Published in final edited form as:
Prog Brain Res. 2008 ; 169: 251–266. doi:10.1016/S0079-6123(07)00015-5.

Persistent neural activity in the prefrontal cortex: a mechanism by which BDNF regulates working memory?

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Abstract

Working memory is the ability to maintain representations of task-relevant information for short periods of time to guide subsequent actions or make decisions. Neurons of the prefrontal cortex exhibit persistent firing during the delay period of working memory tasks. Despite extensive studies, the mechanisms underlying this persistent neural activity remain largely obscure. The neurotransmitter systems of dopamine, NMDA, and GABA have been implicated, but further investigations are necessary to establish their precise roles and relationships. Recent research has suggested a new component: brain-derived neurotrophic factor (BDNF) and its high-affinity receptor, TrkB. We review the research on persistent activity and suggest that BDNF/TrkB signaling in a distinct class of interneurons plays an important role in organizing persistent neural activity at the single-neuron and network levels.

Keywords

TrkB; neurotrophins; plateau potentials; parvalbumin; interneurons; dopamine; ACh; GABA

Introduction: working memory and persistent neuronal firing

Working memory refers to the ability to hold transient representations of task-relevant information to guide subsequent behaviors. Rule learning, planning, decision-making, and many executive functions are likely dependent on this ability. Early lesion studies identified the prefrontal cortex (PFC) as a crucial brain area involved in working memory (Butters and Pandya, 1969). Phylogenetically, the PFC is one of the most recently evolved areas of the brain. The size of the PFC relative to the whole brain increases dramatically in mammals, particularly primates, correlating well with the increasing capacity for more sophisticated executive behaviors. In humans, the PFC is disproportionately large and exceedingly well connected to cortical and subcortical brain regions (for review, see Fuster, 2002). Functional magnetic resonance imaging reveals that the PFC is activated during working memory tasks

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(McCarthy et al., 1994). The importance of the PFC is further manifested in the severe dysfunction in PFC activation and working memory capacity seen in schizophrenia patients (Weinberger and Berman, 1996).

Classic laboratory tests for working memory are the delayed matching (or non-matching) to sample, delayed-alternation, and delayed-response tasks. Ultimately, all these tasks consist of three basic parts: (1) the acquisition of a piece of information (e.g. the location of food); (2) a short delay period during which the subject needs to retain the acquired information while no salient information is present (e.g. the location of the food is obscured); (3) a cue indicating that the subject should respond based on the previously acquired information (e.g. point to the location of the hidden food).

Single unit recordings from neurons in the primate PFC demonstrate that neurons persistently fire during the delay period of a delayed response task (Fuster and Alexander, 1971; Kubota and Niki, 1971), suggesting that these neurons are somehow involved in maintaining the “task-relevant information” for a short period of time. This is further clarified by work showing that neurons in the primate dorsolateral prefrontal cortex (DLPFC) persistently fire during the delay period of a spatial delayed response task in response to stimuli in their preferred spatial field (Funahashi et al., 1989). Given that the persistent firing during the “delay” period does not require stimuli to be sustained, this activity is believed to represent the maintenance and encoding of working memory.

Three mechanisms may contribute to working memory-related persistent activity:

1. intrinsic properties of PFC neurons — individual PFC neurons may have some unique features that allow them to initiate, maintain, and terminate sustained, non-adapting firing;
2. local synaptic network within the PFC — the short term facilitation of excitatory synapses, in addition to the inhibitory control wielded by GABAergic interneurons forms a strong cellular basis for “reverberant” neuronal firing;
3. afferents from subcortical areas — the extensive dopaminergic projections and other inputs to the PFC are likely important for tuning the state of a network and initiating its activity.

In this review, we will discuss research on the mechanisms underlying persistent neuronal firing at each of the three levels highlighted above. Given the emerging evidence that brain-derived neurotrophic factor (BDNF) is a key regulator of neuronal excitability and synaptic plasticity (for review, see Poo, 2001; Lu et al., 2005), we will also discuss a potential role for BDNF in regulating the persistent neuronal activity in the PFC.

Persistent activity and its regulation

Intrinsic properties of PFC neurons

A unique combination of ion channels defines the essential properties of PFC neurons and contributes to their ability to persistently fire. In most parts of the brain, a train of action potentials in pyramidal neurons will display rapid adaptation or accommodation in response

to a sustained depolarization — an undesirable feature for persistent firing of many seconds in duration. Thus, pyramidal neurons in the PFC must be somewhat unique in their intrinsic ion channel properties to allow them to fire persistently.

While few studies have directly examined the contribution of intrinsic properties to persistent firing in the PFC, studies of carbachol-dependent plateau potentials provide strong evidence for the contribution of intrinsic factors to persistent firing (Egorov et al., 2002). Plateau potentials were originally identified in the entorhinal cortex (EC) (Egorov et al., 2002) — another area where delay period persistent activity is observed (Young et al., 1997) — but a similar phenomenon has been observed in the PFC as well (Andrade, 1991; Haj-Dahmane and Andrade, 1998; unpublished results). In this preparation, persistent activity is initiated by a short (500 ms) depolarizing pulse at threshold in the presence of tonic carbachol (10 μM), resulting in a burst of firing and a subsequent afterdepolarization. The afterdepolari-zation results in persistent non-accommodating firing of the neuron, often for an indefinite period of time. Although plateau potentials in EC layer III neurons are resistant to termination by hyperpolarization, a large depolarizing pulse can induce cessation of firing (Tahvildari et al., 2007). In layer V of EC, neurons respond to stimuli in a graded manner, encoding stimulus duration or intensity in the plateau potential firing rate (Egorov et al., 2002). Clearly, this model recapitulates some of the salient features of delay period activity including robust sustained firing and rapid transitions in response to salient input.

Calcium channels and calcium-activated cation or potassium channels may play a role in generating plateau potentials. For instance, blocking L-type calcium channels greatly abbreviates the duration of each plateau potential event. Specifically, during plateau potentials in the EC, continuous application of nifedipine, an L-type calcium channel blocker, greatly decreases the duration of membrane depolarization and curtails all persistent firing (Egorov et al., 2002). In postpubertal rats, D1 type dopamine receptor (D1R) and *N*-methyl-D-aspartate (NMDA) co-activation is sufficient to induce “up states” in PFC slices, a phenomenon related to synchronized persistent activity (Tseng and O’Donnell, 2005). Here too, application of nifedipine greatly reduced the duration and frequency of spontaneous activity.

Perhaps overshadowing the activity of L-type calcium channels, calcium-dependent non-specific cation (CAN) currents and calcium-activated potassium currents (K_{Ca}^{2+}) have proven integral to the generation of plateau potentials in both slice preparations and computational models. Simply blocking CAN currents with flufenamic acid completely abolishes plateau potentials in the EC (Egorov et al., 2002). Furthermore, it has been suggested that the CAN and $K_{Ca}^{2+\leftarrow}$ currents underlie a dynamic attractor for a neuron’s firing rate (Fransen et al., 2006). That is, a balance between the two currents and the presence of two activation states for CAN currents create a system where different firing rates can be stably manifested in response to different stimuli (Fransen et al., 2006). A self-terminating and slightly less robust effect has been similarly reported in PFC layer V pyramidal neurons (Andrade, 1991). It too is significantly dependent on CAN currents (Haj-Dahmane and Andrade, 1998).

Potassium channels are generally strong candidates for permitting persistent activity. As noted earlier, in many neurons sustained firing will result in adaptation and eventual cessation. As mediators of the downward phase of the action potential, faster activation of potassium currents can reduce spike width, perhaps allowing for a non-adapting firing pattern (for review, see Bean, 2007). The inactivation and deactivation of potassium channels may also contribute to the frequency and duration of persistent firing.

While many intrinsic elements are likely to play a role in generating sustained activity, research on the contribution of intrinsic properties in PFC neurons, specifically, to persistent neuronal firing remains in its infancy. More studies must now be done to identify the specific elements pertinent to PFC neurons in manifesting persistent activity. In addition, it is important to determine how these intrinsic properties are regulated by intracortical mechanisms or subcortical afferent inputs.

Intracortical synaptic interactions: GABA, glutamate, and synaptic facilitation

Recurrent models of persistent activity suggest that a balance of excitatory and inhibitory inputs onto pyramidal neurons supports the generation and accuracy of persistent activity (Shu et al., 2003a, b). While the story is probably more complicated (Lau and Bi, 2005; Milojkovic et al., 2005), we now know that the synaptic inputs and network architecture of the PFC are integral to persistent activity, both in vivo and in vitro.

GABAergic control—GABAergic interneurons are the primary provider of inhibition in the PFC. Consequently, delay period persistent activity is critically dependent on gamma-aminobutyric acid (GABA) synaptic inputs. Application of a GABA antagonist to the PFC disrupts the working memory activity (Sawaguchi et al., 1989). Recordings of persistently firing pyramidal neurons and GABAergic inter-neurons reveal that the two cell types have similar receptive fields, and that their responses are phase locked (Wilson et al., 1994). Further work shows that blocking GABA transmission results in a loss of spatial tuning in previously tuned neurons (Rao et al., 2000).

The exact circuit mediating this effect is still unclear, but parvalbumin (PV)-expressing inter-neurons are likely candidates. This group includes both the chandelier and basket neurons, which innervate pyramidal neurons at the axon initial segment (AIS) and proximal to the soma, respectively. The chandelier neurons are perfectly positioned for gating the output of pyramidal neurons to ensure appropriate spike timing. These neurons exert powerful inhibitory controls over a large number of cortical pyramidal neurons by continuously firing at high frequency (fast spiking). It is conceivable that the transient relief of this inhibition would trigger synchronized firing among pyramidal neurons, initiating sustained firing among this population during the delay period of a working memory task. Similarly, basket neuron synapses at or near the soma could help control the gain and timing of pyramidal neuron responses to dendritic and somatic inputs (for review, see Markram et al., 2004). From a broader perspective, both of these could ensure correct encoding of initial stimuli and provide the correct level of inhibition to balance recurrent excitation during persistent firing.

Glutamatergic control—Using the model of up states — spontaneous sustained depolarizations of the membrane potential — excitatory synaptic transmission via alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) and NMDA receptors has been strongly linked to the generation of persistent activity. Both receptors are important for up state activity, but are most likely responsible for different components of the prolonged depolarization associated with up states. A recent work suggests that an AMPA-dependent component is important for initiation of the up state, while the strong inward current present throughout the up state is NMDA dependent (Seamans et al., 2003).

In mice and rats, spontaneous up states can be induced in acute PFC slices via co-activation of dopamine and NMDA receptors (Tseng and O'Donnell, 2005). NMDA by itself causes the membrane potential to maintain a steady depolarization to about — 60 mV. However, NMDA combined with dopamine induces up states in which the potential becomes transiently more depolarized. The importance of NMDA-mediated synaptic inputs and dopaminergic activation in persistent firing was also highlighted in a recent paper by Durstewitz and Gabriel (2007). They suggest that non-linear NMDA conductances induce a potentially meaningful spiking irregularity.

Synaptic facilitation and augmentation—Reverberant network dynamics among assemblies of PFC neurons may yield the sustained synaptic excitation that is thought to underlie persistent activity. Supporting this is the observation that while other cortical areas (such as visual cortex) have synaptic circuits that often exhibit synaptic fatigue or depression, the PFC displays a heterogeneous array of synaptic facilitation, augmentation, and post-tetanic potentiation for a majority of the synapses (Hempel et al., 2000; Wang et al., 2006). These forms of short-term facilitation may help initiate or sustain activity during the delay period of a working memory task. Indeed, in a neurocomputational model of a simple network, synaptic augmentation enables weak recurrent connections to support persistent activity following a transient stimulus (Hempel et al., 2000).

Subcortical afferent inputs

Since most executive functions, including working memory, require the integration of distributed sensory inputs and memory, it is unsurprising that the PFC receives a large number of afferent inputs. Of these, the most prominent are those that release dopamine, norepinephrine, acetylcholine, and serotonin. We will discuss the first three below and simply note that while serotonin has been shown to effect delay period activity and spatial tuning in single neurons (Williams et al., 2002), behavioral data do not indicate a significant effect on delay-dependent working memory (for review, see Ellis and Nathan, 2001).

Dopaminergic afferents—Early studies revealed an apparently simple relationship in which dopamine agonists, especially D1R agonists, increased delay period activity, while antagonists decreased delay period activity (Sawaguchi et al., 1990a, b). However, this picture was soon complicated by behavioral and electrophysiological evidence indicating that optimal dopamine or D1R activation followed an inverted U-shaped tuning curve, in which high or low, but still physiological, levels of dopamine impair working memory (Williams and Goldman-Rakic, 1995; Cai and Arnsten, 1997; Zahrt et al., 1997). A recent

study has demonstrated this effect at the single-neuron level after local application of varying concentrations of D1R agonists onto neurons in the PFC during a working memory task. Assuming that weakly spatially tuned neurons have low levels of endogenous dopamine stimulation and strongly tuned neurons have optimal levels, Vijayraghavan et al. (2007) observed that application of a D1R agonist to the former enhanced spatial tuning, while application to the latter caused either a much smaller increase or actually eroded tuning.

Interestingly, stimulation of the VTA — a primary dopaminergic input to the PFC — can cause D1R-mediated up state transitions in the PFC (Lewis and O'Donnell, 2000). Another work showed that up state depolarizations are synchronized between these two regions, and that inacti-vation of the VTA leaves PFC up states intact, but destroys organized networks of this activity in the PFC (Peters et al., 2004).

The role of dopamine tuning in PFC function is further bolstered by genetic evidence involving a human single nucleotide polymorphism (SNP) in the gene for catechol *O*-methyltransferase (COMT) that results in a substitution of methionine (met) for valine (val) at codon 158 of the protein (for review, see Savitz et al., 2006). COMT is known to facilitate dopamine catabolism and therefore inactivate dopamine after its release. The val form has higher COMT enzymatic activity compared to the met form, resulting in lower dopamine concentration in the cortex (Egan et al., 2001). Furthermore, COMT allelic background determined subject performance in response to amphetamine (a dopamimetic) during a working memory task. Specifically, those with a met/met genotype, who normally perform better in working memory tasks than val/val individuals, exhibited a decrease in working memory performance when treated with amphetamine, while val/val individuals manifested improved working memory performance after amphetamine treatment (Mattay et al., 2003).

Cholinergic afferents—The role of cholinergic inputs to the PFC in persistent activity and working memory is still unclear. Generally, cholinergic agonism appears to enhance prefrontal-dependent memory task performance, while antagonism disrupts it, especially at muscarinic receptors (Ellis and Nathan, 2001; Dalley et al., 2004). However this interaction is confounded by factors such as smoking history and variances in background agonist levels. Perhaps the strongest physiological evidence that acetylcholine may play role in persistent firing again comes from the plateau potential model (Egorov et al., 2002) as this activity is highly dependent on tonic levels of muscarinic receptor activation. However, the exact contribution of acetylcholine to the generation of plateau potentials remains unclear and warrants further investigation.

Norepinephrinergic afferents—A role for norepinephrine in working memory function is evident from studies in non-human primates using a spatial delayed response task. Activation of the α1-adrenoreceptor in the primate DLPFC both impairs spatial working memory performance in primates and attenuates persistent firing in individual neurons for their preferred spatial stimulus (Mao et al., 1999; Birnbaum et al., 2004). Conversely, activation of the α2A–adreno-receptors by the agonist guanfacine in the DLPFC enhances spatial working memory performance and persistent firing (Arnsten et al., 1988; Wang et al., 2007). Recently, it was demonstrated that application of an α2A agonist on individual

neurons on the DLPFC enhanced their spatial tuning, especially if it was initially weak. Furthermore, the same study indicated that α2A enhances tuning by inhibiting cAMP production, consequently causing the closure of hyperpolarization-activated cyclic nucleotide-gated channels, possibly providing a mechanism for selectively activating networks of spatially tuned neurons (Wang et al., 2007).

Possible roles of BDNF in the PFC: from working memory to persistent neural activity

Among members of the neurotrophin family, BDNF stands out for its high levels of expression in the brain and multi-dimensional regulation by neuronal activity. Initially recognized for its role in neural development and survival, it is now well established that the main function of BDNF in the brain is to regulate synaptic plasticity (Poo, 2001; Lu, 2003a, b). The diverse action of BDNF in the brain results from the numerous signaling cascades downstream of BDNF as well as the activity-dependent transcription of BDNF via promoter III (for review, see Lu, 2003a, b; Lu et al., 2005). This coupling of neuronal activity to changes in synaptic structure and function implicates BDNF as an essential regulator of cellular processes that underlie behavior and cognition. Converging lines of evidence are now suggesting that BDNF and its preferred receptor, neurotrophic receptor tyrosine kinase (TrkB), play an integral role in mediating persistent network activity and maintaining normal PFC function (for review, see Lewis et al., 2005; Savitz et al., 2006; Woo and Lu, 2006).

BDNF cell biology

Transcription of the BDNF gene is mediated by multiple (at least four) promoters, each driving a short 5′ exon that is alternatively spliced onto a common 3′ exon (exon V) that contains the coding region (Timmusk et al., 1993). Thus, there are at least four BDNF mRNAs that give rise to exactly the same BDNF protein (West et al., 2001; for review, see Lu, 2003a, b). BDNF is synthesized in the endoplasmic reticulum as a precursor, proBDNF, and then folded and packaged in the Golgi apparatus (Lu, 2003a, b). After this, it is sorted into either a constitutive or activity-dependent secretion pathway (Mowla et al., 1999). In neurons, the BDNF-containing secretory vesicles are transported along axons or dendrites and some of the vesicles are localized to presynaptic terminals or postsynaptic spines (Lu, 2003a, b). ProBDNF may be cleaved either intracellularly or extracellularly yielding mature BDNF (Seidah et al., 1996). Consequent functions of BDNF are mediated by two receptor systems: TrkB and $p75^{NTR}$. Mature BDNF is a strong ligand for TrkB. Activation of this receptor triggers a number of downstream pathways, including the phosphatidylinositol-3-kinase (PI3K), phospholipase C-gamma (PLC-γ), and MEK-MAPK pathways (Huang and Reichardt, 2003). Conversely, if BDNF remains uncleaved, proBDNF binds preferentially to $p75^{NTR}$, leading to activation of signaling cascades including the nuclear factor-kappa B (NF-κB), c-jun kinase, and sphigomyelin hydrolysis pathways (Chao, 2003). Furthermore, it is now believed that pro- and mature BDNF elicit very different and often opposing biological functions (Lu et al., 2005). Clearly, having multiple promoters, a cleavage-dependent protein, two secretory pathways, and two receptor systems with multiple

transduction cascades indicates that BDNF acts in a complex manner and highlights its potential for regulating a number of neuronal processes.

Expression of BDNF and TrkB in the PFC

Expression of BDNF, along with its cognate receptor, TrkB, is widespread in the frontal cortex of mammals, including monkeys and humans (Huntley et al., 1992; Hayashi et al., 2000; Weickert et al., 2003, 2005), as well as rodents (Hofer et al., 1990; Phillips et al., 1990; Connor et al., 1997; Yan et al., 1997a, b; Lipska et al., 2001). In the human dorsolateral PFC, BDNF mRNA is detected in all cortical layers (II–VI). Its expression is developmentally regulated, starting relatively low during infancy, peaking during young adulthood, and then remaining relatively stable throughout later adulthood (Webster et al., 2002). Importantly, BDNF mRNA is expressed in excitatory neurons and not in GABAergic interneurons. The importance of BDNF expression in the PFC is now evident in many CNS disorders where expression levels are significantly altered, including depression, stress-related disorders, and schizophrenia (for review, see Duman and Monteggia, 2006; Castren et al., 2007). As working memory dysfunction is central to the pathology of schizophrenia, we specifically note that expression of BDNF and TrkB is significantly reduced in the dorsolateral PFC of schizophrenic patients (Weickert et al., 2003, 2005; Hashimoto et al., 2005).

In monkeys, BDNF mRNA is highly expressed in large pyramidal neurons of layers III and IV throughout the PFC of fetal and adult monkeys (Huntley et al., 1992). Correspondingly, full-length TrkB receptor immunoreactivity is also expressed in pyramidal cells of layers II, III, V, and VI, and is developmentally regulated (Hayashi et al., 2000). Interestingly, the strongest TrkB immunoreactivity in non-human primates is at six months postnatal, which corresponds to a period of high synapse overproduction in the PFC of macaque monkeys (Bourgeois et al., 1994), suggesting that TrkB and BDNF may play a functional role in synapse formation during development. TrkB mRNA and protein are detected in both excitatory pyramidal neurons and inhibitory interneurons, suggesting that both populations are responsive to BDNF.

An acceptable PFC analogue in rodents has only recently been identified. As a result, much less is known regarding the precise localization of BDNF and TrkB mRNA in this region. However, several recent studies are in agreement that BDNF protein and mRNA are expressed at high levels in the neocortex, particularly the prelimbic and infralimbic cortex (Connor et al., 1997; Yan et al., 1997a, b; Lipska et al., 2001; Blurton-Jones et al., 2004). The situation is similar for TrkB expression, with the anterior cingulate area also showing high expression (Saarelainen et al., 2003; Hashimoto et al., 2005).

While the neurotrophin NT-4 is also a ligand for TrkB and shows relatively similar expression patterns as BDNF, it is expressed at far lower levels (Mori et al., 2004) and its function is less clear.

BDNF/TrkB and PFC-mediated working memory

The discovery of a common SNP resulting in a val to met switch at codon 66 in the pro-domain of the gene encoding for BDNF has greatly facilitated studies on the role of BDNF

in cognitive function (Egan et al., 2003; for review, see Savitz et al., 2006). The met-BDNF allele is associated with decreased hippocampal function in humans, impairments in regulated BDNF secretion and trafficking, and deficits in episodic memory (Egan et al., 2003; Hariri et al., 2003). Carriers of the met-BDNF allele show a reduction in PFC gray matter volume (Pezawas et al., 2004), but generally do not show significant impairments in working memory (Egan et al., 2003; Hansell et al., 2007). However, patients with bipolar disorder who carry the met allele have reduced working memory as reflected by the N-back test, and behavior perseveration as reflected by the Wisconsin Card Sorting Test, as compared to patients homozygous for the val allele (Rybakowski et al., 2003, 2006).

In rodents, extensive studies indicate that BDNF is required for hippocampal-dependent learning and memory, but evidence for a role of BDNF in working memory remains sparse. Intracerebroventricular infusion of an antisense BDNF oligonucleotide impaired both reference and working memory as measured by the radial arm maze test (Mizuno et al., 2000). Furthermore, levels of BDNF in the frontal cortex correlate negatively with the number of working memory errors in aged rats (Bimonte et al., 2003), and in Ts65D mice, an animal model of Down syndrome (Bimonte-Nelson et al., 2003). Finally, mice with a forebrain-specific deletion of the TrkB gene manifest schizophrenic-like cognitive deficits, hyper-locomotion, and stereotyped behaviors (Zorner et al., 2003).

BDNF regulation of GABAergic interneurons

Of particular interest in the PFC are the aforementioned GABAergic interneurons that express PV, which include the basket and chandelier interneurons. They represent a unique class of fast-spiking interneurons, which is important for a number of physiological processes in the mammalian brain, and is regulated by BDNF and TrkB (Woo and Lu, 2006). By innervating the soma and AIS of a large number of pyramidal cells, PV-interneurons are in a powerful position to control persistent and synchronous firing in the PFC (for review, see Markram et al., 2004).

Substantial evidence indicates that BDNF regulates the development of PV-interneurons. In BDNF knockout mice, the number of PV-interneurons is significantly reduced as compared to wild-type counterparts (Jones et al., 1994; Altar et al., 1997). In TrkB hypomorphic mice in which the endogenous TrkB locus is replaced with a floxed TrkB cDNA (Xu et al., 2000), the levels of PV and glutamic acid decarboxylase 67 (GAD67), a GABA synthesizing enzyme, mRNAs were significantly lower in the PFC (Hashimoto et al., 2005). Intriguingly, mice with hypomorphic BDNF expression show no change in GAD67 or PV expression, suggesting that TrkB is more prevalent than BDNF in controlling the GABAergic phenotypes (Monteggia et al., 2004; Hashimoto et al., 2005). This idea is further supported by the observation that PV-interneurons preferentially express TrkB, among other cortical interneurons (Cellerino et al., 1996). Although PV-interneurons do not express BDNF, it is expressed by pyramidal neurons that appear to secrete BDNF only onto local inhibitory neurons, suggesting a tight feedback mechanism (Kohara et al., 2007).

Conversely, in transgenic mice over-expressing BDNF, the maturation of PV-interneurons is significantly accelerated, which is accompanied by an increase in spontaneous network activity (Huang et al., 1999; Aguado et al., 2003). Similarly, application of BDNF to

homogenous cell cultures of fast-spiking PV-interneurons resulted in the accelerated formation of reciprocal connections between these cells (Berghuis et al., 2004). It was also found that exogenous and endogenous TrkB ligands accelerate PV expression via PI3 kinase (Patz et al., 2004).

Evidence for a functional consequence of this interaction between BDNF and PV-interneuron development comes from studies of patients with schizophrenia, who usually have severe working memory deficits. Postmortem studies have indicated that schizophrenia is associated with a reduction in BDNF and TrkB expression (Weickert et al., 2003, 2005; Hashimoto et al., 2005). Similarly, the schizophrenic PFC shows decreased expression of GAD67 in a subset of interneurons that also express PV (Hashimoto et al., 2003). Importantly, the number of PV-interneurons is not decreased; only the amount of GAD67 expressed in them is changed. It remains to be established whether the decreased GAD67 expression in GABAergic neurons is due to a reduction in cortical BDNF. More specifically, chandelier neurons, which form cartridge-like synapses at the AIS of pyramidal neurons, have fewer cartridges with significant GABA membrane transporter 1 (GAT1) expression in the PFC of schizophrenic patients (Pierri et al., 1999). Postsynaptically to these cartridges, an increase in $GABA_A\alpha 2$ receptors is observed, raising the possibility of compensatory changes to GABAergic neurotransmission (Volk et al., 2002).

Studies of the hippocampus indicate that PV-interneurons are functionally integral to organizing network activity and spontaneous firing (for review, see Bartos et al., 2007). Oscillations can be observed both in vitro and in vivo (for review, see Buzsaki and Draguhn, 2004), and PV-interneurons, especially the basket type, show extensive phase locking with hippocampal oscillations (Penttonen et al., 1998; Klausberger et al., 2003; Hajos et al., 2004). Deletion of glutamate receptor subunits in PV expressing interneurons decreased AMPA currents, leading to diminished gamma oscillation power in field recordings and imprecise spike timing in these interneurons. This was correlated with a deficiency in hippocampal dependent behavior seen in these knockout mice (Fuchs et al., 2007). However, it is unknown whether PV-interneurons in the PFC play a similar role in persistent activity.

Acute BDNF regulation of persistent neuronal activity

Although BDNF is involved in normal PFC and PV-interneuron function, it is unclear whether its action is developmental, tonic, or acute, as BDNF can be secreted both constitutively and in an activity-dependent manner. Certainly, in the case of interneuron function, the influence seems largely developmental or tonic, as BDNF/TrkB signaling levels seem to determine the structure of the inhibitory network. However, considering the effect of the val/met substitution on activity-dependent secretion of BDNF, it also seems likely that BDNF also plays an acute role in regulating excitability and plasticity. That is, individual or successive episodes of persistent firing could be modulated by BDNF signaling. Conceptually, BDNF could regulate this at three different levels.

Regulation of intrinsic excitability—An emerging concept is the homeostatic regulation of neuronal plasticity. By stabilizing neuronal activity, homeostatic plasticity

allows neurons to remain responsive to their inputs during periods of change in the strength or number of synaptic inputs. This is accomplished by scaling synaptic strength or intrinsic excitability up or down as a function of activity (LeMasson et al., 1993; Turrigiano et al., 1998; Desai et al., 1999a, b). For example, when tetrodotoxin is chronically applied to cultured cortical neurons, activity is blocked, but, subsequently, their intrinsic excitability is significantly increased (Desai et al., 1999b). Activity-deprived neurons fire in response to smaller current injections and at a higher rate by increasing sodium currents and decreasing persistent potassium currents (Desai et al., 1999b). Interestingly, application of BDNF prevents this increase in excitability, while blocking BDNF/ TrkB signaling caused a similar increase in excitability (Desai et al., 1999a). These observations suggest that BDNF-induced changes in excitability as a result of neuronal activity are mediated by alterations in voltage-gated currents, namely sodium and persistent potassium currents. Such regulation by BDNF could serve to fine-tune the intrinsic properties of PFC neurons, altering their ability to fire persistently.

Control of network excitability: a role in synaptic facilitation—Persistent neuronal activity in the PFC is thought to arise from sustained excitation generated by reverberant activity in an assembly of neurons. Recent work indicates that the PFC is unique among other cortical areas in having a heterogeneous array of synaptic dynamics, including facilitation, augmentation, and post-tetanic potentiation that encourage sustained neuronal firing (Hempel et al., 2000; Wang et al., 2006). In principle, these forms of short-term plasticity may allow PFC neurons to more easily reach a threshold for recurrent excitation and reverberant activity. Therefore, synaptic facilitation may be involved in persistent activity in reverberant networks.

In the hippocampus, BDNF has been shown to facilitate several forms of short-term plasticity including paired pulse facilitation and post-tetanic potentiation (Pozzo-Miller et al., 1999). Particularly relevant is the ability of BDNF to facilitate synaptic responses to high-frequency stimulation (HFS). This is achieved by promoting the mobilization/docking of synaptic vesicles to the active zones, leading to an increase in the readily releasable pool of vesicles. For instance, HFS-induced synaptic fatigue, which is thought to result from vesicle depletion of a readily releasable vesicle pool, is attenuated by a short-term treatment with BDNF (Figurov et al., 1996; Gottschalk et al., 1998, 1999). Moreover, optical imaging techniques using FM dyes show that BDNF enhances release from the immediate releasable pool of synaptic vesicles, evident by a significant increase in the rate of destaining (Tyler et al., 2006). Conversely, scavenging endogenous BDNF with TrkB-IgG or deletion of the BDNF gene causes pronounced synaptic fatigue. Quantitative electron microscopy shows that BDNF knockout mice, which have pronounced synaptic fatigue, have fewer docked vesicles at the active zones of hippocampal CA1 synapses (Pozzo-Miller et al., 1999). Similarly, TrkB knockout animals also have fewer docked vesicles at the active zones (Martinez et al., 1998). Taken together, it is clear that BDNF controls the availability of synaptic responses during successive stimuli by regulating the readily releasable pool and probability of release.

Given the profound importance of BDNF in synaptic dynamics across a broad time course — from vesicle release in milliseconds to potentiation for hours — further studies are

required to determine whether BDNF also critically regulates the release probabilities and short-term plasticity of PFC neurons. Ultimately, BDNF-induced inhibition of synaptic depression or an enhancement of synaptic augmentation represents a potential mechanism for temporarily boosting the efficacy of recurrent synapses and subsequently enhancing persistent states of neuronal firing.

Regulation of ascending inputs—The dopaminergic inputs to the PFC, especially from the VTA, are important for the generation of meaningful persistent activity. Unsurprisingly, BDNF plays an important role in modulating the plasticity of dopaminergic neurons in this area. More interestingly, BDNF may play a role in modulating feedback between the VTA and the PFC. For instance, weak presynaptic stimulation in the rostral VTA, where PFC inputs may be received, is normally not enough to evoke postsynaptic potentiation in VTA dopaminergic neurons. However, potentiation of these synapses occurs in the presence of BDNF (Pu et al., 2006). Furthermore, BDNF and TrkB are expressed in the rat VTA (Seroogy et al., 1994; Numan and Seroogy, 1999).

BDNF is also expressed and transported to fibers and terminals in noradrenergic neurons (Fawcett et al., 1998). Furthermore, pharmacological activation of noradrenergic neurons results in postsynaptic TrkB activation (Aloyz et al., 1999). Work on noradrenergic system antidepressants has suggested that their effect on the anterior cingulate cortex, a rodent analogue of the PFC, is mediated by TrkB activation (Rantamaki et al., 2007).

Similarly tenuous but promising connections exist for the acetylcholine system. As expected, BDNF promotes the survival of cholinergic neurons of the basal forebrain (Nonomura et al., 1995). At the level of plasticity, BDNF enhances the depolarization-evoked release of acetylcholine in cortical-projecting neurons (Sala et al., 1998).

It is not surprising that BDNF has effects on these different ascending systems. However, as more attention is devoted to the role of these ascending systems in working memory, it will be useful to concomitantly examine the role of powerful neuromodulators like BDNF on these systems. At the very least this may provide greater insight into the etiology of psychiatric disorders of a more global nature.

Conclusions

Historically, mechanistic studies of cognitive functions have benefited greatly from the use of cellular models. For example, the synaptic circuit for hippocampal-dependent spatial memory was defined using long-term potentiation as a cellular model, offering tremendous opportunities for in-depth investigations of the cellular, molecular, and genetic mechanisms underlying learning and memory. In contrast, cellular and molecular studies of PFC-mediated working memory remain at the infancy stage. However, the synaptic network subserving working memory is beginning to be unraveled and persistent neural activity has proven to be a promising cellular correlate for working memory.

Examining this correlate, the evidence is compelling that BDNF may play an important role in persistent neural activity and concomitant network activity in the PFC. However, the nature of this role is still unclear. Evidence from patients with working memory dysfunction

suggests that changes to GABAergic synaptic transmission may underlie the etiology of such disorders. Moreover, the changes appear to be targeted at PV-interneurons, which are heavily implicated in organizing network activity and spontaneous firing. Intriguingly, BDNF's high affinity receptor, TrkB, is preferentially expressed in these interneurons and decreased levels of TrkB are associated with GABAergic and working memory dysfunction.

Consequently, we suggest that TrkB plays a role in the modulation of synaptic inputs, by mediating excitability in pyramidal neurons and affecting GABAergic transmission in PV-interneurons. Specifically, we predict that decreases in TrkB signaling in these interneurons may impair GABAergic control of the cortical network, reducing the reliability of firing and fracturing the ensembles of neurons encoding the stimulus.

BDNF may also support the synaptic dynamics required for persistent activity to be sustained in a reverberant network. Modeling suggests that synaptic facilitation may be necessary to initiate persistent firing. Intriguingly, neurons in the PFC are capable of such synaptic facilitation. BDNF is ideally positioned as a modulator of synaptic facilitation and potentiation to play an important role in this mechanism.

We hypothesize that BDNF and TrkB contribute to the etiology of schizophrenia and working memory dysfunction. But, it is not yet clear if they are the keystone of the disease or the result of some upstream modulation. Consequently, much more effort should be directed towards elucidating this process. Modulations of BDNF signaling, especially in PV-expressing interneurons, along with simultaneous single-neuron and network recording, will help identify the role of TrkB in individual neurons, and the role of those neurons in network activity. Furthermore, the relationship between BDNF, high-frequency firing, synaptic augmentation, and persistent firing needs to be more clearly understood. Similarly, BDNF's role as a potent modulator of ascending systems should not be overlooked. Finally, sophisticated behavioral testing of transgenic mice will further clarify the role of these genetic components in working memory and persistent activity.

Acknowledgments

The authors wish to thank the National Institutes of Health — specifically National Institute of Child Health and Human Development and National Institute of Mental Health for funding their work. E.M.G. wishes to thank Elizabeth Zander for helpful discussions.

Abbreviations

AIS	axon initial segment
AMPA	alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid
BDNF	brain-derived neurotrophic factor
CAN	non-specific cation current
COMT	catechol *O*-methyltransferase
D1	dopamine receptor type 1
D1R	D1 receptor

DLPFC	dorsolateral prefrontal cortex
EC	entorhinal cortex
GABA	gamma-aminobutyric acid
GAD67	glutamic acid decarboxylase 67
GAT1	GABA transporter 1
HFS	high-frequency stimulation
$K_{Ca}^{2+\leftarrow}$	calcium-dependent potassium channel
met	methionine
NF-κB	nuclear factor-kappa B
NMDA	*N*-methyl-$_D$-aspartate
$p75^{NTR}$	high-affinity proneurotrophin receptor
PFC	prefrontal cortex
PI3K	phosphatidylinositol-3-kinase
PLC-γ	phospholipase C-gamma
PV	parvalbumin
SNP	single nucleotide polymorphism
TrkB	neurotrophic receptor tyrosine kinase
val	valine
VTA	ventral tegmental area

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