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Synaptic clustering within dendrites: An emerging theory of memory formation

George Kastellakis [a], Denise J. Cai [b], Sara C. Mednick [c], Alcino J. Silva [b], Panayiota Poirazi [a,*]

[a] Institute of Molecular Biology and Biotechnology (IMBB), Foundation for Research and Technology, Hellas (FORTH), P.O. Box 1385, GR 70013 Heraklion, Greece

[b] Departments of Neurobiology, Psychology, Psychiatry, Integrative Center for Learning and Memory and Brain Research Institute, UCLA, 2554 Gonda Center, Los Angeles, CA 90095, United States

[c] Department of Psychology, University of California, 900 University Avenue, Riverside, CA 92521, United States

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ABSTRACT

It is generally accepted that complex memories are stored in distributed representations throughout the brain, however the mechanisms underlying these representations are not understood. Here, we review recent findings regarding the subcellular mechanisms implicated in memory formation, which provide evidence for a dendrite-centered theory of memory. Plasticity-related phenomena which affect synaptic properties, such as synaptic tagging and capture, synaptic clustering, branch strength potentiation and spinogenesis provide the foundation for a model of memory storage that relies heavily on processes operating at the dendrite level. The emerging picture suggests that clusters of functionally related synapses may serve as key computational and memory storage units in the brain. We discuss both experimental evidence and theoretical models that support this hypothesis and explore its advantages for neuronal function.

Contents

Abbreviations: AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; APA, American Psychological Association; BDNF, brain-derived neurotrophic factor; CA1, CornuAmmonis area 1; CA3, CornuAmmonis area 3; ChR2, channel rhodopsin 2; CREB, cAMP response element-binding protein; EPSP, excitatory post-synaptic potential; fMRI, functional magnetic resonance imaging; GluA1, glutamate receptor 1; GluR1, glutamate receptor type 1; HFA, high-functioning autistics; IPSP, inhibitory post-synaptic potential; LTD, long-term depression; LTP, long-term potentiation; MAPK, mitogen-activated protein kinase; mGRASP, mammalian GFP reconstitution across synaptic partners; MLFA, moderately low functioning autistics; mTOR, mechanistic target of rapamycin; NMDA, N-methyl-D-aspartate receptor; PFC, prefrontal cortex; PRPs, plasticity related proteins; STC, synaptic tagging and capture.

* Corresponding author. Tel.: +30 2810391139; fax: +30 2810391101.
E-mail address: poirazi@imbb.forth.gr (P. Poirazi).

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1. Introduction

The ways in which memories are formed and stored in the brain remains one of the most exciting mysteries of neuroscience. While it is generally believed that complex memories are stored in distributed representations throughout the brain (Hübener and Bonhoeffer, 2010; Josselyn, 2010; Lashley, 1950), the mechanisms underlying the formation of these representations are still under intense scrutiny. Powerful new technologies, such as ligand- and light-driven neuronal activation systems, have established that the biophysical correlates of memory (memory *engrams*) consist of ensembles of neurons which undergo plasticity during learning, and are necessary for the expression of memory (Garner et al., 2012; Han et al., 2007; Josselyn, 2010; Kim et al., 2014; Liu et al., 2012).

The storage of memories in neuronal populations is believed to rely on structural and biophysical changes in the synapses between interconnected neurons. Ramon y Cajal was the first to suggest that synaptic contacts between neurons could play a role in memory storage (Ramón y Cajal, 1893) but it wasn't until the 1940s that the synaptic potentiation postulate of Donald Hebb was formulated. According to Hebb's influential theory, synapses between neurons are potentiated when they are concurrently activated, and this mechanism forms the physiological foundation for learning and memory (Hebb, 1949).

Synaptic modifications however are greatly influenced by the biophysical and anatomical complexity of their hosting structures, namely the dendritic branches (Fig. 1). The elaborated morphology together with the rich repertoire of voltage-gated ionic mechanisms found in dendrites (Häusser et al., 2000; Mainen and Sejnowski, 1996; Major et al., 2013; Sjöström et al., 2008; Spruston, 2008) influences the integration of synaptic signals and their forward propagation to the soma, enabling these structures to exhibit compartmentalized regenerative events (Häusser et al., 2000; Larkum et al., 2009; Nevian et al., 2007; Schiller et al., 1997; Wei et al., 2001) and support spatially restricted plasticity (Golding et al., 2002; Hardie and Spruston, 2009; Losonczy et al., 2008; Sjöström et al., 2008). These properties furnish dendrites with the ability to regulate synapse modification in complex, nonlinear ways thus adding another level of complexity in the memory formation process.

Within dendrites, an array of plasticity processes, which include Hebbian long-term potentiation or depression (LTP/LTD), synaptic tagging and capture (STC), plasticity of intrinsic excitability, local homeostasis *etc.*, govern the structural re-organization of synaptic contacts that takes place during memory formation. Many of these processes act locally, at the level of a dendritic branch or even a stretch of a dendritic branch (Zhang and Linden, 2003). Spatially restricted changes in synaptic properties have been proposed to underlie the formation of local groups or *clusters* of synaptic connections in dendritic compartments (Branco and Häusser, 2010). This hypothesis, termed *clustered plasticity*, has been associated with increased storage capacity (Poirazi and Mel, 2001) and feature binding (Govindarajan et al., 2006; Legenstein and Maass, 2011), both of which are important attributes of memory.

On top of it all, global balancing mechanisms, like homeostatic plasticity together with the plasticity of inhibitory connections (Kullmann et al., 2012; Turrigiano and Nelson, 2004; Zhang and Linden, 2003), ensure a smooth running operation of the neuronal circuits that capture, encode and store the life events or skills that we call memories.

In light of the evidence that memory trace formation is governed by plasticity processes operating at multiple levels, existing memory theories are being revised and refined (Branco and Häusser, 2010; Chklovskii et al., 2004; Govindarajan et al., 2006; Jadi et al., 2014; Redondo and Morris, 2011; Rogerson et al., 2014). In the view proposed here, memories are stored in small and distributed overlapping populations of neurons, in which synaptic clusters in dendritic branches encode for 'related' (in time, space or context) memories (Rogerson et al., 2014; Silva et al., 2009). Thus, the formation of a new memory trace does not only result in alterations of the connectivity strengths between neurons in a network, but also in the spatial arrangement of synapses and the excitability properties of dendritic branches where they reside (Chklovskii et al., 2004; Silva et al., 2009; Zhang and Linden, 2003) (see Fig. 3). Evidence for this hypothesis implies a mechanistic link between the expression of memory representations at the neuronal circuit level and the underlying cellular, dendritic and synaptic components that participate in their formation.

In this review, we discuss experimental and computational findings that examine how dendritic non-linearlities in conjunction with local and global plasticity processes shape memory formation in neuronal circuits.

2. Dendritic branches as key computational elements

In neocortical pyramidal neurons, dendritic branches provide the physical substrate where synapses are formed and modified through plasticity operations. Equipped with an array of biophysical mechanisms, *dendrites*[1] can dynamically modulate local voltage responses. This allows them to integrate the excitatory postsynaptic potentials (EPSPs) of the afferent synapses that impinge upon them in sublinear, linear or supralinear ways (Ariav et al., 2003; Branco and Häusser, 2011; Häusser et al., 2003; Longordo et al., 2013; Losonczy and Magee, 2006; Poirazi et al., 2003a; Silver, 2010; Yuste, 2011). On one hand, the elaborated biophysical profile of dendrites, which includes multiple types of voltage-gated conductances, has been postulated to mediate the linear integration of *distributed* synaptic inputs, irrespectively of their location within the neuron (Cash and Yuste, 1999; Yuste, 2011). On the

[1] There are several definitions for the word "Dendrite", depending on the cited papers. According to Wikipedia, *Dendrites* (from Greek δ?νδρον *déndron*, "tree") are the branched projections of a neuron that act to propagate the electrochemical stimulation received from other neural cells to the cell body, or soma, of the neuron from which the dendrites project. We consider as a single "dendritic branch" the section contained within two consecutive branch points (or one branch point and the tip for terminal dendrites) that is not part of trunk.

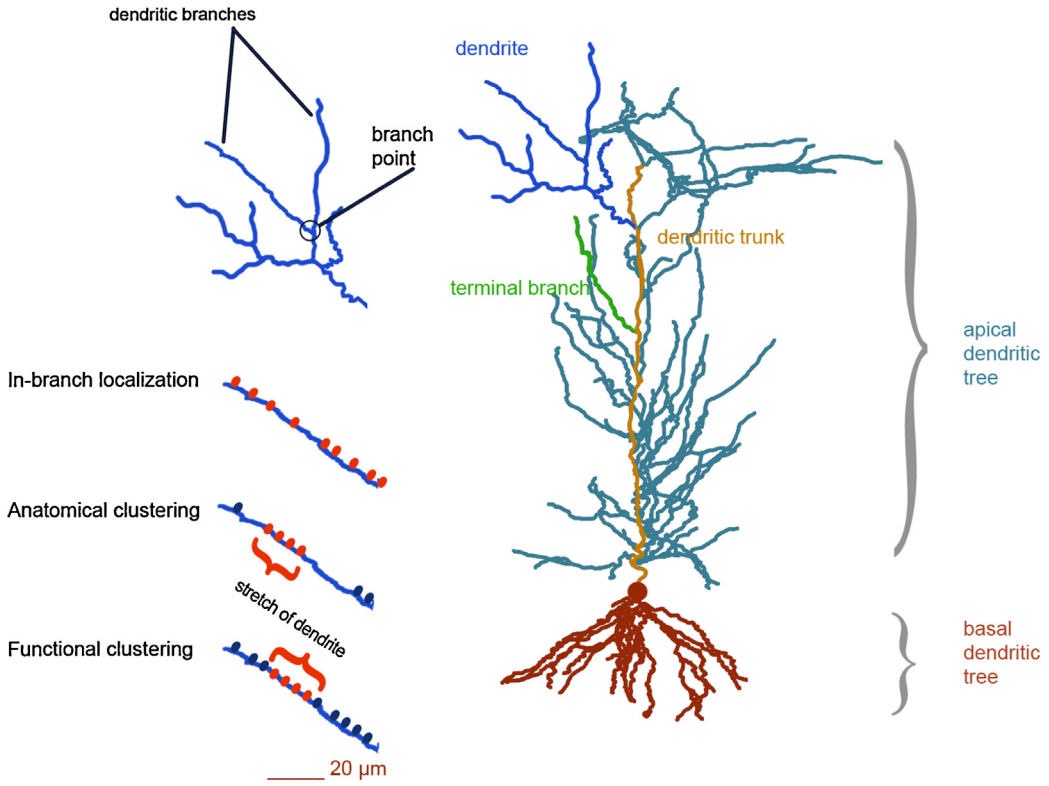

Fig. 1. Dendritic structure and plasticity. Each dendritic tree (apical or basal) in pyramidal neurons can be subdivided to a number of dendrites (dendritic subtrees connected to the apical trunk or the soma). Thin terminal branches are the main targets of excitation in the cerebral cortex. There, synaptic inputs can be organized in the following ways: (1) they can be localized in the same dendritic branch without specific spatial arrangement (in-branch localization), (2) they can form *anatomical clusters*, whereby spines form morphologically distinct groups of several spine heads located in distances less than 5 μm from each other within stretches of a given branch and (3) they can form *functional clusters* where spine density is uniform but nearby synapses (located within 10–20 μm) are activated synchronously. The implications of these different arrangements of connectivity at the dendritic level are discussed in Section 2.

other hand, the ability of dendritic branches in pyramidal and other neuron types to support local electrogenesis, evidenced by the generation of dendritic spikes, has been shown to underlie the non-linear integration of synaptic inputs.

Based on their primary source, dendritic spikes are distinguished in three main types: sodium, calcium and NMDA (N-methyl-D-aspartate) spikes, all of which have been extensively documented in pyramidal neurons both *in vitro* (Ariav et al., 2003; Gasparini et al., 2004; Golding et al., 2002; Kim et al., 2012; Losonczy and Magee, 2006; Makara and Magee, 2013; Nevian et al., 2007; Polsky et al., 2004; Schiller et al., 1997) and *in vivo* (Lavzin et al., 2012; Smith et al., 2013). They are characterized as nonlinear, all-or-none dendritic responses which can propagate actively for some distance and are often confined within the generating branch (Antic et al., 2010; Larkum and Zhu, 2002; Schiller et al., 1997, 2000b). This allows the branch, the dendrite or the neuron to integrate synaptic signals over much longer timescales than passive integration would allow.

Since the processing capabilities of pyramidal neuron dendrites are discussed in several excellent reviews (Branco and Häusser, 2010; Häusser et al., 2003; Major et al., 2013; Segev, 2000; Silver, 2010; Spruston, 2008), we highlight just a few of their key features. Cortical dendrites, perform synaptic integration non-uniformly, with distal inputs within the same branch being amplified over larger time windows compared to proximal ones (Branco and Häusser, 2011). This difference is attributed, by computational models, to the generation of NMDA-dependent dendritic spikes which are facilitated when synapses are located near the tip of a dendritic branch (Branco and Häusser, 2011; Sidiropoulou and Poirazi, 2012). As a result, distal synapses, which are individually too weak to significantly influence the somatic voltage, can act cooperatively to affect the output of the neuron (Schiller et al., 2000a). A similar nonlinearity that serves as a mechanism for coincidence detection also depends on NMDA conductances, this time in the apical tuft dendrites of layer 5 pyramidal neurons (Larkum et al., 2009). The initiation of dendritic spikes and their amplitude is, in turn, determined by the magnitude and location of inhibition that these neurons receive (Jadi et al., 2012).

The above are just a few examples of modeling and experimental studies suggesting that local spikes enable dendritic branches to implement nonlinear integration modes (Mel, 1993; Häusser et al., 2000; Gasparini et al., 2004, Polsky et al., 2004; Losonczy and Magee, 2006; Makara and Magee, 2013), thus conferring enhanced flexibility in neuronal information processing. In order to exploit this additional processing power of nonlinear dendrites, synaptic input should be such that the whole range of possible dendritic responses are explored, including the generation of dendritic spikes. As discussed in Sections 2.1 and 2.2, the spatial arrangement of synaptic inputs in dendritic branches can provide a way to realize this goal.

2.1. Effect of spatial synaptic arrangement on dendritic integration: distributed connectivity and linear integration

Distributed synaptic inputs, irrespectively of their location within the neuron, have been suggested to summate linearly, a result attributed to the elaborated biophysical profile of pyramidal neuron dendrites (Cash and Yuste, 1999; Yuste, 2011). This linear integration mode may be particularly useful when synaptic input is dispersed uniformly throughout the dendritic tree, for example

as a result of an essentially random connectivity between neurons that is dictated by anatomical constraints (Braitenberg and Schüz, 1998). According to this model, the connectivity of neuronal circuits is determined by the overlap of dendritic arbors and axonal processes, as dictated by Peters' rule (Peters et al., 1976). A series of *in vivo* imaging studies in sensory areas has provided indirect support for this model (Chen et al., 2011; Jia et al., 2010; Varga et al., 2011) by showing that neighboring synapses are tuned to apparently random input features (but see Section 2.4.3 for an alternative interpretation).

In a distributed connectivity model like the one discussed above, a large number of synapses must be activated in order to induce a postsynaptic spike. The integration of multiple distributed synaptic inputs within a neuron, however, is negatively affected by membrane dynamics that create an interference problem. Synaptic depolarization causes the opening of membrane conductances, thus lowering the membrane resistance and making the neuron less excitable in response to subsequent synaptic input. Dendritic spines with high electrical neck resistance have been suggested to counteract these effects by isolating synaptic inputs (Segev and Rall, 1998). Alternatively, spatially segregating the synaptic contacts throughout the dendritic tree may serve as a mechanism for implementing linear local summation of incoming signals (Yuste, 2011), however the requirement for a large number of distributed inputs would also lead to shunting effects. The distributed connectivity and linear summation model has inspired a large portion of the early artificial neural network research in the past decades (Hopfield, 1988; Minsky and Papert, 1969). While these models overly simplify the function of neurons, they have been instrumental in studying memory storage and have established synaptic weight changes caused by plasticity as a valid mechanism of learning in artificial neural networks (McClelland and Rumelhart, 1986).

2.2. Effect of spatial synaptic arrangement on dendritic integration: clustering and supralinear integration

The distributed connectivity model presented above has been challenged by findings in several brain regions, including the hippocampus and the cerebral cortex. As detailed in Section 2.4, an increasing number of studies have shown that synaptic contacts can group together within a short stretch of the dendritic branch, forming *anatomical clusters*[2] (Makino and Malinow, 2011; Yadav et al., 2012) and/or create *functional clusters* whereby several neighboring synapses are activated synchronously (Fu et al., 2012; Kleindienst et al., 2011; Takahashi et al., 2012), in the absence of obvious spine density changes. This patterned spatial synaptic arrangement along with concrete evidence of dendritic spike generation both *in vitro* (Ariav et al., 2003; Häusser et al., 2000; Kim et al., 2012; Larkum and Nevian, 2008; Losonczy and Magee, 2006; Makara and Magee, 2013; Nevian et al., 2007; Schiller et al., 2000a) and *in vivo* (Lavzin et al., 2012; Major et al., 2013; Smith et al., 2013), are not accounted for by the distributed connectivity and linear integration model, challenging the traditional view of synaptic weight-based learning. An alternative theory entails that, changes in the spatial wiring of synaptic connections together with dendritic excitability modulation, can serve as additional memory reservoirs in the brain (Chklovskii et al., 2004).

In particular, the spatial arrangement of incoming inputs within active dendrites of both simplified (Mel, 1993; Poirazi and Mel, 2001) and biophysically detailed neurons (Poirazi et al., 2003a,b) was theoretically predicted to influence the dendritic and neuronal output by differentially engaging local conductances. For example, synchronous activation of synapses within the same apical branch (hereby termed *in-branch localization*, see Fig. 1) of a biophysically realistic pyramidal neuron model was predicted to result in supralinear responses while stimulation of the same number of synapses distributed in different branches resulted in linear summation (Poirazi et al., 2003a). This prediction was verified experimentally in L5 neocortical pyramidal neurons (Polsky et al., 2004), highlighting the effect of synapse placement on neuronal output. Supralinearity in this case resulted from the induction of dendritic spikes, a phenomenon that was not seen when synapses were stimulated across different branches.

Similar supralinearities were also found in oblique dendrites of CA1 pyramidal cells, upon stimulation of synapses within individual radial oblique branches (Losonczy and Magee, 2006). In this case, synchronous stimulation of nearby synapses (mimicking *functional clustering*, see Fig. 1) had the same effect as synchronous stimulation of the same number of synapses distributed uniformly within the branch (*in-branch localization*), suggesting that these structures act as single, nonlinear integrative compartments, as predicted by previous modeling work (Poirazi et al., 2003a,b). These dendrites have also been suggested to act as coincidence detectors (Ariav et al., 2003; Gómez González et al., 2011; Losonczy and Magee, 2006) or as detectors of asynchronous bursty inputs (Gómez González et al., 2011), *via* the induction of fast or slow, respectively, dendritic spikes. Evidence of such independent integrative compartments provides support for a 2-stage model of neuronal processing (Katz et al., 2009; Poirazi et al., 2003b), with multiple implications with respect to information processing (for a recent review on the 2-layer model, see Jadi et al. (2014)).

The placement of synapses at different parts (proximal *vs.* distal) of dendritic branches has also been predicted and experimentally evidenced to influence dendritic and neuronal responses (Behabadi et al., 2012; Branco and Häusser, 2011). For example the amplitude of EPSPs and the supralinearity of electrical integration during the stimulation of multiple synapses varies from the base to the tip of a single dendrite. The tip displays both higher EPSP amplitude, higher gain, and higher EPSP supralinearity compared to the base or the middle section of the dendrite (Branco and Häusser, 2011). Moreover, the amplitude and threshold of basal dendritic spikes is affected by the positioning of excitation along the dendrite (Behabadi et al., 2012). Distal excitation lowers the threshold for dendritic spike generation in more proximal inputs, while proximal excitation lowers the threshold and increases the voltage gain of distal inputs.

In sum, models and experiments have shown that the location of any given synapse influences its effective "weight" (*i.e.* its impact on dendritic and neuronal depolarization), since co-activation of neighboring synapses will result in a much larger depolarization than if the particular synapse is activated in isolation. These findings suggest that the spatial organization of synaptic contacts is also likely to have a key role in plasticity processes that underlie learning and memory formation, as detailed in the next session.

2.3. LTP cooperativity in nearby inputs

Beyond spatiotemporal integration, dendritic depolarization and dendritic spikes have a strong effect on Long Term Potentiation (LTP), a form of synaptic plasticity which is believed to play a key role in learning and memory formation. In CA1 pyramidal neurons,

[2] As shown in Fig. 1, there are two major types of synaptic clustering: (a) *anatomical clustering*, whereby spines form morphologically distinct groups of several spine heads located in distances less than 5 μm from each other and (b) *functional clustering*, where spine density is uniform but nearby synapses (located within 10–20 μm) are activated synchronously.

local synaptic depolarization that results in dendritic spikes can induce LTP even in the absence of somatic spiking (Golding et al., 2002; Hardie and Spruston, 2009). In addition, this form of LTP is stronger when paired synaptic inputs are both located in the apical dendrites than if they are separated in the apical and basal trees. This suggests that the large and long lasting dendritic depolarization generated by the activation of spatially proximal synapses is more effective in inducing strong LTP than the pairing of dendritic input with back-propagating action potentials. Where does this difference stem from? Possibly from the ability of spatially close synapses to undergo plasticity in a cooperative manner.

Cooperativity is the ability of multiple activated synapses to collectively overcome the threshold for plasticity and is a characteristic property of LTP that is presumed to be mediated by NMDA calcium influx (Bliss and Collingridge, 1993; Sjöström et al., 2001). Synaptic input which leads to LTP in dendrites initiates complex biochemical signaling cascades in the dendritic region, triggered by the influx of calcium and the elevation of its local concentration (Baudry et al., 2011). Some of these pathways facilitate the cooperativity of LTP at nearby synapses, and this can lead to the coordinated potentiation of neighboring synapses, thus promoting synaptic clustering. For example, the MAPK (mitogen-activated protein kinase) and mTOR (*mechanistic target of rapamycin*) cascades remain active for several minutes after their initial activation (Wu et al., 2001). This prolonged activation allows the spread of proteins and kinases to nearby synapses, thus facilitating their plasticity. The Ras GTPase, which is part of the MAPK signaling pathway and is correlated with increased spine volume during LTP induction, has been shown to spread and invade nearby spines (Harvey et al., 2008). In addition, the RhoA GTPase was found to spread out of stimulated dendritic spines undergoing structural plasticity related to LTP for about 5 μm along the dendrite (Murakoshi et al., 2011). These molecular mechanisms support the cooperative potentiation of synaptic clusters at the spatial scale of <20 μm and are detailed in several excellent reviews (Hering and Sheng, 2001; Patterson and Yasuda, 2011; Winnubst et al., 2012).

Another mechanism that enables local cooperativity of LTP is the activation of 'silent' synapses. Silent synapses contain only NMDA receptors and are blocked by Mg^{2+}ions when the local membrane is in its resting state. Activation of nearby synapses, however, can remove the Mg^{2+} block, allowing these synapses to become conductive. Under a Hebbian plasticity protocol, this could eventually lead to the insertion of AMPA receptors in the synapse, thus 'unsilencing' the synapse (Liao et al., 1995).

Clusters can also be formed by the addition of new synapses near existing ones (Fu et al., 2012), which effectively changes the wiring diagram, however such changes are typically slower as they require the restructuring of neural tissue (Chklovskii et al., 2004; Trachtenberg et al., 2002). Since both synapse formation and elimination are processes that persist in the adult brain (Trachtenberg et al., 2002), it may be possible that LTP cooperativity interacts with synapse formation or the conversion of filopodia to dendritic spines and biases the formation of anatomical synaptic clusters.

The abovementioned evidence indicates that LTP cooperativity in nearby synapses can lead to the formation and stabilization of *functional* and *anatomical* (Fig. 1) clusters of synapses within frequently stimulated dendrites. This clustering may serve as a mechanism for effective wiring, whereby connections are established by sharing protein products, thus saving energy and molecular resources, while at the same time dendritic non-linearities are fully exploited *via* the selective induction of dendritic spikes (Winnubst et al., 2012). Based on this evidence, the *clustered plasticity* hypothesis has been put forward, which proposes that inputs with correlated activity patterns (presumably sharing some functional features), are more likely to be organized in functional and/or anatomical clusters within the dendrites of pyramidal neurons (Govindarajan et al., 2006; Harvey and Svoboda, 2007; Poirazi and Mel, 2001). This view has gradually been gaining experimental support, through the advent of modern imaging methods which allow the detailed mapping of synapses in dendritic arbors. In the following section we summarize the most important experimental findings that support this hypothesis.

2.4. Experimental evidence for synaptic clustering

2.4.1. Anatomical clustering

Evidence for anatomical synapse clustering was first shown in the dendrites of the adaptive microcircuit of the barn owl auditory localization circuit (McBride et al., 2008). Barn owls reared with prismatic spectacles develop an adaptive zone that does not exist in normally reared animals and is a result of the animal's abnormal experience. The experimenters found both increased clustering (contacts located within <20 μm) of axodendritic contacts (potential synapses) in the adaptive zone (presumably a result of the physiological and behavioral adaptation caused by the abnormal experience of the prism) and decreased clustering in the normal zone, indicating that dendritic synapse clustering is correlated with this type of learning (McBride et al., 2008). Importantly, the total number of contacts per dendrite remained constant throughout the experiment, indicating that synaptic contacts were both created and eliminated. Thus, reorganization of the local circuitry during development is accompanied by synaptic clustering.

Assessing the connectivity between neuronal populations with advanced fine-scale circuit mapping methods has also provided evidence that, during development synapses tend to cluster in dendritic domains. Specifically, Druckmann et al. (2014) found that the connectivity between the CA3-CA1 hippocampal neurons is highly structured and clustered both at the neuronal and at the dendritic branch level. By examining pairs of neurons that shared the same neurogenesis and synaptogenesis time window, the authors found exceptionally high anatomical synaptic clustering (five times larger than "normal" or "random" clustering), indicating selective and highly clustered synapse formation between neurons which share the same developmental history.

Anatomical spine clustering has also been documented during learning. By imaging the formation of spines in motor cortex dendrites, Fu et al. analyzed the spine changes that occur during the learning of a motor task that was repeated over multiple days (Fu et al., 2012). During this learning protocol, the majority of new spines that were formed in adjacent positions in the dendrite were more clustered than control spines (in distances <5 μm), and the process was dependent on the activation of NMDA receptors. This study showed that newly formed spines, are highly likely to be added to the existing clusters, thus contributing to the refinement or reinforcement of motor learning. In addition, clustered spines were more stable than isolated ones, implying that the arrangement of synapses in clusters may promote the stability of long-term memories. Increased anatomical clustering of potentiated synapses has also been observed in an *in vitro* study which simulated spaced learning in the hippocampus (Kramár et al., 2012).

Further evidence for anatomical synapse clustering has been provided by the *in vivo* visualization of plasticity-induced receptor trafficking during learning. Makino and Malinow (2011) used fluorescently tagged glutamate receptor type 1 (GluR1) subunits to visualize the trafficking of AMPA receptors during normal sensory experience as well as during sensory deprivation (whisker removal). Normal experience (*e.g.*, whisking) triggers coordinated trafficking of GluR1 subunits to nearby synapses in the dendritic

tree of somatosensory neurons in mice. The authors estimated the size of synaptic potentiation at approximately 8 μm of dendritic length. The clustering of GluR1 subunits was not evident on sensory-deprived mice, indicating that rich sensory experience results in higher clustering. In addition, mutations in GluR1 subunits that render them insensitive to modulation signals induced by LTP cooperativity prevented the coordinated potentiation of nearby synapses in dendritic branches.

Anatomical clustering has also been documented in the primate cortex (Yadav et al., 2012). Analysis of the locations of spines in the prefrontal cortex of rhesus monkeys confirmed the preference for spatial spine clustering. The clustering of spines was concentrated in the terminal branches, which receive the majority of synaptic inputs and the clusters were found to predominantly contain mushroom and stubby-shaped spines.

Finally, an imaging study about memory consolidation after sleep provides new evidence regarding the compartmentalized allocation of spines (Yang et al., 2014). This study showed that different learning tasks cause spine formation on different sets of dendritic branches after sleep consolidation. The formation of these spines depended on the reactivation, during sleep, of the same population of neurons that were active during learning, suggesting that sleep may promote learning and enable the allocation of synapses encoding for different memories to different dendrites.

2.4.2. Functional clustering

Co-activation of neighboring synapses in the absence of profound differences in spine density, termed functional clustering, has also been documented both *in vitro* and *in vivo*, during development and as a result of learning. Using calcium imaging, Kleindienst et al. (2011) investigated the connectivity and activation patterns in organotypic cultures of the developing hippocampus of rats. The authors found that synapses located within a distance of 16 μm had correlated activity, indicating that synapses tended to activate in clusters. This clustered activation of nearby synapses was crucially dependent on neuronal spiking and NMDA receptor activation. In this particular study no evidence was provided regarding the possibility or exclusion of anatomical clustering of co-active synapses.

In vivo imaging also allows the functional mapping of active synapses. By visualizing the synaptic activation of neurons in the barrel cortex of mice, Takahashi et al. found that activated synapses tended to form functional 'assemblets' which were synchronized and locally confined (Takahashi et al., 2012). Specifically, nearby spines were found to be significantly co-activated and tended to form functional synaptic clusters which consisted of groups of synapses (2–12 synapses within <10 μm) in dendritic branches. The spines which participated in these assemblets were larger in size compared to spines that did not form assemblets, indicating that assemblets might have been formed by LTP mechanisms. Indeed, the authors found reduced clustered activation of synapses in tissue that was cultivated in the presence of NMDA receptor antagonist. Moreover, the authors found that the clustered activation results from the concurrent activation of afferent axons which impinge on the synapses. The fact that these afferents synapse in a clustered fashion indicates that synaptic plasticity may have molded a synaptic cluster through either remodeling of the connectivity (*i.e.* the creation of new synapses) or through the cooperative potentiation of synapses that happened to be proximal to each other.

Overall, the large number of studies providing experimental evidence for both anatomical and functional synaptic clustering (some examples are shown in Fig. 2) suggests that clustering may be a common pattern of organization conserved across different brain areas and species (DeBello et al., 2014).

2.4.3. Functional properties of neighboring synapses

In addition to identifying the presence of anatomical or functional synaptic clusters, a number of mapping experiments have examined the coding or tuning features of neighboring synapses in sensory cortices. These experiments show that synapses in nearby spines do not necessarily share the same or similar sensory tuning features as one would expect, but instead the tuning of synapses varies widely along the same dendritic branch without an apparent orderly arrangement. More specifically, combining high-speed 2-photon imaging with electrophysiological recordings in the visual (Jia et al., 2010), auditory (Chen et al., 2011) and barrel (Varga et al., 2011) cortices, it was shown that synapses on nearby spines in dendrites of pyramidal neurons code for seemingly unrelated orientations, sound frequencies or whiskers and whisker combinations, respectively. These findings appear to contradict the hypothesis of synaptic clustering, which predicts that synapses, which carry correlated information, would form functional synaptic clusters in dendrites. This contradiction can be reconciled with the clustering model, however, if we accept that functional clusters of synapses do not code for a continuum of elementary sensory features (*e.g.* subsequent letters of the alphabet) but for combinations of such features which form conceptual entities of behaviorally relevant natural stimuli (*e.g.* words). For example, a functional synapse cluster in the primary auditory cortex could be composed of synapses that are tuned to the frequencies contained in natural speech. As these frequencies vary over a wide range, the tuning of synapses in a functional synaptic cluster which would respond to natural speech would thus reflect this wide range of frequencies. It would be interesting to investigate experimentally the spatial organization of synapses in response to presentation of combinations of input features that are relevant to the animal (*e.g.* frequencies contained in behaviorally relevant sounds) to test this hypothesis.

In sum, the experimental evidence provided above suggests that, although synaptic clustering remains an active area of research, there is considerable evidence for spatial synapse clustering, either anatomical, functional or both, as a result of learning. As described in Section 2, this clustering provides advantages for memory storage by, for example, ensuring the propagation of 'strong' or 'important' signals as opposed to noise *via* the facilitation of nonlinear responses and dendritic spikes. Further experiments are expected to clarify the roles of distributed and clustered connectivity, as well as the range of its functional implications.

2.4.4. A cautionary note

It should be noted that dendritic function and plasticity have been studied at different spatial scales and therefore the role of synaptic clustering in enabling dendritic braches or stretches inside them to act as computational elements remains unclear. On the one hand, whole dendritic branches have been proposed to be elementary units of memory function and storage (Branco and Häusser, 2010; Govindarajan et al., 2006). The level of compartmentalization of function and plasticity in this case is limited by (a) the extent in which local signals can be integrated nonlinearly (*e.g.* in order to generate dendritic spikes) and (b) by the spatial spread of biochemical signaling which would allow cooperative plasticity. In this context, dendritic 'subunits', which represent electrically independent thin terminal branches (receiving the bulk of incoming synaptic connections, Megıas et al., 2001), have been studied theoretically and shown to provide an additional level of computation in the cell (Archie and Mel, 2000; Jadi et al., 2014; Migliore et al., 2008; Poirazi et al., 2003b; Wu and Mel, 2009). This model is corroborated by experiments which show nonlinear synaptic integration at distances <40 μm (Polsky et al., 2004) and studies of synaptic tagging which find LTP cooperativity within

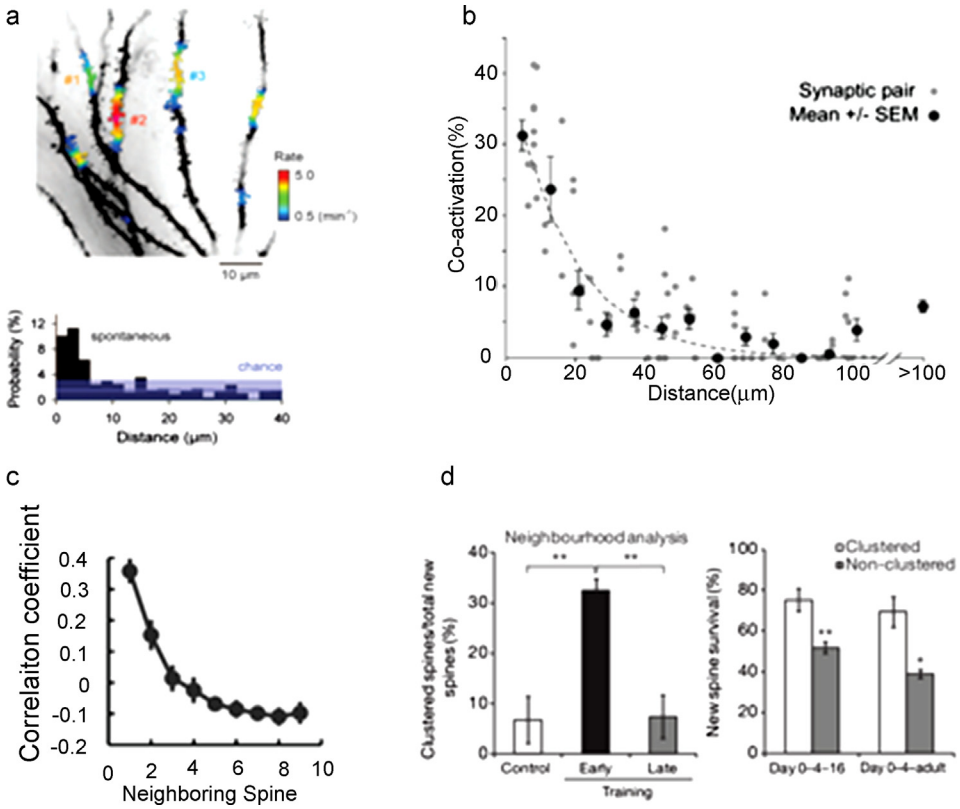

Fig. 2. Evidence for synaptic clustering. (a) Top: Observation of functional synaptic clusters *ex vivo*. Color rate code is the frequency with which these "assemblets" are activated. Bottom: Probability of observing co-activated spines as a function of the inter-spine distance compared to chance level (shaded), as observed *in vivo* in the mouse barrel cortex. Reproduced with permission from (Takahashi et al., 2012). (b) Co-activation of synapse pairs in a developing hippocampal neuron observed *ex vivo* as a function of the distance between pairs of synapses. Reproduced with permission from (Kleindienst et al., 2011). (c) AMPA enrichment is correlated in nearby synapses, as observed using a fluorescently tagged AMPA receptor *in vivo*. Reproduced with permission from (Makino and Malinow, 2011). (d) New Spines formed during learning a repetitive motor task are more likely to form clusters. Additionally, clustered spines have a higher survival rate over a 16-day period. Reproduced with permission from (Fu et al., 2012).

dendritic segments <60 μm (Govindarajan et al., 2011). Importantly, both synaptic integration and synaptic plasticity at dendritic subunits have been found to be relatively isolated between branch points (Govindarajan et al., 2011; Polsky et al., 2004). On the other hand, the computational properties of smaller-scale synaptic interactions which occur at <20 μm have also been theorized to provide computational advantages in learning (Mel, 1992), pattern discrimination (Mel, 1991) and orientation tuning (Mel et al., 1998) and such synaptic arrangements could arise from STDP (Iannella and Tanaka, 2006).

It is yet unclear how the properties of synapse clustering at the microscopic level affect the dendritic-subunit compartmentalization. However, the experimental evidence discussed in Section 2.4 shows that the spatial arrangement of activated synapses within dendritic branches is, in many cases, neither uniform nor random. More experiments are needed to clarify how this spatial clustering influences the ability of dendritic subunits (whether branches or stretches of a branch) to act as independent computational elements.

2.5. Plasticity of dendritic excitability

In parallel with synaptic clustering, synaptic activity can change the conductance of ionic currents which determine the excitability of neuronal membranes. This dynamic adaptation of intrinsic excitability can influence the way dendrites integrate synaptic inputs and consequently affect the neuronal output. Lasting changes in excitation properties are a form of plasticity called *plasticity of intrinsic excitability*, which can be induced by electrical stimulation *in vitro*, or through exposure to an enriched environment. For instance, A-type currents are persistently downregulated after LTP-inducing excitatory stimulation of CA1 pyramidal neurons, leading to increased dendritic excitability (Frick et al., 2004). In addition, LTP and LTD protocols in CA1 result in the increase and decrease, respectively, of the linear summation of postsynaptic responses. This bidirectional plasticity of excitability reflects changes in the hyperpolarization-activated I_h currents and NMDA receptors (Wang et al., 2003). In the latter study, while blockade of both I_h and I_A channels had similar effects in increasing the linearity of synaptic summation, the increase in summation that follows LTP was mainly attributed to modulation of I_h.

The plasticity of intrinsic excitability can be locally restricted to dendritic branches *via* alterations in branch coupling strengths: repeatedly triggering dendritic spikes in a dendrite *in vitro* leads to a slow but long-lasting increase in the coupling strength of the dendrite to the somatic depolarization which is mediated by downregulation of A-type potassium currents (Losonczy et al., 2008). The regulation of dendritic excitability may thus be exploited as a compartmentalized memory storage mechanism during learning. Indeed, it has been shown that exposure of rats to an enriched environment leads to the enhancement of dendritic spike propagation selectively in a subset of dendritic branches of CA1 neurons (Makara et al., 2009).

In the above-mentioned studies, the localized alteration of dendritic excitability was attributed to the activity-dependent regulation of ionic currents. It is not clear however if the plasticity of dendritic excitability requires synaptic input or synaptic

plasticity. To investigate this issue, a recent study tested the plasticity of dendritic excitability using photostimulation of hippocampal dendrites in neurons infected with a channelrhodopsin-2 (ChR2) vector (Labno et al., 2014). Interestingly, the pairing of dendritic photocurrent with somatic spiking induced localized *depression* of excitability. This depression was not dependent on synaptic activation or LTP induction, but was sensitive to calcium. Moreover, the depression was conferred by changes in the A-type potassium current, similarly to the case of branch strength potentiation. These two examples suggest a key role of the A-type K^+ channel in regulating the local intrinsic excitability of pyramidal neuron dendrites.

Taken together, these results indicate that dendritic excitability is a dynamic property which can undergo long-term potentiation or depression in response to specific stimulation protocols, and it can be dissociated from synaptic plasticity. Therefore, the plasticity of dendritic excitability can serve as a mechanism that modulates localized synaptic activity and contributes to localized memory storage, so that it can be considered part of the memory engram (Legenstein and Maass, 2011; Papoutsi et al., 2012; Sjöström et al., 2008; Zhang and Linden, 2003).

Overall, in Section 2, we provided compelling evidence that both synaptic plasticity and the plasticity of intrinsic ionic conductances enhance the flexibility of dendritic responses, endowing dendritic branches, or even membrane stretches inside them, with key computational features that support a pivotal role in memory formation. The molecular processes that may underlie such a model of localized information storage are discussed next.

3. Synaptic consolidation and protein capture

The mechanisms which determine the effect of synaptic plasticity and the resulting changes in connectivity on memory formation are numerous and complex. Indeed, the induction of synaptic plasticity involves networks of signaling cascades and kinase activation which have timescales that vary from seconds to hours (Bhalla, 2011; Citri and Malenka, 2008). Nevertheless, a high-level model of memory consolidation can capture important aspects of memory encoding and its protein dependence. The synaptic tagging and capture model, described in the next section is such a powerful framework for characterizing the role of late-LTP processes in memory encoding and provides the foundation for models of localized, clustered memory storage (Govindarajan et al., 2006; Rogerson et al., 2014).

3.1. The synaptic tagging and capture (STC) model

According to the model of synaptic tagging and capture (Frey and Morris, 1997; Redondo and Morris, 2011), the consolidation of synaptic potentiation which is believed to underlie permanent memory storage occurs in a number of phases. Initially, synaptic plasticity sets a local synaptic tag in the synapse targeted for potentiation or depression. The synthesis of plasticity related proteins (PRPs), which are required for synaptic potentiation, takes place over a period of hours after learning. Finally, the synapses that were tagged capture the synthesized PRPs in order to stabilize their synaptic strengths.

The synaptic tagging and capture (STC) model was initially proposed based on LTP experiments showing that protein-synthesis-dependent LTP could be induced under conditions of protein synthesis inhibition, given that stimulation of a different pathway occurred within a few hours (Frey and Morris, 1997; Reymann and Frey, 2007). The phenomenon was observed by the facilitation of late-LTP in weakly stimulated synapses through the activation of a second strongly stimulated set of synapses (Frey and Morris, 1997). Weak stimulation normally results in early-LTP, a form of LTP that decays after a few hours. As a consequence of the strong stimulus, however, weakly stimulated (but tagged) synapses – which would normally only express early-LTP – can capture the PRPs generated by strong stimulation of the second set of synapses and thus express late-LTP, as observed in synaptic cross-capture experiments (Redondo and Morris, 2011; Sajikumar and Frey, 2004).

The implications of the STC model for learning and memory concern the interactions that are expected to arise between learning events that occur within a defined time horizon. This interaction was tested in behavioral experiments which involved pairing a weak learning protocol with a strong form of learning or environmental novelty. By pairing a weak learning protocol, which normally induces short-term memory, with environmental novelty, it was found that novelty – considered a strong learning event – promotes the formation of long-term memory, presumably through the mechanisms of STC (Ballarini et al., 2009; De Carvalho Myskiw et al., 2013; Moncada and Viola, 2007). Indeed, the memory enhancement was prevented when the protein synthesis inhibitor anisomycin was introduced along with the environmental novelty. These experiments suggested that there are alternative sources of memory-related proteins needed for late-LTP, some of which can be localized within dendritic branches as discussed in the next session.

3.2. STC and local protein synthesis

Synaptic plasticity involves numerous kinases, phosphatases, as well as various molecular signaling pathways (Citri and Malenka, 2008), the activation of which may be spatially constrained. This suggests that molecular signaling cascades may underlie the cooperativity effects observed in plasticity induction within nearby sites in dendrites (Bhalla, 2011; Govindarajan et al., 2011; Harvey et al., 2008; Murakoshi et al., 2011). In addition, the PRPs required for plasticity can be synthesized by the protein synthesis machinery existing in the cell soma, or they may be translated locally by ribosomes which exist in dendritic arbors. Several studies have established the existence of ribosomes, in hippocampal dendrites (Bodian, 1965; Bourne and Harris, 2011; Steward and Levy, 1982; Sutton and Schuman, 2006). These ribosome complexes were found to be near synaptic sites, thus positioned appropriately to facilitate plasticity. Moreover, a large number of mRNAs have been found in hippocampal dendrites and many of those mRNAs code for known synaptic proteins (Cajigas et al., 2012; Steward and Schuman, 2007). This evidence suggests that dendrites may support local forms of plasticity that do not depend on transcription or somatic protein synthesis by sustaining their own protein synthesis which is triggered by local signaling pathways. Dendritic protein synthesis was first identified to be a requirement for rapid synaptic potentiation under exposure to BDNF (Kang and Schuman, 1996) and has since been found to be required for many forms of synaptic plasticity (Sutton et al., 2006).

Based on these observations, it has been proposed that the phenomenon of STC may occur at the dendritic level. In this case, it can lead to LTP interactions and to the generation of activity associations at the dendritic level, *via* the strengthening and stabilization of neighboring synapses, thus facilitating synaptic clustering (Govindarajan et al., 2006; Kelleher et al., 2004; Rogerson et al., 2014). A recent *in vitro* study confirmed that STC can take place at the level of the dendritic branch (Govindarajan et al., 2011). Using glutamate uncaging and two-photon imaging, it was shown that local protein synthesis induced in a synaptic spine could convert the early-LTP of a nearby spine to late-LTP *via* synaptic capture mechanisms. This conversion of early-LTP to late-LTP was dependent on the time interval between the stimulation and protein synthesis and on the distance between

the two spines. The strength of this synaptic cross-capture was inversely proportional to the distance and it did not occur for distances larger than 70 μm on the same dendritic branch or larger than 50 μm when the synapses were placed in sister branches. In addition, the authors found that during LTP consolidation, tagged synapses compete for the capture of available proteins, indicating that the availability of synaptic proteins is a limiting factor for dendritic STC.

It should be noted, however, that certain forms of LTP require gene transcription along with protein synthesis, such as the long-term LTP induced during theta burst stimulation and serotonin application in hippocampal slices (Huang and Kandel, 2007). It is thus possible that different forms of LTP are employed by different brain areas, and/or under different stages of memory consolidation (Izquierdo et al., 2006), which could lead to differential spatial distributions of potentiated synapses (*i.e.* clustered *vs.* distributed). While this is the dominant view of the role of protein synthesis in learning and memory, there are alternative views where protein synthesis plays a more passive role. Protein synthesis may be more peripherally involved in the formation of memories where it is needed to replace proteins 'consumed' by learning or the inhibition of protein synthesis impairs the general well-being of neurons, leading to an inability to deliver resources needed for memory formation (Gold, 2008; Routtenberg and Rekart, 2005). This view suggests that protein synthesis is necessary to just replenish resources that are depleted by memory formation mechanisms.

3.3. STC and memory formation

An intriguing consequence of dendritic STC is that it can become a mechanism for associating temporally close memories, which are expected to form memory representations captured by nearby synapses. This mechanism would result in the generation of functional and/or anatomical clusters of synapses that code for memories that are temporally related over large time frames, defined by the temporal overlap between the life time of the synaptic tag and the upregulation of PRPs. According to such a model, the cross-capture of proteins between synapses that express either LTP or LTD can lead to clustered formation of memory engrams (Govindarajan et al., 2006). As described by previous modeling work, clustered formation of memory engrams whereby synapses with correlated activity are grouped within dendritic branches greatly expands the information storage capacity of neural tissue (Poirazi and Mel, 2001). Moreover, synaptic clustering resulting from STC has been hypothesized to mediate the cellular and behavioral binding of memories that are temporally related (Rogerson et al., 2014; Silva et al., 2009). More studies are needed to investigate the validity and consequences of this hypothesis.

4. Plasticity of inhibition influences dendritic integration

The vast majority of plasticity studies have focused on the plasticity of excitatory connections. However, a significant body of recent work has shown that inhibitory connections are also plastic (Huang et al., 1999; Kullmann et al., 2012), and follow the patterns of excitatory contacts (Chen et al., 2012).

Inhibition plays a major role in shaping neuronal output throughout the brain, and displays significant variability in its magnitude and targeting (Klausberger and Somogyi, 2008). For example, dendritically-targeted inhibition regulates the input–output-transformations in CA1 pyramidal cells and increases the threshold for dendritic spiking, while perisomatic inhibition controls oscillatory activity and suppresses the amplitude of dendritic spikes (Jadi et al., 2012; Lovett-Barron et al., 2012). Thus, neurons can tailor their output by adjusting the location of inhibition that they receive in different dendritic pathways. Importantly, computational modeling suggests that local inhibition can regulate the plasticity of excitatory connections, by controlling calcium influx through the postsynaptic voltage (Bar-Ilan et al., 2012). Indeed, somatostatin-expressing inhibitory neurons exert local compartmentalized control over the Ca^{2+} signals within individual spines, in a way that can directly affect the biochemical signaling of plasticity processes (Chiu et al., 2013). Inhibitory synaptic boutons, on the other hand, have been found to be unstable and are believed to continuously probe the postsynaptic membrane for synapse formation (Schuemann et al., 2013).

In relation to the clustering hypothesis, a recent study examined the dynamics of inhibitory synapses along with the dynamics of spines in the mouse visual cortex (Chen et al., 2012). The authors found that inhibitory synapses made on dendritic spines were more dynamic than inhibitory synapses on dendritic shafts. Importantly, these spines followed closely the arrangements of other dynamic spines within ~10 μm which were presumably excitatory, thus indicating that inhibitory synapses exhibit the same clustered plasticity pattern of excitatory synapses. In addition, inhibitory synapses in spines had different remodeling kinetics during altered sensory experience. These findings show that inhibitory synapses closely follow the spatial arrangement of excitatory synapses, and therefore they are likely to form anatomical clusters with them.

The coordinated plasticity of excitatory and inhibitory connections has been suggested to play a major role in the stability of simulated cortical networks, where a "detailed balance" of excitation/inhibition is required (Vogels and Abbott, 2009).

5. Regulation of synaptic plasticity by local homeostasis

Apart from inhibition, homeostatic plasticity is another major balancing mechanism which acts continuously to regulate synaptic plasticity in the long term. The effect of homeostatic regulation on synaptic clustering and dendritic excitability is thus critical in a model of memory formation where dendritic branches play a key role. Homeostatic phenomena include changes in the intrinsic membrane excitability, the regulation of presynaptic transmitter release, the balancing between excitation and inhibition as well as alterations in neuronal connectivity and modulation of synaptic strengths (Turrigiano and Nelson, 2004). As the focus of this review is synapse clustering, we briefly discuss evidence regarding local homeostasis taking place within dendrites. For a more in-depth discussion on homeostatic plasticity mechanisms we direct the reader to a number of excellent reviews (Abraham, 2008; Pozo and Goda, 2010; Turrigiano and Nelson, 2004).

Homeostatic plasticity can be local, thus regulating only the synapses located within a specific branch (Rabinowitch and Segev, 2008). Such specificity may be critical for the maintenance of existing memory engrams during the continuous formation of new ones. Recent studies have identified forms of homeostatic plasticity which operate at the level of the synapse and/or the branch. Hou et al. found that increasing the presynaptic firing that drives a synapse, caused a selective downregulation of GluA1 receptors in the postsynaptic site (Hou et al., 2011). This indicates a synapse-specific homeostatic regulation mechanism that compensates for increased synaptic input. Another study used a combination of two-photon glutamate uncaging and imaging to show that individual synapses can compensate for changes in their input *via* homeostatic regulation that is independent of their neighboring synapses (Béïque et al., 2011). In this case, homeostatic plasticity was found to require the immediate early gene Arc, which is known to be implicated in synaptic plasticity. The functional role of localized or synapse-specific homeostatic plasticity is not straightforward, as it seems to be a rule that

counters the action of LTP in individual synapses, thus leading to erasure of information. A computational study, on the other hand, has shown that a local form of homeostasis which acts on groups of nearby synapses in dendrites can mediate normalization of responses without disrupting synaptic plasticity (Rabinowitch and Segev, 2008).

Along with the homeostasis of excitatory connectivity, homeostasis of inhibitory connections acts in concert with synaptic potentiation to regulate the strength of inhibition (Echegoyen et al., 2007). At the dendritic level, the dynamic interplay between excitatory and inhibitory synaptic inputs depends on their spatial proximity (Liu, 2004) while at the synaptic level AMPA receptor expression at single synapses is homeostatically regulated under conditions that increase either inhibition or excitation (Hou et al., 2011). The latter indicates the ability of synapses to self-regulate their synaptic potency.

How homeostasis, synaptic plasticity, plasticity of excitability and plasticity of inhibition interact to regulate the action of synapses at the dendritic level is not clear, as these processes have different timescales and roles. Intrinsic excitability appears to positively enhance Hebbian plasticity, while homeostasis provides a form of negative feedback to synaptic action (Sjöström et al., 2008). Interestingly, dendrite-specific LTP coupled with homeostatic depression was computationally predicted to maximize the learning capacity of a medial temporal lobe model implementing online learning (Wu and Mel, 2009). The dendritic learning rules led to an order-of-magnitude increase in the capacity of the network compared to Hebbian learning.

Homeostatic mechanisms provide the final touch in the delicate interplay of local and global factors that oversee the formation of memory representations, starting at synaptic mechanisms and including dendritic, neuronal and network processes. In the following section we discuss how computational models can be used to dissect and/or integrate the roles of different plasticity mechanisms in neuronal function and memory formation.

6. Computational modeling of memory-related neuronal functions: the role of active dendrites and synapse clustering

Computational models have been instrumental in the quest to understand memory functions and particularly the role of synaptic and dendritic processes in memory formation. In this section we review some of the most important computational models that have been proposed over the last few decades to underlie learning and memory formation in the brain. We focus on models taking into account active dendritic processes and plasticity mechanisms that may influence both the strength and the spatial arrangement of synapses.

6.1. Computational models investigating the role of synapse clustering in neuronal function

The ability of neocortical pyramidal neurons to selectively respond to spatially inhomogeneous patterns of synaptic activation (*i.e.* randomly distributed *vs.* spatially clustered activation of synapses) was first predicted by Bartlett Mel, using computational modeling (Mel, 1991, 1992, 1993), and was termed "cluster sensitivity". These early studies identified the boosting provided by the clustered spatial arrangement of synapses and predicted a key role of NMDA conductances in this phenomenon. This effect was found to be robust for a wide range of distributions of active conductances in dendrites. In addition, the author identified the conditions which would cancel the effects of clustering, namely, the high resistance of spine necks, the large synaptic conductances, and the high baseline levels of activity. The advantage of synaptic clustering in the form of in-branch localization (whereby co-active synapses were positioned uniformly within a given branch) for the discrimination and memory capacity of neurons was studied by the same group later on, using theoretical neuron models (Poirazi and Mel, 2001). When dendritic nonlinearities and in-branch localization were taken into account, the pattern discrimination capacity of simplified model neurons and neural networks expanded dramatically, suggesting that synapse clustering could serve as a mechanism for maximizing storage capacity in the brain. Moreover, dendritic nonlinearities and in-branch localization were also predicted by the same group to underlie translation-invariant orientation tuning in visual "complex" cells (Mel et al., 1998). This latter work was the first to predict a key role of dendritic supralinearities in orientation tuning of single neurons in the visual cortex, a prediction that recently received experimental support from *in vivo* experiments (Lavzin et al., 2012; Smith et al., 2013).

A follow-up study using a detailed biophysical model of a CA1 pyramidal cell was able to tease out the mathematical formula underlying "cluster sensitivity". The authors found that the terminal apical dendrites of these neurons summate synaptic inputs nearly independent from each other, using a sigmoidal (or thresholding) activation function (Poirazi et al., 2003a). This prediction has been verified experimentally for the basal dendrites of cortical pyramidal neurons (Polsky et al., 2004) as well as the radial oblique dendrites of CA1 pyramidal cells (Losonczy and Magee, 2006). Moreover, this finding led to the proposal of a "2-layer" model of neuronal integration, according to which, the firing rate of a CA1 pyramidal neuron in response to a large range of synaptic stimuli can be predicted by a two layer mathematical abstraction, in which terminal dendrites act as independent nonlinear thresholding units whose combined output goes through a second thresholding unit at the cell body (Poirazi et al., 2003b). This 2-stage model was recently demonstrated to match the processing of basal trees in cortical pyramidal neurons (Behabadi and Mel, 2014) and has received experimental support based on anatomical findings in CA1 pyramidal cells (Katz et al., 2009). For an extensive discussion on the 2-layer neuronal model please see an excellent recent review (Jadi et al., 2014).

An extension of the 2-layer hypothesis put forward by Hausser and colleagues entails that the interaction between proximal and distal integrative regions of a pyramidal cell may allow for an additional layer of integration, which is multiplicative in nature (Häusser et al., 2003). A different augmented version of the 2-layer model for cortical pyramidal neurons, where basal and apical tuft regions are treated as independent compartments and dendritic responses depend on the spatial arrangement of both excitatory and inhibitory inputs is put forward in (Jadi et al., 2014). Finally, based on the ability of dendrites to release neurotransmitters and neuromodulators, it has been proposed that a neuron may have multiple outputs, with each dendritic subunit performing local integration. In this model, morphology and biophysical properties determine the hierarchical arrangement of dendritic subunits (Branco and Häusser, 2010; Ludwig, 2005).

Overall, the above are a few modeling studies that establish the role of dendritic nonlinearities, which are maximally expressed when synaptic contacts are activated in clusters, in the functioning of neuronal cells and circuits.

6.2. Computational models investigating the role of dendritic nonlinearities and synapse clustering in memory functions

The functional implications of synapse clustering and dendritic nonlinearities which relate explicitly to memory functions have also been modeled in a number of computational studies. Models that included plasticity mechanisms are discussed in the next session. In a single cell model of a layer 5 PFC pyramidal neuron,

working memory was simulated *via* the induction of persistent (beyond the end of the stimulus) activity. It was found that positioning of synapses near the tips of the basal dendrites increased the probability of persistent firing due to the generation of larger, NMDA-dependent, dendritic spikes (Sidiropoulou and Poirazi, 2012). Similar findings were seen at the microcircuit level, whereby NMDA-dependent dendritic spikes were predicted to support persistent activity induction within a group of just a few L5 PFC cells. In the absence of NMDA dendritic spikes, the size of the network required to support persistent activity, the cellular correlate of working memory, increased dramatically (Papoutsi et al., 2013, 2014). In a computational study using realistic neuronal morphologies and active properties, Migliore et al. (2008) examined the role of active dendrites of CA1 neurons in the binding of multiple inputs which arrive at their radial oblique dendrites. Their results suggest that CA1 neurons have a preferred number of radial dendritic inputs that maximizes their capacity to recognize multiple features and propose a link between this number and the well known limitation of short term memory to seven items. Finally, another computational study investigated the role of dendritic function in the spatial working memory circuit by varying the mode of nonlinearity and the configuration of inhibition (Morita, 2008). In this case dendritic compartmentalization enabled the formation of accurate memory that was dependent on the contrast of the external input, but not its intensity. The requirement for this was the existence of either tuned global dendritic inhibition or local dendritic inhibition tuned with global somatic inhibition.

It should be noted that none of the above mentioned studies incorporated synaptic or dendritic plasticity rules. Neuron models with nonlinear dendrites that implement realistic plasticity rules can help investigate memory-related phenomena that go beyond working memory and make predictions about the properties of the resulting memory traces (Clopath et al., 2008; Cutsuridis et al., 2010; Govindarajan et al., 2006; Legenstein and Maass, 2011; Morita, 2008). While the mechanisms of these plasticity rules are not entirely known, models can incorporate simple phenomenological abstractions to study their effect in memory. Only few studies, however, have explicitly examined how active dendritic properties in combination with local plasticity rules can shape memory engram formation.

Wu and Mel explored the capacity of the monosynaptic pathway from Schaffer collaterals to CA2 pyramidal dendrites for "online" (one-shot) learning (Wu and Mel, 2009). This study found that dendritic-specificity of LTP, along with homeostatic depression, enables efficient memory utilization. The learning rules which enabled this CA3-to-CA1 system to perform online learning include a dual-threshold LTP, sparse synaptic plasticity, binary synaptic weight values and the co-occurrence of homeostatic depression and LTP as all-or-none phenomena. Using a model of nonlinear dendrites in combination with the branch strength potentiation (BSP), a computational study showed how nonlinear dendrites could be used to bind combinations of multiple features in dendritic subunits (Legenstein and Maass, 2011). The branch strength potentiation rule induced a competition between dendrites, which allow a neuron to become part of multiple memory traces. In this model, branch strength potentiation enables neurons to specialize in the binding of specific combinations of input features, which could represent the unique characteristics of objects. By inducing competition, a single neuron is thus able to store multiple such combinations in separate dendritic domains. Another recent study examined the implications of the spatial patterning of plasticity proteins in memory using a simplified model of memory consolidation with dendritic domains (O'Donnell et al., 2014). The spatial patterning of protein synthesis led to the consolidation of memories selectively, even when other events occured simultaneously and were represented by the same neuronal populations. Based on this function, the authors proposed a model for selective memory generalization during sleep.

6.3. Creating predictive models of dendritic function

Reliable and predictive modeling of dendritic properties and function requires that models can be constrained well by experimental data. As the study of dendrites is an active area of research, our knowledge of dendritic function and synaptic plasticity is only partially complete. For example, both the size and the spatial extent of functional and/or anatomical dendritic synapse clusters can only be inferred with imaging methods such as calcium imaging, immunolabeling or electron microscopy (Kleindienst et al., 2011; Makino and Malinow, 2011; Takahashi et al., 2012; Yadav et al., 2012). Similarly, the temporal constraints related to synaptic capture, plasticity protein production and homeostatic mechanisms can be found in relevant studies (Govindarajan et al., 2011; Hou et al., 2011; Losonczy et al., 2008). Although recent research has provided a wealth of data at an unprecedented level of detail, much remains to be discovered regarding particular aspects of memory storage. For example, the extent of LTP cooperativity, the protein dependence of LTP consolidation, the ability for dendritic protein synthesis, the molecular basis of synaptic tagging are parameters that crucially affect the properties of memory formation. However, even with our current knowledge of these mechanisms, we can generate predictive models of memory formation. As knowledge accumulates, these models will be continuously refined, generating more interesting and accurate predictions. Their ability to integrate data and mechanisms that operate at different levels, as well as to separately characterize the contribution of each of these mechanisms, will not only further our understanding of memory functions but also point to new avenues for experimental investigations.

7. Perspective

A large body of experimental studies has recently revealed detailed information about the existence and possible manipulation of memory representations at the cellular level (Silva et al., 2009; Josselyn, 2010; Rogerson et al., 2014). In parallel, multiple lines of evidence suggest that the plasticity underlying learning and memory acts at multiple levels: fast spine dynamics are shaped by synaptic activity, dendritic branch excitation properties are regulated by activity and homeostatic mechanisms, neuronal excitability is affected by previous learning, *etc.* (Fig. 3). To complete the picture, the excitability of networks is also controlled by several factors including the plasticity of GABA-mediated inhibition. These findings challenge the old view whereby synapses are considered as independent and elementary units of plasticity. Dendritic branches now emerge as semi-independent units of function and plasticity (Branco and Häusser, 2010). The observation of functional and/or anatomical synaptic clusters within dendritic branches implies that synapses may act in groups, formed by cooperative plasticity and local protein synthesis, which exert a nonlinear effect on the output of the cell (Mel, 1992; Mel, 1993; Poirazi et al., 2003; Poirazi and Mel, 2001; Govindarajan et al., 2006; Rogerson et al., 2014). The size of synaptic clusters and their spatial extent can be defined based on observations. The limited experimental evidence that is currently available suggests that even clusters of 2 synapses are functionally relevant (Fu et al., 2012; Takahashi et al., 2012). Based on a variety of biochemical and electrophysiological data, we can at least estimate the spatial proximity necessary between synapses to receive facilitation of

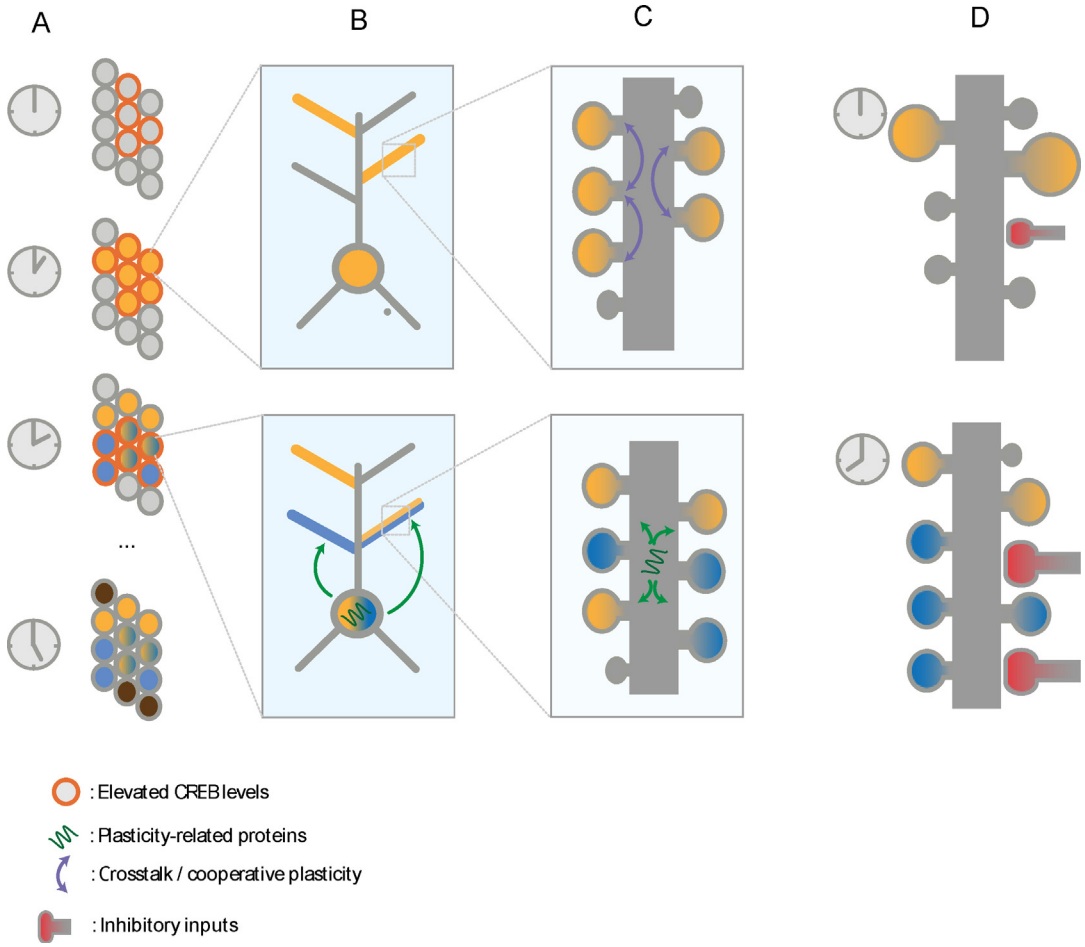

Fig. 3. Memory allocation across multiple temporal and spatial scales. (A) Increased CREB levels (orange outline) make these cells more likely to be engaged in the formation of upcoming memory representations (yellow cells). Engagement of cells in memory leads to increased CREB levels for a given time period (orange outline), increasing the probability that these cells will take part in subsequent learning (yellow/blue cells). This does not happen if learning occurs much later (brown). (B) Intrinsic plasticity mechanisms can regulate excitability locally in branches (*e.g.* branch strength potentiation) allowing neural cells to compartmentalize storage. Additionally, synaptic tagging and capture that depends on nuclear protein production (green arrows) can enhance cooperativity across branches. (C) Synaptic crosstalk and plasticity cooperativity act locally in branches, enabling the formation of synaptic clusters (top, purple arrows). Additionally, synaptic tagging and capture that occurs within branches can allow the binding of different memories/features in clusters (bottom, green arrows). (D) Homeostatic processes act in longer timescales, fine tuning synaptic integration, normalizing excitation and balancing excitatory and inhibitory inputs in order to prevent runaway excitation or silencing of neurons.

plastic events. Examples include LTP facilitation due to shared protein synthesis within 50–70 μm of a dendritic branch (and its sister) (Govindarajan et al., 2006, 2011) and diffusion of activated GTPases within 5–10 μm within a dendritic branch (Harvey and Svoboda, 2007; Harvey et al., 2008; Murakoshi et al., 2011; Murakoshi and Yasuda, 2012).

The effect of synaptic clustering on neuronal output is in turn modulated by intrinsic plasticity mechanisms that modify the excitability properties of dendritic branches where groups of synapses reside (Zhang and Linden, 2003). *The emerging picture suggests that clusters of functionally related synapses, which are formed within dendritic branches under the influence of local activity-dependent and homeostatic mechanisms, are likely to serve as a key computational and memory storage unit in the brain.* The time is ripe for undertaking the obvious challenge, namely to design experiments that test the implications of this idea at the behavioral level.

For example, it would be critical to know whether manipulations that do not disrupt canonical synaptic plasticity processes, but interfere with dendritic synaptic clustering alter or disrupt learning and memory at a behavioral level (Lavzin et al., 2012). Furthermore, is there a clinical consequence of abnormal clustering for episodic memory in animals and humans? For example, episodic memory representations require a certain degree of independence from each other to allow for accurate pattern separation and specificity. At the same time, memories must be richly connected for a sequence of experiences to be recalled together. Excessive or hyper-connectedness between each memory may result in the activation of overlapping networks of neurons, dendritic branches or synapses for every memory. This is likely to lead to a lack of pattern separation between memories and poor episodic recall or even catastrophic forgetting (*i.e.* interference between all memories resulting in no recall). In contrast, if events are too sparsely connected, memory for individual details might be extremely accurate but the general context and relatedness between items will be lost. These extremes can be captured by either over- or under-clustering of synapses, or neurons related to a set of memories (Fig. 4).

Predictions can be made for performance profiles that lie along the clustering continuum. On the extremes, over-clustering should present as an increase in associative thinking but with poor episodic memory due to a lack of pattern separation and increased interference between memories. Schizophrenia is characterized as having a looseness of association of ideas (Bleuler and Zinkin,

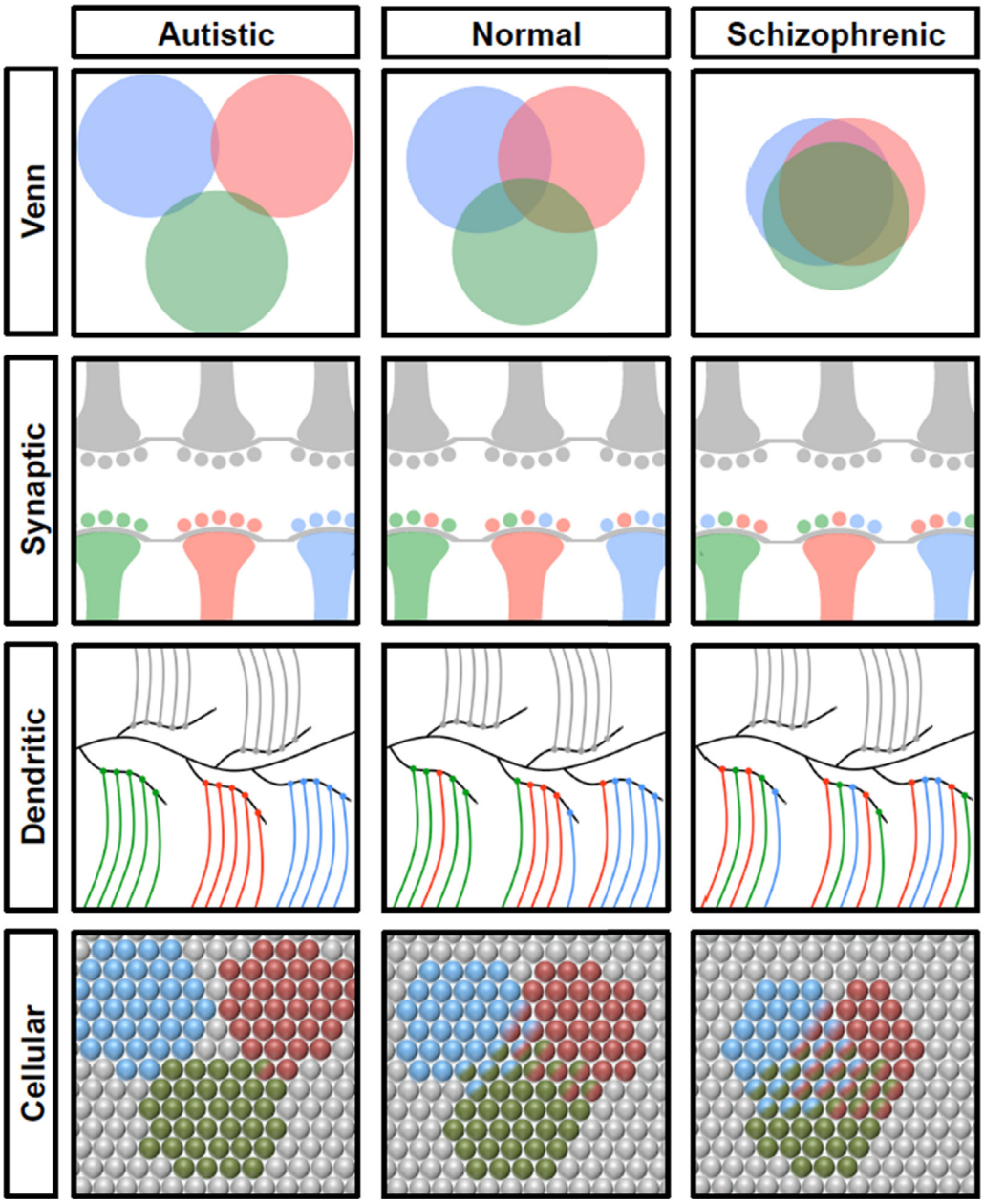

Fig. 4. The Impact of Clustering on Neurological Disease. Clustering in the normal cortex is balanced between the benefits of associativeness and distinctiveness of episodic memories. Memories are spatially segregated with a moderate degree of overlap. Over-clustering between memories predicts reduced spatial segregation, decreased resolution of individual episodic memories, and the intrusion of remote associations as seen in schizophrenia. Under-clustering is characterized by autonomous spatial arrangements that increase the capacity for distinct episodic memories at the cost of reduced relatedness between memories and/or knowledge domains, as seen in autism. These principles are represented above, in which three distinct memories that share a temporal context are represented in red, blue and green. The Venn diagrams illustrate the general concept of under-clustering in autistics, average clustering in normally-developed brains, and over-clustering in schizophrenics. Synaptic level cross-talk between intracellular signaling cascades during synaptic tagging and capture is illustrated. Dendritic level clustering shows the degree of spatial segregation of synapses within a dendritic branch that results in the formation of multiple processing units. At the cellular level, distinct memories may be allocated to networks of neurons whose overlap may predict the degree of relatedness between them.

1950), and patients perform better than controls on tasks that favor highly associative thinking (Manschreck et al., 1988; Poljakov, 1973). However, on tests of episodic memory, specifically pattern separation, schizophrenics typically perform poorly (Das et al., 2014). This is what would be predicted if the associative memory deficit were due to over-clustering. In this case, the encoding of new events activates a normal spread of neurons or dendrites in a network. However, with each subsequent episodic event, a highly redundant, overlapping network is activated, causing interference between events. Consequently, cueing a single event stimulates recall of multiple memories and performance fails.

In contrast, too little clustering would produce normal or even superior episodic memory for individual items, but poor contextual or relational processing. In the case of autism, numerous studies show that performance on recognition memory tests of individual items using a variety of nonsocial stimuli is unimpaired and occasionally superior in autistic patients compared with normal controls (Boucher et al., 2005; Bowler et al., 2000; Salmond et al., 2005; Williams et al., 2006). On the other hand, autistics have

difficulty with integrative thinking and contextual processing, such as using semantically-related words to probe contextual processing (Bowler et al., 1997, 2010; Smith et al., 2007), or categorical information to improve recall of semantically-related words (Smith et al., 2007). The extreme case of savants is a profound example of a highly localized knowledge that does not generalize nor associate to any other knowledge domain within the individual (Treffert, 2009). Mechanistically, rather than a string of events clustering together to create contextual and temporal meaning, each new experience would stimulate a separate and autononomous pattern of activation, which could strengthen access to each event, and weaken connectivity between events. This could explain how individuals with low cognitive skills and poor performance on some intelligence tests might still display talent in a restricted domain (O'Connor and Hermelin, 1988).

Although these hypothetical, clinical examples of over- and under-clustering have little direct evidence as to their mechanistic explanation, they point to the need for computational models that capture the complexity of nonlinear dendritic properties and make predictions that can be tested in behaving animals and humans. In years to come, experimental and theoretical approaches will have to work side-by-side in unraveling and testing hypotheses concerning the basic dendritic rules that underlie the formation of memory representations in the brain.

In the last twenty years a plethora of approaches, including transgenic mice, have established the importance of stable long-lasting changes in synaptic function in learning and memory (Lee and Silva, 2009). We are now able to explore the behavioral implications of dendritic processing rules. This daunting task will require all of the tools at our disposal, including new computational approaches, optogenetics, *in vivo* 2-photon imaging, *in vivo* whole-cell and dendritic recordings, multi-electrode high resolution recordings, *etc.* We will also need to develop new behavioral tools specifically designed to test the implications of changes in the electrophysiological and structural properties of dendrites, imaging methods paired with neuroinformatics tools that will allow us to track and characterize the dendritic activation patterns of neuronal networks in behaving animals, molecular tools that will inducibly manipulate individual synaptic molecular components in single synapses of spine clusters, fluorescent tags that will make it possible to image the very molecular events that trigger, filter, stabilize, modify and maintain synaptic clusters, *etc.* Importantly, all of these developments may only be a heart-beat away (if not here already). Experimentalists will need simple and predictive computational models that they can use to design the behavioral-based dendritic clustering experiments that seem impossibly complex today, but that undoubtedly will be routine tomorrow. It is both sobering and enormously exciting that the tools and results described here are bringing us closer than ever to understanding one of the greatest mysteries of all times: how experiences shape our memories and the very core of who we are as individuals.

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