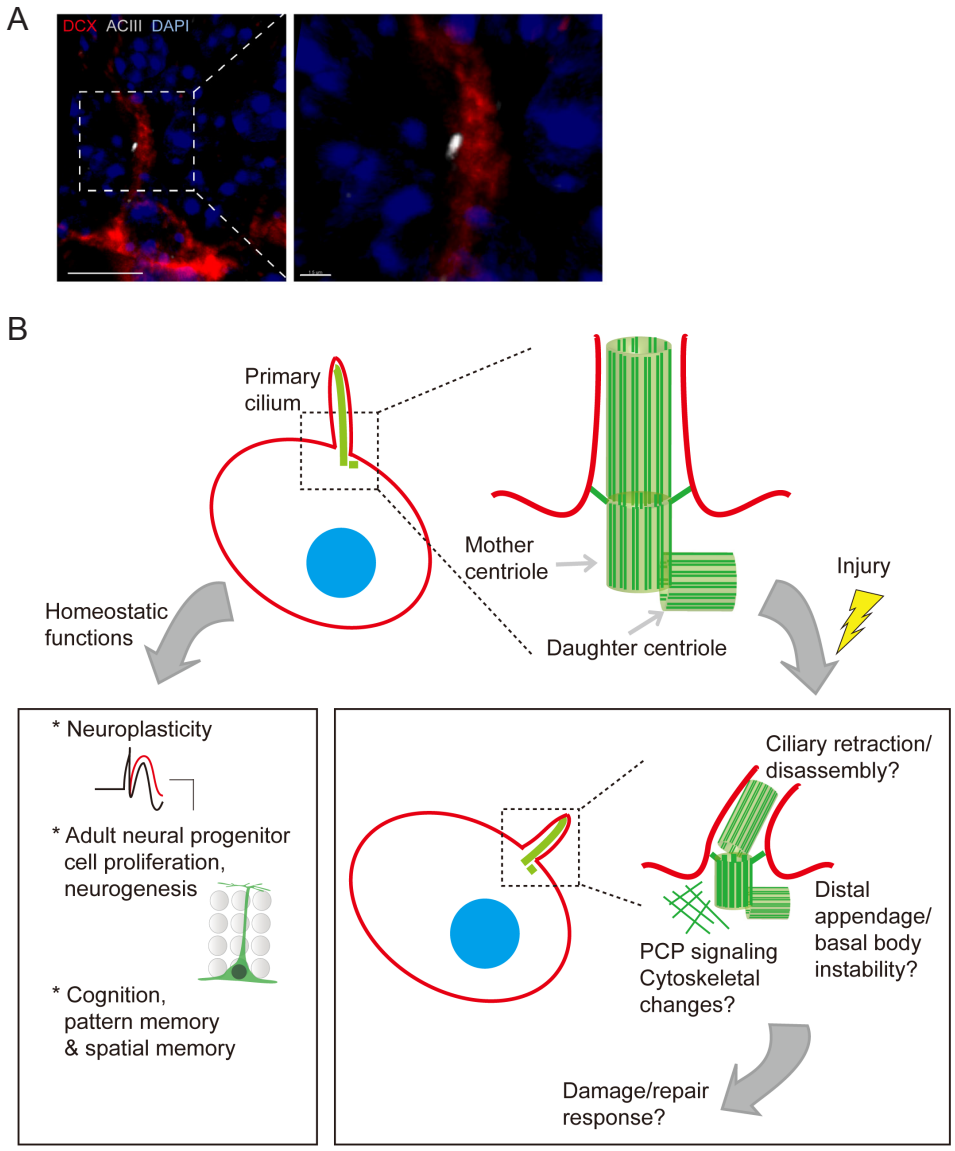

Figure 1 Functions of adult neuronal primary cilia, and potential disruptions following CNS injury.
(A) A representative image of the neuronal primary cilium of an adult-born dentate granule neuron in the hippocampus (stained with the immature neuronal marker double cortin, DCX). Adenylyl cyclase III (ACIII) labels primary cilia. The left and right scale bars are 10 and 1.5 μm, respectively. (B) An intact primary cilium, anchored by the basal body composed of one of the two centrioles, and tethered to the cell membrane *via* distal appendage proteins. Its physiological functions are listed at the left. A proposed pathological response is portrayed at the right. CNS: Central nervous system; PCP: planar cell polarity.

adapted to study primary cilia in the nervous system in response to electrical or chemical stimuli will be interesting to explore. Finally, novel technologies such as cilia-APEX, which selectively biotinylates cilia-specific proteins for subsequent proteomic analysis, may facilitate discovery of the unique protein makeup of cilia across different cell types and brain areas (Mick et al., 2015). It will be exciting to see our understanding of cilia structural/functional diversity blossom as these and other innovations allow us to answer a series of fundamental questions that currently remain unresolved.

Identify novel therapeutic agents to promote or restore cilia signaling under disease conditions

Aside from our incomplete understanding of how neural cilia signal under physiological conditions, we do not currently know whether structurally compromised primary cilia are still able to signal, and if so, how this signaling may differ from their homeostatic functions. As shown in **Table 1**, primary cilia of the CNS indeed express an array of receptors including GPCRs, which may suffice as a starting point, however the precise downstream signaling cascades of these receptors, as well as those of as-of-yet unidentified receptors, will require extensive characterization. As it stands, we now appreciate some of the important functions of adult neural primary cilia, and so the next step will be to elucidate the underlying mechanisms using pharmacological or genetic tools. If we can engineer such tools, we may be able to fine-tune ciliary signaling, with the potential to either facilitate repair following neural injury, or identify candidate therapies for the treatment of primary ciliopathies. For example, a recent high-throughput screen of small molecules targeting ciliary signaling *via* Hedgehog identified a number of small molecules that prevented aberrant Hedgehog signaling in a pancreatic ductal adenocarcinoma model, impeding the transition from G1 to S phase of the cell cycle and hence retarding cancer cell proliferation (Jung et al., 2016). More preclinical small molecule screening studies for neurological diseases (especially those involving aberrant cell proliferation or migration) will likely prove instrumental in such endeavors.

The field of adult primary cilia biology is ripe with potential to discover novel approaches to address common as well as rare neurological diseases. The primary cilium acts as a central sensory hub that concentrates receptors and signaling molecules, coordinates intracellular programs, and synchronizes the migration, morphogenesis, and homeostasis of cellular neighbors during development and into maturity. Our knowledge of the breadth of ciliary signaling is still limited in the realm of normal physiology, let alone pathophysiology. In particular, the importance of neural primary cilia in adult brain circuits and behavior is just starting to be illuminated. Thus, we hope to see the field continue to advance rapidly with the advent of more refined and specific tools to probe neural primary cilia and unleash their reparative/regenerative potential.

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