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Isolating pathogenic mechanisms embedded within the hippocampal circuit

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Abstract

Some of the most common and devastating disorders of the brain target the hippocampal formation. The hippocampal formation is a complex circuit of interconnected regions, and it is assumed that clues into the causes of these disorders are embedded within the circuit. Neuroimaging tools have been optimized to interrogate the malfunctioning hippocampal circuit, and by applying these tools to patients in the earliest stages of disease and to animal models, patterns of regional dysfunction have been established for Alzheimer's disease, schizophrenia and cognitive aging. More recently, studies have begun deciphering the cellular and molecular reasons underlying regional dysfunction. Collectively, this information clarifies the pathophysiology of these disorders and informs on therapeutic strategies.

INTRODUCTION

So deeply ingrained as to seem eternal, 'anatomical localization' is a relatively new concept in the annals of Medicine. It is easily forgotten that throughout most of Medicine's history diseases were thought to reflect diffuse processes caused by imbalances of bodily substances or fluids. The shift toward an anatomical basis of disease began slowly during the late renaissance and was only fully articulated in 1761 when the anatomist Giovanni Morgagni published his textbook, "On the seats and causes and disease through an investigation of anatomy" (Morgagni, 1761). This landmark textbook formulated what subsequently became a first principle in modern Medicine: Localizing the anatomical site of pathology is an important first step towards better understanding, diagnosing and ultimately curing any disease. Cell theory and its medical offshoot 'cellular pathology', pioneered by Rudolf Virchow (Virchow, 1863) and others in 19th century, refined the target of disease localization. With the introduction of the idea that 'sick cells' are the basic unit of disease, localization needed to scale down, from an organ or structure to the level of afflicted cells.

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Besides providing a basis for disease classification and improving diagnostic accuracy, the ultimate promise of disease localization is mechanistic. Answering why one group of cells are afflicted by a disease while a neighboring group is not, promises to shed light on pathogenic causes. Although the logic of disease localization has been validated—zooming in from anatomy to cells and down to molecular mechanisms-- it has only recently been applied to complex disorders that affect the hippocampal formation. Notably, the fact that the hippocampal formation is a circuit made up interconnected regions, each housing a distinct group of neurons, was first suggested by Ramon Y Cajal (Cajal, 1911) (Fig. 1), whose research was performed in the cell theory spirit of the 19th century. (Indeed, compared to other organs, the brain was the last holdout in defiance of cell theory). Subsequent cellular, electrophysiological and molecular studies have further characterized the distinct properties of neurons contained within each region of the hippocampal circuit—the entorhinal cortex, the dentate gyrus, the cornu ammonis (CA) subfields, and the subiculum (Fig. 1). Adding a further level of complexity, the functional and molecular properties of neurons within each region vary across the hippocampal long-axis (as reviewed in (Small et al., 2011)). This diversity within the hippocampal circuit accounts for how the circuit can be a ‘seat’ to a range of mechanistically distinct disorders. Its molecular diversity in particular has led to the hypothesis that different regions of the hippocampal circuit will be preferentially targeted by different disorders (Small, 2001).

While a plausible hypothesis, pinpointing regional dysfunction for many disorders that involve the hippocampal circuit presents a challenge. Most disorders start subtly, in ‘preclinical’ or ‘prodromal’ stages that then worsen and spread over time, and so mapping the anatomy of the earliest stages of disease is often elusive by the time patients come to autopsy. Furthermore, although some disorders develop dramatic cell death and other clear histological findings, nearly all disorders begin in a ‘cell sickness’ stage—that is neuronal dysfunction occurs before neuronal loss. Mapping neuronal dysfunction is tricky using the time-honored approach of postmortem examination.

In principle, *in vivo* functional imaging is well suited to overcome these challenges, but it was only at the turn of the 21st century that MRI-based techniques began to be optimized, enabling individual regions of the hippocampal circuit to be visualized (Davachi and Wagner, 2002; Gabrieli et al., 1997; Kirwan et al., 2007; Small et al., 2000; Small et al., 2004; Small et al., 1999; Zeineh et al., 2000). Ultimately, by allowing the full circuit to be interrogated during the earliest stages of diseases these tools have been able to localize hippocampal regions preferentially affected by—and, just as importantly, resistant to-- many disorders.

We have previously reviewed how the anatomical organization of the hippocampal circuit provides a framework for characterizing and investigating hippocampal dysfunction, among the surprisingly numerous and diverse range of diseases that target this circuit (Small et al., 2011). The primary purpose of this perspective is to review recent evidence that illustrates how this framework has been successfully applied in isolating pathogenic mechanisms. To date the clearest patterns of regional dysfunction within the hippocampal circuit have been established for Alzheimer’s disease, schizophrenia and cognitive aging, and it is for these

disorders that patterns of hippocampal dysfunction have been mechanistically most illuminating.

It should be pointed out that other areas outside the hippocampal circuit are affected in all three disorders, and as previously reviewed (Small et al., 2011) many are directly linked to the circuit (for example, the posterior parietal lobe and the precuneus in Alzheimer's disease, the ventral striatum in schizophrenia, and the prefrontal cortex in cognitive aging). We have previously reviewed how connectivity with extra-hippocampal areas might account for phenotypic diversity among the range of disorders in which the hippocampal circuit is implicated (Small et al., 2011). In this perspective, with an eye on mechanism, I will focus exclusively on the hippocampal circuit, and demonstrate how the well-characterized organization of the circuit can be used in an effort to follow the first principle of disease localization. As I will discuss, by performing molecular studies designed to address why one region of the circuit is affected and another neighboring region is resistant to a particular disorder, the circuit can be used as an anatomical 'Rosetta stone' in trying to decipher pathogenic mechanisms.

Alzheimer's Disease and endosomal transport

Although Alzheimer's disease (AD) is a neurodegenerative disorder, it too is thought to begin in a cell sickness stage (Selkoe, 2002), assumed to occur years before cell death. Postmortem maps of neuronal loss have mapped an anatomical pattern of disease, showing that the entorhinal cortex is the hippocampal region most vulnerable to the earliest stages of AD (Gomez-Isla et al., 1996), while suggesting that the neighboring dentate gyrus is the one that appears most resistant to the disease (Braak et al., 2006; Schonheit et al., 2004; West et al., 1994; West et al., 2000). Aside from confirming this pattern of dysfunction in living patients, including the relative resistance of the dentate gyrus (Moreno et al., 2007), the main contribution of neuroimaging is showing that entorhinal cortex dysfunction exists during the earliest preclinical stages of disease (Huijbers et al., 2014; Khan et al., 2014; Miller et al., 2013; Whitwell et al., 2007; Whitwell et al., 2008). Functional neuroimaging has been able to detect entorhinal cortex dysfunction in mouse models of disease (Khan et al., 2014; Moreno et al., 2007), notable for manifesting cell sickness without cell death, thereby validating that these some of these neuroimaging tools can in principle capture the earliest pathophysiological stage of disease

Guided by this pattern of dysfunction, we performed a molecular profiling study on postmortem tissue harvested from the entorhinal cortex as the 'target' region and the dentate gyrus as the 'within-subject control' region, from brains with and without AD. A statistical model was used to identify molecular correlates that might help explain why the entorhinal cortex is targeted by AD, but the neighboring dentate gyrus is relatively preserved. Molecules linked to the retromer emerged as the primary findings (Small et al., 2005), which were found to be affected in the entorhinal cortex but unaffected in the dentate gyrus. The retromer is an assembly of proteins that work in unison to orchestrate cargo transport out of endosomes (Burd and Cullen, 2014), either to the trans-golgi network or back to the cell surface. As originally suggested (Small et al., 2005), retromer has been found to transport the amyloid-precursor protein (APP) out of endosomes via VPS10-containing receptors, in

particular Sorl1 (also called Sorla) (Fjorback et al., 2012). Although this study suggests that retromer defects are a molecular correlate of entorhinal cortex dysfunction, they do not explain why these defects occur in the entorhinal cortex in the first place. This remains an outstanding question that we are currently pursuing.

A pathogenic link to AD has been established by genetic studies led by Richard Mayeux, Peter St. George Hyslop, Lindsay Farrer and their colleagues. Collectively, these studies have identified variants in SORL1 (Rogaeva et al., 2007), genes encoding other VPS10-containing receptors (Reitz et al., 2013), and genes encoding other key elements of retromer (Vardarajan et al., 2012). The importance of SORL1 in particular has been confirmed by a recent large-scale genetic meta-analysis (Lambert et al., 2013). Further support for a pathogenic role has been provided by genetically modified retromer deficient animal models (Muhammad et al., 2008; Wen et al., 2011). It is within endosomes that APP is most likely to be cleaved by BACE1 (beta-site APP cleaving enzyme 1) (Small and Gandy, 2006), a β-secretase that initiates the ‘amyloidogenic’ processing of APP leading to the accumulation of the neurotoxic fragments β-CTF (β C-terminal fragment) and Aβ (amyloid β). Defects in retromer-mediated transport leads to the accumulation of these neurotoxic fragments by increasing the resident time of APP in endosomes (Bhalla et al., 2012; Mecozzi et al., 2014).

The observed defects in the retromer transport pathway should be interpreted in the context of a growing body of evidence that have more broadly implicated endosomal transport defects in the disease. Primary evidence pinpointing the endosome as the intracellular site of dysfunction was described in a seminal series of histological studies performed by Randy Nixon and his colleagues (Cataldo et al., 2000). They showed that endosomes in the entorhinal cortex and the CA subfields of the hippocampal circuit are abnormally enlarged during the earliest stages of disease. Remarkably, the distribution of abnormally enlarged endosomes was nearly diagnostic of the disease, with very little overlap in the size of endosomes observed in age-matched controls. Additionally, Nixon and colleagues showed that carrying the APOE4 gene, the strongest genetic risk factor for late-onset disease, further enhanced endosomal enlargement, and that abnormal enlargement did not occur as part of normal aging. The near uniformity of the abnormality in patients with late-onset ‘sporadic’ AD, suggests a convergence of pathogenic mechanisms leading to endosomal enlargement. Furthermore, they observed enlarged endosomes in brain regions that were relatively free of evidence of Aβ pathology (Cataldo et al., 1997; Cataldo et al., 2000), which agrees with an emerging view that endosomal abnormalities are upstream to Aβ accumulation. The fact that enlarged endosomes represent a cell-biological phenotype of AD has recently been validated in neurons derived via IPSC (induced pluripotent stem cells) from patients (Israel et al., 2012). Furthermore, studies using IPSC-derived neurons have also showed that APP mutations mis-traffic APP to endosomes (Muratore et al., 2014), similar to the effect caused by retromer defects.

Endosomes are a hub of membrane trafficking, and mechanistically it can be assumed that they become enlarged either because of accelerated delivery, via cell-surface endocytosis, or by reducing the transport out of endosomes. Indeed, Nixon and his colleagues provided the first evidence for increased endocytosis in AD (Cataldo et al., 1997), while retromer defects (Bhalla et al., 2012) and an AD-associated deficiency in phosphatidylinositol-3-phosphate

(PI3P) (Morel et al., 2013), a lipid that regulates transport of cargo out of endosomes, cause enlarged endosomes. Interestingly, one of many affects of APOE4 is to increase the endocytosis of cargo including APP from the surface membrane (Ye et al., 2005; Yu et al., 2014), which can explain why APOE4 is associated with enlarged endosomes. More generally, additional evidence that endosomal dysfunction plays an upstream role in AD pathology comes from large-scale genetic studies that have identified a group of endosomal transport genes that have emerged as a unified genetic factor linked to AD (Lambert et al., 2013).

Besides accounting for how APP fragments can be misprocessed in late onset AD, recent studies are beginning to link endosomal transport defects to other core features of the disease. For example, retromer defects has been found in microglia of AD patients (Lucin et al., 2013), and this same study showed how these defects reduces the cell surface transport of AD-linked microglia receptors. Of course, besides amyloid accumulation, neurofibrillary tangles, and their constituent abnormal tau species, are the second defining histological feature of AD. While amyloid accumulation, particularly its soluble forms (Lue et al., 1999; Naslund et al., 2000), begins to accumulate in the entorhinal cortex during the early disease stages, it is tau related abnormalities that are very prominent histological features found in this region. Might endosomal dysfunction be linked to tau toxicity? This remains an open question, but recent evidence suggests that it is while tau is translocated to endosomes that the processing to tau pathology is triggered(Michel et al., 2014). Additionally, recent studies have begun finding associations of AD-linked endosomal genes with tau pathology (Ando et al., 2013; Chapuis et al., 2013).

Taken together, these observations establish that endosomal dysfunction is a pathogenic mechanism, and validate endosomal transport as a ‘cell biological’ target for drug discovery. Providing proof-of-principle for this idea, in a collaboration with Greg Petsko and Dagmar Ringe, we has recently isolated a novel class of pharmacological chaperones (Mecozzi et al., 2014) that increases the stability and function of retromer, shunts APP away from endosomes, and decreases the abnormal processing of APP. In principle, there are numerous other pharmacological approaches that can correct endosomal transport defects, and future studies will determine whether these novel classes of drugs will prove efficacious whey applied to early stages of AD.

Schizophrenia and glutamate production or catabolism

In schizophrenia, to contrast with AD, the histological abnormalities observed within the hippocampal circuit are subtler, primarily involving a mild loss of GABAergic interneurons in the CA regions (Benes and Berretta, 2001) (Fig. 2). Neuroimaging has therefore played a more important role in implicating the hippocampal circuit in the disease. This was originally documented using relatively low-resolution techniques, showing dominant hippocampal atrophy in the disease (as reviewed in (Adriano et al., 2012)), and studies suggesting that that the hippocampus is characterized by an abnormal hypermetabolic state (Friston et al., 1992; Heckers et al., 1998; Kawasaki et al., 1992; Malaspina et al., 2004; Medoff et al., 2001; Schobel et al., 2009). A recent study, combining high-resolution functional and structural MRI applied to patients in the earliest stages of the disease, more

precisely mapped the spatial and temporal profile of abnormalities within the hippocampal circuit (Schobel et al., 2013). These studies suggest that hypermetabolism occurs first, observed during prodromal stages and is localized to the CA1 region of the hippocampal circuit. With progression to the psychosis stage of disease, hypermetabolism is followed by atrophy, and this too is localized predominantly to the CA1 (Fig. 2).

The remarkable anatomical concordance suggested that hypermetabolism drives the ensuing atrophy and it was hypothesized that elevations in extracellular glutamate might act as the pathogenic driver of both indicators of hippocampal dysfunction (Schobel et al., 2013). This hypothesis was based on the fact that NMDA-blocking agents, which cause an increase in extracellular glutamate (Moghaddam et al., 1997), recapitulate the disease's full spectrum of symptoms (Krystal et al., 1994), and because mouse fMRI studies suggested that the CA1 region is differentially sensitive to alterations in glutamate (Gaisler-Salomon et al., 2009). This hypothesis was confirmed when the same high-resolution functional and structural MRI techniques which were originally used to establish the disease's imaging-phenotype were applied to mice who were administered NMDA-blocking agents (Schobel et al., 2013). These studies established that elevations in extracellular glutamate phenocopied the disease-- first causing selective CA1 hypermetabolism followed more slowly by atrophy. Furthermore, the MRI-detected atrophy was shown to be associated with GABAergic interneuron loss, thereby phenocopying the histological findings of the disease (Schobel et al., 2013). This interpretation is bolstered by a recent study combining magnetic resonance spectroscopy (MRS) and structural MRI (Kraguljac et al., 2013), showing that glutamate elevations in the hippocampus of patients are correlated with CA1 atrophy.

What then causes the elevations in extracellular glutamate? One idea is that there is a relative redistribution of glutamate from the intracellular to the extracellular space. This interpretation might be problematic, however, because the glutamate elevations observed by MRS cannot be caused by a simple redistribution of glutamate. Rather, these neuroimaging findings suggest that there is a net increase in glutamate levels, either by increased production or decreased catabolism. The production and catabolism of glutamate is tightly regulated by a group of enzymes distributed in astrocytes and neurons (Erecinska and Silver, 1990; Maciejewski and Rothman, 2008)—including, glutamate dehydrogenase, glutaminase, glutamine synthetase, glutamic acid decarboxylase, GABA transaminase, and Aspartate & Alanine aminotransferase. It is hypothesized therefore that these enzymes might be defective in schizophrenia. Alterations in this group of enzymes might occur genetically—either directly by genes encoding these enzymes (Jia et al., 2010) or secondarily by genetic links to the glutamatergic system (Walsh et al., 2008; Wilson et al., 2006; Winchester et al., 2014)-- or via environmental stressors and risk factors (e.g.(Matrisciano et al., 2012)).

Although this hypothesis awaits further confirmation, the imaging studies summarized above suggest that glutamate elevation itself is a valid drug target and that glutamate-reducing agents might be an effective therapeutic intervention. An important implication of the imaging studies is that these agents should be given during prodromal stages of disease, before the loss of interneurons and its imaging correlate atrophy (Fig. 2). Indeed, recent failures of clinical trials using the glutamate-reducing agent Pomaglumetad (LY2140023)

(Adams et al., 2014) might be explained by the fact that they were tested in patients who were already in advanced stages of the disease.

Cognitive aging and CREB-dependent histone acetylation

Perhaps more than any other process that targets the hippocampal circuit, mapping the effects of normal aging is most challenging, as there are a number of diseases that target the aging hippocampal circuit, including AD, vascular disease, and diabetes (Wu et al., 2008). Insofar that it is still difficult to completely exclude these disorders when investigating the hippocampal circuit in aging populations, isolating an anatomical pattern of dysfunction linked to aging per se presents a unique challenge.

One approach in addressing this challenge is to apply high-resolution functional MRI tools in a comparative cross-species manner. The hippocampal circuit is remarkably homologous across mammals (Fig. 1) and all develop age-related hippocampal dysfunction. As non-human mammals do not develop AD, vascular disease or diabetes, it is assumed that mechanisms by which aging affects the hippocampal circuit is preserved from rodents, through nonhuman primates, to humans. If true, then patterns of age-related regional dysfunction should also be preserved. Guided by this reasoning, we have applied high-resolution functional MRI tools first to healthy humans across the life span (Small et al., 2002), and then tested whether these patterns are observed in aging rhesus monkeys (Small et al., 2004), rats, and wildtype mice (Moreno et al., 2007). Together, these results have suggested that the dentate gyrus is the dominant region affected by aging, while the entorhinal cortex is the region that shows the greatest resistance. Notably, dentate gyrus dysfunction appears to begin in the fourth decade of life and to gradually worsen thereafter (Fig. 2).

Other studies using alternative forms of functional (Yassa et al., 2011b) or structural MRI (Wisse et al., 2014) largely agree with this conclusion, and in fact some studies suggest that aging is associated with a mild loss of interneurons selectively in the dentate gyrus (West, 1993). With a greater appreciation of the distinct cognitive operations performed by the dentate gyrus, notably pattern separation (Yassa and Stark, 2011), memory tests have been developed that can assess dentate gyrus function using cognitive measures. By applying these cognitive tools, a growing number of studies have confirmed that the dentate gyrus is a dominant ‘seat’ of age-related hippocampal dysfunction (Gracian et al., 2013; Holden et al., 2012; Yassa et al., 2011a).

Guided by this pattern of dysfunction, we performed a molecular profiling study on postmortem tissue harvested from the dentate gyrus as the ‘target’ region and the entorhinal cortex as the ‘within-subject control’ region, from healthy brains across the adult lifespan. A statistical model was used to identify molecular correlates that might help explain why the dentate gyrus is targeted by aging, but the neighboring entorhinal cortex is relatively preserved. Results implicated the histone-binding protein RbAp48 (Pavlopoulos et al., 2013), which was found to undergo selective age-related deficiency in the dentate gyrus. By interacting with the CREB-Binding Protein (CBP) (Zhang et al., 2000), RbAp48 regulates CREB-dependent histone acetylation and transcription (CREB = cAMP Response Element–Binding Protein). In a collaborative study with Eric Kandel, we first confirmed that RbAp48

is, like in humans, selectively deficient in the dentate gyrus of aging wildtype mice. More importantly, Kandel's lab developed a mouse model that expressed a dominant-negative inhibitor of RbAp48. These mice were found to phenocopy the cognitive, neuroimaging, and histone acetylation defects characteristics of the aging hippocampal circuit. Providing further causal confirmation, overexpressing RbAp48 selectively in the dentate gyrus of aging wildtype mice rescued age-related memory decline (Pavlopoulos et al., 2013).

Another recent study provided further causal confirmation that the dentate gyrus is the seat of age-related memory decline, and for its underlying molecular mechanism (Villeda et al., 2014). This study used heterochronic parabiosis to transfer the blood of young to old mice. Young blood was found to rescue the electrophysiological and behavior phenotypes of the aging hippocampus, and it did so by increasing spine density selectively in the dentate gyrus. Moreover, the induced increase in dentate gyrus spine density was found to be mediated by the CREB pathway.

Perhaps the strongest pathogenic link between CREB-dependent histone acetylation and cognitive aging in humans comes from a recent genetic study performed by Richard Mayeux and his colleagues (Barral et al., 2014). They tested whether variants in genes encoding RbAp48, CREB1 and CBP are associated with memory performance cognitively healthy elderly. While associations were detected in variants encoding all three proteins, the strongest and most reliable association was for variants encoding CBP (Barral et al., 2014)

These findings suggest interventions for ameliorating age-related memory decline. While age-related memory decline is to some degree universal, and therefore has extremely high prevalence, the symptoms associated with aging are not nearly as devastating as those caused by disease. Nevertheless, with increasing longevity, even mild memory decline has a negative impact on older individuals who are not only living longer but who want to remain engaged in cognitively demanding lifestyles.

There is a pharmacopeia of agents that target the CREB pathway and these might be worth testing in aging populations. Indeed, the FDA has recently opined that age-related memory decline is an approved indication for clinical trials. At the same time, because age-related memory decline is considered a normal process, behavioral or dietary interventions might be more appropriate. Aerobic exercise is one such intervention, as neuroimaging studies have found that it enhances dentate gyrus function (Pereira et al., 2007). Dietary interventions might also work, as Fred Gage and his colleagues have showing that a diet enriched in the flavanol epicatechin improves dentate gyrus function in mice (van Praag et al., 2007). Accordingly, we have initiated a randomized-controlled clinical trial, testing the effect a high flavanol diet has on the hippocampal circuit in healthy aging individuals.

Summary

Giovanni Morgagni was quoted as saying that when presented with a disease one should listen to the "cry of a suffering organ". With the introduction of 'cell theory' and its clinical correlate 'cellular pathology', listening needed to be fine-tuned, to detect the cry of suffering cells. High-resolution functional and structural MRI has turned out to be very good listening devices that can isolate the group of neurons preferentially afflicted by, and relatively

resistant to, various disorders that target the hippocampal circuit. Moreover, neuroimaging studies have *de novo* established or re-affirmed that disorders can start in a cell sickness stage before progressing to cell death, a later stage that must be considered more intractable to therapeutic interventions (Fig. 2).

While these neuroimaging tools might be useful in improving diagnostic capabilities, disease localization is most important for isolating pathogenic mechanisms. As reviewed in this perspective, insight into cellular pathophysiology and molecular mechanisms can be used to develop novel interventions. Human genetics or animal models have at least partially validated many of the mechanisms discussed. Nevertheless, the ultimate validation of any hypothesis about disease is showing that an intervention that targets the proposed cellular site or molecular mechanism treats the actual disease. This ultimate validation awaits future studies for all disorders that affect the hippocampal circuit.

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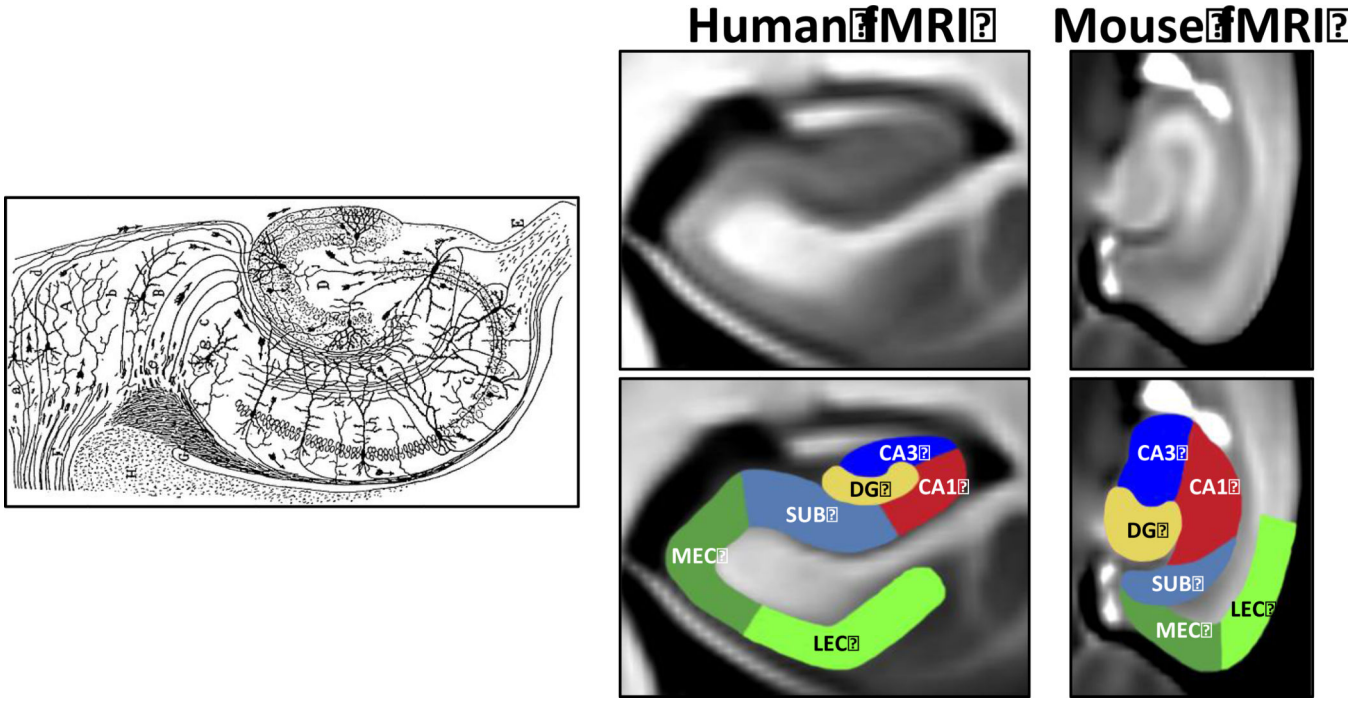

Figure 1. Visualizing the hippocampal circuit

In 1911, Ramon Y Cajal used the Golg-staining technique applied to the postmortem rabbit (left panel) to first show that regions of the hippocampal formation comprise distinct neurons and that the regions are connected to form a circuit (Cajal, 1911). Approximately a hundred years later, functional imaging techniques were optimized to visualize the regions of the hippocampal circuit in living humans (middle panel) and living mice (right panel). In the examples shown, fMRI images were generated with an exogenous contrast agent allowing submillimeter resolution (Adapted from (Khan et al., 2014). (LEC=lateral entorhinal cortex; MEC=medial entorhinal cortex; DG=dentate gyrus; SUB=subiculum)

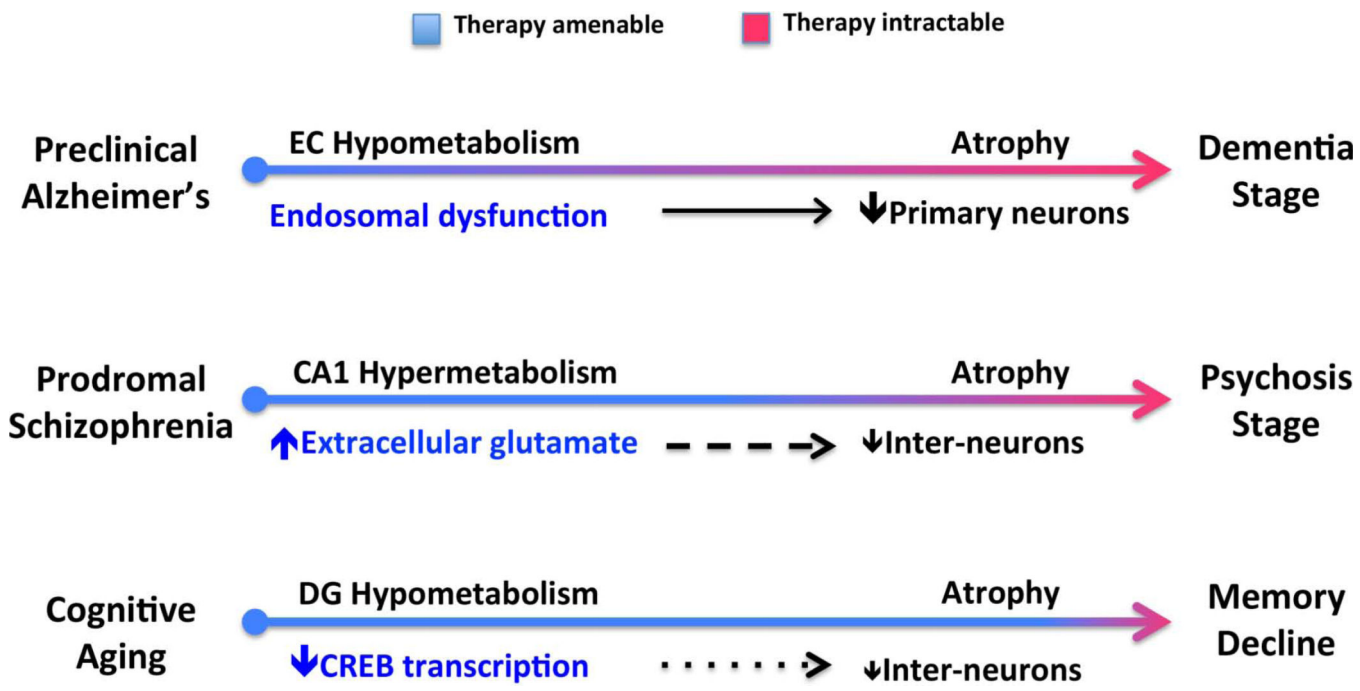

Figure 2. Pathogenic mechanisms and the progression of hippocampal-based disorders

Alzheimer's disease starts in a 'preclinical stage' before progressing to dementia. Hypometabolism during the preclinical stage has been localized to the entorhinal cortex (EC), in which defects in retromer-mediated endosomal transport have been isolated. Schizophrenia starts in a 'prodromal stage' before progressing to psychosis. Hypermetabolism during the prodromal stage has been localized to the CA1 region, and has been linked to increases in extracellular glutamate. Cognitive aging starts in the fourth decade of life and progresses gradually to memory decline. Hypometabolism during normal aging has been localized to the dentate gyrus (DG), in which defects in CREB-dependent histone acetylation have been isolated. During the progression of each entity, a primary 'cell sickness' stage is thought to antedate a 'cell death' stage. (A dramatic loss of primary neurons in Alzheimer's disease, a more subtle loss of GABAergic interneurons in schizophrenia, and a subtle loss of hilar interneurons in cognitive aging). Accordingly, the disorders are anticipated to be most amenable to therapeutic interventions during the earliest pathophysiological stage.