Functions and Dysfunctions of Adult Hippocampal Neurogenesis

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Abstract

Adult neurogenesis, a developmental process of generating functionally integrated neurons, occurs throughout life in the hippocampus of the mammalian brain and showcases the highly plastic nature of the mature central nervous system. Significant progress has been made in recent years to decipher how adult neurogenesis contributes to brain functions. Here we review recent findings that inform our understanding of adult hippocampal neurogenesis processes and special properties of adult-born neurons. We further discuss potential roles of adult-born neurons at the circuitry and behavioral levels in cognitive and affective functions and how their dysfunction may contribute to various brain disorders. We end by considering a general model proposing that adult neurogenesis is not a cell-replacement mechanism, but instead maintains a plastic hippocampal neuronal circuit via the continuous addition of immature, new neurons with unique properties and structural plasticity of mature neurons induced by new-neuron integration.

Contents

INTRODUCTION 244
PROCESSES OF ADULT HIPPOCAMPAL NEUROGENESIS 245
Synaptic Inputs 247
Synaptic Outputs 248
SPECIAL PROPERTIES OF ADULT-BORN DENTATE GRANULE NEURONS 249
Distinct Cellular Properties 249
Distinct Circuitry Properties 249
POTENTIAL MODES OF ADULT-BORN NEURON CONTRIBUTION TO BRAIN FUNCTIONS 250
FUNCTIONS OF ADULT HIPPOCAMPAL NEUROGENESIS IN COGNITION AND MOOD REGULATION 252
Cognitive Functions 252
Mood Regulation 254
DYSFUNCTION OF ADULT HIPPOCAMPAL NEUROGENESIS IN BRAIN DISORDERS 254
Dysfunction via Loss-of-Function 255
Dysfunction via Gain-of-Function 255
CONCLUSION 256

INTRODUCTION

One major advance in modern neuroscience is the appreciation of the extent of plasticity in the mature nervous system. Many critical functions of the nervous system depend on its mutability: its ability to process external information, to encode novel associations among events and objects in the world, and to generate adaptive behavior. Plasticity thought to underlie these functions occurs at multiple levels, from epigenetic modifications of gene expression, to neuronal activity-dependent modulation of synaptic strength, to tuning of integrated circuits that carry multimodal sensory information. Perhaps the most striking form of structural plasticity in the adult nervous system is the de novo generation and integration of new neurons into the existing circuitry through a process known as adult neurogenesis (Kempermann & Gage 1999). Originally thought to occur only during embryonic development, active adult neurogenesis has now been shown in almost all mammalian species examined so far (Lledo et al. 2006, Ming & Song 2005). Active neurogenesis occurs in two discrete regions: the subventricular zone of the lateral ventricle, from where newborn neurons migrate to the olfactory bulb or striatum (Ernst et al. 2014) and differentiate mostly into interneurons, and the dentate gyrus of the hippocampus, where newborn granule cells are integrated into the local circuitry (Ming & Song 2011) (**Figure 1*a***). Significant progress has been made in the past decade to understand the generation, development, and integration of adult-born neurons, molecular and regulatory mechanisms, and potential contributions of adult neurogenesis to brain function and dysfunction (Ming & Song 2011, Zhao et al. 2008).

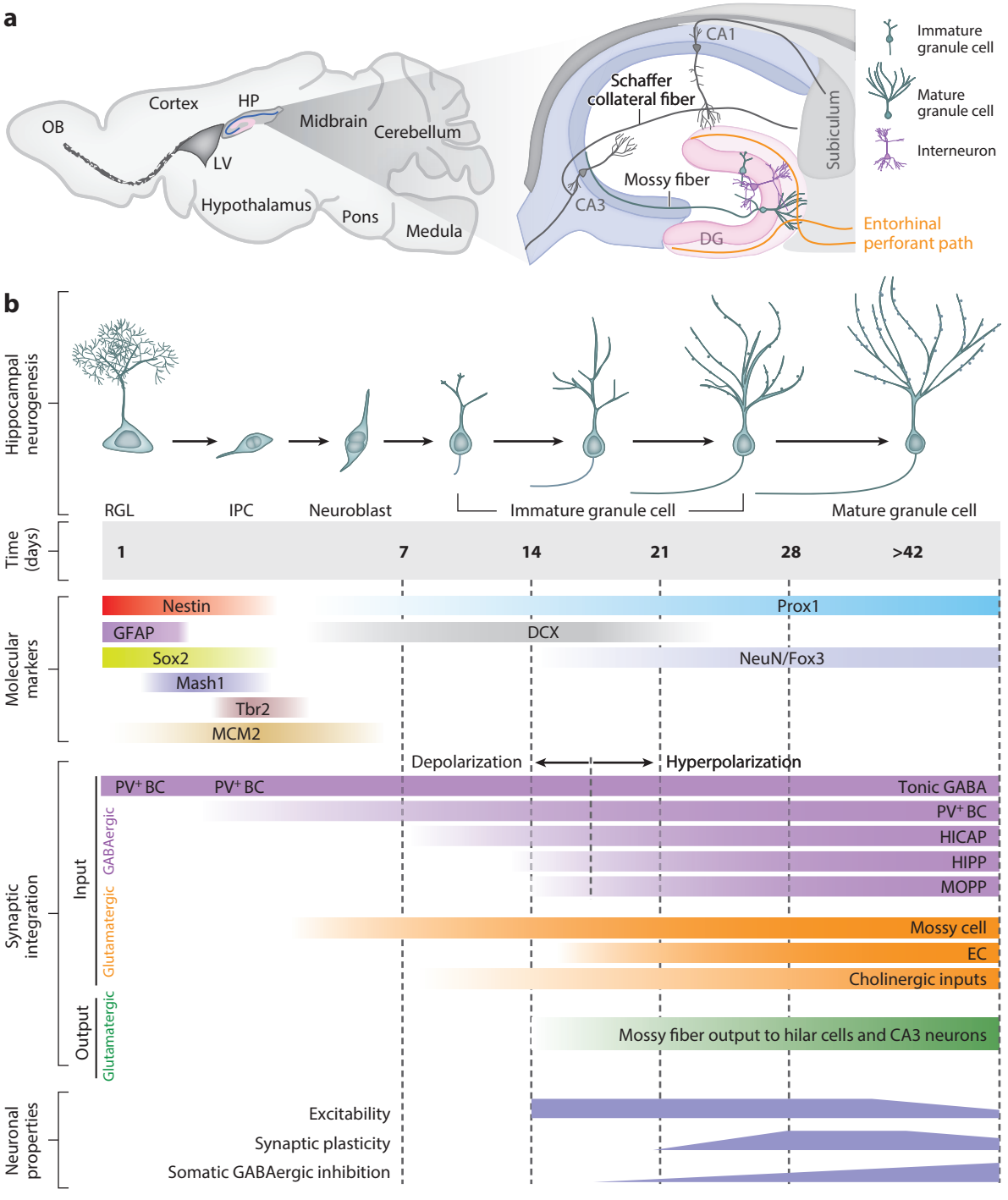
Adult hippocampal neurogenesis has garnered significant interest because of its potential to influence information processing in the medial temporal lobe, a neural substrate for many forms of learning and memory and a site of pathophysiology associated with various neurological disorders

(Squire 1992). The canonical signaling network of the hippocampus consists of synaptically connected principal neurons located in three major subregions to form the trisynaptic circuit: granule cells in the dentate gyrus and pyramidal neurons in CA1 and CA3 (**Figure 1*a***). Information flows from the entorhinal cortex through medial and lateral perforant pathways to the dentate gyrus, then to CA3 pyramidal cells via mossy fiber axons of granule cells, then to CA1 pyramidal cells via Schaffer collateral projections of CA3 neurons, and finally to the subiculum and back to the entorhinal cortex. This primary hippocampal circuit forms a closed loop wherein sensory information from specific cortical areas converges onto the entorhinal cortex, is processed through the hippocampal circuitry, and returns to the region of origin in the entorhinal cortex. In addition, there are direct projections from the entorhinal cortex to CA3 and CA1 and multiple modulatory inputs from other brain regions to the hippocampus. The dentate gyrus also contains diverse γ-aminobutyric acid (GABA)-ergic inhibitory neurons within the hilus region and the molecular layer, which mediate feedforward and feedback inhibition, and hilar glutamatergic mossy cells, which receive inputs primarily from granule cells and then innervate granule cells and local interneurons.

Within the hippocampus, dentate granule cells are the only neurons to be continuously generated. Young adult rats generate an estimated 9,000 new cells each day in the dentate gyrus, about 6% of the total granule cell population each month (Cameron & McKay 2001), whereas adult humans add 700 new neurons in each hippocampus per day, corresponding to an annual turnover of 1.75% of the renewing neuronal population (Spalding et al. 2013). The significant number of new neurons, together with dynamic regulation of adult neurogenesis by various physiological and pathological stimuli (Ma et al. 2009), suggests that adult neurogenesis may be integral to certain brain functions. Indeed, behavior analyses in animal models support a critical role for dentate newborn neurons in several hippocampus-dependent functions (Aimone et al. 2011). Electrophysiological analyses have identified special properties of immature adult-born neurons (Ge et al. 2007, Schmidt-Hieber et al. 2004, Snyder et al. 2001), providing a mechanistic basis for their unique contributions to neural processes. In addition, many studies have implicated dysfunction of adult hippocampal neurogenesis in an increasing number of brain disorders (Braun & Jessberger 2013, Ming & Song 2009, Sahay & Hen 2007, Winner et al. 2011). Focusing on adult hippocampal neurogenesis in this review, we start with a summary of the recent progress in our understanding of the adult neurogenesis processes and special properties of newborn neurons and follow with a discussion of models for how adult neurogenesis contributes to circuit regulation and behavior under normal and pathological conditions. Interested readers can consult other recent reviews on general topics of adult neural stem cells and neurogenesis (Bonaguidi et al. 2012, Gage & Temple 2013, Göritz & Frisen 2012, Kriegstein & Alvarez-Buylla 2009, Ming & Song 2011) and functions of olfactory bulb adult neurogenesis (Lepousez et al. 2013).

PROCESSES OF ADULT HIPPOCAMPAL NEUROGENESIS

Tremendous progress has been made in recent years, mostly using rodents as experimental models, in understanding the origin of newborn neurons and their development, maturation, and integration into the existing neuronal circuitry in the adult hippocampus. Genetic fate-mapping studies have demonstrated that neural precursors located within the subgranular zone, between the granule cell layer and the hilus, are the source of newborn neurons in the dentate gyrus (Dhaliwal & Lagace 2011). Clonal lineage-tracing analyses have further identified radial glia-like precursors as multipotent neural stem cells, capable of repeated self-renewal and generation of both neurons and astrocytes but not oligodendrocytes (Bonaguidi et al. 2011). During neurogenic cell



division, these neural stem cells give rise to intermediate progenitor cells, which in turn give rise to proliferating neuroblasts, postmitotic immature neurons, and finally mature dentate granule cells (**Figure 1*b***). Nonradial precursors within the subgranular zone can also give rise to newborn neurons, although their identity remains unclear (Bonaguidi et al. 2012). The majority of the newborn cells in rodents die within the first four days of their birth (Sierra et al. 2010) or within one to three weeks after birth (Tashiro et al. 2006). Ultimately, less than 25% of newborn neurons survive to become mature neurons and synaptically integrate under normal conditions. Significant efforts have been devoted to understanding how newborn neurons become integrated into existing circuits.

Synaptic Inputs

Studies using oncoretroviruses for birth-dating and labeling have shown that newborn granule cells in young adult mice develop a single primary dendrite with multiple branches that reaches the molecular layer within 7 days and exhibits rapid growth between 7 and 17 days, followed by modest growth for at least two months (Sun et al. 2013). Functional electrophysiological characterization of labeled newborn neurons in acute slices has revealed a stereotypic integration process in which GABAergic synapses precede glutamatergic synapse formation (Espósito et al. 2005, Ge et al. 2006, Overstreet-Wadiche et al. 2006b). Although radial glia-like precursors exhibit functional $GABA_A$ receptors and tonic responses to ambient GABA (Song et al. 2012), the first functional synaptic inputs appear to form onto proliferating neuroblasts within four days of birth (Song et al. 2013, Tozuka et al. 2005). Postmitotic newborn neurons continue to exhibit tonic GABA responses while their GABAergic synaptic responses mature (Espósito et al. 2005, Ge et al. 2006). Several recent studies, using paired recording (Markwardt et al. 2011), optogenetics (Song et al. 2013), and rabies virus–based retrograde transsynaptic tracing (Deshpande et al. 2013, Li et al. 2013, Vivar et al. 2012), have identified multiple interneuron subtypes that innervate newborn neurons within weeks of birth (**Figure 1*b***), including parvalbumin-expressing basket cells, somatostatin-expressing HIPP (hilar perforant path-associated) cells, HICAP cells (hilar interneuron with commissural-associational pathway-associated axon terminals), and MOPP (molecular layer perforant pathway) cells, such as neurogliaform cells/Ivy cells. The sequence of GABAergic synapse formation by various interneuron subtypes remains unknown. Notably, newborn neurons exhibit initial depolarizing responses to GABA, which gradually shift to hyperpolarizing responses within two to three weeks of birth (Ge et al. 2006, Overstreet Wadiche et al. 2005). Depolarizing GABAergic signaling promotes survival, maturation, and synapse formation and activation in newborn neurons (Chancey et al. 2013, Ge et al. 2006, Pontes et al. 2013, Song et al. 2013, Tozuka et al. 2005). Initial GABAergic synaptic inputs are not sufficient to elicit action potentials and are therefore unlikely to be directly involved in information processing. Instead, new neuron outputs

Figure 1

Summary of basic processes of neurogenesis in the young adult mouse hippocampus. (*a*) A sagittal section view of an adult rodent brain highlighting two restricted regions that exhibit active adult neurogenesis—the hippocampus (HP) and lateral ventricle (LV)—which generate new neurons that mostly migrate into the olfactory bulb. More detailed hippocampal structure is further illustrated with the primary trisynaptic circuit formed by three principal neuronal subtypes. (*b*) Summary of the developmental processes of adult hippocampal neurogenesis, including time course of marker expression, developmental stages, synaptic integration, and special neuronal properties associated with different stages. BC, basket cells; DG, dentate gyrus; EC, entorhinal cortex; HICAP, hilar interneuron with commissural-associational pathway-associated axon terminals; HIPP, hilar perforant path-associated interneurons; IPCs, intermediate progenitor cells; MOPP, molecular-layer perforant pathway cells; OB, olfactory bulb; PV^+, parvalbumin-expressing interneurons; RGL, radial glia-like cell.

are controlled by glutamatergic synaptic inputs. Electrophysiological analyses have shown that the first detectable glutamatergic synaptic responses emerge in 11–14-day-old newborn neurons, and these responses mature over the next several weeks, accompanied by increased density of dendritic spines (Chancey et al. 2014, Espósito et al. 2005, Ge et al. 2006). Recent optogenetic and rabies virus–based retrograde transsynaptic tracing suggested that glutamatergic synaptic inputs onto newborn neurons originating from mossy cells form ahead of those by perforant pathway fibers from the entorhinal cortex (**Figure 1*b***) (Chancey et al. 2014, Deshpande et al. 2013, Kumamoto et al. 2012). In addition, studies revealed inputs from cholinergic septal neurons at early stages (Deshpande et al. 2013, Vivar et al. 2012). Upon maturation, adult-born granule cells appear to exhibit general properties that are indistinguishable from developmentally born granule cells (Ge et al. 2007; Laplagne et al. 2006, 2007), although differences in some specific characteristics cannot be ruled out.

Synaptic Outputs

Newborn neurons extend a single axon from the base of the cell body that follows a stereotypic pathway through the hilus to reach CA3 within 7 days and establishes mature primary projection patterns within 21 days (Sun et al. 2013). Electron microscopic analyses of retrovirally labeled newborn neurons have shown synaptic structures associated with cells in both hilus and CA3 within 14 days and mossy fiber en passant boutons reaching morphological maturation within 8 weeks (Faulkner et al. 2008, Toni et al. 2008). Optogenetic activation of newborn neurons confirmed functional glutamatergic synaptic outputs onto hilar mossy cells and interneurons and CA3 neurons (Gu et al. 2012, Toni et al. 2007). Two- to four-week-old adult-born neurons synthesize and corelease GABA, in addition to glutamate (Cabezas et al. 2012, 2013). However, this GABA release appears to modulate presynaptic mossy fiber excitability only by activating $GABA_B$ autoreceptors and GABAergic postsynaptic responses have not been detected (Cabezas et al. 2012). In general, we know much less about properties of synaptic outputs of newborn neurons compared with their inputs, information critically needed to better understand adult neurogenesis functions. Future studies using new tools, such as optogenetics, anterograde transsynaptic tracing, and whole-mount imaging, are needed to provide a more complete picture about different targets of adult-born neurons and temporal dynamics of functional synapse formation.

A common feature of pre- and postsynaptic integration of newborn neurons is the apparent competition with mature granule cells for innervation from afferent axons and efferent connections to invade and replace preexisting synapses (Toni et al. 2007, 2008). Therefore, adult neurogenesis not only continuously adds new individual units to the dentate gyrus, but also induces structural plasticity of mature neurons, including mature granule cells and hilar mossy cells and interneurons, presynaptic terminals of entorhinal inputs, and postsynaptic sites on CA3 neurons.

Basic characterization of the adult hippocampal neurogenesis process has provided critical information on when and how newborn neurons could contribute to brain functions. For example, 14-day-old adult-born neurons already exhibit functional glutamatergic synaptic inputs and outputs and can therefore participate in neural processing during immature stages. Developmental and synaptic integration patterns of adult-born neurons are largely consistent with those described for dentate granule cells generated during development (Liu et al. 1996, Overstreet-Wadiche et al. 2006a, Zhao et al. 2006); therefore, it seems that adult-born neurons may participate in the same neuronal circuits as do preexisting ones. A fundamental question follows: How can a small population of adult-born neurons make meaningful contributions to brain functions in the presence of millions of mature neurons of the same type?

SPECIAL PROPERTIES OF ADULT-BORN DENTATE GRANULE NEURONS

One significant advance in the field came from discoveries of special properties of adult-born neurons while they were immature. These distinct cellular and circuit-level properties work together to determine their potential to make a functional contribution.

Distinct Cellular Properties

Electrophysiological analyses showed that, compared with mature neurons, immature adult-born neurons are highly excitable (Dieni et al. 2013, Mongiat et al. 2009). As a result, they are very efficient in generating action potentials, even with weak glutamatergic inputs (Marín-Burgin et al. 2012). Immature newborn neurons also exhibit a lower induction threshold and larger amplitude of associative long-term potentiation (LTP) of perforant path synaptic inputs compared with mature granule cells in acute slices under identical conditions (Ge et al. 2007, Schmidt-Hieber et al. 2004). This enhanced synaptic plasticity is partially due to a lack of strong GABAergic inhibition in immature neurons (Ge et al. 2008). Adult-born neurons exhibit such properties only during a critical period between approximately three and six weeks after birth and depend on developmentally regulated synaptic expression of NR2B-containing *N*-methyl-D-aspartate (NMDA) receptors (Ge et al. 2007). Similarly, in vivo field recordings showed that four-week-old newborn neurons exhibit enhanced LTP at mossy fiber synaptic outputs onto CA3 neurons (Gu et al. 2012). Therefore, adult-born neurons have distinct cellular properties compared with mature neurons, and the transient nature of such properties may provide a fundamental mechanism allowing adult-born neurons within this critical period to serve as major mediators of experience-induced plasticity.

Distinct Circuitry Properties

One major difference between immature and mature granule neurons is in GABAergic inputs and, in particular, a lack of strong perisomatic inhibition of immature neurons (Ge et al. 2008, Li et al. 2012, Marín-Burgin et al. 2012). As a result, four-week-old newborn neurons exhibit a lower firing threshold owing to an enhanced excitation/inhibition balance involving feedforward inhibitory circuitry. Combined with higher intrinsic excitability, weak afferent activity recruits a substantial proportion of immature neurons while activating few mature granule cells, as shown by calcium imaging in acute slices (Marin-Burgin et al. 2012). These observations suggest a model in which immature neurons with a low activation threshold and input specificity comprise a population of integrators that are broadly tuned during a finite developmental period and may encode most features of the incoming afferent information. However, mature granule cells generated during both development and adult neurogenesis, owing to their high activation thresholds and input specificity, serve as pattern separators. In this model, activity patterns entering the dentate gyrus could undergo differential encoding through immature neuronal cohorts that are highly responsive and integrative and, in parallel, through a large population of mature granule cells with sparse activity and high input specificity.

Long-distance modulatory inputs may also differentially affect immature and mature granule cells and impact information processing. Dentate granule cells are known to receive dopaminergic inputs from the ventral tegmental area (Gasbarri et al. 1997). Dopamine causes a long-lasting attenuation of medial perforant path inputs to newborn neurons through D1-like receptors and decreases their capacity to express LTP, whereas dopamine activation via D2-like receptors suppresses synaptic inputs onto mature granule cells but does not influence their LTP expression

(Mu et al. 2011). Whether other long-projection modulatory inputs differentially regulate newborn and mature granule cells remains to be determined.

These studies, mostly in vitro characterizations in acute slice preparations, have demonstrated differential properties of adult-born neurons during immature stages and provided the framework for how adult-born neurons could make unique contributions to specific brain functions. Indeed, many computational modeling and animal behavior studies support the immature neuron model of how adult neurogenesis may contribute to hippocampal functions (Deng et al. 2010). This model does not rule out potential contributions of mature adult-born neurons because these neurons are also plastic in response to neuronal activity and could be involved in different aspects of learning and memory (Lemaire et al. 2012, Ramirez-Amaya et al. 2006). One critical parameter of this model is the rate of new-neuron maturation or the duration of immature states. The entire neurodevelopmental process takes an estimated eight weeks in young adult mice (Ge et al. 2007, Zhao et al. 2006). This maturation rate is affected by numerous environmental, pathological, and pharmacological factors (Piatti et al. 2011, Zhao et al. 2006) and exhibits significant differences among species (Brus et al. 2013). Notably, neuronal maturation in the dentate gyrus of adult macaque monkeys appears to be longer than six months (Kohler et al. 2011). It is tempting to speculate that the lengthened time course for adult-born neuron maturation in nonhuman primates, and possibly in humans, may help to maintain immature neuronal properties over a longer life span.

Much remains to be learned about basic properties of adult-born neurons. One major roadblock is the lack of effective approaches to directly examine physiological properties of newborn neurons in awake behaving animals. Our current methodology is limited to immediate early gene expression as an indirect readout of neuronal activation, which has produced conflicting results on whether adult-born neurons are preferentially recruited into active networks over preexisting neurons upon specific behavioral stimulation (Ramirez-Amaya et al. 2006, Stone et al. 2011). Future studies of newborn neurons in vivo, such as targeted recording of firing properties (Leutgeb et al. 2007; Neunuebel & Knierim 2012, 2014) or calcium imaging using miniature microscopes (Ziv et al. 2013), will provide essential new information and significantly advance the field.

POTENTIAL MODES OF ADULT-BORN NEURON CONTRIBUTION TO BRAIN FUNCTIONS

Adult-born neurons could impact brain functions directly via two modes: first, as an information-processing unit and, second, as an active modulator of local circuitry to shape mature neuron firing, synchronization, and network oscillations (**Figure 2**). One hallmark of the dentate gyrus is its sparse activation as shown by both in vivo recording of putative granule cells and immediate early gene expression (Neunuebel & Knierim 2012, 2014; Ramírez-Amaya et al. 2005). Although these neurons are small in absolute number, preferential recruitment of excitable immature neurons with enhanced plasticity would allow this population to be a major player in information processing in the trisynaptic circuit.

In the second mode, newborn neurons could actively modulate local circuit activity, for example, maintaining a basal tone of excitation/inhibition or facilitating information encoding by increasing signal to noise in the region and/or by priming circuits to respond (**Figure 2**). Immature newborn neurons target hilar basket cells (Toni et al. 2008), which provide strong inhibition of a large number of mature granule cells and regulate network oscillations (Freund 2003). Indeed, in vivo recordings from the dentate gyrus in anesthetized mice have shown that elimination of adult neurogenesis leads to decreased amplitude of perforant path–evoked responses and a marked increase in both the amplitude of spontaneous γ-frequency bursts in the dentate gyrus and the

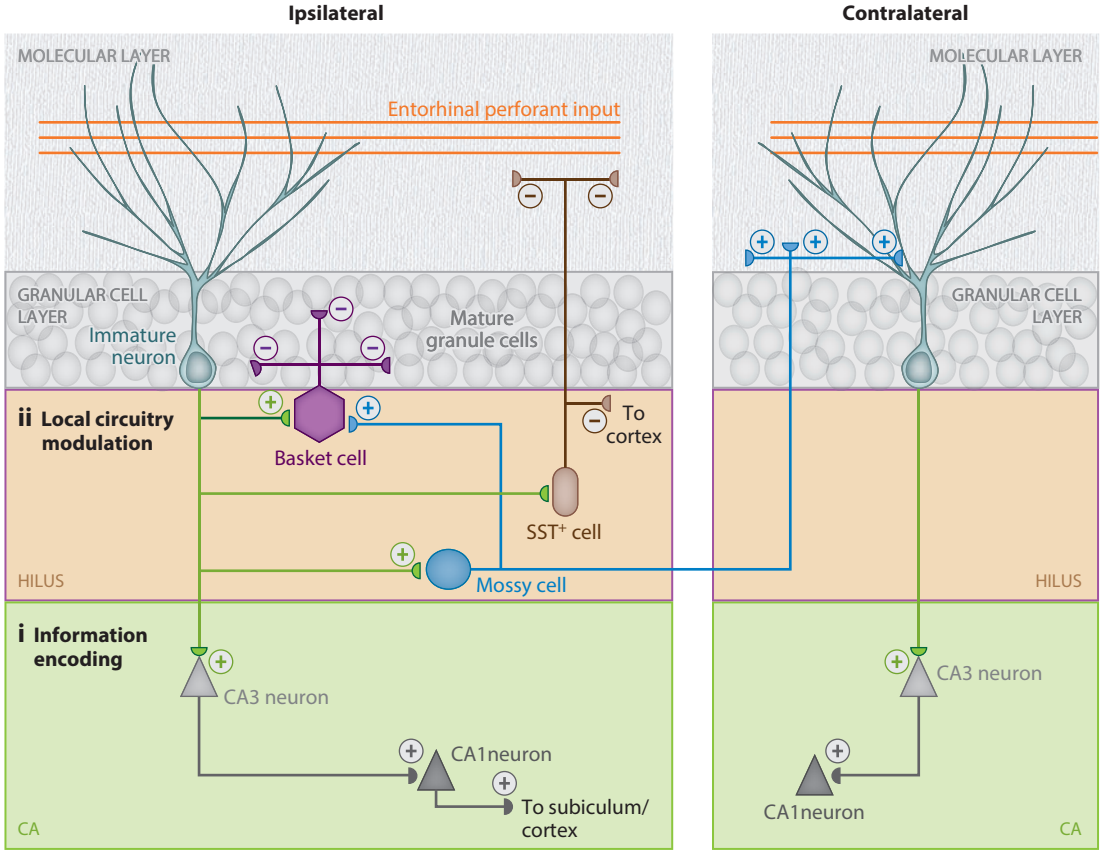


Figure 2

Circuitry properties of newborn neurons in the adult hippocampus. A schematic illustration of connectivity of newborn neurons in the adult dentate gyrus, highlighting the two modes by which newborn neurons can contribute to hippocampal functions, direct information processing via CA3 neurons (*i*, direct pathway) and modulation of local circuitry via hilar interneurons and mossy cells (*ii*, indirect pathway). SST^+ neurons, somatostatin-expressing interneurons.

synchronization of dentate neuron firing to these bursts (Lacefield et al. 2012). Immediate early gene expression analysis has also shown increased activation of dentate granule cells in response to specific learning tasks after ablation of adult neurogenesis (Burghardt et al. 2012). In addition to interneurons, newborn neurons also innervate hilar mossy cells (Toni et al. 2008), which are glutamatergic and activate local interneurons and contralateral newborn and mature granule cells. Together, a modulator mode provides an amplification mechanism that allows a small number of newborn neurons to impact the global function of the dentate gyrus across both hemispheres. In addition, hippocampal somatostatin-expressing interneurons, including those in the hilus, send distal projections and directly modulate inhibition in the entorhinal cortex (Melzer et al. 2012). This finding raises the intriguing possibility that newborn neurons shape network properties well beyond the dentate gyrus by regulating these long projection interneurons. More studies are needed to investigate potential roles of new neurons as an active modulator of proximal and distal circuitry, especially in awake behaving animals.

Adult neurogenesis could also contribute indirectly to brain functions through alternations in structure properties of the circuitry, a possibility that has been rarely tested experimentally (**Figure 2**). For example, adult neurogenesis disrupts existing synapses of mature neurons owing to competition during new-neuron synaptic integration (Toni et al. 2007, 2008). The impact of such structural plasticity of mature neurons on brain functions is not well understood. In addition, adult hippocampal neurogenesis generates astrocytes that migrate into the hilus, the granule cell layer, and the molecular layer (Bonaguidi et al. 2011, Encinas et al. 2011). Given the critical role of astrocytes in regulating various brain functions (Clarke & Barres 2013), including adult hippocampal neurogenesis (Song et al. 2002), this is a largely untapped area that warrants future exploration.

FUNCTIONS OF ADULT HIPPOCAMPAL NEUROGENESIS IN COGNITION AND MOOD REGULATION

Immediately after the initial discovery of neurogenesis in the postnatal rat hippocampus, Altman (1967) postulated that newborn neurons are critical for learning and memory. Studies have since shown that hippocampus-dependent learning and memory (Gould et al. 1999), experience, mood, behavioral states, and antidepressants dynamically regulate multiple adult hippocampal neurogenesis processes (Deng et al. 2010, Sahay & Hen 2007). The first experimental evidence in mammals of a casual role of adult neurogenesis in generation or modification of specific behaviors came from a study in which blockade of neurogenesis in the adult mouse by an antimitotic agent disrupts trace eye-blink conditioning and trace fear conditioning, but not contextual feature conditioning and spatial memory (Shors et al. 2001). Since then, the field has gradually transitioned from correlative studies with manipulations that lack specificity to more sophisticated genetic and optogenetic approaches with enhanced temporal and spatial resolution and targeted behavioral protocols. Computational modeling has also been instrumental in framing possible functions of adult hippocampal neurogenesis and its underlying mechanisms (Aimone & Gage 2011). Although the idea is still under debate, the dorsal and ventral hippocampus are likely involved in fine-tuned, spatially discrete memory processes and affective behaviors, respectively, and adult hippocampal neurogenesis has been implicated in both functions (Deng et al. 2010, Kitabatake et al. 2007, Sahay et al. 2011b).

Cognitive Functions

A central dogma regarding information processing through the trisynaptic circuit of the hippocampus has been that the dentate gyrus mediates pattern separation, the ability to distinguish similar stimuli and contexts, whereas CA3 mediates pattern completion, the reinstatement of activity patterns correlated with complete contexts and associations using only partial or degraded information. Building on Marr's description of the information-processing capacity of the hippocampus based on its structure and intrinsic connectivity, an emergent model proposed that the densely packed dentate gyrus can support the orthogonalization of inputs arriving from the entorhinal cortex (pattern separation) (Marr 1971, Treves & Rolls 1994). The dentate gyrus, in turn, directly projects to CA3, a hippocampal subregion with extensive recurrent connections and thus the putative capacity to reactivate stored patterns using partial inputs (pattern completion). The idea that the dentate gyrus could support pattern separation received empirical support following the observation that cells in the dentate gyrus region are sparsely activated and have very low firing rates. Many behavioral assays of the dentate gyrus and CA3 function have been designed to test this hypothesis, and indeed results suggest that each of these regions may play a role in

pattern separation and completion, respectively (Hunsaker & Kesner 2013). Recent evidence also supports an essential role for newborn granule neurons in mediating pattern separation, as inferred from behavioral deficits in mnemonic discrimination when adult neurogenesis is impaired (Aimone et al. 2011, Sahay et al. 2011b). For example, ablation of adult neurogenesis via irradiation impairs the ability of the mice to discriminate stimuli with little spatial separation, but not stimuli widely separated in space, in two spatial memory tasks (Clelland et al. 2009). Conversely, increasing the number of adult-born neurons by deleting the proapoptotic gene *Bax* from adult neural precursors and their progeny enhances their ability to differentiate between overlapping contextual representations (Sahay et al. 2011a). In one striking example, mice engineered to block synaptic release via tetanus toxin light-chain expression in mature dentate granule cells, but not in most immature neurons younger than four weeks, exhibit improved discrimination of very similar contexts in a fear-conditioning test, and blockade of adult neurogenesis via irradiation impairs context discrimination, suggesting a predominant role of immature neurons in mediating pattern separation (Nakashiba et al. 2012). However, these mice exhibit defects in the water-maze task and fear-conditioning tasks with partial cues presented, which suggests a critical role for mature granule cells in rapid pattern completion. One must recognize that the computational definition of pattern separation and completion implies a strict input–output relationship at the neural level that is not necessarily congruent with the use of this concept to describe behavior (Santoro 2013). It is still not clear, for example, that an animal that appears to pattern complete by behaving indistinguishably in a full-cue versus partial-cue context is doing so by using attractor dynamics in the CA3 region or by engaging mechanisms that compensate for the activation of only a subset of synapses to recruit the full complement of synapses involved in encoding (Knierim & Zhang 2012). Likewise, it is not clear that similar contexts are encoded by minimally overlapping ensembles of dentate granule cells.

Adult hippocampal neurogenesis has also been implicated in other aspects of contextual and spatial memory (Deng et al. 2010). By varying the timing between adult neurogenesis ablation and behavioral tests, studies have also pinpointed essential roles of adult-born immature neurons at various stages for these functions, especially when the task is difficult (Deng et al. 2009, Denny et al. 2012). These results corroborate findings of special cellular properties associated with immature stages and support the immature neuron model of the contribution of adult neurogenesis to brain functions. Adult neurogenesis has also been implicated in memory consolidation and the reorganization of memory traces to extrahippocampal structures, such as the prefrontal cortex (Kitamura et al. 2009). One study has shown that decreased adult hippocampal neurogenesis is accompanied by a prolonged period of hippocampus-dependent associative fear memory, whereas increased adult neurogenesis is associated with accelerated reorganization of memory traces that rely less on the hippocampus. In another interesting study, longitudinal activity data were collected on a large number of inbred mice, which shared one large enriched environment, to explore the relationship among cognitive challenges, adult hippocampal neurogenesis, and the development of individual behavioral traits. The size of the roaming area explored by an individual mouse was positively correlated with the amount of hippocampal neurogenesis (Freund et al. 2013), suggesting that one function of adult neurogenesis may be to shape the neuronal circuitry according to individual needs and improve adaptability over the life course of the individual.

There are many inconsistencies in the current literature regarding effects of various manipulations of adult neurogenesis levels on behavioral test outcomes, which have been summarized in previous reviews (Deng et al. 2010, W.R. Kim et al. 2012). Many possible factors contribute to these contradictory findings, such as differences in the genetic background, experimental manipulation, and behavioral paradigms. One major limitation of traditional approaches is the chronic nature of manipulations that affect adult neurogenesis throughout multiple phases of the learning

process; therefore, it is not always clear whether adult-born neurons contribute to encoding, consolidation, storage, and/or retrieval processes. In addition, compensatory network changes may occur following ablation of adult neurogenesis (Singer et al. 2011). Newly available tools now allow for specific manipulation of the activity of adult-born neurons at distinct stages of maturation and during specific stages of learning and recall (W.R. Kim et al. 2012). One recent study of retrovirally targeted newborn neurons in the adult mouse dentate gyrus showed that optogenetic suppression of four-week-old, but not two- or eight-week-old, newborn neurons during recall trials impairs contextual fear memory and spatial memory retrieval (Gu et al. 2012). Given the increasing availability of sophisticated genetic models to target specific populations of neural progenitor subtypes or newborn neurons at specific maturation stages, combined with optogenetic and pharmacogenetic tools to manipulate neuronal activity with spatial and temporal precision, future studies will be able to directly address questions of how and when newborn neurons contribute to neural function.

Mood Regulation

It is now well-established that stress negatively regulates progenitor proliferation and new-neuron survival (Gould et al. 1992), whereas clinical antidepressant treatments, including electroconvulsive therapy and chemical antidepressants (Malberg et al. 2000), promote proliferation of neural progenitors and maturation of newborn neurons during adult hippocampal neurogenesis (Sahay & Hen 2007, Warner-Schmidt & Duman 2006). Such effects are evolutionarily conserved from rodents to nonhuman primates (Perera et al. 2007) and potentially to humans (Boldrini et al. 2009). Ablation of adult neurogenesis does not appear to alter affective phenotypes at basal levels but abolishes some antidepressant-induced behaviors in rodents (Santarelli et al. 2003) and nonhuman primates (Perera et al. 2011). Emerging evidence suggests a critical role of adult hippocampal neurogenesis in the stress response by suppressing the hypothalamic-pituitary-adrenal (HPA) axis. In mice with adult neurogenesis ablated, mild stress leads to increased levels of stress hormones and greater stress responses in behavioral tests (Schloesser et al. 2009, Snyder et al. 2011). Furthermore, blockade of adult neurogenesis abolishes the antidepressant effect of hippocampal regulation of the HPA axis after chronic stress (Surget et al. 2011). The mechanism by which adult-born neurons regulate the HPA axis under basal conditions and upon antidepressant treatment remains to be determined. Anatomical studies have revealed that whereas the dorsal hippocampus projects primarily to cortical areas that mediate cognitive processes such as learning and memory and navigation and exploration, the ventral hippocampus projects to the limbic system, including the amygdala, the nucleus accumbens, and the hypothalamus (Fanselow & Dong 2010). Future studies are needed to address how adult-born neurons, especially those in ventral regions, influence neural pathways involved in emotional experience and affective states. It will also be interesting to test the immature neuron model of adult neurogenesis function in the context of mood regulation. Development of optogenetic and pharmacogenetic approaches to target newborn neurons at specific maturation stages in the dorsal or ventral dentate gyrus will facilitate these efforts (Kheirbek et al. 2013).

DYSFUNCTION OF ADULT HIPPOCAMPAL NEUROGENESIS IN BRAIN DISORDERS

The dentate gyrus is vulnerable to cell death; but as one of the most labile structures in the brain in terms of population dynamics, it is also subject to the consequences of dysregulated adult neurogenesis. A substantial body of literature addresses changes of adult hippocampal neurogenesis

in rodents, and limited reports in humans, in the context of various pathophysiological conditions, including aging, epilepsy, stroke, degenerative neurological disorders, and neuropsychiatric disorders (Kempermann et al. 2008, Parent 2003, Sahay & Hen 2007, Winner et al. 2011). In most cases, whether these changes represent adaptive responses to various pathophysiological conditions, or are part of the pathophysiology that contributes to the condition, is unknown. Examples in animal models now suggest that dysfunction of adult hippocampal neurogenesis may play a causal role in brain disorders. There are two modes by which dysregulated adult hippocampal neurogenesis can contribute to dysfunction of the hippocampus: a loss-of-function mode due to decreased new-neuron production and integration, and a gain-of-function mode due to aberrant development and integration of new neurons.

Dysfunction via Loss-of-Function

Fragile X syndrome, the most common form of inherited intellectual disability, is caused by the functional loss of fragile X mental retardation protein (FMRP). *Fmrp* null mice exhibit deficits in some forms of hippocampus-dependent learning, accompanied by reduced adult hippocampal neurogenesis due to impaired neuronal differentiation and survival (Luo et al. 2010). Deletion of *Fmrp* specifically in adult neural progenitor cells using *nestin-CreER^{T2}* mice recapitulates defects in both adult neurogenesis and hippocampus-dependent learning, and furthermore, restoration of *Fmrp* expression in adult neural progenitors alone is sufficient to rescue learning deficits in *Fmrp* null mice (Guo et al. 2011). These striking results suggest a causal role of adult neurogenesis dysfunction in learning impairments associated with fragile X syndrome, at least in animal models. Whether this is generalizable to other disorders remains to be seen.

One major regulator of adult hippocampal neurogenesis is aging. Over the subject's lifetime, the rate of adult neurogenesis decreases dramatically, from rodents to primates, which may contribute to the dysfunction of hippocampus (Ming & Song 2011). The rate of decline of adult neurogenesis during aging is much more robust in rodents (about tenfold) than in humans (about fourfold) (Spalding et al. 2013).

Dysfunction via Gain-of-Function

Dentate granule cells may play a central role in the pathogenesis of temporal lobe epilepsy, one of the most common human seizure-related disorders (Houser 1992). In animal models of epilepsy, pilocarpine-induced status epilepticus leads to a dramatic and prolonged increase in dentate neural progenitor proliferation (Parent et al. 1997). However, many of these newborn neurons integrate aberrantly, displaying hilar basal dendrites with spines, ectopic hilar localization of the cell body, and mossy fiber sprouting (Jessberger et al. 2007, Kron et al. 2010), similar to what has been observed in postmortem dentate gyri of patients with temporal lobe epilepsy (Houser 1992). Eliminating cohorts of newborn neurons decreases status epilepticus–induced mossy fiber sprouting and ectopic granule cells (Kron et al. 2010) and attenuates spontaneous recurrent seizures in mice (Jung et al. 2004). Separately, deletion of PTEN (phosphatase and tensin homolog deleted on chromosome ten) in a small percentage of dentate granule cells born postnatally is sufficient to cause spontaneous seizure within four weeks, accompanied by aberrant granule cell morphology seen in epilepsy (Pun et al. 2012). Collectively, these studies provide strong evidence that dysfunction of adult hippocampal neurogenesis plays a causal role in epileptogenesis.

In another gain-of-function example, retrovirus-mediated knockdown of *Disrupted in Schizophrenia I* (*DISC1*), a risk gene for major mental illness (Thomson et al. 2013), leads to aberrant integration of newborn dentate granule neurons in the adult mouse hippocampus, including

ectopic location of the cell body to the outer granule cell layer and molecular layer, aberrant axonal targeting beyond CA3, hyperexcitability, and aberrant formation of synaptic inputs and outputs, due in part to hyperactivation of the mTOR pathway in newborn neurons (Duan et al. 2007; Faulkner et al. 2008; J.Y. Kim et al. 2009, 2012). Dysregulated adult hippocampal neurogenesis following DISC1 knockdown in one cohort of newborn neurons is sufficient to cause several behavioral phenotypes, including pronounced learning and memory deficits (in the object-place recognition task and the spatial version of the Morris water maze), as well as clear anxiety and depression-like phenotypes (in the forced-swim test and elevated plus maze) (Zhou et al. 2013). Inactivation of these aberrant neurons reverses specific behavioral phenotypes, indicating a causal role of adult neurogenesis dysfunction in behavioral impairments.

Notably, the impact of adult neurogenesis dysfunction due to gain-of-function on animal behavior is generally more pronounced than that seen in loss-of-function conditions. This finding may not be surprising because the complete absence or removal of a system may trigger the recruitment of alternative pathways to compensate (Singer et al. 2011), whereas miswiring of newborn neurons can be more detrimental, especially given their high excitability and unique properties. These findings have significant implications for future cell-replacement therapy in which correct wiring of transplanted neurons could be essential for functional benefits and for avoiding potential side effects.

CONCLUSION

In the past decade we have witnessed rapid advances in the adult neurogenesis field, with significant progress in (*a*) the characterization of this phenomenon in different species, including humans; (*b*) the delineation of neurogenic processes and properties of adult-born neurons; (*c*) exploration of its function at circuitry and behavioral levels; and (*d*) an appreciation of how dysfunction of adult neurogenesis may contribute to brain disorders. Despite these tremendous findings, understanding the function of adult hippocampal neurogenesis remains a central goal in the field. Perhaps one of the most frequently asked questions is why it occurs in the dentate gyrus. The dentate gyrus is one of the two regions with continuous neurogenesis from rodents to humans. Fully addressing these questions will require a multidisciplinary approach and new technologies. First, we need to know more about basic properties of the dentate gyrus and how it processes information and contributes to hippocampal functions, which will provide the framework to delineate the contribution of adult neurogenesis. Second, we need to have a better knowledge of the dentate circuitry, especially synaptic outputs of newborn neurons. Third, recordings of newborn neurons at different maturation stages in awake behaving animals will provide critical information to test current models of how adult-born neurons contribute to brain functions and dysfunctions. Fourth, the field needs to address contradictory results from behavioral analyses using newly available tools with better cell-type specificity and higher temporal and spatial resolution. Fifth, we need to consider how other plasticity associated with adult neurogenesis also contributes to brain functions, such as the generation of new astrocytes and induced structural changes in mature neurons. Sixth, comparative studies of two primary neurogenic regions in different species have proven highly informative, and ultimately, we want to understand the function of adult neurogenesis in humans.

It was originally proposed that adult neurogenesis is not a cell-replacement mechanism in which dying individual neurons are functionally replaced by new neurons, but instead continuously provides new cohorts of immature neurons with properties and information-processing capacities that are distinct from those of existing mature neurons (Ge et al. 2007). This immature neuron model of the adult neurogenesis contribution to brain function has gained significant support over the past few years from additional comparisons of immature and mature neurons, computational

modeling, and animal behavioral analyses. Building on this model is the plastic dentate gyrus hypothesis: Adult neurogenesis represents a continuous developmental process that maintains a highly plastic dentate circuitry, collectively with the addition of immature neurons with unique properties and new astrocytes and with the continued structural plasticity of associated mature neurons in broader brain regions. The heterogeneous nature of the dentate gyrus, with a small immature neuronal cohort that is highly plastic and excitable and with a large population of mature granule cells that is sparsely activated with high input specificity, offers unique information-processing power that can adapt to dynamic needs over the lifetime.

Understanding the physiological function of adult neurogenesis not only provides a new prospective on the plasticity of the mature nervous system, but also has significant implications for our understanding of several brain disorders and regenerative medicine. Recent evidence supports a critical contribution of dysfunctional postnatal neurogenesis, via both loss-of-function and gain-of-function modes, to developmental disorders and may be a crucial mechanism that initiates the onset of disorders such as autism and schizophrenia (Ming & Song 2009). Recent animal model studies have suggested that treating molecular deficits underlying neurodevelopmental disorders could result in significant amelioration of associated behavioral phenotypes, even when treatments were initiated in adults (Ehninger et al. 2008). Therefore, targeting adult neurogenesis could be a novel potential therapeutic strategy for these disorders. Basic principles learned from normal and dysregulated adult neuronal development and synaptic integration of newborn neurons will also provide invaluable information for the future development of cell-replacement therapy.

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Annual Review of Neuroscience

Volume 37, 2014

Contents

Embodied Cognition and Mirror Neurons: A Critical Assessment
Alfonso Caramazza, Stefano Anzellotti, Lukas Strnad, and Angelika Lingnau 1

Translational Control in Synaptic Plasticity and Cognitive Dysfunction
Shelly A. Buffington, Wei Huang, and Mauro Costa-Mattioli 17

The Perirhinal Cortex
Wendy A. Suzuki and Yuji Naya 39

Autophagy and Its Normal and Pathogenic States in the Brain
Ai Yamamoto and Zhenyu Yue 55

Apolipoprotein E in Alzheimer's Disease: An Update
Jin-Tai Yu, Lan Tan, and John Hardy 79

Function and Dysfunction of Hypocretin/Orexin: An Energetics Point of View
Xiao-Bing Gao and Tamas Horvath 101

Reassessing Models of Basal Ganglia Function and Dysfunction
Alexandra B. Nelson and Anatol C. Kreitzer 117

A Mitocentric View of Parkinson's Disease
Nele A. Haelterman, Wan Hee Yoon, Hector Sandoval, Manish Jaiswal, Joshua M. Shulman, and Hugo J. Bellen 137

Coupling Mechanism and Significance of the BOLD Signal: A Status Report
Elizabeth M.C. Hillman 161

Cortical Control of Whisker Movement
Carl C.H. Petersen 183

Neural Coding of Uncertainty and Probability
Wei Ji Ma and Mehrdad Jazayeri 205

Neural Tube Defects
Nicholas D.E. Greene and Andrew J. Copp 221

Functions and Dysfunctions of Adult Hippocampal Neurogenesis
Kimberly M. Christian, Hongjun Song, and Guo-li Ming 243

Emotion and Decision Making: Multiple Modulatory Neural Circuits
Elizabeth A. Phelps, Karolina M. Lempert, and Peter Sokol-Hessner 263

Basal Ganglia Circuits for Reward Value–Guided Behavior
Okihide Hikosaka, Hyoung F. Kim, Masaharu Yasuda, and Shinya Yamamoto 289

Motion-Detecting Circuits in Flies: Coming into View
Marion Silies, Daryl M. Gohl, and Thomas R. Clandinin 307

Neuromodulation of Circuits with Variable Parameters: Single Neurons and Small Circuits Reveal Principles of State-Dependent and Robust Neuromodulation
Eve Marder, Timothy O'Leary, and Sonal Shruti 329

The Neurobiology of Language Beyond Single Words
Peter Hagoort and Peter Indefrey 347

Coding and Transformations in the Olfactory System
Naoshige Uchida, Cindy Poo, and Rafi Haddad 363

Chemogenetic Tools to Interrogate Brain Functions
Scott M. Sternson and Bryan L. Roth 387

Meta-Analysis in Human Neuroimaging: Computational Modeling of Large-Scale Databases
Peter T. Fox, Jack L. Lancaster, Angela R. Laird, and Simon B. Eickhoff 409

Decoding Neural Representational Spaces Using Multivariate Pattern Analysis
James V. Haxby, Andrew C. Connolly, and J. Swaroop Guntupalli 435

Measuring Consciousness in Severely Damaged Brains
Olivia Gosseries, Haibo Di, Steven Laureys, and Mélanie Boly 457

Generating Human Neurons In Vitro and Using Them to Understand Neuropsychiatric Disease
Sergiu P. Paşca, Georgia Panagiotakos, and Ricardo E. Dolmetsch 479

Neuropeptidergic Control of Sleep and Wakefulness
Constance Richter, Ian G. Woods, and Alexander F. Schier 503

Indexes

Cumulative Index of Contributing Authors, Volumes 28–37 533

Cumulative Index of Article Titles, Volumes 28–37 537

Errata

An online log of corrections to *Annual Review of Neuroscience* articles may be found at http://www.annualreviews.org/errata/neuro