

Synaptic Plasticity and AMPA Receptor Trafficking

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ABSTRACT: Alterations in neuronal activity can elicit long-lasting changes in the strength of synaptic transmission at excitatory synapses and, as a consequence, may underlie many forms of experience-dependent plasticity, including learning and memory. The best-characterized forms of such synaptic plasticity are the long-term depression (LTD) and long-term potentiation (LTP) observed at excitatory synapses in the CA1 region of the hippocampus. It is now well accepted that the trafficking of AMPA receptors to and away from the synaptic plasma membrane plays an essential role in both LTP and LTD, respectively. Here we review current models of AMPA receptor trafficking and how this trafficking may be regulated at the molecular level in order to produce the observed changes in synaptic strength. We also review recent work from our lab suggesting that synaptic plasticity in the mesolimbic dopamine system may contribute importantly to the neural adaptations elicited by drugs of abuse.

KEYWORDS: AMPA receptor; synaptic transmission; LTD; LTP; VTA; nucleus accumbens

INTRODUCTION

Long-lasting, activity-dependent changes in synaptic strength at excitatory synapses are thought to be critical for virtually all forms of experience-dependent plasticity, including learning and memory. Among the most widely studied and accepted models of synaptic plasticity in the mammalian brain are the long-term depression (LTD) and long-term potentiation (LTP) that are generated at excitatory synapses on hippocampal CA1 pyramidal cells. Both of these synaptic phenomena share the characteristic that they are triggered by a rise in postsynaptic calcium concentration due to activation of NMDA receptors.¹ Presumably different properties of the postsynaptic calcium signal, primarily its magnitude and perhaps its time course, activate different postsynaptic signaling cascades that lead to either LTP or LTD.²

Over the last 20 years, the specific cellular and molecular mechanisms responsible for LTP and LTD have been the object of intense study and debate. While much remains to be elucidated, recent studies have provided compelling evidence that

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Ann. N.Y. Acad. Sci. 1003: 1–11 (2003). © 2003 New York Academy of Sciences.
doi: 10.1196/annals.1300.001

alterations in synaptic activity lead to the regulated trafficking of AMPA receptors both to and from synapses and that this importantly contributes to the changes in synaptic strength during LTP and LTD. Here, we will briefly review this rapidly moving field. For more comprehensive reviews, see References 3–5.

AMPA RECEPTOR PROTEIN–PROTEIN INTERACTIONS

AMPA receptors are a subclass of ionotropic glutamate receptors found at virtually all excitatory synapses. They are multimeric protein assemblies likely consisting of combinations of four different subunits termed GluR1–4 or GluRA–D.^{6–8} In

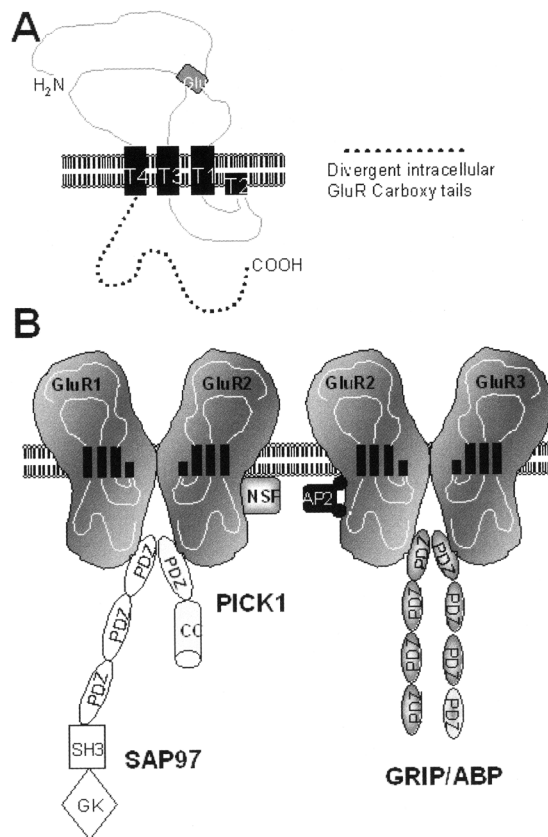


FIGURE 1. Diagrams showing the main protein–protein interactions of AMPA receptor subunits. **(A)** Schematic of membrane topology of AMPA receptor subunits. All subunits have a large extracellular N-terminus and an intracellular C-terminus of varying length. The ligand binding site is also shown. **(B)** The major forms of endogenous AMPA receptors (GluR1/2 and GluR2/3 heteromers) are shown with the domain structures of their main binding partners. GluR1 interacts with the PDZ protein SAP97. GluR2/3 interacts with the PDZ proteins GRIP/ABP and PICK1. GluR2 also interacts with NSF. The clathrin adaptor complex AP2 binds to GluR2 as well as to all other subunits.

the mature hippocampus, two types of AMPA receptors appear to dominate: heteromers consisting of GluR1 and 2, or GluR2 and 3.⁹ The topology of each subunit is similar, consisting of four transmembrane domains (one of which does not completely transverse the membrane) and a large extracellular N-terminus (FIG. 1). Importantly, the individual subunits have intracellular C-termini that are unique in that they interact with different intracellular binding partners. As a consequence, the detailed subunit composition of AMPA receptors may greatly influence their trafficking and surface expression.

Many of the known protein–protein interactions of AMPA receptors involve intracellular proteins that contain so-called PDZ domains.¹⁰ GluR1 appears to interact specifically with the PDZ containing protein SAP97, while GluR2 and GluR3 interact through a different class of PDZ domain with GRIP, ABP, and PICK1^{4,5,11} (FIG. 1). Although many details remain to be worked out, the interactions of AMPA receptors with these various PDZ containing proteins appear to importantly influence both the targeting and clustering of AMPA receptors to specific subcellular regions as well as the stabilization of AMPA receptors both on the neuronal cell surface and in intracellular pools. Thus these interactions are thought to play key roles in determining how AMPA receptors are restricted from synaptic sites and how they may be delivered in an activity-dependent manner in order to respond to changes in synaptic inputs and elicit long-lasting changes in synaptic strength.

Another protein that plays an important role in AMPA receptor trafficking and hence synaptic plasticity is NSF (NEM-sensitive factor), which was originally identified as an ATPase that is required for membrane fusion processes during intracellular protein trafficking and presynaptic vesicle exocytosis.¹² NSF interacts with the intracellular C-terminus of GluR2 and is thought to be important for the delivery of AMPA receptors to the synaptic plasma membrane and/or their stabilization within the membrane.^{4,5}

CONSTITUTIVE CYCLING OF AMPA RECEPTORS

An interesting aspect of the trafficking of membrane proteins is that they are often capable of undergoing constitutive as well as regulated insertion and removal. It appears that AMPA receptors also exhibit both forms of trafficking and that their basal rate of insertion and removal as well as the activity-dependent modulation of their trafficking are dependent upon their subunit composition (see below). The evidence for constitutive cycling derives from the observation that loading CA1 pyramidal cells with peptides that presumably inhibit specific protein–protein interactions involving AMPA receptors causes a “run-up” or “run-down” of synaptic responses. For example, a peptide that interferes with the NSF-GluR2 interaction causes a run-down of EPSCs as does NEM itself.^{13,14} Conversely, peptides that interfere with the GluR2-GRIP/ABP interaction can cause a run-up of EPSCs^{15,16} as do inhibitors of dynamin,¹⁷ a GTPase that is involved in many forms of endocytosis (see below). Examination of the trafficking of recombinant receptor subunits in cultured hippocampal neurons has also yielded results that are consistent with the idea that AMPA receptors constitutively cycle into and out of the synaptic plasma membrane with a time course of minutes.^{4,5} Thus it has become accepted that a significant proportion of synaptic AMPA receptors are continually being replaced via this mechanism.

The movement of AMPA receptors from the cytosol to the dendritic plasma membrane and subsequently to the synapse may involve an additional critical protein termed *stargazin*.^{18,19} Stargazin was originally identified as the mutant protein that is responsible for the neurologic deficits in the stargazer mutant mouse. Cerebellar granule cells prepared from these mice lack functional synaptic and extrasynaptic AMPA receptors on their surface. Acute expression of stargazin in these mutant granule cells rescues both synaptic responses and the response to exogenous application of glutamate, indicating that stargazin is required for the normal surface expression of AMPA receptors. Biochemical and mutagenesis studies revealed that stargazin interacts with both AMPA receptor subunits and PDZ proteins, including PSD-95, which was originally identified based on its interaction with NMDA receptors.²⁰ Interestingly, a mutant form of stargazin lacking the PDZ-binding domain still is capable of delivering AMPA receptors to the cell surface but not to synapses. This and other observations have led to a model proposing that stargazin-AMPA receptor interactions are critical for the delivery of AMPA receptors to the cell surface and that a subsequent interaction between stargazin and PSD-95 (or other synaptic PDZ proteins) is required for their movement into synapses.^{18,19}

AMPA RECEPTOR TRAFFICKING AND LTP

Almost two decades ago Lynch and Baudry proposed that LTP involved an increase in the number of synaptic glutamate receptors.²¹ This idea was largely ignored over the next 10 years as a vigorous debate concerning whether LTP was primarily due to pre- or postsynaptic modifications took place. The idea was resurrected when electrophysiological evidence for the existence of “silent synapses” was presented.^{22,23} Silent synapses are synapses that contain no or very small numbers of AMPA receptors but an easily detectable complement of NMDA receptors. Thus they are functionally silent at normal resting membrane potentials. Evidence was also presented that LTP involved the conversion of “silent” to “functional” synapses presumably due to the delivery of AMPA receptors to the silent synapses and their insertion into the synaptic plasma membrane. Consistent with this idea, loading cells with inhibitors of membrane fusion events was found to block LTP.²⁴

The “silent synapse hypothesis” subsequently stimulated a major effort by a large number of groups to determine whether AMPA receptor trafficking contributed to LTP and LTD and the molecular mechanisms responsible for this activity-dependent trafficking. For LTP an important assumption of this model is that there are sufficient nonsynaptic stores of AMPA receptors that can be delivered rapidly to synapses. Indeed, both light and electron microscopic studies have provided evidence for intracellular stores of AMPA receptors as well as the existence of extrasynaptic receptors in the plasma membrane.^{4,5}

There is also now reasonably strong evidence in support of the hypothesis that LTP involves the insertion of new AMPA receptors into the synaptic plasma membrane. In cultured hippocampal neurons, pharmacological manipulations that mimic LTP induction cause a rapid increase in the level of surface expression of AMPA receptors.^{25,26} Similarly, in hippocampal slice cultures, a GFP-GluR1 fusion protein was “delivered” to dendritic spines in an activity- and NMDA receptor-dependent manner.²⁷ Most convincingly, when overexpressed in slice cultures, GluR1 forms

homomeric channels that can be detected electrophysiologically when they are inserted into the synapse because, unlike normal endogenous synaptic AMPA receptors, they exhibit a profound inward rectification. Normally these overexpressed receptor subunits are not found at synapses, but, in response to LTP-inducing stimuli, they are rapidly incorporated into synapses such that they respond to synaptically released glutamate.²⁸ This delivery can also be triggered by overexpression of an active form of CaMKII,²⁸ a protein kinase known to be required for the triggering of LTP.²⁹ Consistent with the importance of GluR1 for the synaptic delivery of AMPA receptors during LTP, overexpression of a portion of the GluR1 intracellular tail, which presumably acts as a dominant negative inhibitor of GluR1 protein-protein interactions, blocked LTP.³⁰ Furthermore, knockout mice lacking GluR1 do not express LTP, at least in mature hippocampus.³¹ Surprisingly, the critical substrate for the CaMKII-dependent delivery of AMPA receptors does not appear to be GluR1 itself but some other as yet unidentified protein.²⁸

While GluR1 appears to be required for the activity-dependent delivery of AMPA receptors during LTP, GluR2/3 subunits may play a complementary role in the constitutive delivery pathway. Specifically, it has been proposed that the “rules” governing AMPA receptor trafficking are related to the length of the carboxyl tail. AMPA receptors with “long” cytoplasmic tails, such as GluR1 as well as GluR4, may normally be restricted from the synapse but can be delivered to the synapse during periods of enhanced synaptic activity (i.e., as would be seen during LTP). In contrast, GluR2/3 AMPA receptors may continually replace preexisting synaptic AMPA receptors in an activity-independent manner.^{4,5} Indeed the molecular stoichiometry of AMPA receptors may influence whether they are inserted directly into the postsynaptic density (GluR2/3) or rather first get inserted into adjacent extrasynaptic plasma membrane and then diffuse laterally within the plasma membrane to synaptic sites (GluR1).^{32,33}

A final additional complexity is the observation that early during postnatal development, LTP in the hippocampus does not require CaMKII or GluR1.^{34,35} Instead LTP requires activation of PKA,³⁵ which appears to cause the delivery of GluR4, the expression of which is developmentally regulated with robust expression in early postnatal hippocampus and minimal expression in older hippocampus.³⁶

LONG-TERM DEPRESSION AND AMPA RECEPTOR ENDOCYTOSIS

An obvious corollary of the hypothesis that LTP involves synaptic delivery of AMPA receptors is that LTD involves the removal or loss of synaptic AMPA receptors. That this, in fact, can occur was first demonstrated using epitope-tagged recombinant AMPA receptor subunits and chronic manipulations of activity.³⁷ Subsequently, it was found that pharmacological activation of either AMPA receptors or NMDA receptors with agonist can elicit robust internalization/endocytosis of AMPA receptors.³⁸ This was shown to be a dynamin- and clathrin-dependent process³⁸ and likely involves direct binding of the AP2 clathrin adaptor complex to AMPA receptor subunits themselves.³⁹

That AMPA receptor endocytosis does indeed play a critical role in LTD is supported by several lines of evidence. First, generation of LTD in cultured hippocampal neurons is accompanied by a decrease in the number of synaptic AMPA receptors.⁴⁰

Second, manipulations that cause the loss of surface AMPA receptors, such as the injection of the NSF inhibitory peptide, prevent the subsequent expression of LTD.^{13,41} Third, loading the cell with reagents that inhibit dynamin-dependent endocytosis blocks hippocampal LTD.¹³ Interestingly, LTD at other synaptic connections also appears to involve endocytosis of AMPA receptors, specifically at parallel fiber-Purkinje cell synapses in the cerebellum⁴² and excitatory synapses on dopamine cells in the ventral tegmental area.⁴³ These data suggest that AMPA receptor trafficking may be a fairly universal mechanism by which activity can modify synaptic strength.

In terms of intracellular signaling mechanisms, the regulated endocytosis of AMPA receptors in hippocampal neurons appears to share properties with synaptically evoked LTD. Both depend on rises in postsynaptic calcium concentration and are blocked by pharmacological inhibition of the calcium-dependent protein phosphatase calcineurin as well as protein phosphatase 1.^{1,44,45} The critical required targets of these protein phosphatases are unknown. One hypothesis is that calcineurin acts on components of the endocytic machinery and enhances their functions.³ Another obvious possibility is that dephosphorylation of specific AMPA receptor subunits is required for AMPA receptor endocytosis. Consistent with this idea, AMPA receptors appear to be dephosphorylated following LTD,⁴⁶ and a mouse expressing a mutant form of GluR1 with its major phosphorylation sites deleted does not express LTD.⁴⁷ However, the mechanisms controlling AMPA receptor endocytosis appear to be much more complicated, in that LTD in the cerebellum and in the ventral tegmental area both require AMPA receptor endocytosis but are due, at least in part, to activation of PKC and PKA, respectively.^{42,43} Thus there may be multiple mechanisms by which AMPA receptor endocytosis can be enhanced, perhaps because of the existence of different subsets of binding partners in different cell types.

Because LTD is a long-lasting and presumably stable form of synaptic plasticity, an important question is whether the endocytosed AMPA receptors are targeted for degradation via the lysosome or are eventually recycled back to the cell surface. A study that measured the fate of surface biotinylated AMPA receptors in cultured hippocampal neurons found that whether internalized AMPA receptors were degraded or recycled back to the plasma membrane was influenced by the stimulus that triggered the endocytosis in the first place.⁴⁵ This observation lends additional complexity to the trafficking of AMPA receptors but also provides additional sites that may be subject to activity-dependent modulation.

SYNAPTIC PLASTICITY AND DRUGS OF ABUSE

Although AMPA receptor trafficking is clearly implicated in phenomena such as hippocampal LTP and LTD, which are primarily studied *in vitro*, a critical question is whether these mechanisms actually play a role *in vivo* in mediating various forms of experience-dependent plasticity. It has been shown that LTP and LTD generated *in vivo* in the hippocampus are accompanied by decreases and increases, respectively, in the level of AMPA receptors that were measured biochemically in fractions enriched in synaptic membranes.⁴⁸ More recently, using virally mediated overexpression of AMPA receptor subunits *in vivo* in somatosensory (barrel) cortex, it was found that alterations in sensory experience could stimulate the synaptic de-

livery and incorporation of the recombinant AMPA receptors.⁴⁹ This provides important evidence that the mechanisms of AMPA receptor trafficking elucidated from the study of reduced *in vitro* preparations likely apply to the intact, functioning brain.

We have attempted to examine whether synaptic plasticity mechanisms analogous to hippocampal LTP and LTD occur *in vivo* by examining the synaptic changes elicited by drugs of abuse. A prominent hypothesis in the addiction field is that cellular mechanisms, such as synaptic plasticity, which are used during adaptive forms of experience-dependent plasticity, may also be important for the neural adaptations generated by acute and chronic exposure to drugs of abuse.^{50,51} An important advantage of using administration of drugs of abuse as a model for experience-dependent plasticity is that the critical sites of action that are responsible for mediating the addictive properties of drugs of abuse have been extensively studied and clearly include the mesolimbic dopamine system, the chief components of which are the nucleus accumbens (NAc) and the ventral tegmental area (VTA). Thus we explored the hypothesis that *in vivo* exposure to drugs of abuse may elicit changes in synaptic strength at excitatory synapses in these brain regions due to synaptic plasticity mechanisms.

We first examined excitatory synaptic responses recorded from the VTA dopamine neurons in slices prepared from cocaine-treated animals and obtained evidence that a single *in vivo* exposure to cocaine caused a significant increase in synaptic strength using a mechanism that involved modification of AMPA receptors.⁵² We also found evidence that this increase may share mechanisms with LTP. More recently we have found that not only cocaine but multiple different classes of drugs of abuse (i.e., amphetamine, morphine, nicotine, and ethanol) all cause an increase in strength at excitatory synapses on midbrain dopamine neurons when administered *in vivo*.⁵³ Importantly, nonabused psychoactive drugs, such as fluoxetine and carbamazepine, did not cause a change. Because stress has a profound facilitatory effect on the initiation and reinstatement of drug self-administration,⁵⁴ the effect of an acute stress was examined and, like drugs of abuse, was also found to cause an increase in synaptic strength in midbrain dopamine cells.⁵³

These results suggest that plasticity at excitatory synapses on dopamine cells may be a key neural adaptation contributing to addiction and its interactions with stress. Since external stimuli that are associated with the firing of midbrain dopamine cells are granted high appetitive or motivational significance, we would suggest that by increasing synaptic drive onto these cells, drugs of abuse or stress enhance the motivational significance of drugs themselves as well as stimuli closely associated with drug seeking and self-administration. The detailed molecular mechanisms that are responsible for the observed synaptic changes are unknown. One intriguing hypothesis is that they are due to an LTP-like mechanism that involves the trafficking of GluR1-containing AMPA receptors to synapses. Indeed, overexpression of GluR1 in the VTA has been found to enhance the locomotor-stimulatory and rewarding properties of morphine.⁵⁵ This and several other observations have led to the specific hypothesis that elevated levels of GluR1 in the midbrain are an important trigger for the behavioral sensitization elicited by drugs of abuse.⁵⁶

Because some of the long-term behavioral sequella of chronic administration of drugs of abuse clearly involve the NAc,⁵¹ we also performed a similar study that involved preparing slices of this structure from animals who had been administered cocaine *in vivo*. In contrast to the changes observed in the VTA, chronic *in vivo* ad-

ministration of cocaine was required to elicit detectable effects. Specifically, we examined synaptic strength at excitatory synapses in NAc slices that were prepared 10–14 days after repeated (5-day) *in vivo* administration of cocaine—a treatment that caused robust behavioral sensitization.⁵⁷ Neurons in the shell, but not the core region of NAc slices prepared from the cocaine-treated animals, showed a decrease in strength at excitatory synapses made by prelimbic cortical afferents. LTD was also diminished in these slices, suggesting that the decrease was due to mechanisms shared with LTD. As is the case for the synaptic changes in the VTA, the detailed mechanisms responsible for this drug-induced synaptic plasticity in the NAc are unclear. One intriguing hypothesis is suggested by the finding that persistent upregulation of the Δ FosB transcription factor, which is known to occur following repeated cocaine treatment, induces NAc expression of the AMPA receptor subunit GluR2.⁵⁸ Due to conductance differences in GluR2-containing versus non-GluR2-containing AMPA receptors, increases in GluR2 expression could potentially reduce AMPA receptor-mediated responses. This scenario, however, depends on the existence of a significant population of non-GluR2-containing synaptic AMPA receptors prior to cocaine exposure. If such a population existed, it should be identifiable due to the strong inward rectification of non-GluR2-containing receptors. Although this hypothesis remains intriguing, preliminary studies have failed to detect inward-rectifying AMPA receptor-mediated responses in NAc medium spiny neurons, suggesting that GluR2 incorporation does not explain the cocaine-induced depression. Another possibility is suggested by the fact that the acute administration of amphetamine to slices blocks LTP in the NAc.⁵⁹ This effect disappears in slices prepared from animals that have been repeatedly exposed to amphetamine. If this also occurs after *in vivo* cocaine exposure, such an action could initially enhance the likelihood of generating LTD.

CONCLUSIONS

We have briefly reviewed some of the evidence supporting the idea that activity-dependent modulation of the trafficking of AMPA receptors plays an important role in the expression of NMDA receptor-dependent LTP and LTD in the hippocampus (FIG. 2). On the basis of ultrastructural examination of synapses in the hippocampus (see, e.g., Ref. 60) and work in other systems, such as the neuromuscular junction,⁶¹ it is attractive to speculate that the activity-dependent regulation of the number of synaptic AMPA receptors is an initial step in a more comprehensive and long-lasting reorganization of the entire ultrastructure of the synapse, processes that may involve the production of new synaptic connections and the pruning away of preexisting ones.⁶²

We have also reviewed evidence that *in vivo* administration of drugs of abuse causes changes in excitatory synaptic strength in the NAc and VTA, two main components of the mesolimbic dopamine system, and that this may occur due to activation of the mechanisms that underlie LTP and LTD in these structures. While this latter work is still in its infancy, it, we hope, illustrates that the powerful *in vivo* effects of drugs of abuse may be a valuable model for studying the role of synaptic plasticity in mediating experience-dependent plasticity. Indeed, it is already apparent that, like other forms of experience-dependent plasticity, such as learning and

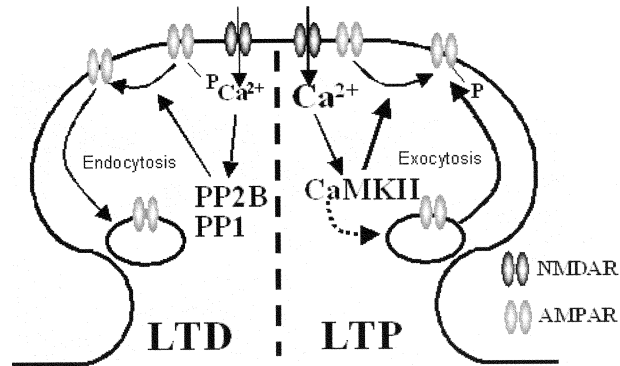


FIGURE 2. Simplified model of the intracellular pathways involved in LTD and LTP. LTD is triggered by a modest rise in calcium that activates protein phosphatase 2B (calcineurin) and protein phosphatase 1. This leads to the endocytosis of synaptic AMPA receptors as well as to their dephosphorylation. LTP is triggered by a large rise in calcium that activates CaMKII. This causes the delivery (exocytosis) of intracellular AMPA receptors to the synapse. CaMKII may also phosphorylate AMPA receptors directly, although this may not be required for their synaptic delivery.

memory, persistent drug-induced behavioral changes likely occur, in part, because of their ability to elicit long-lasting changes in synaptic weights in crucial brain circuits. Furthermore, it is important to note that the mesolimbic dopamine system did not evolve to respond to drugs of abuse but rather plays very important roles in adaptive behaviors, including various types of learning and memory. Thus examining the neural adaptations elicited by drugs of abuse will not only inform us about the pathophysiology of addiction but will also provide important information about how neural circuit modifications in the NAc and VTA contribute to normal, motivated behavior.

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