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Microglia: A new frontier for synaptic plasticity, learning and memory, and neurodegenerative disease research

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ABSTRACT

We focus on emerging roles for microglia in synaptic plasticity, cognition and disease. We outline evidence that ramified microglia, traditionally thought to be functionally "resting" (i.e. quiescent) in the normal brain, in fact are highly dynamic and plastic. Ramified microglia continually and rapidly extend processes, contact synapses in an activity and experience dependent manner, and play a functionally dynamic role in synaptic plasticity, possibly through release of cytokines and growth factors. Ramified microglial also contribute to structural plasticity through the elimination of synapses via phagocytic mechanisms, which is necessary for normal cognition. Microglia have numerous mechanisms to monitor neuronal activity and numerous mechanisms also exist to prevent them transitioning to an activated state, which involves retraction of their surveying processes. Based on the evidence, we suggest that maintaining the ramified state of microglia is essential for normal synaptic and structural plasticity that supports cognition. Further, we propose that change of their ramified morphology and function, as occurs in inflammation associated with numerous neurological disorders such as Alzheimer's and Parkinson's disease, disrupts their intricate and essential synaptic functions. In turn altered microglia function could cause synaptic dysfunction and excess synapse loss early in disease, initiating a range of pathologies that follow. We conclude that the future of learning and memory research depends on an understanding of the role of non-neuronal cells and that this should include using sophisticated molecular, cellular, physiological and behavioural approaches combined with imaging to causally link the role of microglia to brain function and disease including Alzheimer's and Parkinson's disease and other neuropsychiatric disorders.

1. Synapses are multicellular

Cajal and Sherrington introduced a new era in neuroscience with their work on neurons as the central node of cognition in the brain, leading to the concept of a 'bi-partite' synapse (Cajal, 1888; Pearce, 2004). Leaping forward 100 years, in the 1990s there was a significant increase in our understanding of the molecular contributors to synapse function. Modern techniques employed by influential figures such as Eric Kandel, Mark Mayford, Alcino Silva and Susumu Tonegawa, among numerous other outstanding researchers, enabled many of the molecular underpinnings of memory, specifically related to neuronally expressed molecules, to be clarified (Bailey, Bartsch, & Kandel, 1996; Bannerman, Good, Butcher, Ramsay, & Morris, 1995; Bourtchuladze et al., 1994; Chen & Tonegawa, 1997; Elgersma & Silva, 1999; Kandel, 2001; Kandel, 2009; Maren, Aharonov, Stote, & Fanselow, 1996; Martin, Grimwood, & Morris, 2000; Mayford & Kandel, 1999; Mayford, Siegelbaum, & Kandel, 2012; Mayford et al., 1996; Silva, Kogan, Frankland, & Kida, 1998; Silva, Paylor, Wehner, & Tonegawa, 1992; Tsien, Huerta, & Tonegawa, 1996; Winder, Mansuy, Osman, Moallem, & Kandel, 1998). A major advance in the field of synaptic physiology and learning, introduced by these and other scientists, was to use regional and cell specific gene expression and knockout (KO) approaches, to investigate the role of specific molecular and cellular processes at the synapse. Further, using behavioural approaches these processes were elegantly related to higher level cognitive function. For an excellent review on the cellular and molecular techniques used to study memory mechanisms see Mayford et al., 2012.

Since these initial seminal studies, numerous investigators, including ourselves (Daniel, Galbraith, Iacovitti, Abdipranoto, & Vissel, 2009; Vissel, Krupp, Heinemann, & Westbrook, 2001; Vissel and Royle, et al., 2001; Wiltgen et al., 2010), have used similar approaches to deeply investigate various neuron specific processes

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important in synaptic physiology. With more than a decade of additional research, however, it is becoming evident that these neuron specific studies should be usefully added to by exploring the contribution of two other major cell types in the brain, microglia and astrocytes, to synaptic plasticity mechanisms and learning and memory in both the normal and diseased brain.

In our and other investigators' view the prevailing vision of the synapse as a structure involving pre- and post-synaptic connections between two or more neurons has constrained our thinking of synaptic function and plasticity, and its role in cognition. The emerging concepts of the "tri-partite" synapse (Araque, Parpura, Sanzgiri, & Haydon, 1999) and even the "quad-partite" synapse (Bennett, 2007; Schafer, Lehrman, & Stevens, 2013; Tremblay & Majewska, 2011) may better describe recent evidence indicating that there are multiple cell types working together at synapses. However, while highly exciting in advancing the concept of a multi-cellular synapse, terms like tri- or quard-partite could inadvertently be as constraining as the view that synapses are neuron-specific. For example, a role for the extracellular matrix as an integral member of the synapse has also been proposed and needs to be considered (Dityatev & Rusakov, 2011; Tsien et al., 2013). For this reason we prefer simply to say that we must not limit our view of the synapse and instead strive to understand it as a complex, dynamic and often transient structure involving several cells interacting within a sophisticated extracellular matrix and milieu.

Astrocytes initially caught attention as players in synaptic plasticity in the late 1990s when they were shown to increase intracellular Ca^{2+} levels in response to synaptic transmission, creating a feedback loop on transmission (Araque et al., 1999). Astrocytes physically contact synapses, with up to 2 million synapses contacted by a single astrocyte in the human brain (Oberheim, Goldman, & Nedergaard, 2012). Furthermore, overexpression of an astrocytic specific S100B was found to impair learning and memory, strongly implicating these cells in behavioural processes (Gerlai, Wojtowicz, Marks, & Roder, 1995). More recently, engraftment of human astrocytes into mice enhanced long-term potentiation (LTP, a molecular model of learning and memory), and performance on cognitive tests (Han et al., 2013). This further illustrated that human astrocytes, acting through releasing tumour necrosis factor (TNF), are essential for synaptic plasticity, and showed that human astrocytes may help enhance cognitive abilities compared to those of other mammals. Several recent reviews cover the current state of knowledge regarding the role of astrocytes at the synapse and their potential roles in information processing in the brain (Allen & Barres, 2005; Barker & Ullian, 2010; Nedergaard & Verkhratsky, 2012; Pannasch & Rouach, 2013; Perea, Navarrete, & Araque, 2009).

Here we focus on reviewing a role for a second non-neuronal cell type, microglia, in synaptic and structural plasticity and learning and memory. The reader is also referred to other excellent reviews on the roles of microglia at the synapse (Kettenmann, Kirchhoff, & Verkhratsky, 2013; Schafer et al., 2013; Tremblay & Majewska, 2011). We concentrate on recent evidence suggesting that these cells, which have typically been investigated for their immunological roles in an activated state, actually have critical roles at the synapse in their "resting" state. We suggest these ramified microglia have a critical role in regulating synaptic and structural plasticity at specific synapses during learning and memory. Finally, we consider how loss of the maintenance of normal "resting" microglial phenotype and function could trigger synaptic dysfunction as an important and early event in disorders of cognition, such as Alzheimer's disease. A key point, we will conclude, is that most of the exceptional approaches that have to date been used to elucidate molecular processes involved in learning and memory should now be applied to study the more complex multi-cellular synapse involving microglia and astrocytes, a next frontier in learning and memory research.

1.1. Origin of the bi-partite synapse concept

In his influential 1888 publication, Ramon S. Cajal was the first to describe the existence of dendritic spines, where others had deemed them artefacts of the Golgi staining process (Cajal, 1888). Cajal later proposed that dendritic spines are responsible for contacting axons and dendrites (Cajal, 1891), thereby serving as the substrate for the formation of adhesion between neurons. The term 'synapse' was given to these areas of adhesion in 1897 by Sir Charles Scott Sherrington (Pearce, 2004) but it was not until 1959 that Gray, using electron microscopy, finally confirmed that dendritic spines are the sites of neuronal connection (Gray, 1959). The complexity of neuronal connections in the brain is extensive, with single neurons containing 5000–10,000 synapses (Tang, Nyengaard, De Groot, & Gundersen, 2001), and the human brain containing $>10^{13}$ spines (Alvarez & Sabatini, 2007).

1.2. The contribution of spines to synapse structure and function

Dendritic spines are small protrusions on the dendrites of various types of neurons (Rochefort & Konnerth, 2012), connected to the main dendrite by a thin neck (Kasai, Fukuda, Watanabe, Hayashi-Takagi, & Noguchi, 2010). Post-synaptic densities are thought to convert to synapses when a pre-synaptic specialisation develops opposite them, giving rise to dendritic spines. Spinogenesis has been reviewed in detail (Garcia-Lopez, Garcia-Marin, & Freire, 2010). The pre- and post-synaptic densities are separated by a region termed the synaptic cleft, through which neurotransmitters pass from the pre- to the post-synapse. Dendritic spines are the major postsynaptic sites for excitatory synaptic transmission, with the majority of spines in the cortex forming Gray's type I asymmetric excitatory synapses (Colonnier, 1968) utilising glutamate as the primary neurotransmitter in the brain (Klemann & Roubos, 2011). Synapses can also be inhibitory, known as symmetric Gray's type II symmetric synapses, which mostly terminate on dendritic shafts rather than spines (Tashiro & Yuste, 2003; Yuste & Majewska, 2001).

Structurally, spines are highly specialised compartments primarily designed for the transmission of chemical signals (Nimchinsky, Sabatini, & Svoboda, 2002). They are variable in shape and size, likely the result of functional differences (Rochefort & Konnerth, 2012). Three morphologies are commonly described: long thin spines with small bulbs, mushroom shaped spines with thick stalks and large bulbs and short stubby spines with no stalks (Peters & Kaiserman-Abramof, 1970). Long thin spines that lack a bulbous head are found on developing neurons. They possess a transient structure termed filopodia (Fiala, Feinberg, Popov, & Harris, 1998; Miller & Peters, 1981). Thin spines are more transient than thick spines, appearing and disappearing over the course of days. In contrast, mushroom spines are long-lasting and contain more molecular machinery for long-term maintenance (Bourne & Harris, 2007). A detailed review on the structure and function of spines is available (Rochefort & Konnerth, 2012). In the hippocampus and neocortex 65% of spines appear thin, and 25% are mushroom spines. The remaining 10% are immature stubby, multisynaptic, filopodial or branched shapes (Bourne & Harris, 2007). Alterations in the structure of spines ultimately modify the strength of connections between neurons as the strength of transmission is directly correlated to spine size (Tashiro & Yuste, 2003).

1.3. Function of the synapse: synaptic plasticity

The term synaptic plasticity is used to describe the ability of synapses to change the strength of their connections. The 'strength' of a synapse refers to the response that is generated in a post-synapse as a result of activity of the pre-synapse (Atwood &

Karunanithi, 2002). Changes in both the molecular expression of synaptic molecules and structural changes of synapses can increase, or decrease, the response produced in a target cell by stimulation of a pre-synaptic terminal, and these changes can occur in both pre- and post-synaptic dendritic spines (Atwood & Karunanithi, 2002). Plasticity can occur over short timescales, utilising a variety of molecular mechanisms to alter synaptic strength, remove and modify, and add new synaptic connections (Bear, 1999; Bliss & Collingridge, 1993; Holtmaat et al., 2005; Katz & Shatz, 1996; Luscher & Malenka, 2012). Synapses can also refine their connectivity via synaptic scaling, a form of homeostasis which involves uniform adjustments in the strength of all synapses in a cell. This occurs as the result of long-term changes in the electrical activity of a cell, by either enhancing or depressing firing of synapses for the purposes of stabilising neuronal connections (Turrigiano, 2008). Synaptic plasticity is therefore an important feature for modifying neural networks and has long been thought to represent the basis of learning and memory (Mayford et al., 2012), remarkably suggested by Ramon Cajal in the late 19th century (Cajal, 1894).

How does synaptic plasticity occur? The influential psychologist, Donald Hebb, laid the groundwork for the current understanding of synaptic plasticity. Hebb's famous law can be summarised with the common phrase "cells that fire together, wire together", which requires simultaneous pre- and post-synaptic activity (Hebb, 1949). The discovery of a phenomenon known as long-term potentiation (LTP) provided the first evidence of Hebb's law in action (Bliss & Lomo, 1973). LTP is induced by brief trains of high-frequency stimulation (a tetanus) delivered to excitatory synapses, causing a sustained increase in transmission (Bliss & Collingridge, 1993; Cooke & Bliss, 2006). It increases the recruitment of ionotropic glutamate receptors including the N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors to the synaptic membrane and usually depends on Ca^{2+} influx through NMDA receptors (Luscher & Malenka, 2012; Matsuzaki, Honkura, Ellis-Davies, & Kasai, 2004), although neurons can express multiple distinct forms of LTP (Johnston, Williams, Jaffe, & Gray, 1992; Mayford et al., 2012). A related phenomenon, long-term depression (LTD), was discovered later (Lynch, Dunwiddie, & Gribkoff, 1977). Whereas LTP enhances the strength of a synapse, LTD results in the internalisation of AMPA receptors (Man et al., 2000), activation of perisynaptic NMDA receptors and lower increases in intracellular Ca^{2+}, ultimately inhibiting synaptic activity. LTD can also be dependent on metabotropic type glutamate receptor (mGluR) activation (Snyder et al., 2005; Xiao, Zhou, & Nicoll, 2001). LTP and LTD, as models of synaptic plasticity therefore reveal that molecular changes in synapses can drive the plasticity of existing synapses, thought to be important for learning and memory mechanisms.

Classical views of synaptic plasticity, including LTP and LTD, are of course constantly evolving into increasingly sophisticated views (Mozzachiodi & Byrne, 2010). Accordingly, mechanisms which control synaptic plasticity, including metaplasticity and particularly synaptic tag and capture theory, are now taking centre stage in behavioural neuroscience and in a number of prominent theories concerning the physical substrates of learning and memory (Abraham & Bear, 1996; Finnie & Nader, 2012; Hulme, Jones, & Abraham, 2013; Redondo & Morris, 2011).

1.4. Synaptic plasticity drives structural alterations at the synapse

Synaptic plasticity does not only occur via molecular changes in existing synapses, but can also involve structural changes through modification, formation and elimination of existing synapses, a process termed 'structural plasticity'. Consistent with this idea, the classical correlate of plasticity LTP, described above, appears to promote global increases in the volume of synaptically activated spines (Lang et al., 2004; Maletic-Savatic, Malinow, & Svoboda, 1999), converting thin spines to thicker mushroom shaped spines (Kopec, Li, Wei, Boehm, & Malinow, 2006; Matsuzaki et al., 2004) and inducing the formation of new spines (Engert & Bonhoeffer, 1999). In contrast, LTD appears to promote shrinkage and retraction of spines (Chen, Bourne, Pieribone, & Fitzsimonds, 2004; Lee, Liu, Wang, & Sheng, 2002; Linden & Connor, 1995; Luscher et al., 1999; Massey & Bashir, 2007; Mulkey & Malenka, 1992; Nagerl, Eberhorn, Cambridge, & Bonhoeffer, 2004; Zhou, Homma, & Poo, 2004). Thus synaptic plasticity drives structural plasticity.

1.5. Structural plasticity provides an exciting potential substrate for encoding memory

Does structural plasticity provide the physical mechanism for learning and memory? Only recently have we begun to understand the importance of synapse modulation, formation and elimination for cognitive processes (Holtmaat & Svoboda, 2009). It has been suggested that alterations in the morphology of dendritic spines may provide the physical basis for the transition between learning and memory, with thin and more transient spines suggested to be 'learning spines' and thick longer-lasting spines being 'memory spines' (Bourne & Harris, 2007). A particularly important advance was the observation that learning induces dynamic formation and elimination of dendritic spines in response to novel experience and learning, and that the extent of this turnover correlates with behavioural improvement after learning (Yang, Pan, & Gan, 2009). Furthermore, a small subset of spines are stably maintained after learning and throughout the lifetime of an animal, providing a physical basis for long-term retention of memory. Remarkably one study showed that during contextual fear conditioning, synaptic elimination occurred in activated hippocampal neurons only (Sanders, Cowansage, Baumgartel, & Mayford, 2012). A more recent study extended on these remarkable findings by directly correlating dendritic spine formation and elimination along the same dendritic branch of individual neurons, to the opposing behavioural effects of cued fear conditioning, extinction and reconditioning (Lai, Franke, & Gan, 2012). Thus mechanisms of synapse formation, and particularly elimination, are emerging as critical players for encoding and storing memory traces.

Despite the fact that structural alterations are very likely candidates for the physical basis of learning and memory, the factors that control spine formation, maturation and elimination remain poorly understood. In particular, it remains unclear how new spines are formed, how they are eliminated, and how they reach and form physical connections with pre-synaptic bulbs from neighbouring neurons. Although it is likely that the neurons themselves are able to respond to external cues and thereby enact structural alterations in their cytoskeletal structure to allow for spine formation and elimination, in what follows below we propose that other cell types in the vicinity, namely microglia, may play a crucial role in these functions and may thus have active and indispensable roles in the modulation of neural networks that support learning and memory.

2. Microglia as essential mediators of synaptic plasticity, structural plasticity and memory

2.1. Microglia infiltrate the CNS during embryogenesis

Microglia, of the same lineage as monocytes and macrophages, originate in the bone marrow and infiltrate the CNS during early embryogenesis, with precursors invading from the yolk-sac (Ginhoux et al., 2010; Kierdorf et al., 2013; McKercher et al., 1996; Ransohoff & Cardona, 2010). Once in the CNS, microglial

progenitors are thought to be essentially cut off from their bone marrow progenitor niches, forming their own self-renewing colony (Kierdorf et al., 2013; Saijo & Glass, 2011). Microglial cells self-renew through cell division (Lawson, Perry, & Gordon, 1992), although they mainly appear to be long-lived cells in the uninjured brain, with a low rate of turnover (Lawson et al., 1992). Although present in all areas of the brain, microglia are not uniformly distributed, with a variation of between 0.5% and 16.6% of the total proportion of cells for each region in humans and mice (Lawson, Perry, Dri, & Gordon, 1990; Mittelbronn, Dietz, Schluesener, & Meyermann, 2001). Their mesodermal origin differentiates them from the neuroectodermal derived astrocytes and neurons, and they retain many of the features of macrophages throughout their lifecycle. For instance, one of the major functions of microglial cells in the brain is to survey for damage and protect neural material (Rivest, 2009).

2.2. Traditional view of microglia: the brains innate immune cell

We argue below that microglia are not simply the brain's inflammatory cell, however we first note that microglia can and do act in this capacity under certain circumstances (Graeber, Li, & Rodriguez, 2011; Krause & Muller, 2010; Streit, Mrak, & Griffin, 2004). Although it was once thought that the brain was an immune privileged organ due to the blood–brain barrier, an absence of lymphatic drainage and its tolerance to transplanted tissue, it is now clear that, through microglia, the brain has a capacity for an innate immune response (Oemichen, 1978; Rivest, 2009). However, the role that microglia play in inflammation, and how these cells interact with other cell types to contribute to an inflammatory response, is not at all well understood and remains to be elucidated.

In their resting state in the mature brain microglia are highly ramified with long processes and small cell bodies (Kettenmann, Hanisch, Noda, & Verkhratsky, 2011), and have traditionally been thought to be functionally quiescent. Microglia become 'activated' in response to many types of injury and pathogenic events in the CNS (Thomas, 1992), changing their morphology from the highly ramified "resting" state to a globular "amoeboid" activated form through a series of distinct steps (Kitamura, Tsuchihashi, & Fujita, 1978; Stence, Waite, & Dailey, 2001), with the ability to migrate to sites of damage (Nolte, Moller, Walter, & Kettenmann, 1996; Stence et al., 2001) and phagocytose cellular debris (Kettenmann, 2007; Kierdorf et al., 2013; Kreutzberg, 1996). These activated cells are also known to be capable of performing neuroprotective functions (Streit, 2005), support neurogenesis, direct the invading vasculature, remove apoptotic cells, influence synaptogenesis and control developmental apoptosis (for full reviews see (Bessis, Béchade, Bernard, & Roumier, 2007; Ransohoff & Cardona, 2010; Saijo & Glass, 2011)). Activation states have been defined as the classical M1 and the alternative M2 states, adopted from descriptions used for peripheral macrophage activation (Ransohoff & Cardona, 2010; Ransohoff & Perry, 2009; Saijo & Glass, 2011). However, activation state is likely more complex than this, and the relevance of these constrained definitions is not yet clear (Colton, 2009; Fagan, 2013).

2.3. An emerging view of microglia: "resting" microglia are highly dynamic in the normal brain

In general it is still the case that the innate immune functions of "activated" microglia dominate research into this cell type (Section 2.2) (van Rossum & Hanisch, 2004). As described above, in this view ramified microglia in normal physiological conditions are functionally inert and hence described as "quiescent" or "resting". A major challenge to this argument came with two publications identifying the fine processes of ramified microglia are highly dynamic surveyors of the healthy brain (Davalos et al., 2005; Nimmerjahn, Kirchhoff, & Helmchen, 2005), earning them the new title of "surveillant" microglia, and indicating the definition of these cells as "resting" is now redundant. Due to the highly sensitive nature of microglia (they are activated in response to the slightest CNS damage) (Petersen & Dailey, 2004; Streit, Walter, & Pennell, 1999), studies of their resting functions have been technically very difficult. For instance, microglia, become activated in hippocampal slice preparations (Haynes et al., 2006; Kurpius, Wilson, Fuller, Hoffman, & Dailey, 2006). However, Nimmerjahn et al. and Davalos et al. bypassed the possibility of *in vitro* activation of microglial by employing a novel technique to thin, but not penetrate, the skull of mice (Davalos et al., 2005; Nimmerjahn et al., 2005). This enabled the visualisation of "resting" microglia in the adult cortex through the thin-skulled preparation using *in vivo* two-photon microscopy.

Although the cell bodies and main branches mostly remain static, the thin processes of "resting" ramified microglia are in fact highly mobile in the normal brain (Davalos et al., 2005; Nimmerjahn et al., 2005). They transiently appear and disappear, form bulbous structures at their ends and sometimes stall for short periods. Each microglia samples its own microenvironment specifically, not extending into other microglial cell territories. The microglia appear to contact neighbouring astrocytes, neuronal cell bodies and blood vessels, sometimes even engulfing tissue components, and also increase their surveillance in response to neuronal activity. The thin microglial processes are particularly fast moving, quicker in fact than structural changes seen in neurons and astrocytes (Nimmerjahn et al., 2005). Both Nimmerjahn et al. and Davalos et al. were also able to visualise the rapid activation of microglia in response to neuronal injury, with the number of microglia responding correlating with the severity of injury, and with microglial processes migrating to the site of injury without any movement from the cell body.

2.4. Microglia have numerous mechanisms to detect neuronal activity

Microglia express most of the major classes and subtypes of excitatory and inhibitory neurotransmitter receptors and ion channels classically found at neuronal synapses (for recent reviews refer to Kettenmann et al., 2011; Pocock & Kettenmann, 2007). Many studies have assessed the role of these receptors and ion channels in terms of their impact on microglial responses to inflammatory insults (Pocock & Kettenmann, 2007). For example, blocking NMDA receptors can reduce the inflammatory response of microglial cells to insults such as lipopolysaccharide (LPS) (Glezer, Zekki, Scavone, & Rivest, 2003) and microglia NMDA receptor activation promotes increases in oxidative stress, cytokines and chemokines *in vitro* (Kaindl et al., 2008, 2012). Results such as these suggest that the classical synaptic receptors found in microglia can regulate microglial responses to inflammation.

However as we elaborate below, ramified microglia are also essential to normal synaptic function. Yet, surprisingly, little is known about the role of the neurotransmitter and ion channel receptors in ramified microglia. In our view it is likely that these receptors and ion channels exist in microglia as a highly ordered mechanism for sampling the extra-cellular matrix and milieu, for monitoring, assessing and responding to neuronal activity and, for participating at the synapse. It therefore remains an open and intriguing question as to how these receptors and ion channels are organized in ramified microglia. It is tempting to suggest that ramified microglia may have organized synaptic specializations not dissimilar to those found in neuronal synapses to sense, monitor and interact with neurons at synapses. This area remains open to investigation.

2.5. Microglial motility is activity dependent in the normal brain

Recent research has shown that microglial process motility is not passive but controlled by neuronal activity (Schafer et al., 2012; Tremblay, Lowery, & Majewska, 2010; Wake, Moorhouse, Jinno, Kohsaka, & Nabekura, 2009). For example the motility of microglial processes can be regulated *ex vivo* by ionotropic glutamatergic neurotransmission and decreased by ionotropic GABAergic neurotransmission (Fontainhas et al., 2011). Microglial process motility has also been linked to the release of extracellular ATP and recognition of this by purinergic receptors on microglia (Davalos et al., 2005; Haynes et al., 2006; Kurpius, Nolley, & Dailey, 2007). This is consistent with findings, mentioned in Section 2.4, that microglia express a variety of neurotransmitter receptors (Domercq, Vazquez-Villoldo, & Matute, 2013; Kettenmann et al., 2011; Pocock & Kettenmann, 2007), ion channels (Farber & Kettenmann, 2005), and an array of purinoceptors (Farber & Kettenmann, 2006), which may allow them to respond to neural activity, however this is still a subject of debate (Chen, Koga, Li, & Zhuo, 2010; Schafer et al., 2012; Tremblay et al., 2010; Wake et al., 2009; Wu & Zhuo, 2008).

2.6. Microglial processes contact synapses in an experience-dependent manner

If microglia survey the brain in an activity dependent manner, what are their processes specifically sampling, and why are they so restless? Again employing the thin-skulled window strategy in mice (6–10 weeks of age), and by fluorescently labelling both neurons and microglia, Wake et al. elegantly answered these questions using two-photon microscopy. This research showed that microglial processes make direct transient contacts with synapses for 5 min periods once every hour in an activity-dependent manner (Wake et al., 2009). An important observation was made that the time of contact with synapses was extended to ~1 h after transient cerebral ischaemia, and that this could be followed by loss of the contacted pre-synaptic bouton, implicating microglial processes in synaptic removal (see Section 3.2).

Importantly, further evidence has demonstrated that microglial processes are in association with synapses during visual experience, including contacting axon terminals, dendritic spines, perisynaptic astrocytic processes and synaptic clefts (Tremblay et al., 2010), in a similar way to the known position of astrocyte contacts at the synapse (the tri-partite synapse (Araque et al., 1999)). In this experimental paradigm, microglial processes appeared to localise to small, transiently growing dendritic spines in the visual cortex of juvenile mice in response to light stimulus. When the light stimulus was removed microglia became less motile and contacted a different, larger subset of spines. Thus microglial contact with dendritic spines is related not only to neuronal activity but also more broadly to sensory experience, suggesting by extension that it could also be exquisitely regulated during more complex cognitive processes such as learning and memory.

More recently, a thorough electron microscope study has suggested that microglial processes predominantly contact pre-synaptic elements in the adult rat brain and that these contacts are relatively rare during normal physiology (Sogn, Puchades, & Gundersen, 2013). The authors interpreted this result to suggest microglia have a limited role in synaptic plasticity. However the low percentage of contacts seen under electron microscopy likely represent the fact that contact is transient, directed by activity and experience, and is only directed to specific subsets of active synapses as shown by Tremblay et al. (2010). Furthermore, given the rapid motility of microglial processes, it is conceivable the process of anaesthetising and sacrificing the animals used by most investigators in anatomical and electron microscopy studies could lead to rapid retraction of microglial contact with synapses immediately prior to tissue fixation. Live imaging studies in the healthy brain using minimally invasive approaches are going to be important for addressing such issues in future.

3. The role of microglia in synaptic and structural plasticity and learning and memory

If microglia processes contact synapses in an experience-dependent manner, what functions do they perform and what molecular mechanisms do they employ to achieve these effects? We review evidence that microglia have important roles in synaptic as well as structural plasticity. By extension we implicate these microglia-controlled processes in learning and memory. The following sections are devoted to discussing both known and potential mechanisms by which they might mediate these effects.

3.1. The relevance of inflammatory cytokines to synaptic plasticity and learning

The most well-known mechanism by which both active and resting microglia could contribute to synaptic plasticity is via their release of various synaptically active molecules including cytokines (Hanisch, 2002; Mallat & Chamak, 1994; Streit & Xue, 2012). Cytokines, comprising a functionally-connected group of peptides, phylogenetically very old (Beutler & Van Huffel, 1994), and including TNF and interleukin-1 (IL-1), are generated by cells of the macrophage/microglial lineage, noted above, as well as a wide range of cell types both sides of the blood–brain barrier. Neurons and astrocytes are cerebral examples of cells that release cytokines (Pan et al., 1997). Cytokines are commonly, but not very precisely, termed the inflammatory cytokines, in that they also have primary roles in physiology, innate and acquired immune responses and wound healing, as well as the pathogenesis of inflammation, and inflammatory disease (Clark, Alleva, & Vissel, 2010; Clark, Atwood, Bowen, Paz-Filho, & Vissel, 2012). They operate in networks and cascades, and regulate cellular activity in an autocrine, paracrine and hormonal manner (Beutler & Van Huffel, 1994).

These same cytokines have central physiological roles in synaptic plasticity, neurogenesis and learning and memory in the normal brain (Albensi & Mattson, 2000; Aloe et al., 1999; Beattie et al., 2002; Bernardino et al., 2008; Cacci, Claasen, & Kokaia, 2005; Iosif et al., 2006; Ogoshi et al., 2005; Santello & Volterra, 2012). For instance, IL-1β is induced in the learning process and is important for consolidation of memory (Goshen et al., 2007), and at least one cellular source are the microglia (Williamson, Sholar, Mistry, Smith, & Bilbo, 2011). TNF, interleukin-6 (IL-6), prostaglandins, complement cascade proteins (C1q and C3) and major histocompatibility complex class I family members (MHCI) are also implicated in learning processes (for recent in depth reviews refer here (Blank & Prinz, 2013; Boulanger, 2009; Yirmiya & Goshen, 2011)). These effects are mediated by neuronal activity, and involve microglia and astrocytes, although predominantly are mediated by microglia (Yirmiya & Goshen, 2011). It has been suggested that cytokine expression in the brain may play a role in the regulation of dendritic spine dynamics, and by extension learning and memory (Bitzer-Quintero & Gonzalez-Burgos, 2012). Microglia are also thought to play a role in the process of synaptic scaling (described in Section 1.3), through secretion of TNF (Pascual, Ben Achour, Rostaing, Triller, & Bessis, 2012; Stellwagen & Malenka, 2006). Thus the cytokines released from microglia and other brain cells manipulate fine control of synaptic plasticity (Bitzer-Quintero & Gonzalez-Burgos, 2012; Brynskikh, Warren, Zhu, & Kipnis, 2008; Garay & McAllister, 2010; Ishii & Mombaerts, 2008; Pocock & Kettenmann, 2007;

Rivest, 2009; Romo-González, Chavarría, & Pérez-H, 2012; Streit & Xue, 2012; Yirmiya & Goshen, 2011).

3.2. Microglia can eliminate synapses in the normal brain

Microglia need not only influence the plasticity of existing synapses but may also contribute to more profound structural plasticity mechanisms. In particular, we propose that they may be able to phagocytose specific subsets of synapses activated during learning and memory. Although evidence for such a view is at present scarce, in what follows, we argue in favour of this idea by demonstrating that microglia are entirely capable of eliminating synapses in development (termed synaptic 'pruning' (Section 3.3) and also in disease conditions in the adult (termed synaptic 'stripping', Section 3.4). We therefore suggest that microglia could be performing similar functions at a much more controlled level in physiological conditions of learning and memory in the adult.

3.3. Microglia remove synapses during periods of synaptic maturation in development

Structural plasticity is highly active during development, with the rate of spine elimination exceeding the rate of spine formation (Holtmaat et al., 2005). This is known as synaptic pruning and is thought to be essential for forming efficient neural connections during development. Synapse formation and elimination in the adult brain is muted, with spines more stable in the adult brain (Grutzendler, Kasthuri, & Gan, 2002; Majewska, Newton, & Sur, 2006), lasting for up to 18 months, virtually the entire lifespan of a mouse (Zuo, Lin, Chang, & Gan, 2005). This area has been well reviewed (Holtmaat & Svoboda, 2009).

Using PSD95, a marker of excitatory post-synaptic densities, colocalisation of GFP-labelled microglial processes and PSD95 immunoreactivity has been found in the mouse hippocampus during the period of synaptic maturation (Paolicelli et al., 2011). These data provide some of the strongest evidence to date that not only do microglia contact synapses, they may actually phagocytose them during development, playing a role in synaptic pruning. Paolicelli et al. also provided further evidence for a role of microglia in synaptic pruning, and implicated a potential signalling mechanism by which this may occur, by finding that mice lacking the fractalkine receptor (CX3CR1) had deficits in synaptic pruning and decreased frequency of spontaneous excitatory post-synaptic currents, suggesting immature connectivity in knockout mice. Neurons release the chemokine fractalkine during periods of synapse maturation. Findings from this study support the theory that soluble fractalkine may promote the migration of microglia into the brain during development, since microglia numbers are indeed lower in CX3CR1 knockout mice (Paolicelli et al., 2011). As the mice mature however, microglia and synapse numbers return to normal levels, although the long-term behavioural effect of the knockout on hippocampal-dependent functions were not tested. This study highlights the importance of microglia pruning in the maturing brain, with dysfunctional pruning possibly delaying brain maturation. Since these experiments were performed on hippocampal tissue, an area of the brain involved in the formation and consolidation of memory, the outcome suggests that microglia are active in the hippocampus during developmental synaptic pruning, and therefore plausibly play a role in this region in the adult hippocampus.

Recent evidence has implicated complement cascade proteins as mediators of microglial-controlled synaptic pruning during development. The best evidence, in summary, is that mice deficient in the complement cascade protein C1q, or a downstream complement protein C3 have excess synaptic connections in the mouse retinogeniculate system, a commonly studied area for researching developmental synaptic elimination (Stevens et al., 2007). Both C1q and C3 localise to synapses during development, suggesting complement proteins tag synapses removal. The C3 receptor, complement receptor 3 (CR3/CD11b–CD18/Mac-1) is specifically expressed on microglia in the CNS, and in a follow-up study this group identified that signalling between C3 and this phagocytic receptor is a critical mechanism by which microglia recognise synapses to prune in the developing retinogeniculate system (Schafer et al., 2012). Critically, this paper established that synaptic pruning by microglia was dependent on neural activity (see Section 2.5). These studies firmly established the C1q/C3/CR3 axis as an integral mechanism for synaptic pruning by microglia. Another important observation made in this study was that microglia preferentially target 'weak' synapses. This finding is consistent with those of Tremblay and co-workers who in 2010 showed that in response to sensory activity, microglia target smaller spines thought to represent 'weaker' spines, which are then frequently removed 2 days after association with microglial processes (Tremblay et al., 2010).

3.4. Microglia 'strip' synapses following synaptic damage

A role for microglia in removing damaged synapses was found as far back as 1968 (Blinzinger & Kreutzberg, 1968). Activated microglia were shown to closely adjoin dendrites, and physically separate pre- and post-synaptic boutons, following cleavage of the axon of facial nerve motor neurons, although the function of this was unknown at the time. This is now known as 'synaptic stripping' and is thought to represent a neuroprotective function by reducing synaptic activity and promoting synaptic reorganisation (Gehrmann, Matsumoto, & Kreutzberg, 1995; Kettenmann et al., 2013; Moran & Graeber, 2004; Schiefer, Kampe, Dodt, Zieglgansberger, & Kreutzberg, 1999; Trapp et al., 2007). Pre-synaptic inhibition of glutamate release may precede the association of microglia with synapses, and subsequent synaptic stripping, suggesting microglia are indeed sensing changes in neuronal activity and acting to remove synapses as a result (Yamada et al., 2008). As mentioned earlier (Section 2.6) the contact time of microglia with synapses is increased in response to ischaemia, and synapses are often lost following this contact (Wake et al., 2009). Evidence for synaptic stripping has also been found in a human case of severe peripheral facial nerve paresis (Graeber, Bise, & Mehraein, 1993). It is unclear exactly how synaptic stripping occurs, and what phenotype of microglia is responsible for this process as microglia can also strip synapses when early stages of activation and proliferation are inhibited (Kalla et al., 2001). Thus the phenotype of microglia that strip damaged synapses may actually be the ramified form which, due to its surveillant functions, could allow the brain greater sensitivity in eliminating individually diseased connections. Consistent with the idea that resting microglia are able to phagocytose neural components, so-called "resting" microglia have been shown to shape hippocampal neurogenesis by phagocytosing many new-born neuroblasts in the subgranular zone (Sierra et al., 2010). Crucially, this study established that microglial processes can perform this phagocytosis themselves, separately from the cell body. This links well with research showing microglia can clear apoptotic neurons without inflammation (Takahashi, Rochford, & Neumann, 2005).

Together these studies of synaptic pruning and synaptic stripping, as controlled by microglia, strongly implicate microglial cells in structural plasticity. When placed in the context that synaptic elimination and formation are important for learning and memory (Section 1), this allows us to propose the testable hypothesis that structural plasticity induced by microglia, in response to neuronal activity, has a role in learning and memory processes in the normal brain.

3.5. Maintaining ramified microglial function is important for synaptic plasticity and cognition

As we intimated earlier, the term "resting microglia" should perhaps be considered as an oxymoron, since as we pointed out, it is apparent that microglia are not physically or functionally resting when they are in the "resting" ramified state (Section 2.3). It is not surprising therefore that numerous mechanisms exist to maintain microglia in their ramified state. This allows them to perform their normal functions, surveying and modifying synapses, and prevents them becoming aberrantly activated. By extension, based on our hypothesis that synaptic elimination by microglia is important for learning and memory, it follows that maintaining the fine control of microglial phenotype in the normal brain is also important for learning and memory. In this section we therefore briefly mention the mechanisms that maintain microglia in a ramified state and suggest that this is important for normal cognition.

Neurons suppress the activation of microglia via the CX3C-chemokine ligand 1 (CX3CL1/fractalkine), and its cognate receptor on microglia CX3CR1 (Cardona et al., 2006; Lyons et al., 2009). Activation of microglia may therefore involve removal of this inhibition, a hypothesis supported by another study (Paolicelli et al., 2011). CX3CR1 also controls the release of inflammatory mediators IL-1β, TNF, and IL-6 (Rogers et al., 2011), each important for memory as described in detail earlier. Intriguingly a knockout of CX3CR1 receptors leads to developmental deficits in synapse number (see Section 3.3) (Paolicelli et al., 2011). In turn, adult CX3CR1 deficient animals also have cognitive deficits in hippocampal-dependent fear learning and memory and significant impairments in LTP (Rogers et al., 2011).

Another mechanism inhibiting microglia activation is CD200, expressed on neurons, which binds to its receptor CD200R on the microglial surface (Barclay, Wright, Brooke, & Brown, 2002; Hoek et al., 2000; Walker, Dalsing-Hernandez, Campbell, & Lue, 2009). CD200 knockout mice have microglia with an activated phenotype, and more rapid inflammatory responses. Interestingly, hippocampal slices prepared from $CD200^{-/-}$ mice show reduced LTP (Costello et al., 2011), implicating CD200–CD200R interactions as important for synaptic plasticity, possibly via an aberrant activation of microglia, and therefore a loss of resting function.

Recent research has also implicated traditional innate immune receptors, which can control the activation of microglia, in learning and memory. A particularly interesting molecule in this regard is toll-like receptor 4 (TLR4), which in healthy brain has only been detected on microglia (Pascual et al., 2012), and has been shown to have a developmental role in learning and memory (Okun et al., 2012). Microglial activation has also been suggested to modulate neuronal activity through TLR4 (Pascual et al., 2012).

Together, the above studies indicate there are a range of mechanisms involved in the fine control of the activation state of microglia and that these mechanisms are in turn important for learning and memory. These molecules may affect learning and memory by modulating the level of secretion of molecules involved in synaptic plasticity, or by controlling the phagocytic capabilities of ramified microglia, allowing controlled regulation of synaptic and structural plasticity by microglia in the normal brain.

4. Microglia in disease

4.1. The effect of inflammation on microglial signalling

We have reviewed a role for microglial derived cytokines in synaptic plasticity, and have implicated microglia in synaptic elimination in development and disease. Furthermore we have established that maintaining resting microglial phenotype is important for learning and memory. A specific link between the control of synaptic elimination and secretion of cytokines may be provided by research indicating that cytokines are involved in synaptic elimination (Kubota et al., 2009; Tonelli & Postolache, 2005), although this has yet to be linked to secretion of cytokines from the branched processes of resting microglia, and moreover has not yet been directly implicated in learning and memory. What happens when the fine balance of cytokine secretion by resting microglia is perturbed, as occurs in disease? Furthermore what happens when microglia lose their quiescence, and retract their fine processes, becoming "activated" and amoeboid? As we will illustrate in the following sections, disruption of cytokine signalling, and failure of the signalling mechanisms maintaining the phenotype of microglia in the normal brain, may contribute to learning and memory dysfunction and synaptic pathologies such as Alzheimer's disease.

Most, if not all of the cytokines implicated in synaptic plasticity also, when over-supplied, can cause brain pathology (Griffin et al., 2006; Iosif et al., 2008; Stellwagen, Beattie, Seo, & Malenka, 2005). If cytokines secreted by microglia are critical to normal brain plasticity it follows in turn that aberrant levels of cytokines, as occurs in inflammatory states associated with diseases like Alzheimer's and Parkinson's (Akiyama et al., 2000; Clark et al., 2010, 2012; Tuppo & Arias, 2005; Wersinger & Sidhu, 2002; Wilms et al., 2007; Wright et al., 2013; Wyss-Coray & Rogers, 2012), will impair synaptic plasticity and potentially drive structural plasticity into harmful directions. This would explain the profound early synaptic pathology seen in Alzheimer's.

As with macrophages in the rest of the body the inflammatory nature of activated microglia can disturb the fine balance needed to preserve normal physiology such as synaptic plasticity functions, and exacerbations in inflammatory mediators in the brain as a result of a number of risk factors can increase the rate of neurodegeneration (Perry, Cunningham, & Holmes, 2007) with grave implications for maintaining normal synaptic plasticity and learning and memory. This may come about via a microglial priming mechanism (Norden & Godbout, 2013), as evidenced by systemic infections and neuroinflammation being able to exacerbate neurodegeneration and concurrent memory loss (Perry et al., 2007). Stress, trauma, infection and seizures may increase neural-immune cross talk (Cunningham, Wilcockson, Campion, Lunnon, & Perry, 2005; Garay & McAllister, 2010), with adverse implications for glia-neuron interactions, controlled by immune molecules, during synaptic plasticity. Furthermore, recent evidence indicates aberrant activation of microglia in the hypothalamus, via the TNF they secrete, controls physiological aging, and its concomitant shortening lifespan and weakening cognition (Zhang et al., 2013). Indeed it was shown that artificially minimizing glial activation in the hypothalamus increased lifespan and raised the cognitive performance of mice (Zhang et al., 2013). Fortunately there are safeguards to prevent aberrant neuroinflammation causing unnecessary damage to neural circuits (Biber, Neumann, Inoue, & Boddeke, 2007), with a variety of signals maintaining microglia in a quiescent state in the adult brain and therefore maintaining their resting functions, which are only just becoming recognised (discussed in Section 3).

4.2. Altered resting microglial function as a cause of cognitive disorders and Alzheimer's disease

As we noted in Section 3, microglia rapidly scan and interact with a set of defined cells in their vicinity, playing a role in regulating synaptic and structural plasticity. It is well known that microglia can exhibit an inflammatory – non-ramified – phenotype in early AD and in other neurodegenerative diseases (McGeer & McGeer, 2003). This change in microglial phenotype involves the retraction of processes that are believed necessary in the healthy

brain for maintaining and regulating synaptic integrity. Consequently, we propose that dementia, at least in some of its forms, and perhaps also a number of other cognitive and neurodegenerative disorders, is at its onset a result of a failure to maintain microglia in their ramified state, which is important to exquisitely control synapse function and plasticity. Further, at least in neurodegenerative diseases, we suggest that microglia, either concurrently or subsequently to a change of phenotype, can develop a pathological role wherein they contribute to an increased rate of synaptic elimination compared to synaptogenesis, possibly as a prelude to neurodegeneration and other pathologies (Walsh & Selkoe, 2004). We hope that this set of ideas will provide an interesting model and/or initial framework for explaining the early synapse loss and cognitive impairment seen in diseases like Alzheimer's, which can occur many years in advance of the extensive pathology seen later in the disease (Davies, Mann, Sumpter, & Yates, 1987; Fiala, Spacek, & Harris, 2002; Masliah et al., 1994; Scheff & Price, 2003; Scheff, Price, Schmitt, DeKosky, & Mufson, 2007; Scheff, Price, Schmitt, & Mufson, 2006; Selkoe, 2002; Terry et al., 1991).

It is clear from a number of studies that subtle changes in microglia function can have quite profound consequences on synapses and on the behaviour of an organism. We consider that it is no coincidence that perturbations in many molecules controlling microglial activation, some of which we mentioned above, are implicated in Alzheimer's disease. Nor is it a coincidence that Alzheimer's disease is characterized by changes at synapses long in advance of pathology (Penzes, Cahill, Jones, VanLeeuwen, & Woolfrey, 2011). It seems likely that failure of signalling required for maintaining microglial in a ramified state, likely important for preserving surveillant functions, may have consequences that play a role in Alzheimer's pathogenesis by altering the exquisite microglial regulation of synaptic plasticity and function.

The importance of the recent finding that TREM2 genotype is a strong risk factor for sporadic Alzheimer's disease (Golde, Streit, & Chakrabarty, 2013; Guerreiro et al., 2013; Jonsson et al., 2012) must be seen in this context. Not unexpectedly, it has been suggested that TREM2 may have a potential role for housekeeping in the CNS by modulating microglial activity (Neumann & Takahashi, 2007; Takahashi et al., 2005), similar to its role in macrophages (Turnbull et al., 2006). A rare autosomal genetic disorder termed Nasu–Hakola disease is brought about by mutations in either one of two microglial proteins, DAP12 and TREM2. These mutations result in early onset dementia with or without bone cysts and fractures (Thrash, Torbett, & Carson, 2009). This shows that a major perturbation of signalling that affects microglia function can drive the pathogenesis of brain disorders (Bianchin, Martin, de Souza, de Oliveira, & de Mello Rieder, 2010). By inference, more subtle perturbations in this signalling, e.g. through subtle changes in TREM2 function, could result in a slower pathology onset and chronic slow onset of disease such as occurs in Alzheimer's. It is therefore not surprising that recent work associates TREM2 variants with Alzheimer's disease risk and in turn implicates innate immunity in cognitive disorders.

This case is strengthened by considering the host of other molecules that have been implicated in both maintaining microglial quiescence and are now known to also be factors implicated in Alzheimer's disease. This includes molecules such as CD200 and CD200R (Ransohoff & Cardona, 2010; Walker et al., 2009), CX3CR1 (Cardona et al., 2006; Fuhrmann et al., 2010), MicroRNA mir-124 (Lukiw, 2007; Ponomarev et al., 2011) and toll-like receptor-4 (Cameron & Landreth, 2010) to name just a few.

Furthermore, a gain in synaptic elimination could occur by overexpression of the molecules which tag synapses for elimination by microglia. As mentioned earlier, a C1q/C3 receptor system appears to control the removal of synapses by microglia during developmental pruning (Schafer et al., 2012; Stevens et al., 2007). There is aberrant expression of complement receptor factors in the Alzheimer's brain (Fischer et al., 1995). The interpretation of a role for microglial elimination in Alzheimer's disease has mainly been limited by evidence of synaptic elimination, by microglia, not being required for synaptic stripping in a mouse model of prion disease (Perry & O'Connor, 2010; Siskova et al., 2010). However the question needs to be explored before deeper conclusions are drawn.

Finally, it has been suggested that loss of microglial resting phenotype could occur as a result of microglial senescence during aging, and may thereby contribute to the pathogenesis of Alzheimer's disease (Damani et al., 2011; Streit & Xue, 2010, 2012; Streit et al., 2004a; Tremblay, Zettel, Ison, Allen, & Majewska, 2012; Wong, 2013). Loss of resting microglial phenotype can also be driven by systemic infections and inflammation, which are linked to the pathogenesis of synaptic disorders such as Alzheimer's disease (Combrinck, Perry, & Cunningham, 2002; Cunningham et al., 2005). Perry, Nicoll, & Holmes, (2010) provides a recent review of the role of microglia in neurodegenerative disease. In Alzheimer's disease microglial cells undergo changes such as deramification, increased cell body volume, fragmentation of cytoplasm, spheroid formation and gnarling (Krabbe et al., 2013; Streit, Braak, Xue, & Bechmann, 2009; Streit et al., 2004), and this correlates with amyloid-β deposition (Krabbe et al., 2013). Importantly, glial senescence during aging can impact normal synapse function (Streit & Xue, 2010; Wong, 2013). This could cause a loss of their normal resting function of routinely surveying synapses, and thus result in aberrant connectivity between neurons.

We propose that these combined observations raise the distinct possibility that dementia, in at least some of its forms, is a disorder caused by a failure of the maintenance of normal ramified microglial function. This failure may be driven by inflammation (Abdipranoto, Wu, Stayte, & Vissel, 2008; Abdipranoto-Cowley et al., 2009; Clark et al., 2010, 2012; Wright et al., 2013). We therefore suggest a hypothesis for the pathogenesis of cognitive function in diseases such as Alzheimer's results in the first instance from a loss of maintenance of microglial surveillant functions and/or a gain in microglial activation that drives synaptic pathology, one of the earliest pathogenic events in Alzheimer's disease. We also suggest that many of the hallmarks of Alzheimer's can logically be inferred to follow.

Microglia dysfunction is not constrained to memory disorders such as Alzheimer's disease, which we have chosen to focus on here. In particular, studies of autism and schizophrenia, which are considered synaptic disorders, have also been linked to dysfunctional microglia (Frick, Williams, & Pittenger, 2013; Maezawa & Jin, 2010; Monji, Kato, & Kanba, 2009; Munn, 2000). In fact it is quite conceivable that failure to maintain the exquisite control of ramified microglial function, possibly as a result of inflammatory stimuli, could underlie a number of neurological disorders including Parkinson's disease, or at least components of the disease. There are also related syndromes with currently unknown causes, such as progressive supranuclear palsy (PSP) that could be investigated in these terms.

5. Future directions

Clearly, a comprehensive model of learning and memory will not be achievable without incorporating the role of non-neuronal cells. A key point of this review is that microglia (and astrocytes) play a fundamental role at the synapse, and that perturbations in the functions of these cells would lead to diseases such as Alzheimer's or dementia more broadly. This is a testable hypothesis that needs attention in the field of learning and memory. The implications extend to a wide range of neurological and psychiatric disease in which aberrant synapse function and structure have been noted.

Cajal's influence on today's thinking about synapses is not lost on neuroscientists. In the last 50 years, the field of learning and memory has made enormous headway through studying synapses and brain plasticity using cellular and molecular approaches combined with electrophysiology, imaging and behavioural assays. It is imperative now that we start to apply these same approaches to studying microglia and astrocytes in order to gain an understanding of their role in learning and memory. The obvious starting point is to ablate critical synaptic and other paracrine or intracellular signalling molecules from microglia and astrocytes specifically, such as through cre/loxP specific knockout systems. Such approaches would allow the study of the functional role of microglia and astrocytes, using the now well-established behavioural, electrophysiological and other widely used and established paradigms.

An important qualifier to the above has recurred throughout this review. Many paradigms used to investigate neuronal function in neuroscience are performed *ex vivo*, and most cause microglia to alter their activation state and therefore likely their roles and functions. The study of microglia and their role at the synapse in the normal brain will require highly innovative approaches that ensure they maintain their normal range of morphologies.

One particularly appealing avenue is to combine the cre/loxP KO approach (Sauer, 1998), to knockout specific genes in microglia (Cho et al., 2008; Clausen et al., 1999; Wolf et al., 2013) and astrocytes (Ganat et al., 2006; Mobley & McCarty, 2012), with high-end *in vivo* imaging (Nimmerjahn, 2012). Viewing microglia in contact with, and structurally altering specific ensembles of neurons and synapses when activated during learning, will provide further evidence of the concepts presented in this review. Even then, there will still be limitations to overcome. *In vivo* imaging of deeper brain structures is technically challenging, especially when attempting non-invasive approaches to prevent aberrant activation of microglial cells, and increased turnover of synapses in response to glial activation (Xu, Pan, Yang, & Gan, 2007). In fact, many of the results presented in this review have largely viewed synapses and microglia in outer layers of the cerebral cortex, and in the visual system. As such our interpretation of microglial function in deeper brain structures is limited, as microglia can be phenotypically different in different brain regions. Two-photon microscopy has been used to successfully visualise hippocampal neurons *in vivo*, however this required removal of cortical tissue above the hippocampus which is likely to perturb resting microglia and limit interpretation of their resting roles (Mizrahi, Crowley, Shtoyerman, & Katz, 2004). New techniques are emerging which may make it possible to visualise microglia in deeper brain structures *in vivo* using less invasive approaches in the not too distant future (Kawakami et al., 2013).

We have also highlighted the intriguing observation that microglia express a battery of ion channels and receptors that are associated with the synapse in neurons. It is time to start considering that these receptors in ramified microglia may be highly organized as part of a structural specialisation that can sense, monitor and interact with neurons at synapses. In this model, microglia would serve as dynamic players in the neuronal circuit and would be expected to show rapid plasticity of the molecular architecture that associates with synapses. Much is known about the sophisticated molecular organization of neuronal synapses (Ottersen et al., 1997; Schoch & Gundelfinger, 2006; Sheng & Kim, 2011; Sheng & Lin, 2001) and this could serve as a model in the first instance to guide investigations of the molecular organisation of receptors, channels and signalling molecules in microglia at the synapse.

In studying the mechanisms of microglial dysfunction in Alzheimer's disease and neurological diseases, understanding how failure of maintenance of normal ramified microglia function (i.e. when microglia switch phenotype) effects synapse plasticity, is an important avenue to research. Further, how and why synaptic elimination is initiated, and how this relates to the perturbation of microglial function is unknown. Finally it is important to determine the mechanisms which maintain microglial in a functional ramified state, capable of interacting with synapses during normal physiology. This might provide a valuable path to considering therapeutic strategies.

In sum, we propose that it is now the time to open an intriguing new chapter of research in learning and memory. Many of the approaches used to study the molecular mechanisms involved in learning and memory have largely to date focussed on neuron specific communication. These excellent studies now provide us with a framework by which we can begin to investigate the contribution of non-neuronal cells, including microglia and astrocytes, to synaptic plasticity, structural plasticity, and learning and memory in the brain.

6. Conclusions

We can no longer constrain our view of the synapse to considering it as a structure of neurons. We must instead strive to understand it as a complex, dynamic and often transient structure involving several cells interacting within a sophisticated extracellular matrix and milieu. Herein we have presented several lines of evidence supporting a role for microglia in synaptic and structural plasticity. The functions of microglia are determined by both its cellular morphology and by its molecular expression profiles. These studies all strongly imply that microglia, traditionally only thought of as the brains innate immune cells, are critical players in the mechanisms of normal learning and memory in the brain.

Finally, it is clear that many mechanisms which act to maintain microglia in their normal ramified and surveying state in the brain are important for normal learning and memory and are perturbed in learning and memory disorders such as Alzheimer's disease. This suggests a hypothesis for Alzheimer's disease is a loss of the maintenance of the normal microglial state, possibly driven in some instances by inflammation, leading to alterations in microglial effects on synapses early in disease pathogenesis. While there are likely other pathways to synaptic elimination and the pathogenesis of Alzheimer's, the novel roles of microglia in structural plasticity should be included in future discussions on synaptic deficits in Alzheimer's disease.

Only through understanding the complex interactions between the different cell types at the synapse, and the role of the extracellular matrix, will we truly understand synaptic plasticity, learning, memory and cognition. The implication will of course be to understand how perturbations in these interactions contribute to brain diseases. As such, microglia, and indeed astrocytes, represent a further frontier in learning and memory research.

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References

Abdipranoto, A., Wu, S., Stayte, S., & Vissel, B. (2008). The role of neurogenesis in neurodegenerative diseases and its implications for therapeutic development. *CNS & Neurological Disorders Drug Targets, 7*(2), 187–210.

Abdipranoto-Cowley, A., Park, J. S., Croucher, D., Daniel, J., Henshall, S., Galbraith, S., et al. (2009). Activin A is essential for neurogenesis following neurodegeneration. *Stem Cells, 27*(6), 1330–1346.

Abraham, W. C., & Bear, M. F. (1996). Metaplasticity: The plasticity of synaptic plasticity. *Trends in Neurosciences, 19*(4), 126–130.

Akiyama, H., Barger, S., Barnum, S., Bradt, B., Bauer, J., Cole, G. M., et al. (2000). Inflammation and Alzheimer's disease. *Neurobiology of Aging, 21*(3), 383–421.

Albensi, B. C., & Mattson, M. P. (2000). Evidence for the involvement of TNF and NF-kappaB in hippocampal synaptic plasticity. *Synapse, 35*(2), 151–159.

Allen, N. J., & Barres, B. A. (2005). Signaling between glia and neurons: Focus on synaptic plasticity. *Current Opinion in Neurobiology, 15*(5), 542–548.

Aloe, L., Properzi, F., Probert, L., Akassoglou, K., Kassiotis, G., Micera, A., et al. (1999). Learning abilities, NGF and BDNF brain levels in two lines of TNF-alpha transgenic mice, one characterized by neurological disorders, the other phenotypically normal. *Brain Research, 840*(1–2), 125–137.

Alvarez, V. A., & Sabatini, B. L. (2007). Anatomical and physiological plasticity of dendritic spines. *Annual Review of Neuroscience, 30*, 79–97.

Araque, A., Parpura, V., Sanzgiri, R. P., & Haydon, P. G. (1999). Tripartite synapses: Glia, the unacknowledged partner. *Trends in Neuroscience, 22*(5), 208–215.

Atwood, H. L., & Karunanithi, S. (2002). Diversification of synaptic strength: Presynaptic elements. *Nature Reviews Neuroscience, 3*(7), 497–516.

Bailey, Craig H., Bartsch, Dusan, & Kandel, Eric R. (1996). Toward a molecular definition of long-term memory storage. *Proceedings of the National Academy of Sciences, 93*(24), 13445–13452.

Bannerman, D. M., Good, M. A., Butcher, S. P., Ramsay, M., & Morris, R. G. (1995). Distinct components of spatial learning revealed by prior training and NMDA receptor blockade. *Nature, 378*(6553), 182–186.

Barclay, A. N., Wright, G. J., Brooke, G., & Brown, M. H. (2002). CD200 and membrane protein interactions in the control of myeloid cells. *Trends in Immunology, 23*(6), 285–290.

Barker, Al. J., & Ullian, E. M. (2010). Astrocytes and synaptic plasticity. *The Neuroscientist, 16*(1), 40–50.

Bear, M. F. (1999). Homosynaptic long-term depression: A mechanism for memory? *Proceedings of the National Academy of Sciences, 96*(17), 9457–9458.

Beattie, E. C., Stellwagen, D., Morishita, W., Bresnahan, J. C., Ha, B. K., Von Zastrow, M., et al. (2002). Control of synaptic strength by glial TNFalpha. *Science, 295*(5563), 2282–2285.

Bennett, M. R. (2007). Synaptic P2X7 receptor regenerative-loop hypothesis for depression. *Australian and New Zealand Journal of Psychiatry, 41*(7), 563–571.

Bernardino, L., Agasse, F., Silva, B., Ferreira, R., Grade, S., & Malva, J. O. (2008). Tumor necrosis factor-alpha modulates survival, proliferation, and neuronal differentiation in neonatal subventricular zone cell cultures. *Stem Cells, 26*(9), 2361–2371.

Bessis, A., Béchade, C., Bernard, D., & Roumier, A. (2007). Microglial control of neuronal death and synaptic properties. *Glia, 55*(3), 233–238.

Beutler, B., & Van Huffel, C. (1994). An evolutionary and functional approach to the TNF receptor/ligand family. *Annals of the New York Academy of Sciences, 730*, 118–133.

Bianchin, Marino M., Martin, Kelin C., de Souza, Ana C., de Oliveira, Marina A., & de Mello Rieder, Carlos R. (2010). Nasu–Hakola disease and primary microglial dysfunction. *Nature Reviews Neurology, 6*(9).

Biber, K., Neumann, H., Inoue, K., & Boddeke, H. W. G. M. (2007). Neuronal on and off signals control microglia. *Trends in Neurosciences, 30*(11), 596–602.

Bitzer-Quintero, O. K., & Gonzalez-Burgos, I. (2012). Immune system in the brain: A modulatory role on dendritic spine morphophysiology? *Neural Plasticity, 2012*, 348642.

Blank, T., & Prinz, M. (2013). Microglia as modulators of cognition and neuropsychiatric disorders. *Glia, 61*(1), 62–70.

Blinzinger, K., & Kreutzberg, G. (1968). Displacement of synaptic terminals from regenerating motoneurons by microglial cells. *Z Zellforsch Mikrosk Anat, 85*(2), 145–157.

Bliss, T. V., & Collingridge, G. L. (1993). A synaptic model of memory: Long-term potentiation in the hippocampus. *Nature, 361*(6407), 31–39.

Bliss, T. V., & Lomo, T. (1973). Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. *The Journal of Physiology, 232*(2), 331–356.

Boulanger, L. M. (2009). Immune proteins in brain development and synaptic plasticity. *Neuron, 64*(1), 93–109.

Bourne, J., & Harris, K. M. (2007). Do thin spines learn to be mushroom spines that remember? *Current Opinion in Neurobiology, 17*(3), 381–386.

Bourtchuladze, R., Frenguelli, B., Blendy, J., Cioffi, D., Schutz, Gr., & Silva, A. J. (1994). Deficient long-term memory in mice with a targeted mutation of the cAMP-responsive element-binding protein. *Cell, 79*(1), 59–68.

Brynskikh, A., Warren, T., Zhu, J., & Kipnis, J. (2008). Adaptive immunity affects learning behavior in mice. *Brain, Behavior, and Immunity, 22*(6), 861–869.

Cacci, E., Claasen, J. H., & Kokaia, Z. (2005). Microglia-derived tumor necrosis factor-alpha exaggerates death of newborn hippocampal progenitor cells in vitro. *The Journal of Neuroscience Research, 80*(6), 789–797.

Cajal, S. R. (1888). Estructura de los centros nerviosos de las aves. *Revista Trimestral de Histología Normal y Patológica, 1*, 1–10.

Cajal, S. R. (1891). Significación fisiológica de las expansiones protoplásmicas y nerviosas de la sustancia gris. *Revista Trimestral de Histología Normal y Patológica, 22*, 23.

Cajal, Santiago Ramon Y. (1894). The croonian lecture: la fine structure des centres nerveux. *Proceedings of the Royal Society of London, 55*(331–335), 444–468.

Cameron, B., & Landreth, G. E. (2010). Inflammation, microglia, and Alzheimer's disease. *Neurobiology of Disease, 37*(3), 503–509.

Cardona, A. E., Pioro, E. P., Sasse, M. E., Kostenko, V., Cardona, S. M., Dijkstra, I. M., et al. (2006). Control of microglial neurotoxicity by the fractalkine receptor. *Nature Neuroscience, 9*(7), 917–924.

Chen, Y., Bourne, J., Pieribone, V. A., & Fitzsimonds, R. M. (2004). The role of actin in the regulation of dendritic spine morphology and bidirectional synaptic plasticity. *Neuroreport, 15*(5), 829–832.

Chen, T., Koga, K., Li, X. Y., & Zhuo, M. (2010). Spinal microglial motility is independent of neuronal activity and plasticity in adult mice. *Molecular Pain, 6*, 19.

Chen, C., & Tonegawa, S. (1997). Molecular genetic analysis of synaptic plasticity, activity-dependent neural development, learning, and memory in the mammalian brain. *Annual Review of Neuroscience, 20*(1), 157–184.

Cho, I. H., Hong, J., Suh, E. C., Kim, J. H., Lee, H., et al. (2008). Role of microglial IKKbeta in kainic acid-induced hippocampal neuronal cell death. *Brain, 131*(Pt 11), 3019–3033.

Clark, I. A., Alleva, L. M., & Vissel, B. (2010). The roles of TNF in brain dysfunction and disease. *Pharmacology & Therapeutics, 128*(3), 519–548.

Clark, I., Atwood, C., Bowen, R., Paz-Filho, G., & Vissel, B. (2012). Tumor necrosis factor-induced cerebral insulin resistance in Alzheimer's disease links numerous treatment rationales. *Pharmacological Reviews, 64*(4), 1004–1026.

Clausen, B. E., Burkhardt, C., Reith, W., Renkawitz, R., & Forster, I. (1999). Conditional gene targeting in macrophages and granulocytes using LysMcre mice. *Transgenic Res, 8*(4), 265–277.

Colonnier, M. (1968). Synaptic patterns on different cell types in the different laminae of the cat visual cortex. An electron microscope study. *Brain Research, 9*(2), 268–287.

Colton, C. A. (2009). Heterogeneity of microglial activation in the innate immune response in the brain. *Journal of Neuroimmune Pharmacology, 4*(4), 399–418.

Combrinck, M. I., Perry, V. H., & Cunningham, C. (2002). Peripheral infection evokes exaggerated sickness behaviour in pre-clinical murine prion disease. *Neuroscience, 112*(1), 7–11.

Cooke, S. F., & Bliss, T. V. (2006). Plasticity in the human central nervous system. *Brain, 129*(Pt 7), 1659–1673.

Costello, D. A., Lyons, A., Denieffe, S., Browne, T. C., Cox, F. F., & Lynch, M. A. (2011). Long term potentiation is impaired in membrane glycoprotein CD200-deficient mice: A role for Toll-like receptor activation. *The Journal of Biological Chemistry, 286*(40), 34722–34732.

Cunningham, C., Wilcockson, D. C., Campion, S., Lunnon, K., & Perry, V. H. (2005). Central and systemic endotoxin challenges exacerbate the local inflammatory response and increase neuronal death during chronic neurodegeneration. *The Journal of Neuroscience, 25*(40), 9275–9284.

Damani, M. R., Zhao, L., Fontainhas, A. M., Amaral, J., Fariss, R. N., & Wong, W. T. (2011). Age-related alterations in the dynamic behavior of microglia. *Aging Cell, 10*(2), 263–276.

Daniel, J. A., Galbraith, S., Iacovitti, L., Abdipranoto, A., & Vissel, B. (2009). Functional heterogeneity at dopamine release sites. *The Journal of Neuroscience, 29*(46), 14670–14680.

Davalos, D., Grutzendler, J., Yang, G., Kim, J. V., Zuo, Y., Jung, S., et al. (2005). ATP mediates rapid microglial response to local brain injury in vivo. *Nature Neuroscience, 8*(6), 752–758.

Davies, C. A., Mann, D. M., Sumpter, P. Q., & Yates, P. O. (1987). A quantitative morphometric analysis of the neuronal and synaptic content of the frontal and temporal cortex in patients with Alzheimer's disease. *Journal of the Neurological Sciences, 78*(2), 151–164.

Dityatev, A., & Rusakov, D. A. (2011). Molecular signals of plasticity at the tetrapartite synapse. *Current Opinion in Neurobiology, 21*(2), 353–359.

Domercq, M., Vazquez-Villoldo, N., & Matute, C. (2013). Neurotransmitter signaling in the pathophysiology of microglia. *Frontiers in Cellular Neuroscience, 7*, 49.

Elgersma, Y., & Silva, A. J. (1999). Molecular mechanisms of synaptic plasticity and memory. *Current Opinion in Neurobiology, 9*(2), 209–213.

Engert, F., & Bonhoeffer, T. (1999). Dendritic spine changes associated with hippocampal long-term synaptic plasticity. *Nature, 399*(6731), 66–70.

Fagan, T. (2013). Microglia activation—Venusberg meeting Questions M1, M2 Designations. <http://www.alzforum.org/new/detail.asp?id=3426> (Retrieved 15.07.2013).

Farber, K., & Kettenmann, H. (2005). Physiology of microglial cells. *Brain Research Reviews, 48*(2), 133–143.

Farber, K., & Kettenmann, H. (2006). Purinergic signaling and microglia. *Pflugers Arch, 452*(5), 615–621.

Fiala, J. C., Feinberg, M., Popov, V., & Harris, K. M. (1998). Synaptogenesis via dendritic filopodia in developing hippocampal area CA1. *The Journal of Neuroscience, 18*(21), 8900–8911.

Fiala, J. C., Spacek, J., & Harris, K. M. (2002). Dendritic spine pathology: Cause or consequence of neurological disorders? *Brain Research Reviews, 39*(1), 29–54.

Finnie, P. S. B., & Nader, K. (2012). The role of metaplasticity mechanisms in regulating memory destabilization and reconsolidation. *Neuroscience & Biobehavioral Reviews, 36*(7), 1667–1707.

Fischer, B., Schmoll, H., Riederer, P., Bauer, J., Platt, D., & Popa-Wagner, A. (1995). Complement C1q and C3 mRNA expression in the frontal cortex of Alzheimer's patients. *Journal of Molecular Medicine, 73*(9), 465–471.

Fontainhas, A. M., Wang, M., Liang, K. J., Chen, S., Mettu, P., Damani, M., et al. (2011). Microglial morphology and dynamic behavior is regulated by ionotropic glutamatergic and GABAergic neurotransmission. *PLoS One, 6*(1), e15973.

Frick, L. R., Williams, K., & Pittenger, C. (2013). Microglial dysregulation in psychiatric disease. *Clinical and Developmental Immunology, 2013*, 10.

Fuhrmann, M., Bittner, T., Jung, C. K. E., Burgold, S., Page, R. M., Mitteregger, G., et al. (2010). Microglial Cx3cr1 knockout prevents neuron loss in a mouse model of Alzheimer's disease. *Nature Neuroscience, 13*(4), 411–413.

Ganat, Y. M., Silbereis, J., Cave, C., Ngu, H., Anderson, G. M., Ohkubo, Y., et al. (2006). Early postnatal astroglial cells produce multilineage precursors and neural stem cells in vivo. *The Journal of Neuroscience, 26*(33), 8609–8621.

Garay, P. A., & McAllister, A. K. (2010). Novel roles for immune molecules in neural development: Implications for neurodevelopmental disorders. *Frontiers in Synaptic Neuroscience, 2*, 136.

Garcia-Lopez, P., Garcia-Marin, V., & Freire, M. (2010). Dendritic spines and development: Towards a unifying model of spinogenesis–a present day review of Cajal's histological slides and drawings. *Neural Plasticity, 2010*, 769207.

Gehrmann, J., Matsumoto, Y., & Kreutzberg, G. W. (1995). Microglia: Intrinsic immuneffector cell of the brain. *Brain Research Reviews, 20*(3), 269–287.

Gerlai, R., Wojtowicz, J. M., Marks, A., & Roder, J. (1995). Overexpression of a calcium-binding protein, S100 beta, in astrocytes alters synaptic plasticity and impairs spatial learning in transgenic mice. *Learning and Memory, 2*(1), 26–39.

Ginhoux, F., Greter, M., Leboeuf, M., Nandi, S., See, P., Gokhan, S., et al. (2010). Fate mapping analysis reveals that adult microglia derive from primitive macrophages. *Science, 330*(6005), 841–845.

Glezer, I., Zekki, H., Scavone, C., & Rivest, S. (2003). Modulation of the innate immune response by NMDA receptors has neuropathological consequences. *The Journal of Neuroscience, 23*(35), 11094–11103.

Golde, T. E., Streit, W. J., & Chakrabarty, P. (2013). Alzheimer's disease risk alleles in TREM2 illuminate innate immunity in Alzheimer's disease. *Alzheimer's Research & Therapy, 5*(3), 24.

Goshen, I., Kreisel, T., Ounallah-Saad, H., Renbaum, P., Zalzstein, Y., Ben-Hur, T., et al. (2007). A dual role for interleukin-1 in hippocampal-dependent memory processes. *Psychoneuroendocrinology, 32*(8–10), 1106–1115.

Graeber, M. B., Bise, K., & Mehraein, P. (1993). Synaptic stripping in the human facial nucleus. *Acta Neuropathologica, 86*(2), 179–181.

Graeber, M. B., Li, W., & Rodriguez, M. L. (2011). Role of microglia in CNS inflammation. *FEBS Letters, 585*(23), 3798–3805.

Gray, E. G. (1959). Axo-somatic and axo-dendritic synapses of the cerebral cortex: An electron microscope study. *Journal of Anatomy, 93*, 420–433.

Griffin, R., Nally, R. l., Nolan, Y., McCartney, Y., Linden, J., & Lynch, M. A. (2006). The age-related attenuation in long-term potentiation is associated with microglial activation. *Journal of Neurochemistry, 99*(4), 1263–1272.

Grutzendler, J., Kasthuri, N., & Gan, W. B. (2002). Long-term dendritic spine stability in the adult cortex. *Nature, 420*(6917), 812–816.

Guerreiro, R., Wojtas, A., Bras, J., Carrasquillo, M., Rogaeva, E., Majounie, E., et al. (2013). TREM2 variants in Alzheimer's disease. *New England Journal of Medicine, 368*(2), 117–127.

Han, X., Chen, M., Wang, F., Windrem, M., Wang, S., Shanz, S., et al. (2013). Forebrain engraftment by human glial progenitor cells enhances synaptic plasticity and learning in adult mice. *Cell Stem Cell, 12*(3), 342–353.

Hanisch, U.-K. (2002). Microglia as a source and target of cytokines. *Glia, 40*(2), 140–155.

Haynes, S. E., Hollopeter, G., Yang, G., Kurpius, D., Dailey, M. E., Gan, W.-B., et al. (2006). The P2Y12 receptor regulates microglial activation by extracellular nucleotides. *Nature Neuroscience, 9*(12), 1512–1519.

Hebb, D. O. (1949). *The organization of behavior*. New York: Wiley.

Hoek, R. M., Ruuls, S. R., Murphy, C. A., Wright, G. J., Goddard, R., Zurawski, S. M., et al. (2000). Down-regulation of the macrophage lineage through interaction with OX2 (CD200). *Science, 290*(5497), 1768–1771.

Holtmaat, A., & Svoboda, K. (2009). Experience-dependent structural synaptic plasticity in the mammalian brain. *Nature Reviews Neuroscience, 10*(9), 647–658.

Holtmaat, A. J. G. D., Trachtenberg, J. T., Wilbrecht, L., Shepherd, G. M., Zhang, X., Knott, G. W., et al. (2005). Transient and persistent dendritic spines in the neocortex in vivo. *Neuron, 45*(2), 279–291.

Hulme, S. R., Jones, O. D., & Abraham, W. C. (2013). Emerging roles of metaplasticity in behaviour and disease. *Trends in Neurosciences, 36*(6), 353–362.

Iosif, R. E., Ahlenius, H., Ekdahl, C. T., Darsalia, V., Thored, P., Jovinge, S., et al. (2008). Suppression of stroke-induced progenitor proliferation in adult subventricular zone by tumor necrosis factor receptor 1. *Journal of Cerebral Blood Flow & Metabolism, 28*(9), 1574–1587.

Iosif, R. E., Ekdahl, C. T., Ahlenius, H., Pronk, C. J., Bonde, S., Kokaia, Z., et al. (2006). Tumor necrosis factor receptor 1 is a negative regulator of progenitor proliferation in adult hippocampal neurogenesis. *The Journal of Neuroscience, 26*(38), 9703–9712.

Ishii, T., & Mombaerts, P. (2008). Expression of nonclassical Class I major histocompatibility genes defines a tripartite organization of the mouse vomeronasal system. *The Journal of Neuroscience, 28*(10), 2332–2341.

Johnston, D., Williams, S., Jaffe, D., & Gray, R. (1992). NMDA-receptor-independent long-term potentiation. *Annual Reviews Physiology, 54*, 489–505.

Jonsson, T., Stefansson, H., Ph, D. Ss, Jonsdottir, I., Jonsson, P. V., Snaedal, J., Stefansson, K. (2012). Variant of TREM2 Associated with the Risk of Alzheimer's Disease. New England *Journal of Medicine*.

Kaindl, A. M., Degos, V., Peineau, S., Gouadon, E., Chhor, V., Loron, G., et al. (2012). Activation of microglial N-methyl-D-aspartate receptors triggers inflammation and neuronal cell death in the developing and mature brain. *Annals of Neurology, 72*(4), 536–549.

Kaindl, A. M., Degos, V., Peineau, S., Gouadon, E., Loron, G., Lombet, A., et al. (2008). Microglia express functional NMDA receptors: A novel finding and a promise for innovative treatment of excitotoxic and inflammatory brain disease. *Neuropediatrics, 39*(05), V23.

Kalla, R., Liu, Z., Xu, S., Koppius, A., Imai, Y., Kloss, C. U., et al. (2001). Microglia and the early phase of immune surveillance in the axotomized facial motor nucleus: Impaired microglial activation and lymphocyte recruitment but no effect on neuronal survival or axonal regeneration in macrophage-colony stimulating factor-deficient mice. *Journal of Comparative Neurology, 436*(2), 182–201.

Kandel, E. R. (2001). The molecular biology of memory storage: A dialogue between genes and synapses. *Science, 294*(5544), 1030–1038.

Kandel, E. R. (2009). The biology of memory: A forty-year perspective. *The Journal of Neuroscience, 29*(41), 12748–12756.

Kasai, Haruo, Fukuda, Masahiro, Watanabe, Satoshi, Hayashi-Takagi, Akiko, & Noguchi, Jun (2010). Structural dynamics of dendritic spines in memory and cognition. *Trends in Neurosciences, 33*(3), 121–129.

Katz, L. C., & Shatz, C. J. (1996). Synaptic activity and the construction of cortical circuits. *Science, 274*(5290), 1133–1138.

Kawakami, R., Sawada, K., Sato, A., Hibi, T., Kozawa, Y., Sato, S., et al. (2013). Visualizing hippocampal neurons with in vivo two-photon microscopy using a 1030 nm picosecond pulse laser. *Scientific Reports, 3*, 1014.

Kettenmann, H. (2007). Neuroscience: The brain's garbage men. *Nature, 446*(7139), 987–989.

Kettenmann, H., Hanisch, U. K., Noda, M., & Verkhratsky, A. (2011). Physiology of microglia. *Physiological Reviews, 91*(2), 461–553.

Kettenmann, Helmut., Kirchhoff, Frank., & Verkhratsky, Alexei. (2013). Microglia: New roles for the synaptic stripper. *Neuron, 77*(1), 10–18.

Kierdorf, K., Erny, D., Goldmann, T., Sander, V., Schulz, C., Perdiguero, E. G., et al. (2013). Microglia emerge from erythromyeloid precursors via Pu.1- and Irf8-dependent pathways. *Nature Neuroscience, 16*(3), 273–280.

Kitamura, T., Tsuchihashi, Y., & Fujita, S. (1978). Initial response of silver-impregnated "resting microglia" to stab wounding in rabbit hippocampus. *Acta Neuropathologica, 44*(1), 31–39.

Klemann, C. J. H. M., & Roubos, E. W. (2011). The gray area between synapse structure and function—Gray's synapse types I and II revisited. *Synapse, 65*(11), 1222–1230. http://dx.doi.org/10.1002/syn.20962.

Kopec, C. D., Li, B., Wei, W., Boehm, J., & Malinow, R. (2006). Glutamate receptor exocytosis and spine enlargement during chemically induced long-term potentiation. *The Journal of Neuroscience, 26*(7), 2000–2009.

Krabbe, G., Halle, A., Matyash, V., Rinnenthal, J. L., Eom, G. D., Bernhardt, U., et al. (2013). Functional impairment of microglia coincides with Beta-amyloid deposition in mice with Alzheimer-like pathology. *PLoS One, 8*(4), e60921.

Krause, D. L., & Muller, N. (2010). Neuroinflammation, microglia and implications for anti-inflammatory treatment in Alzheimer's disease. *International Journal of Alzheimer's Disease*.

Kreutzberg, G. W. (1996). Microglia: A sensor for pathological events in the CNS. *Trends in Neurosciences, 19*(8), 312–318.

Kubota, K., Inoue, K., Hashimoto, R., Kumamoto, N., Kosuga, A., Tatsumi, M., et al. (2009). Tumor necrosis factor receptor-associated protein 1 regulates cell adhesion and synaptic morphology via modulation of N-cadherin expression. *Journal of Neurochemistry, 110*(2), 496–508.

Kurpius, D., Nolley, E. P., & Dailey, M. E. (2007). Purines induce directed migration and rapid homing of microglia to injured pyramidal neurons in developing hippocampus. *Glia, 55*(8), 873–884.

Kurpius, D., Wilson, N., Fuller, L., Hoffman, A., & Dailey, M. E. (2006). Early activation, motility, and homing of neonatal microglia to injured neurons does not require protein synthesis. *Glia, 54*(1), 58–70.

Lai, C. S., Franke, T. F., & Gan, W. B. (2012). Opposite effects of fear conditioning and extinction on dendritic spine remodelling. *Nature, 483*(7387), 87–91.

Lang, C., Barco, A., Zablow, L., Kandel, E. R., Siegelbaum, S. A., & Zakharenko, S. S. (2004). Transient expansion of synaptically connected dendritic spines upon induction of hippocampal long-term potentiation. *Proceedings of the National Academy of Sciences, 101*(47), 16665–16670.

Lawson, L. J., Perry, V. H., Dri, P., & Gordon, S. (1990). Heterogeneity in the distribution and morphology of microglia in the normal adult mouse brain. *Neuroscience, 39*(1), 151–170.

Lawson, L. J., Perry, V. H., & Gordon, S. (1992). Turnover of resident microglia in the normal adult mouse brain. *Neuroscience, 48*(2), 405–415.

Lee, S. H., Liu, L., Wang, Y. T., & Sheng, M. (2002). Clathrin adaptor AP2 and NSF interact with overlapping sites of GluR2 and play distinct roles in AMPA receptor trafficking and hippocampal LTD. *Neuron, 36*(4), 661–674.

Linden, D. J., & Connor, J. A. (1995). Long-term synaptic depression. *Annual Review of Neuroscience, 18*, 319–357.

Lukiw, W. J. (2007). Micro-RNA speciation in fetal, adult and Alzheimer's disease hippocampus. *Neuroreport, 18*(3), 297–300.
Luscher, C., & Malenka, R. C. (2012). NMDA receptor-dependent long-term potentiation and long-term depression (LTP/LTD). *Cold Spring Harbor Perspectives in Biology, 4*(6).
Luscher, C., Xia, H., Beattie, E. C., Carroll, R. C., von Zastrow, M., Malenka, R. C., et al. (1999). Role of AMPA receptor cycling in synaptic transmission and plasticity. *Neuron, 24*(3), 649–658.
Lynch, G. S., Dunwiddie, T., & Gribkoff, V. (1977). Heterosynaptic depression: A postsynaptic correlate of long-term potentiation. *Nature, 266*(5604), 737–739.
Lyons, A., Lynch, A. M., Downer, E. J., Hanley, R., O'Sullivan, J. B., Smith, A., et al. (2009). Fractalkine-induced activation of the phosphatidylinositol-3 kinase pathway attentuates microglial activation in vivo and in vitro. *Journal of Neurochemistry, 110*(5), 1547–1556.
Maezawa, I., & Jin, L. W. (2010). Rett syndrome microglia damage dendrites and synapses by the elevated release of glutamate. *The Journal of Neuroscience, 30*(15), 5346–5356.
Majewska, A. K., Newton, J. R., & Sur, M. (2006). Remodeling of synaptic structure in sensory cortical areas in vivo. *The Journal of Neuroscience, 26*(11), 3021–3029.
Maletic-Savatic, M., Malinow, R., & Svoboda, K. (1999). Rapid dendritic morphogenesis in CA1 hippocampal dendrites induced by synaptic activity. *Science, 283*(5409), 1923–1927.
Mallat, M., & Chamak, B. (1994). Brain macrophages: Neurotoxic or neurotrophic effector cells? *Journal of Leukocyte Biology, 56*(3), 416–422.
Man, H. Y., Lin, J. W., Ju, W. H., Ahmadian, G., Liu, L., Becker, L. E., et al. (2000). Regulation of AMPA receptor-mediated synaptic transmission by clathrin-dependent receptor internalization. *Neuron, 25*(3), 649–662.
Maren, S., Aharonov, G., Stote, D. L., & Fanselow, M. S. (1996). N-methyl-D-aspartate receptors in the basolateral amygdala are required for both acquisition and expression of conditional fear in rats. *Behavioral Neuroscience, 110*(6), 1365–1374.
Martin, S. J., Grimwood, P. D., & Morris, R. G. (2000). Synaptic plasticity and memory: An evaluation of the hypothesis. *Annual Review of Neuroscience, 23*, 649–711.
Masliah, E., Mallory, M., Hansen, L. A., Richard, D. T., Alford, M. l., & Terry, R. D. (1994). Synaptic and neuritic alterations during the progression of Alzheimer's disease. *Neuroscience Letters, 174*(1), 67–72.
Massey, P. V., & Bashir, Z. I. (2007). Long-term depression: Multiple forms and implications for brain function. *Trends in Neurosciences, 30*(4), 176–184.
Matsuzaki, M., Honkura, N., Ellis-Davies, G. C., & Kasai, H. (2004). Structural basis of long-term potentiation in single dendritic spines. *Nature, 429*(6993), 761–766.
Mayford, M., Bach, M. E., Huang, Y. Y., Wang, L., Hawkins, R. D., & Kandel, E. R. (1996). Control of memory formation through regulated expression of a CaMKII transgene. *Science, 274*(5293), 1678–1683.
Mayford, M., & Kandel, E. R. (1999). Genetic approaches to memory storage. *Trends in Genetics, 15*(11), 463–470.
Mayford, M., Siegelbaum, S. A., & Kandel, E. R. (2012). Synapses and memory storage. *Cold Spring Harbor Perspectives in Biology, 4*(6).
McGeer, E. G., & McGeer, P. L. (2003). Inflammatory processes in Alzheimer's disease. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 27*(5), 741–749.
McKercher, S. R., Torbett, B. E., Anderson, K. L., Henkel, G. W., Vestal, D. J., Baribault, H., et al. (1996). Targeted disruption of the PU.1 gene results in multiple hematopoietic abnormalities. *The EMBO Journal, 15*(20), 5647–5658.
Miller, M., & Peters, A. (1981). Maturation of rat visual cortex. II. A combined Golgi-electron microscope study of pyramidal neurons. *The Journal of Comparative Neurology, 203*(4), 555–573.
Mittelbronn, M., Dietz, K., Schluesener, H. J., & Meyermann, R. (2001). Local distribution of microglia in the normal adult human central nervous system differs by up to one order of magnitude. *Acta Neuropathologica, 101*(3), 249–255.
Mizrahi, A., Crowley, J. C., Shtoyerman, E., & Katz, L. C. (2004). High-resolution in vivo imaging of hippocampal dendrites and spines. *The Journal of Neuroscience, 24*(13), 3147–3151. doi: monj.
Mobley, A. K., & McCarty, J. H. (2012). Use of Cre-lox technology to analyze integrin functions in astrocytes. *Methods Mol Biol, 814*, 555–570.
Monji, A., Kato, T., & Kanba, S. (2009). Cytokines and schizophrenia: Microglia hypothesis of schizophrenia. *Psychiatry and Clinical Neurosciences, 63*(3), 257–265.
Moran, L. B., & Graeber, M. B. (2004). The facial nerve axotomy model. *Brain Research Reviews, 44*(2–3), 154–178.
Mozzachiodi, R., & Byrne, J. H. (2010). More than synaptic plasticity: Role of nonsynaptic plasticity in learning and memory. *Trends in Neurosciences, 33*(1), 17–26.
Mulkey, R. M., & Malenka, R. C. (1992). Mechanisms underlying induction of homosynaptic long-term depression in area CA1 of the hippocampus. *Neuron, 9*(5), 967–975.
Munn, N. A. (2000). Microglia dysfunction in schizophrenia: An integrative theory. *Medical Hypotheses, 54*(2), 198–202.
Nagerl, U. V., Eberhorn, N., Cambridge, S. B., & Bonhoeffer, T. (2004). Bidirectional activity-dependent morphological plasticity in hippocampal neurons. *Neuron, 44*(5), 759–767.
Nedergaard, M., & Verkhratsky, A. (2012). Artifact versus reality—How astrocytes contribute to synaptic events. *Glia, 60*(7), 1013–1023.
Neumann, H., & Takahashi, K. (2007). Essential role of the microglial triggering receptor expressed on myeloid cells-2 (TREM2) for central nervous tissue immune homeostasis. *Journal of Neuroimmunology, 184*(1–2), 92–99.
Nimchinsky, E. A., Sabatini, B. L., & Svoboda, K. (2002). Structure and function of dendritic spines. *Annual Review of Physiology, 64*, 313–353. http://dx.doi.org/10.1146/annurev.physiol.64.081501.160008.
Nimmerjahn, A. (2012). Two-photon imaging of microglia in the mouse cortex in vivo. *Cold Spring Harbor Protocols, 2012*(5), pdb.prot069294.
Nimmerjahn, A., Kirchhoff, F., & Helmchen, F. (2005). Resting microglial cells are highly dynamic surveillants of brain parenchyma in vivo. *Science, 308*(5726), 1314–1318.
Nolte, C., Moller, T., Walter, T., & Kettenmann, H. (1996). Complement 5a controls motility of murine microglial cells in vitro via activation of an inhibitory G-protein and the rearrangement of the actin cytoskeleton. *Neuroscience, 73*(4), 1091–1107.
Norden, D. M., & Godbout, J. P. (2013). Review: Microglia of the aged brain: Primed to be activated and resistant to regulation. *Neuropathology and Applied Neurobiology, 39*(1), 19–34.
Oberheim, N. A., Goldman, S. A., & Nedergaard, M. (2012). Heterogeneity of astrocytic form and function. *Methods in Molecular Biology, 814*, 23–45.
Oemichen, M. (1978). Mononuclear phagocytes in the central nervous system. Origin, mode of distribution, and function of progressive microglia, perivascular cells of intracerebral vessels, free subarachnoidal cells, and epiplexus cells. *Schriftenreihe Neurologie, 21*(I–X), 1–167.
Ogoshi, F., Yin, H. Z., Kuppumbatti, Y., Song, B., Amindari, S., & Weiss, J. H. (2005). Tumor necrosis-factor-alpha (TNF-α) induces rapid insertion of $Ca2^{+}$-permeable α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA)/kainate (Ca-A/K) channels in a subset of hippocampal pyramidal neurons. *Experimental Neurology, 193*(2), 384–393.
Okun, E., Barak, B., Saada-Madar, R., Rothman, S. M., Griffioen, K. J., Roberts, N., et al. (2012). Evidence for a developmental role for TLR4 in learning and memory. *PLoS One, 7*(10), e47522.
Ottersen, O. P., Chaudhry, F. A., Danbolt, N. C., Laake, J. H., Nagelhus, E. A., Storm-Mathisen, J., et al. (1997). Molecular organization of cerebellar glutamate synapses. *Progress in Brain Research, 114*, 97–107.
Pan, W., Zadina, J. E., Harlan, R. E., Weber, J. T., Banks, W. A., & Kastin, A. J. (1997). Tumor necrosis factor-alpha: A neuromodulator in the CNS. *Neuroscience and Biobehavioral Reviews, 21*(5), 603–613.
Pannasch, U., & Rouach, N. (2013). Emerging role for astroglial networks in information processing: From synapse to behavior. *Trends in Neurosciences, 36*(7), 405–417.
Paolicelli, R. C., Bolasco, G., Pagani, F., Maggi, L., Scianni, M., Panzanelli, P., et al. (2011). Synaptic pruning by microglia is necessary for normal brain development. *Science, 333*(6048), 1456–1458.
Pascual, O., Ben Achour, S., Rostaing, P., Triller, A., & Bessis, A. (2012). Microglia activation triggers astrocyte-mediated modulation of excitatory neurotransmission. *Proceedings of the National Academy of Sciences, 109*(4), E197–205.
Pearce, J. M. (2004). Sir Charles Scott Sherrington (1857–1952) and the synapse. *Journal of Neurology, Neurosurgery & Psychiatry, 75*(4), 544.
Penzes, P., Cahill, M. E., Jones, K. A., VanLeeuwen, J.-E., & Woolfrey, K. M. (2011). Dendritic spine pathology in neuropsychiatric disorders. *Nature Neuroscience, 14*(3), 285–293.
Perea, G., Navarrete, M., & Araque, A. (2009). Tripartite synapses: Astrocytes process and control synaptic information. *Trends in Neurosciences, 32*(8), 421–431. doi: al.
Perry, V. H., Cunningham, C., & Holmes, C. (2007). Systemic infections and inflammation affect chronic neurodegeneration. *Nature Reviews Immunology, 7*(2), 161–167.
Perry, V. H., Nicoll, J. A. R., & Holmes, C. (2010). Microglia in neurodegenerative disease. *Nature Reviews Neurology, 6*(4), 193–201.
Perry, V. H., & O'Connor, V. (2010). The role of microglia in synaptic stripping and synaptic degeneration: A revised perspective. *ASN Neuro, 2*(5), e00047.
Peters, A., & Kaiserman-Abramof, I. R. (1970). The small pyramidal neuron of the rat cerebral cortex. The perikaryon, dendrites and spines. *American Journal of Anatomy, 127*(4), 321–355.
Petersen, M. A., & Dailey, M. E. (2004). Diverse microglial motility behaviors during clearance of dead cells in hippocampal slices. *Glia, 46*(2), 195–206.
Pocock, J. M., & Kettenmann, H. (2007). Neurotransmitter receptors on microglia. *Trends in Neurosciences, 30*(10), 527–535.
Ponomarev, E. D., Veremeyko, T., Barteneva, N., Krichevsky, A. M., & Weiner, H. L. (2011). MicroRNA-124 promotes microglia quiescence and suppresses EAE by deactivating macrophages via the C/EBP-[alpha]-PU.1 pathway. *Nature Medicine, 17*(1), 64–70.
Ransohoff, R. M., & Cardona, A. E. (2010). The myeloid cells of the central nervous system parenchyma. *Nature, 468*(7321), 253–262.
Ransohoff, R. M., & Perry, V. H. (2009). Microglial physiology: Unique stimuli, specialized responses. *Annual Review of Immunology, 27*, 119–145.
Redondo, R. L., & Morris, R. G. M. (2011). Making memories last: The synaptic tagging and capture hypothesis. *Nature Reviews Neuroscience, 12*(1), 17–30.
Rivest, S. (2009). Regulation of innate immune responses in the brain. *Nature Reviews Immunology, 9*(6), 429–439.
Rochefort, N. L., & Konnerth, A. (2012). Dendritic spines: From structure to in vivo function. *EMBO Reports, 13*(8), 699–708.
Rogers, J. T., Morganti, J. M., Bachstetter, A. D., Hudson, C. E., Peters, M. M., Grimmig, B. A., et al. (2011). CX3CR1 deficiency leads to impairment of hippocampal cognitive function and synaptic plasticity. *The Journal of Neuroscience, 31*(45), 16241–16250.

Romo-González, T., Chavarría, A., & Pérez-H, J. (2012). Central nervous system: A modified immune surveillance circuit? *Brain, Behavior, and Immunity, 26*(6), 823–829.

Saijo, K., & Glass, C. K. (2011). Microglial cell origin and phenotypes in health and disease. *Nature Reviews Immunology, 11*(11), 775–787.

Sanders, J., Cowansage, K., Baumgartel, K., & Mayford, M. (2012). Elimination of dendritic spines with long-term memory is specific to active circuits. *The Journal of Neuroscience, 32*(36), 12570–12578.

Santello, M., & Volterra, A. (2012). TNFalpha in synaptic function: Switching gears. *Trends in Neurosciences, 35*(10), 638–647.

Sauer, B. (1998). Inducible gene targeting in mice using the Cre/lox system. *Methods, 14*(4), 381–392.

Schafer, D. P., Lehrman, E. K., Kautzman, A. G., Koyama, R., Mardinly, A. R., Yamasaki, R., et al. (2012). Microglia sculpt postnatal neural circuits in an activity and complement-dependent manner. *Neuron, 74*(4), 691–705.

Schafer, D. P., Lehrman, E. K., & Stevens, B. (2013). The "quad-partite" synapse: Microglia-synapse interactions in the developing and mature CNS. *Glia, 61*(1), 24–36.

Scheff, S. W., & Price, D. A. (2003). Synaptic pathology in Alzheimer's disease: A review of ultrastructural studies. *Neurobiology of Aging, 24*(8), 1029–1046.

Scheff, S. W., Price, D. A., Schmitt, F. A., DeKosky, S. T., & Mufson, E. J. (2007). Synaptic alterations in CA1 in mild Alzheimer disease and mild cognitive impairment. *Neurology, 68*(18), 1501–1508.

Scheff, S. W., Price, D. A., Schmitt, F. A., & Mufson, E. J. (2006). Hippocampal synaptic loss in early Alzheimer's disease and mild cognitive impairment. *Neurobiology of Aging, 27*(10), 1372–1384.

Schiefer, J., Kampe, K., Dodt, H. U., Zieglgansberger, W., & Kreutzberg, G. W. (1999). Microglial motility in the rat facial nucleus following peripheral axotomy. *Journal of Neurocytology, 28*(6), 439–453.

Schoch, S., & Gundelfinger, E. D. (2006). Molecular organization of the presynaptic active zone. *Cell and Tissue Research, 326*(2), 379–391.

Selkoe, D. J. (2002). Alzheimer's disease is a synaptic failure. *Science, 298*(5594), 789–791.

Sheng, M., & Kim, E. (2011). *The postsynaptic organization of synapses*. Cold Spring Harbor Perspectives in Biology.

Sheng, M., & Lin, J. W. (2001). *Glutamatergic synapses: Molecular organization eLS*. John Wiley & Sons, Ltd..

Sierra, A., Encinas, J. M., Deudero, J. J. P., Chancey, J. H., Enikolopov, G., Overstreet-Wadiche, L. S., et al. (2010). Microglia shape adult hippocampal neurogenesis through apoptosis-coupled phagocytosis. *Cell Stem Cell, 7*(4), 483–495.

Silva, A. J., Kogan, J. H., Frankland, P. W., & Kida, S. (1998). Creb and memory. *Annual Review of Neuroscience, 21*(1), 127–148.

Silva, A. J., Paylor, R., Wehner, J. M., & Tonegawa, S. (1992). Impaired spatial learning in alpha-calcium-calmodulin kinase II mutant mice. *Science, 257*(5067), 206–211.

Siskova, Z., Mahad, D. J., Pudney, C., Campbell, G., Cadogan, M., Asuni, A., et al. (2010). Morphological and functional abnormalities in mitochondria associated with synaptic degeneration in prion disease. *The American Journal of Pathology, 177*(3), 1411–1421.

Snyder, E. M., Nong, Y., Almeida, C. G., Paul, S., Moran, T., Choi, E. Y., et al. (2005). Regulation of NMDA receptor trafficking by amyloid-beta. *Nature Neuroscience, 8*(8), 1051–1058.

Sogn, C. J., Puchades, M., & Gundersen, V. (2013). Rare contacts between synapses and microglial processes containing high levels of Iba1 and actin – A postembedding immunogold study in the healthy rat brain. *The European Journal of Neuroscience*.

Stellwagen, D., Beattie, E. C., Seo, J. Y., & Malenka, R. C. (2005). Differential regulation of AMPA receptor and GABA receptor trafficking by tumor necrosis factor-α. *The Journal of Neuroscience, 25*(12), 3219–3228.

Stellwagen, D., & Malenka, R. C. (2006). Synaptic scaling mediated by glial TNF-alpha. *Nature, 440*(7087), 1054–1059.

Stence, N., Waite, M., & Dailey, M. E. (2001). Dynamics of microglial activation: A confocal time-lapse analysis in hippocampal slices. *Glia, 33*(3), 256–266.

Stevens, Beth, Allen, Nicola J., Vazquez, Luis E., Howell, Gareth R., Christopherson, Karen S., Nouri, Navid, et al. (2007). The classical complement cascade mediates CNS synapse elimination. *Cell, 131*(6), 1164–1178.

Streit, W. J. (2005). Microglia and neuroprotection: Implications for Alzheimer's disease. *Brain Research Brain Research Reviews, 48*(2), 234–239.

Streit, W. J., Braak, H., Xue, Q. S., & Bechmann, I. (2009). Dystrophic (senescent) rather than activated microglial cells are associated with tau pathology and likely precede neurodegeneration in Alzheimer's disease. *Acta Neuropathologica, 118*(4), 475–485.

Streit, W. J., Mrak, R. E., & Griffin, W. S. (2004). Microglia and neuroinflammation: A pathological perspective. *Journal of Neuroinflammation, 1*(1), 14.

Streit, Wolfgang J., Sammons, Nicole W., Kuhns, Amanda J., & Sparks, D. Larry (2004a). Dystrophic microglia in the aging human brain. *Glia, 45*(2), 208–212.

Streit, W. J., Walter, S. A., & Pennell, N. A. (1999). Reactive microgliosis. *Progress in Neurobiology, 57*(6), 563–581.

Streit, W. J., & Xue, Q. S. (2010). The brain's aging immune system. *Aging and Disease, 1*(3), 254–261.

Streit, W. J., & Xue, Q. S. (2012). Alzheimer's disease, neuroprotection, and CNS immunosenescence. *Frontiers in Pharmacology, 3*, 138.

Takahashi, K., Rochford, C. D. P., & Neumann, H. (2005). Clearance of apoptotic neurons without inflammation by microglial triggering receptor expressed on myeloid cells-2. *The Journal of Experimental Medicine, 201*(4), 647–657.

Tang, Y., Nyengaard, J. R., De Groot, D. M., & Gundersen, H. J. (2001). Total regional and global number of synapses in the human brain neocortex. *Synapse, 41*(3), 258–273.

Tashiro, A., & Yuste, R. (2003). Structure and molecular organization of dendritic spines. *Histology and Histopathology, 18*(2), 617–634.

Terry, R. D., Masliah, E., Salmon, D. P., Butters, N., DeTeresa, R., Hill, R., et al. (1991). Physical basis of cognitive alterations in alzheimer's disease: Synapse loss is the major correlate of cognitive impairment. *Annals of Neurology, 30*(4), 572–580.

Thomas, W. E. (1992). Brain macrophages: Evaluation of microglia and their functions. *Brain Research Reviews, 17*(1), 61–74.

Thrash, J. C., Torbett, B. E., & Carson, M. J. (2009). Developmental regulation of TREM2 and DAP12 expression in the murine CNS: Implications for Nasu–Hakola disease. *Neurochemical Research, 34*(1), 38–45.

Tonelli, L. H., & Postolache, T. T. (2005). Tumor necrosis factor alpha, interleukin-1 beta, interleukin-6 and major histocompatibility complex molecules in the normal brain and after peripheral immune challenge. *Neurological Research, 27*(7), 679–684.

Trapp, B. D., Wujek, J. R., Criste, G. A., Jalabi, W., Yin, X., Kidd, G. J., et al. (2007). Evidence for synaptic stripping by cortical microglia. *Glia, 55*(4), 360–368.

Tremblay, M. E., Lowery, R. L., & Majewska, A. K. (2010). Microglial interactions with synapses are modulated by visual experience. *PLoS Biology, 8*(11), e1000527.

Tremblay, M. E., & Majewska, A. K. (2011). A role for microglia in synaptic plasticity? *Communicative & Integrative Biology, 4*(2), 220–222.

Tremblay, M. E., Zettel, M. L., Ison, J. R., Allen, P. D., & Majewska, A. K. (2012). Effects of aging and sensory loss on glial cells in mouse visual and auditory cortices. *Glia, 60*(4), 541–558.

Tsien, J. Z., Huerta, P. T., & Tonegawa, S. (1996). The essential role of hippocampal CA1 NMDA receptor-dependent synaptic plasticity in spatial memory. *Cell, 87*(7), 1327–1338.

Tsien, R. Y. (2013). Very long-term memories may be stored in the pattern of holes in the perineuronal net. Proceedings of the National Academy of Sciences of the United States of America.

Tuppo, E. E., & Arias, H. R. (2005). The role of inflammation in Alzheimer's disease. *The International Journal of Biochemistry & Cell Biology, 37*(2), 289–305.

Turnbull, I. R., Gilfillan, S., Cella, M., Aoshi, T., Miller, M., Piccio, L., et al. (2006). Cutting edge: TREM-2 attenuates macrophage activation. *Journal of Immunology, 177*(6), 3520–3524.

Turrigiano, G. G. (2008). The self-tuning neuron: synaptic scaling of excitatory synapses. *Cell, 135*(3), 422–435.

van Rossum, D., & Hanisch, U. K. (2004). Microglia. *Metabolic Brain Disease, 19*(3–4), 393–411.

Vissel, B., Krupp, J. J., Heinemann, S. F., & Westbrook, G. L. (2001a). A use-dependent tyrosine dephosphorylation of NMDA receptors is independent of ion flux. *Nature Neuroscience, 4*(6), 587–596.

Vissel, B., Royle, G. A., Christie, B. R., Schiffer, H. H., Ghetti, A., Tritto, T., et al. (2001b). The role of RNA editing of kainate receptors in synaptic plasticity and seizures. *Neuron, 29*(1), 217–227.

Wake, H., Moorhouse, A. J., Jinno, S., Kohsaka, S., & Nabekura, J. (2009). Resting microglia directly monitor the functional state of synapses in vivo and determine the fate of ischemic terminals. *The Journal of Neuroscience, 29*(13), 3974–3980.

Walker, D. G., Dalsing-Hernandez, J. E., Campbell, N. A., & Lue, L. F. (2009). Decreased expression of CD200 and CD200 receptor in Alzheimer's disease: A potential mechanism leading to chronic inflammation. *Experimental Neurology, 215*(1), 5–19.

Walsh, D. M., & Selkoe, D. J. (2004). Deciphering the molecular basis of memory failure in Alzheimer's disease. *Neuron, 44*(1), 181–193.

Wersinger, C., & Sidhu, A. (2002). Inflammation and Parkinson's disease. *Current Drug Targets Inflammation and Allergy, 1*(3), 221–242.

Williamson, L. L., Sholar, P. W., Mistry, R. S., Smith, S. H., & Bilbo, S. D. (2011). Microglia and memory: Modulation by early-life infection. *The Journal of Neuroscience, 31*(43), 15511–15521.

Wilms, H., Zecca, L., Rosenstiel, P., Sievers, J., Deuschl, G., & Lucius, R. (2007). Inflammation in Parkinson's diseases and other neurodegenerative diseases: Cause and therapeutic implications. *Current Pharmaceutical Design, 13*(18), 1925–1928.

Wiltgen, B. J., Royle, G. A., Gray, E. E., Abdipranoto, A., Thangthaeng, N., Jacobs, N., et al. (2010). A role for calcium-permeable AMPA receptors in synaptic plasticity and learning. *PLoS One, 5*(9).

Winder, D. G., Mansuy, I. M., Osman, M., Moallem, T. M., & Kandel, E. R. (1998). Genetic and pharmacological evidence for a novel, intermediate phase of long-term potentiation suppressed by calcineurin. *Cell, 92*(1), 25–37.

Wolf, Y., Yona, S., Kim, K-W., & Jung, S. (2013). Microglia, seen from the CX3CR1 angle. Frontiers in Cellular Neuroscience, 7.

Wong, W. T. (2013). Microglial aging in the healthy CNS: Phenotypes, drivers, and rejuvenation. *Frontiers in Cellular Neuroscience, 7*, 22.

Wright, A. L., Zinn, R., Hohensinn, B., Konen, L. M., Beynon, S. B., Tan, R. P., et al. (2013). Neuroinflammation and neuronal loss precede abeta plaque deposition in the hAPP-J20 mouse model of Alzheimer's disease. *PLoS One, 8*(4), e59586.

Wu, L.-J., & Zhuo, M. (2008). Resting microglial motility is independent of synaptic plasticity in mammalian brain. *Journal of Neurophysiology, 99*(4), 2026–2032.

Wyss-Coray, T., & Rogers, J. (2012). Inflammation in Alzheimer disease—A brief review of the basic science and clinical literature. *Cold Spring Harbor Perspectives in Medicine, 2*(1).

Xiao, M. Y., Zhou, Q., & Nicoll, R. A. (2001). Metabotropic glutamate receptor activation causes a rapid redistribution of AMPA receptors. *Neuropharmacology, 41*(6), 664–671.

Xu, H.-T., Pan, F., Yang, G., & Gan, W.-B. (2007). Choice of cranial window type for in vivo imaging affects dendritic spine turnover in the cortex. *Nature Neuroscience, 10*(5), 549–551.

Yamada, J., Hayashi, Y., Jinno, S., Wu, Z., Inoue, K., Kohsaka, S., et al. (2008). Reduced synaptic activity precedes synaptic stripping in vagal motoneurons after axotomy. *Glia, 56*(13), 1448–1462.

Yang, G., Pan, F., & Gan, W. B. (2009). Stably maintained dendritic spines are associated with lifelong memories. *Nature, 462*(7275), 920–924.

Yirmiya, R., & Goshen, I. (2011). Immune modulation of learning, memory, neural plasticity and neurogenesis. *Brain, Behavior, and Immunity, 25*(2), 181–213.

Yuste, R., & Majewska, A. (2001). On the function of dendritic spines. *Neuroscientist, 7*(5), 387–395.

Zhang, G., Li, J., Purkayastha, S., Tang, Y., Zhang, H., Yin, Y., et al. (2013). Hypothalamic programming of systemic ageing involving IKK-beta, NF-kappaB and GnRH. *Nature, 497*(7448), 211–216.

Zhou, Q., Homma, K. J., & Poo, M. M. (2004). Shrinkage of dendritic spines associated with long-term depression of hippocampal synapses. *Neuron, 44*(5), 749–757.

Zuo, Y., Lin, A., Chang, P., & Gan, W. B. (2005). Development of long-term dendritic spine stability in diverse regions of cerebral cortex. *Neuron, 46*(2), 181–189.