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Functional Differentiation of Adult-Born Neurons along the Septotemporal Axis of the Dentate Gyrus

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Over the past several decades, the proliferation and integration of adult-born neurons into existing hippocampal circuitry has been implicated in a wide range of behaviors, including novelty recognition, pattern separation, spatial learning, anxiety behaviors, and antidepressant response. In this review, we suggest that the diversity in behavioral requirements for new neurons may be partly caused by separate functional roles of individual neurogenic niches. Growing evidence shows that the hippocampal formation can be compartmentalized not only along the classic trisynaptic circuit, but also along a longitudinal septotemporal axis. We suggest that subpopulations of hippocampal adult-born neurons may be specialized for distinct mnemonic- or mood-related behavioral tasks. We will examine the literature supporting a functional and anatomical dissociation of the hippocampus along the longitudinal axis and discuss techniques to functionally dissect the roles of adult-born hippocampal neurons in these distinct subregions.

Since the presence of dividing cells in the mostly postmitotic adult brain was first described (Altman and Das 1965), the generation of new neurons in adulthood has been proposed to be involved in a variety of behaviors (Doetsch and Hen 2005; Becker and Wojtowicz 2007; Sahay and Hen 2007; Deng et al. 2010; Ming and Song 2011; Miller and Hen 2014). Adult neurogenesis in the healthy mammalian brain is consistently seen in the subventricular zone (SVZ) of the lateral ventricles and the subgranular zone (SGZ) of the hippocampal dentate gyrus

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(DG). Recent studies have implicated hippocampal neurogenesis in learning- and memory-related tasks, such as contextual discrimination and spatial navigation and, specifically, in behavioral pattern separation (Clelland et al. 2009; Sahay et al. 2011; Nakashiba et al. 2012; Niibori et al. 2012; see also reviews in Deng et al. 2010; Ming and Song 2011; Marin-Burgin and Schinder 2012), but also in some behavioral effects of antidepressants (Santarelli et al. 2003; see also reviews in Sahay and Hen 2007; Kheirbek et al. 2012; Tanti and Belzung 2013). However, the exact role of adult hippocampal neurogenesis in some of these behaviors has been debated as some studies have shown no effects of altering adult neurogenesis on spatial navigation or antidepressant response. Proposed explanations have included differences in the behavioral tasks used to measure cognition or emotion, motivational state of subjects, species differences, or in how neurogenesis is defined, either as proliferation, survival, or differentiation (see reviews in Zhao et al. 2008; Aimone et al. 2011; Petrik et al. 2012b; Miller and Hen 2014).

It must also be noted, however, that these hippocampal neurons are not born into a singular structure. Work in the past several decades has shown that the hippocampus can be divided, not only along the classic trisynaptic loop, but also longitudinally along a septotemporal axis. The septal (dorsal in rodents; posterior in primates) and temporal (ventral in rodents; anterior in primates) poles, as well as potential intermediate zones of the hippocampus, have different anatomic connections and electrophysiological properties, express a gradient of molecular markers, and play different functional roles, such as performance in spatial learning tasks and stress responses (see reviews in Moser and Moser 1998; Fanselow and Dong 2010). Consequently, adult-born neurons in the hippocampal DG may also be segregated along this longitudinal axis, and conflicting functional roles for neurogenesis may be a result of attempting to examine hippocampal neurogenesis as a unitary phenomenon. It is possible that there are intrinsic, cell-autonomous differences in adult-born neurons generated at opposite poles of the DG. An alternative, although not mutually exclusive, hypothesis is that progenitor cells are initially identical, but differentiate in a dissimilar manner as a result of integration into distinct network circuitry. We will, therefore, first discuss heterogeneity of the hippocampus along its longitudinal axis before reviewing differences in neurogenesis between the septal and temporal poles of the DG. As these topics have been reviewed extensively elsewhere (Moser and Moser 1998; Deng et al. 2010; Fanselow and Dong 2010; Koehl and Abrous 2011; Samuels and Hen 2011; Kheirbek et al. 2012; Petrik et al. 2012b), we will not try to exhaustively cover all the current literature. Rather, we attempt to gather key studies examining a septotemporal gradient of the hippocampus and hippocampal neurogenesis. We will then suggest possible approaches to examine neurogenesis in specific subregions of the hippocampal DG. Finally, a short section will examine segregation of the DG along its transverse axis.

SEPTOTEMPORAL HETEROGENEITY OF THE HIPPOCAMPUS

Anatomic Connections

Although the trisynaptic organization of the hippocampal formation is preserved through the rostrocaudal extent of the brain, the temporal and septal poles of the hippocampus receive afferents from and send efferents to distinct neural nuclei (Fig. 1A) (Witter et al. 1989). Retrograde tracers injected in the septal third of DG reveal afferent connections from the superficial and deep layers of the dorsolateral and caudomedial subdivisions of the entorhinal cortex (EC) (Dolorfo and Amaral 1998). These caudal subnuclei of the EC, in turn, receive projections from the postrhinal and caudal perirhinal cortices (Burwell and Amaral 1998), which are themselves innervated by midline and lateral thalamic nuclei and parietal, somatosensory, and occipital cortices (Deacon et al. 1983; Burwell and Amaral 1998). Efferent projections from the septal hippocampus consist largely of recurrent connections to the EC (Dolorfo and Amaral 1998), as well as projections to the

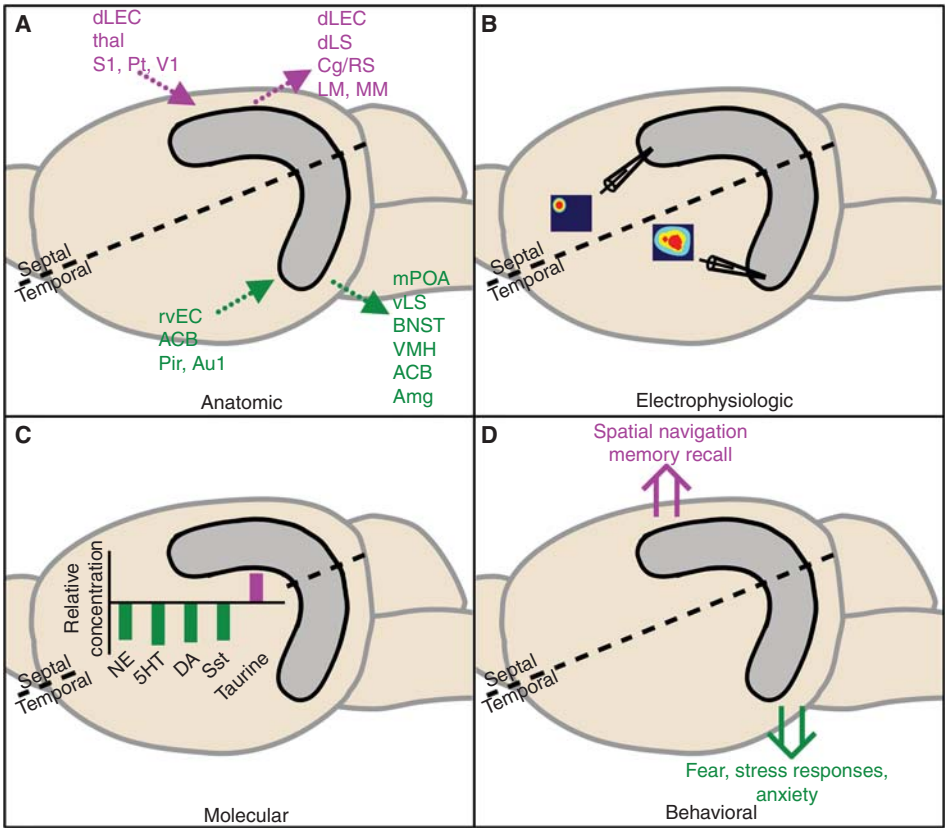

Figure 1. Segregation of the hippocampus along the septotemporal axis. Septal (purple) and temporal (green) subregions of the hippocampus can be dissociated anatomically, electrophysiologically, molecularly, and behaviorally. (*A*) Dotted arrows represent anatomic efferents and afferents. ACB, Nucleus accumbens; Amg, amygdala; Au1, auditory cortex; BNST, bed nucleus of the stria terminalis; Cg/RS, cingulate/retrosplenial cortex; dLEC, dorsolateral entorhinal cortex; dLS, dorsolateral septum; LM, lateral mammillary nucleus; MM, medial mammillary nucleus; mPOA, medial preoptic area; Pir, piriform cortex; Pt, parietal cortex; rvEC, rostroventral entorhinal cortex; S1, somatosensory cortex; thal, thalamus; V1, visual cortex; vLS, ventro lateral septum; VMH, ventromedial hypothalamus. (*B*) Representative spatial place cell firing maps are shown in cartoon form, demonstrating a sharper receptive field in the septal and lower spatial resolution in the temporal hippocampus. (*C*) Relative levels of norepinephrine (NE), serotonin (5HT), γ-aminobutyric acid (GABA), glutamate (Glu), dopamine (DA), and somatostatin (Sst) are higher in the temporal hippocampus, whereas taurine is expressed at a higher level in the septal hippocampus. (*D*) Double arrows depict putative dissociations in behavioral functions along the longitudinal axis.

dorsolateral septum, retrosplenial area of the cingulate, and, via the fimbria and fornix, the mammillary complex (Swanson and Cowan 1977; Cenquizca and Swanson 2007).

The temporal third of the DG receives afferents from the rostroventral EC (Dolorfo and Amaral 1998), which is innervated subcortically by the amygdaloid complex and nucleus accumbens (Vaudano et al. 1991; Burwell and Amaral 1998). Cortical afferents to the rostroventral EC include the auditory association and piriform cortices (Burwell and Amaral 1998). Projections from the temporal hippocampus, again, include recurrent connections to afferent regions, but also connections to the lateral and medial preoptic area, ventrolateral septum, bed nucleus of the stria terminalis, ventromedial nucleus of the hypothalamus, amygdala, and nu-

cleus accumbens shell (Swanson and Cowan 1977; Pitkanen et al. 2000; Cenquizca and Swanson 2006). This divergence in physical connections suggests that the septal and temporal hippocampus likely participate in separate cognitive and emotional circuits, respectively. It must also be noted, however, that mossy cells do send projections across the longitudinal axis, which possibly provides for communication between the septal and temporal hippocampus (Amaral and Witter 1989; Buckmaster et al. 1996; Blasco-Ibanez and Freund 1997), suggesting that the two regions may not exist in absolute isolation.

Electrophysiological Properties

In addition to differences in anatomical projections, cells along the longitudinal axis of the hippocampus have distinct electrophysiological properties. Mean amplitude of evoked potentials is higher in slices taken from the temporal pole of the hippocampus at baseline conditions (Gilbert et al. 1985; Maggio and Segal 2007). At higher K^+ concentrations, epileptiform bursting was induced in all slices, but there was a higher likelihood of burst firing in temporal slices as compared with septal ones (Gilbert et al. 1985; Bragdon et al. 1986). In contrast, the threshold for long-term potentiation (LTP) induction appears to be lower in slices taken from the septal pole of CA1 (Elul 1964). LTP induction is also both larger and longer lasting in septal slices (Maggio and Segal 2007). Additionally, hilar mossy cells in the septal hippocampus have more spontaneous excitatory postsynaptic potentials (EPSPs) with higher maximum amplitude, but lower intrinsic rhythmic bursting than those in the temporal hippocampus (Jinno et al. 2003).

Firing of hippocampal place cells in response to spatial environments also appears to shift along the septotemporal axis (Fig. 1B). When rats were tested along a large linear track, place cell representation changed from a receptive field of <1 m at the septal hippocampal pole to >10 m in the temporal CA3 (Kjelstrup et al. 2008). Spatial resolution of temporal place cells also appears to be lower when animals are placed in a square arena representation, and the total number of complex spike cells that had place fields dropped from 45% in the septal to 18% in the temporal hippocampus (Jung et al. 1994). This change in receptive field seems to parallel an overall shift away from representation of spatial information along the septotemporal axis. Buzsaki and colleagues showed that when rats were placed in either radial arm or zigzag mazes, place cells at the temporal pole of the hippocampus fire in response to reward or goal representations rather than geographical locations (Royer et al. 2010), suggesting that, in addition to spatial representations, cells in the temporal hippocampus may also host nonspatial functions. Cells in the temporal CA3 also appear to be less synchronized as recordings of local field potentials revealed reduced θ modulation, as well as an overall reduced rhythmicity in this region, further supporting a decline in spatial representation in the temporal region of the hippocampus.

Molecular Markers

One explanation for these differences in firing patterns could be a gradient of cell types in the hippocampus. Kosaka and colleagues examined inhibitory and excitatory cells along the septotemporal axis of the hippocampus in mice. Staining for GAD67 immunoreactivity revealed a higher numerical density and cell size of inhibitory neurons in the temporal third of the hippocampus compared with the septal third. When separated by laminar subdivision, this septotemporal difference persists in both CA3 and DG, but not CA1 (Jinno et al. 1998). The number of γ-aminobutyric acid (GABA)ergic interneurons immunoreactive for somatostatin, cholecystokinin, and vasoactive intestinal polypeptide was also higher in the temporal hippocampus (Jinno and Kosaka 2003). Conversely, numerical densities of granule and pyramidal cells expressing GluR2/3 are higher in the septal third of the DG, CA1, and whole hippocampus compared with the temporal third (Jinno and Kosaka 2010). Consequently, examination of GABAergic and glutamatergic neurons in 300-μm-thick hippocampal slices revealed at least a

twofold increase in the ratio of inhibitory to excitatory neurons in temporal compared with septal slices. This increased excitatory tone may explain why more cells are active in the septal DG in baseline conditions (Snyder et al. 2009) and may provide for differential network circuitry surrounding adult-born hippocampal cells.

Modulatory neurotransmitters are also distributed along a longitudinal gradient (Fig. 1C). Gage and colleagues showed higher concentrations of norepinephrine (NE) and serotonin (5-HT) in the temporal half of the rat hippocampus (Gage et al. 1978), along with a corresponding increase in the distribution of NE and 5-HT nerve terminals (Gage and Thompson 1980). This analysis has also been extended to multiple classes of neurotransmitters (Hortnagl et al. 1991). Temporally enriched markers included concentrations of GABA, glutamate, dopamine, noradrenaline and its metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG), serotonin and its metabolite 5-hydroxyindoleacetic acid (HIAA), levels of somatostatin, and enzymatic activity of choline acetyltransferase, acetylcholinesterase, and glutamate decarboxylase. Levels of neuropeptide Y and concentrations of glycine and aspartate were equally distributed across the septotemporal axis. Only concentrations of the amino acid taurine were higher in the septal hippocampus (Hortnagl et al. 1991). The investigators suggest that these results may indicate a denser innervation of the temporal hippocampus raising the possibility that systemic neurotransmitter administration may preferentially alter signaling in the temporal hippocampus. Consistent with this hypothesis, multiple serotonin receptor subtypes (including Htr7, Htr2c, Htr2a, and Htr1a) are preferentially expressed in the temporal, compared with septal, CA3 (Htr1a is preferentially expressed in the temporal DG, but also in the septal CA1) (Tanaka et al. 2012), in which increased serotonin release has been shown following retrieval of fear memory (Ohmura et al. 2010) or forced swim-induced stress (Yoshitake et al. 2004).

This apparent neurochemical demarcation of hippocampal subregions also suggests that genetic markers may be useful in defining molecular boundaries between the septal and temporal hippocampus. Recent studies have begun to use microarray technology to identify gene expression patterns specific to septal or temporal CA1 (Leonardo et al. 2006; Dong et al. 2009), CA3 (Thompson et al. 2008), and DG (Christensen et al. 2010; Fanselow and Dong 2010). A sample list of candidate genes includes: wolframin, Eph receptor A7 (septal CA1), titin, flavin-containing monooxygenase 1, protein kinase C delta (septal CA3), adipocyte-specific adhesion molecule, histidine decarboxylase, cocaine, and amphetamine-regulated transcript (septal DG), decorin, neuronatin, synaptotagmin XVII, serotonin receptor 2C, gastrin-releasing peptide (temporal CA1), Rab3b, tissue inhibitor of metalloproteinase 2, and somatostatin receptor 1 (temporal DG). Further characterization of molecular markers needs to be performed, however, especially if these markers are to be used to functionally target-specific subpopulations of the hippocampus and neurogenic niches.

Behavioral Roles

Functional segregation of the hippocampus as a whole has been studied with double dissociated lesioning strategies in the rat (see reviews in Moser and Moser 1998; Fanselow and Dong 2010). Excitotoxic lesions of either the complete or septal half of the hippocampus result in decreased performance on the T-maze nonmatch to position task, as well as the Morris water maze (Bannerman et al. 2002; Kjelstrup et al. 2002). Behavioral performance in these tasks was spared in animals with temporal lesions. In contrast, temporal, but not septal, hippocampal lesions result in deficits in predator-induced freezing (Phillips and LeDoux 1992), cued fear conditioning (Maren and Holt 2004), and novelty-induced hyponeophagia (Bannerman et al. 2002). Effects of partial lesions on elevated plus maze performance has been equivocal, with some groups showing decreased measures of anxiety only in temporally lesioned animals (Kjelstrup et al. 2002; Trent and Menard 2010), and others demonstrating

deficits resulting from both temporal and septal lesions (Bannerman et al. 2002). Regardless, when taken together, these functional results again complement anatomical and cellular divisions of the hippocampus along its longitudinal axis, suggesting a role for the septal hippocampus in cognitive tasks and the temporal hippocampus in mood- and anxiety-related behaviors (Fig. 1D). Accordingly, behavior in conditioned place preference tasks is impaired in animals with septal hippocampal lesions, but improved in temporally lesioned animals (Ferbinteanu and McDonald 2001). Recent work using optogenetic strategies has, in fact, shown a double dissociation in DG function following acute activation of granule cells. Stimulation of dentate granule cells in the septal hippocampus specifically suppresses contextual encoding and retrieval, likely because of altered activity in downstream dorsal CA3. Conversely, activation of temporal, but not septal, dentate granule cells results in suppression of innate anxiety without altering contextual learning or memory behavior (Kheirbek et al. 2013).

Septotemporal dissociation of the hippocampus has also been examined in humans using functional imaging of hippocampal volumes, with more complex results. Septal hippocampal volume appears to be associated with spatial memory as London taxi drivers, who have an extensive spatial map of the city, have significantly increased gray matter in the septal hippocampus compared with London bus drivers (Maguire et al. 2006). This increase in posterior hippocampal volume, at the expense of the anterior hippocampus, correlates with years of taxi driving and consequent integration of the mental spatial map. Increased volume of the septal hippocampus is also associated with increased recollection memory ability in young adults (Poppenk and Moscovitch 2011). Patients suffering from posttraumatic stress disorder have reduced septal hippocampal volume (Bonne et al. 2008), which the investigators suggest may correlate with maladaptive memory associations commonly observed in the disorder. However, the volume of the septal hippocampus was also seen to be positively associated with degree of psychopathy (Laakso et al. 2001), suggesting that this region may also be implicated in emotional processing. Conversely, the temporal hippocampus appears to be implicated in stress- and mood-related changes as self-reported stress levels and presentation of schizophrenic episodes were both associated with decreased temporal hippocampal volumes (Szeszko et al. 2003, 2006). Older chronic alcoholics also appear to have decreased temporal, but not septal, hippocampal volume (Sullivan et al. 1995), whereas increased exercise correlates with an increase solely in temporal hippocampal volume in older healthy subjects (Erickson et al. 2011). Daily exercise also appeared to correlate with an increase in spatial memory in healthy subjects. Additionally, performance on both contextual (Rajah et al. 2010) and verbal (Hackert et al. 2002) memory tasks has been associated with temporal hippocampus volume. Activation of the temporal hippocampus has also been observed in contextual fear-conditioning tasks (Alvarez et al. 2008). Other studies have suggested that both the temporal and septal regions of the hippocampus are implicated in memory tasks, but that the septal hippocampus is associated with familiarity and the retrieval of information, whereas the temporal hippocampus is preferentially involved in novelty and the encoding of information (Lepage et al. 1998; Strange et al. 1999). Taken together, this suggests multiple degrees of functional specialization along the septotemporal axis of the hippocampus that may be more complex in humans than in rodents.

SEPTOTEMPORAL SEGREGATION OF HIPPOCAMPAL NEUROGENESIS

As adult-born neurons in the SGZ mature, they migrate along a transverse axis from the hilar border of the granule cell layer (GCL) toward the molecular layer (Kempermann et al. 2003; Li et al. 2009), but appear to stay in the same longitudinal plane. Given the evidence demonstrating a dissociation of the septal and temporal hippocampal poles, it is therefore likely that new neurons may also be similarly segregated along the longitudinal axis of the hippocampus depending on the environment into which they integrate.

Baseline and Manipulated Levels of Neurogenesis

Studies in multiple rodent species have revealed differences in baseline neurogenesis along the longitudinal axis of the DG. More cells were labeled with 5-bromo-2′-deoxyuridine (BrdU), a marker of DNA synthesis, in the septal DG one (Dawirs et al. 1998) and two (Ferland et al. 2002) weeks following BrdU administration in the gerbil and mouse, respectively. This may be a result of increased survival of newborn cells rather than changes in proliferation as there is no difference in expression of proliferation cell nuclear antigen (PCNA), an endogenous marker of proliferation (Jinno 2011). Rather, the number of cells expressing doublecortin (DCX), a marker of immature neurons, is higher in the septal DG compared with the temporal. Studies in the rat, however, have been more equivocal. Examination of proliferating cells has revealed either no difference (Banasr et al. 2006; Olariu et al. 2007; Felice et al. 2012), more labeled cells in the temporal DG (Silva et al. 2006), or increased proliferation in the septal DG (Snyder et al. 2009). In contrast to mice, survival of new neurons in rats appears to be equivalent across the septotemporal axis (Banasr et al. 2006; Felice et al. 2012; Snyder et al. 2012). It is possible that these discrepancies are caused by species variation, as baseline neurogenesis has previously been shown to depend on mouse strain (Kempermann et al. 1997). An additional caveat is a lack of standardized boundaries of septal and temporal subdivisions of the DG. Bisection of the DG was performed relative to the third ventricle (Silva et al. 2006), thalamus (Ferland et al. 2002), interaural line (Banasr et al. 2006), or a combination of landmarks (Snyder et al. 2012). Using molecular markers to define septotemporal boundaries may be one way to resolve these differences.

Levels of neurogenesis along the longitudinal axis of the DG can also be differentially manipulated. Although cell proliferation was increased in both the septal and temporal DG of Balb/C mice following 6 wk of environmental enrichment, the number of new neurons was significantly higher only in the septal hippocampus (Tanti et al. 2012). Conversely, chronic environmental stress or chronic administration of the stress hormone corticosterone appears to preferentially decrease proliferation and neurogenesis in the temporal, but not the septal DG (Jayatissa et al. 2006; Brummelte and Galea 2010; Tanti et al. 2012), although some groups have reported impaired neurogenesis in both the temporal and septal hippocampus (Rainer et al. 2011; Nollet et al. 2012). Interestingly, recent work has shown that acute stress increases the number of proliferating cells in the septal, but not temporal, DG via increased astrocytic fibroblast growth factor (FGF)-2 secretion (Kirby et al. 2013), which the investigators suggest may indicate a beneficial response to acute stress, conferring cognitive plasticity.

Regional differences following pharmacologic induction of neurogenesis have also been reported. LTP (Bruel-Jungerman et al. 2006) and seizures (Parent and Lowenstein 2002) are known to induce neurogenesis, and administration of the seizure-inducing compound flurothyl leads to increased neurogenesis specifically in the septal DG (Ferland et al. 2002). Septal neurogenesis also appears to be preferentially induced following administration of the neuroleptic haloperidol in gerbils (Dawirs et al. 1998). Neurogenic effects of antidepressants appear to be more ambiguous however (see reviews in Tanti and Belzung 2013). The $GABA_B$ antagonist CGP52432 preferentially increases proliferation, but not survival, in the temporal DG (Felice et al. 2012), whereas the selective serotonin reuptake inhibitor escitalopram induces proliferation specifically in the septal SGZ (Jayatissa et al. 2006). One explanation may be that neurogenic effects of antidepressants are dependent on whether they are administered in baseline conditions or in the context of prior stress. Although chronic administration of the antidepressant fluoxetine increases both cell proliferation and neurogenesis throughout the septotemporal extent of the DG at baseline (Malberg et al. 2000; Santarelli et al. 2003), fluoxetine appears to induce neurogenesis preferentially in the temporal DG following unpredictable chronic mild stress (Tanti et al. 2012). Similarly, agomelatine, a combined melatonin

receptor agonist and serotonin 2C receptor antagonist, increases dendritic maturation across the septotemporal axis of the DG at baseline conditions in the mouse, but appears to have a temporal-specific effect following chronic corticosterone administration (Rainer et al. 2011). Taken together, these studies suggest that behavioral manipulations may differentially alter levels of adult neurogenesis in the septal or temporal DG depending on how the manipulation may have changed the molecular landscape and/or functional roles of the local surrounding hippocampal network.

Circuit-Mediated Maturation of Immature Neurons

Newborn neurons in the DG have unique electrophysiological properties. As adult-born neurons mature and integrate into the existing DG circuitry, they are more easily excitable and, as in the developing hippocampus, can be excited by GABA inputs (Esposito et al. 2005). The threshold for LTP induction is also lower and amplitude of induced potentiation is higher in immature neurons (Ge et al. 2007). However, expression of immediate early genes, such as Arc, used as markers of cellular activity, cannot be induced in adult-born cells until 2 wk after birth or later (Jessberger and Kempermann 2003). Once fully mature, adult-born neurons are indistinguishable from developmentally born granule cells (Laplagne et al. 2006; Toni et al. 2008).

Two recent studies have shown that maturation of new neurons depends on the local circuitry, in which the adult-born neurons are located. New neurons in the septal DG start expressing the immediate early gene, Arc, and the neuronal marker, NeuN, earlier than those in the temporal hippocampus (Snyder et al. 2012), suggesting earlier maturation of septal neurons. Schinder and colleagues also showed that new neurons in the septal DG mature at a faster rate than those in the temporal DG (Piatti et al. 2011). Three-week-old cells in the septal hippocampus have a higher spontaneous excitatory postsynaptic current (sEPSC) frequency, characteristic of mature granule cells, compared with temporal cells. These neurons also have a higher spine density and a higher percentage of them express markers of mature neurons at 3 wk of age, although adult-born neurons in the septal and temporal DG are indistinguishable by 8 wk of age. This altered maturation rate appears to be caused by increased electrical activity in the septal DG, which is consistent with the overall decrease in inhibitory tone seen in the septal compared with temporal hippocampus as a whole. However, voluntary exercise, which has been shown to increase proliferation and survival of neural precursor cells (van Praag et al. 2002), led to an increase in the number of active dentate granule cells and faster maturation rate of adult-born cells solely in the temporal DG, although it is possible that this dissociation is a result of a ceiling effect in the septal DG. It will be interesting to determine whether these temporal DG-specific effects on maturation rate extend to other parameters of adult neurogenesis, including proliferation, survival, and differentiation following voluntary exercise.

Taken together, this suggests that the differentiation of new neurons along the longitudinal axis of the hippocampus may be specified by the local environmental network activity or molecular and cellular landscape. However, it is also possible that there are intrinsic differences in the progenitor cells of the two subregions. In the SVZ of the lateral ventricle, for example, adult neural stem cells differentiate according to cell-autonomous factors established in progenitors during perinatal development rather than environmental signals present during neuronal differentiation (Merkle et al. 2007). Surprisingly, although cultured SGZ-derived progenitors differentiate into olfactory or hippocampal neurons when transplanted into the SVZ or SGZ, respectively (Suhonen et al. 1996), SVZ-derived progenitors differentiate into neurons only when transplanted into the olfactory bulb, and not hippocampus (Herrera et al. 1999), suggesting that both cell-autonomous and environmental factors play a role in the differentiation of adult-born neurons. It will be interesting to examine neuronal differentiation following transplantation of neural stem cells

from the septal SGZ into the temporal DG and vice versa.

Schinder and colleagues (Piatti et al. 2011) suggest that differences in maturation time may allow for memory encoding along a graded timescale, such that events that occur closer together in time are represented at a more detailed level by adult-born neurons in the septal DG, whereas events that are separated in time are more generally represented by temporal adult-born dentate granule cells (Aimone et al. 2006). This is reminiscent of speculation by McNaughton and colleagues (Jung et al. 1994) that neurons, regardless of age, in the septal hippocampus may encode high-resolution representations of small spaces, whereas temporal hippocampal neurons represent low-resolution information about larger environments. Taken together, this suggests that neurons in the septal hippocampus, whether developmentally or adult-born, may be specialized for more finely tuned representations or tasks, such as, perhaps, pattern separation.

Functional Roles

Behavioral deficits following ablation of hippocampal adult-born neurons have included both memory- and emotion-related effects, similar to lesion studies. Adult neurogenesis is required for contextual discrimination, spatial memory, and spatial pattern separation (Clelland et al. 2009; Arruda-Carvalho et al. 2011; Sahay et al. 2011; Denny et al. 2012; Nakashiba et al. 2012; Niibori et al. 2012; see Abrous and Wojtowicz 2015 for in-depth discussion). A role for adult-born neurons in relation to emotion was first proposed with the observation that changes in adult neurogenesis correlate with mood-related manipulations in both negative (Gould et al. 1992) and positive directions (Malberg et al. 2000; van Praag et al. 2002) (especially in the temporal DG). However, rather than mediating the etiology of depression- or anxiety-related behavior, adult hippocampal neurogenesis is thought to be required for some behavioral effects of antidepressants (Santarelli et al. 2003; Surget et al. 2008; David et al. 2009; Perera et al. 2011) or for appropriate stress responses in the context of preexisting disorder (Snyder et al. 2012; for review, see Petrik et al. 2012b). Such preexisting conditions could include social pressures as socially stressed nonhuman primates are more likely to become depressed compared with nonstressed controls (Shively and Willard 2012). Some work has also suggested that an individual's social status in a dominance hierarchy is correlated with levels of adult hippocampal neurogenesis (Kozorovitskiy and Gould 2004; Wu et al. 2014). Interestingly, although the number of neural progenitor cells (NPCs) in the DG is unchanged in human patients with major depressive disorder (MDD) compared with controls, NPC number is increased in MDD patients administered antidepressants compared with untreated patients, particularly in the septal DG (Boldrini et al. 2012).

Given the contribution of adult neurogenesis to these divergent tasks, it is likely that specific subpopulations of adult-born neurons mediate distinct behaviors such that adult neurogenesis in the septal DG plays a role in cognitive tasks, whereas adult-born neurons in the temporal DG regulate mood-related behaviors. Alternately, it may be that adult-born neurons do not themselves mediate distinct tasks, but effect differential behaviors by nature of altering the local network circuitry (Burghardt et al. 2012; Lacefield et al. 2012), which is itself functionally dissociated. To wit, recent work has shown an interaction between depressive-like state and performance on neurogenesis-dependent memory tests (Dery et al. 2013; Shelton and Kirwan 2013), indicating that the contribution of adult hippocampal neurogenesis to depression and anxiety disorders may, in fact, be because of deficits in correct emotional responses to appropriate contextual stimuli (Becker and Wojtowicz 2007; Kheirbek et al. 2012). Wojtowicz and colleagues propose that adult neurogenesis provides for "contextual gating," which suggests that differential memory- or mood-related behavioral roles for these adult-born neurons are simply a result of divergent downstream connections from the septal and temporal hippocampus to cortical and hypothalamic regions, respectively. We have proposed that

impaired encoding functions of the DG, such as pattern separation-completion balances, might result in ineffective gating of downstream circuits subserving fear and stress responses (Kheirbek et al. 2012). Accordingly, recent work has shown that temporary loss of hippocampal neurogenesis in adolescence, although not adulthood, blocks susceptibility to chronic social defeat in adulthood (Kirshenbaum et al. 2014).

In a similar vein, it has been shown that adult-born neurons serve to confer behavioral flexibility in changing environments (Garthe et al. 2009; Burghardt et al. 2012), a process that may modulate either cognition, emotion, or both, depending on whether these neurons are located in the septal or temporal DG. Given the proposed role for differential maturation in high- versus low-resolution representational encoding (Jung et al. 1994; Aimone et al. 2006; Piatti et al. 2011), the loss of contextual encoding or cognitive flexibility in the temporal DG may then lead to more general, long-term behavioral consequences, such as depression or anxiety.

To assess functional contributions of specific subsets of hippocampal adult-born neurons, precise targeting of these subpopulations is critical. As yet, however, few studies have solely targeted neurogenic subpopulations along the septotemporal axis. Perhaps the most straightforward method is via anatomic targeting of new neurons in either the septal or temporal DG. Retroviral vectors preferentially infect dividing cells (van Praag et al. 2002), and retroviral delivery of the inward rectifier Kir2.1 has already been used to selectively silence adult-born neurons (Piatti et al. 2011). Retroviral vectors encoding the cytotoxic subunit of diphtheria toxin (DTA) have been used to ablate human cancer cells (Qiao and Caruso 2002) and can potentially be directed toward adult-born neurons. Stereotactic targeting of these viruses to distinct subregions along the septotemporal gradient of the DG would either silence or ablate adult-born neurons in circumscribed anatomical regions, allowing for behavioral assessment of the functional roles of these neurons. Additionally, recent work has shown that increased survival of new neurons improves performance on certain learning- and memory-related tasks (Sahay et al. 2011). Local injection of retroviral vectors encoding Cre recombinase (Tashiro et al. 2006) in mice expressing a conditional allele of the proapoptotic gene, Bax (Takeuchi et al. 2005), would allow for examination of behavioral consequences of increased survival of subsets of adult-born neurons.

Optogenetic strategies (Zhang et al. 2007) have also been used to examine effects of directed activation of adult-born neurons in the olfactory bulb (Bardy et al. 2010; Alonso et al. 2012). Retroviral injection of the light-gated cation channel channelrhodopsin (ChR2) into the hippocampus has allowed for acute stimulation of adult-born neurons in slice culture (Toni et al. 2008). Optically activated channels could be targeted to dividing cells along the septotemporal axis via stereotaxic injection of retroviral vectors. Alternately, tamoxifen-inducible Cre recombinase under the control of the nestin (Imayoshi et al. 2006; Lagace et al. 2007; Dranovsky et al. 2011) or DCX (Zhang et al. 2010) promoters could be used to drive Cre-dependent opsin expression (Madisen et al. 2012) in neural stem cell or immature neurons, respectively, at precise time points. Implantation of fiber optic light sources along the septotemporal axis of the hippocampus would then allow for acute stimulation or inhibition of discrete subpopulations of new neurons. Indeed, dissociable behavioral effects following optogenetic manipulation of granule cells along the septotemporal DG, regardless of maturity, have recently been shown (Kheirbek et al. 2013).

X-irradiation has also routinely been used to ablate progenitor cells specifically in the SGZ (Santarelli et al. 2003; Raber et al. 2004; Winocur et al. 2006; Surget et al. 2008). Recent technology has been used to precisely direct X-ray beams to areas as small as 0.5 mm in diameter (Wong et al. 2008; Armour et al. 2010). Using computed tomography to first visualize the brain of individual animals to guide irradiation treatment, two groups have targeted neurogenic niches specifically in the right hippocampus (Ford et al. 2011) or hypothalamus (Lee et al. 2012). We have used X-irradiation to target

small windows of dividing cells, allowing us to specifically ablate subpopulations of neural stem cells along the septotemporal axis, and have shown a double dissociation wherein adult hippocampal neurogenesis in the septal DG is critical for normal acquisition of a contextual discrimination task, whereas anxiolytic/antidepressant effects of fluoxetine require adult-born neurons in the temporal DG (Wu and Hen 2014).

Additionally, epigenetic mechanisms, which have been implicated in both mnemonic- and mood-related behaviors, are well known to modulate adult hippocampal neurogenesis (see reviews in Hsieh and Eisch 2010; Mateus-Pinheiro et al. 2011; Lv et al. 2013). It will be interesting to examine chromatin marks in microdissected septal or temporal regions of the DG following stressful interventions or memory tasks to determine whether a dissociation exists in epigenetic modifications along the longitudinal axis of the hippocampus. One could also imagine a scenario in which genes implicated in the stress response, such as the glucocorticoid receptor, are actively repressed in the septal but not temporal hippocampus, allowing for region-specific downstream gene expression.

A caveat of these anatomic approaches is that they still depend on arbitrary separations of the hippocampal formation. There are currently no standardized landmarks to divide the hippocampus along its longitudinal axis, and the inherent curvature of the structure makes it difficult to define a single dividing plane (Snyder et al. 2009). One more stringent way to define these boundaries would be to use molecular markers. A necessary first step, therefore, is to characterize the molecular phenotype of adult-born neurons along the longitudinal axis of the DG. Recent work has coupled microarray technology with fluorescent activated cell sorting (FACS) techniques to identify the molecular profile of adult-born neurons (Bracko et al. 2012; Petrik et al. 2012a). Microdissected septal and temporal DG from mice expressing GFP under the control of the nestin promoter in an inducible manner (Lagace et al. 2007; Dranovsky et al. 2011) could be sorted and screened to determine whether distinct expression profiles exist. Candidate genes could then be used to direct expression of Kir2.1 or DTA as above. It is possible that new neurons in the septal or temporal DG are molecularly indistinguishable, and intersectional approaches (Imayoshi et al. 2009) will be required for specific targeting of immature neurons localized in distinct environmental networks.

One potential method to pharmacogenetically silence pools of adult-born neurons would take advantage of the heteromeric chloride channel GluClαβ (Lerchner et al. 2007). Coexpression of both α and β subunits is required for functional activation of the modified ivermectin-gated channel. Nestin promoter-directed expression of the inducible Cre recombinase (Imayoshi et al. 2006; Lagace et al. 2007; Dranovsky et al. 2011) could be used to drive expression of the GluClα subunit, preceded by a loxP-flanked stop cassette, in adult-born neurons with temporal control achieved on systemic administration of tamoxifen. By directing expression of the GluClβ subunit to either the septal or temporal DG with specific promoters as identified in microarrays, functional channels would then be expressed only in adult-born cells within tissue-specific regions, allowing for acute targeted silencing of these cells with systemically administered ivermectin.

SEGREGATION ALONG THE TRANSVERSE AXIS OF THE DG

Although we have focused on a septotemporal dissociation of the hippocampus, a transverse segregation between the suprapyramidal blade of the DG, enclosed between areas CA1 and CA3, and the infrapyramidal blade, located on the opposite side of the DG hilus, also exists. Cells in the suprapyramidal, or upper, blade appear to be preferentially activated following exploration of either the Morris water maze (Snyder et al. 2009) or a novel environment (Chawla et al. 2005; Satvat et al. 2012). However, it has also been suggested that the infrapyramidal, or lower, blade is hyperexcitable compared with the suprapyramidal blade and this phenomenon can be enhanced following seizure induction (Scharfman et al. 2002). Consistent with this,

the ratio of inhibitory basket cells to dentate granule cells has also been shown to be higher in the suprapyramidal blade (Seress and Pokorny 1981). Overall, these differences may be attributable to increased plasticity in the suprapyramidal blade as dendrites are longer and harbor a higher density of spines in this blade as compared with the infrapyramidal blade (Desmond and Levy 1985; Claiborne et al. 1990).

Additionally, there appears to be increased adult neurogenesis at baseline in the suprapyramidal compared with the infrapyramidal blade (Ambrogini et al. 2000; Kempermann et al. 2003; Ramirez-Amaya et al. 2006; Dranovsky et al. 2011; Jinno 2011; although, see also Snyder et al. 2009, 2012). This is, again, consistent with increased adult neurogenesis in a subregion with increased local circuit activity. However, it is unclear whether behavioral manipulations, such as environmental enrichment or spatial learning, increase proliferation predominantly in the suprapyramidal (Tashiro et al. 2007) or infrapyramidal blade (Ambrogini et al. 2000). Interestingly, acute administration of cannabinoids leads to both increased cell number and total dendritic length in the infrapyramidal blade (Lawston et al. 2000). Increased neurogenesis in the infrapyramidal blade is also seen following chronic fluoxetine administration (Satvat et al. 2012), which the investigators suggest may account for the dampened effects of fluoxetine seen on spatial learning and memory.

Taken together, this suggests a dissociation of the transverse axis of the DG similar to that seen along the longitudinal axis. However, the literature examining differences between the supra- and infrapyramidal regions of the hippocampus is less extensive, and whether a similar functional dissociation exists such that the suprapyramidal blade of the DG mediates memory-related tasks, whereas the infrapyramidal blade is preferentially involved in anxiety-related behaviors, remains to be determined. There is also likely to be an interaction between the longitudinal and transverse axes as forebrain ischemia induces neurogenesis in both blades of the septal DG, but only in the infrapyramidal blade of the temporal DG (Choi et al. 2003).

CONCLUSION

Adult-born neurons in the hippocampus are required in multiple behavioral paradigms. Although it is clear that the hippocampus can be segregated into discrete zones with distinct anatomy, physiology, and functions, specialization of hippocampal neurogenic niches has only recently been examined. Potential subpopulations of NPCs will need to be individually defined, characterized, and targeted to fully comprehend the functional role of these neural stem cells.

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