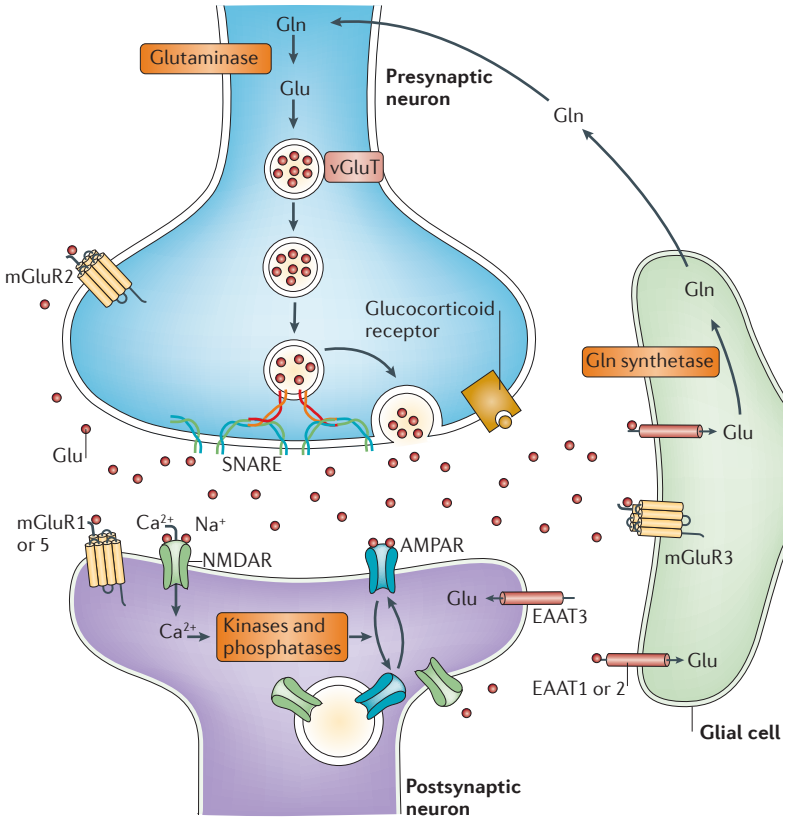

Figure 1 | **The tripartite glutamate synapse.** Neuronal glutamate (Glu) is synthesized *de novo* from glucose (not shown) and from glutamine (Gln) supplied by glial cells. Glutamate is then packaged into synaptic vesicles by vesicular glutamate transporters (vGluTs). SNARE complex proteins mediate the interaction and fusion of vesicles with the presynaptic membrane. After release into the extracellular space, glutamate binds to ionotropic glutamate receptors (NMDA receptors (NMDARs) and AMPA receptors (AMPARs)) and metabotropic glutamate receptors (mGluR1 to mGluR8) on the membranes of both postsynaptic and presynaptic neurons and glial cells. Upon binding, the receptors initiate various responses, including membrane depolarization, activation of intracellular messenger cascades, modulation of local protein synthesis and, eventually, gene expression (not shown). Surface expression and function of NMDARs and AMPARs is dynamically regulated by protein synthesis and degradation and receptor trafficking between the postsynaptic membrane and endosomes. The insertion and removal of postsynaptic receptors provide a mechanism for long-term modulation of synaptic strength. Glutamate is cleared from the synapse through excitatory amino acid transporters (EAATs) on neighbouring glial cells (EAAT1 and EAAT2) and, to a lesser extent, on neurons (EAAT3 and EAAT4). Within the glial cell, glutamate is converted to glutamine by glutamine synthetase and the glutamine is subsequently released by System N transporters and taken up by neurons through System A sodium-coupled amino acid transporters to complete the glutamate–glutamine cycle.

and modulate glutamate receptor activity in order to ensure optimal neurotransmission and prevent potential excitotoxicity (FIG. 1).

Glutamate can be synthesized *de novo* from glucose in astrocytes via the Krebs cycle, followed by transamination or reductive amination of α-oxoglutarate, and it can be recycled through the glutamate–glutamine cycle[21]. Exocytotic vesicular release of glutamate, which underlies the vast majority of excitatory neurotransmission in the brain, is a strictly regulated process in which the synaptic vesicles that store glutamate merge and then fuse with the presynaptic membrane in response to stimulation. In glutamatergic synapses, presynaptic terminals are normally associated with specialized postsynaptic structures (dendritic spines), unlike synapses at which monoaminergic neurotransmitters (dopamine, noradrenaline, adrenaline, serotonin and histamine) are released.

The core of the presynaptic machinery for vesicular neurotransmitter release, including glutamate release, is the so-called SNARE complex. The SNARE complex is formed by the interaction of two synaptic membrane proteins (syntaxin 1 or syntaxin 2 and SNAP25) and a vesicular protein (synaptobrevin 1 or synaptobrevin 2), and is thought to mediate the fusion of synaptic vesicles with the presynaptic membrane[22–24].

Glutamate regulates synaptic transmission and plasticity by activating ionotropic glutamate receptors (AMPA and NMDA) and metabotropic glutamate receptors (mGluR1 to mGluR8). The number and stability of these receptors at the synaptic membrane is an important factor in determining excitatory synaptic efficacy. Several mechanisms have been proposed to control the surface expression of NMDARs and AMPARs, including PDZ domain-mediated interactions between channel subunits and synaptic scaffolding proteins[25–27], clathrin-dependent endocytosis regulated by phosphorylation[28–30], and motor protein-based transport along microtubule or actin cytoskeletons[31–33]. Members of the RAB family of small GTPases, which function as key regulators for all stages of membrane traffic[34], are involved in the internalization, recycling and delivery of NMDARs and AMPARs to the spine[35,36]. The synthesis and degradation of postsynaptic glutamate receptors are dynamically regulated[37,38].

Glutamate is cleared from the extracellular space by high-affinity excitatory amino acid transporters (EAATs), which are located on neighbouring glial cells (EAAT1 and EAAT2) and, to some extent, on neurons (EAAT3 and EAAT4)[39]. In glial cells, glutamate is converted into glutamine by glutamine synthetase. Glutamine is then transported back into the glutamatergic neuron, where it is hydrolysed into glutamate by glutaminase[21]. Owing to the lack of degradative enzymes in the synapse, uptake by EAATs is the primary mechanism through which the action of extracellular glutamate is terminated. The following sections will discuss evidence that stress and glucocorticoids can influence glutamate neurotransmission through actions at several sites within the system, namely at the levels of glutamate release, ionotropic glutamate receptor activity and glutamate clearance and metabolism.

Stress effects on glutamate release

Acute stress and glucocorticoids increase extracellular glutamate levels. Glucocorticoids secreted during the diurnal rhythm and during stress (BOX 1) affect the basal release of glutamate in several limbic and cortical areas, including the hippocampus, amygdala and PFC[40,41]. Converging lines of evidence from animal studies suggest that acute exposure to stress or administration of glucocorticoids rapidly increases glutamate release in these brain areas[40,42–45]. For example, *in vivo* microdialysis studies have shown that exposure of rats to tail-pinch, forced-swim or restraint stress induces a marked, transient increase of extracellular glutamate levels in the

SNARE complex
Soluble NSF (*N*-ethylmaleimide-sensitive factor) attachment protein (SNAP) receptor complex.