Spine dynamics in the brain, mental disorders and artificial neural networks

Haruo Kasai[1,2]✉, *Noam E. Ziv*[3], *Hitoshi Okazaki*[1,2], *Sho Yagishita*[1,2] *and Taro Toyoizumi*[4,5]

Abstract | In the brain, most synapses are formed on minute protrusions known as dendritic spines. Unlike their artificial intelligence counterparts, spines are not merely tuneable memory elements: they also embody algorithms that implement the brain's ability to learn from experience and cope with new challenges. Importantly, they exhibit structural dynamics that depend on activity, excitatory input and inhibitory input (synaptic plasticity or 'extrinsic' dynamics) and dynamics independent of activity ('intrinsic' dynamics), both of which are subject to neuromodulatory influences and reinforcers such as dopamine. Here we succinctly review extrinsic and intrinsic dynamics, compare these with parallels in machine learning where they exist, describe the importance of intrinsic dynamics for memory management and adaptation, and speculate on how disruption of extrinsic and intrinsic dynamics may give rise to mental disorders. Throughout, we also highlight algorithmic features of spine dynamics that may be relevant to future artificial intelligence developments.

The major sites of synaptic change in the mammalian brain are dendritic spines (FIG. 1a), small protrusions that extend laterally from dendrites and that are the postsynaptic sites of most excitatory glutamatergic synapses[1–3]. The spine is characterized by a bulbous head with a volume between 0.005 and 1 μm^3, shaped by actin-based scaffolds. The spine head contains a postsynaptic density (PSD) that anchors glutamate receptors and other signalling molecules to the postsynaptic membrane. The PSD, in turn, is juxtaposed across the synapse with a presynaptic axonal bouton. The spine head is connected to the dendritic shaft by a narrow neck with a diameter of 0.1–0.5 μm and a length of 0.1–2.5 μm. There are estimated to be 100 trillion spines in the human cortex, vastly outnumbering the 175 billion synapses in the largest deep neural networks in current-use artificial intelligence (AI)[4,5]. Thousands of dendritic spines decorate the dendrites of major neuron types in the brain, reaching densities of one to ten spines per micrometre and constituting 70% of synapses in the cortex. Dendritic spines are densest in principal (projection) neurons of vertebrates, but can be found in insects[6,7] and even in nematodes[8].

Spines are not fixed structures: new spines form while others are eliminated, and spines grow larger and smaller and change shape. Some of these dynamics are directly linked to major forms of synaptic plasticity such as long-term potentiation (LTP) and long-term depression (LTD) of functional connectivity. Although such changes have been reported in many synapses[9,10], it is only at the spine synapses that synapse-specific and weight changes lasting a day or so have been directly demonstrated. These dynamics, as well as many additional functional and structural properties of spines, are mediated by hundreds of gene products found at these minute synaptic specializations, subtle variations of which affect mental function. It follows that dendritic spines are involved in virtually all mental functions and in many mental disorders.

Recent progress in machine learning and AI is largely based on artificial neural networks (ANNs), whose architectures were inspired by, and share similarities with, those of the brain. ANNs are composed of feedforward or recurrently connected 'neurons', in which the 'synapses' connecting the neurons have tuneable weights (strengths). Typically, these weights are set during a training phase in which errors (differences between the actual output and the desired output) are propagated from the output backward throughout the network (via 'backpropagation'). Although it is not clear whether this highly effective procedure is used in the brain, it has been suggested that it might be in some form[11]. Regardless, the synapse is a central, common denominator of ANNs and brains, the seat of fundamental mental functions in humans and animals. Although ANNs are radically simplified variants of their biological counterparts, lessons learned in this field might provide important frameworks for understanding brain function[12].

Reinforcement learning (RL) is another biologically inspired machine learning field. In RL, agents exploring interactive environments learn action models that

[1]*Laboratory of Structural Physiology, Center for Disease Biology and Integrative Medicine, Faculty of Medicine, The University of Tokyo, Tokyo, Japan.*

[2]*International Research Center for Neurointelligence (WPI-IRCN), UTIAS, The University of Tokyo, Bunkyo-ku, Tokyo, Japan.*

[3]*Technion Faculty of Medicine and Network Biology Research Labs, Technion City, Haifa, Israel.*

[4]*Laboratory for Neural Computation and Adaptation, RIKEN Center for Brain Science, Saitama, Japan.*

[5]*Department of Mathematical Informatics, Graduate School of Information Science and Technology, The University of Tokyo, Tokyo, Japan.*

✉*e-mail: hkasai@m.u-tokyo.ac.jp*

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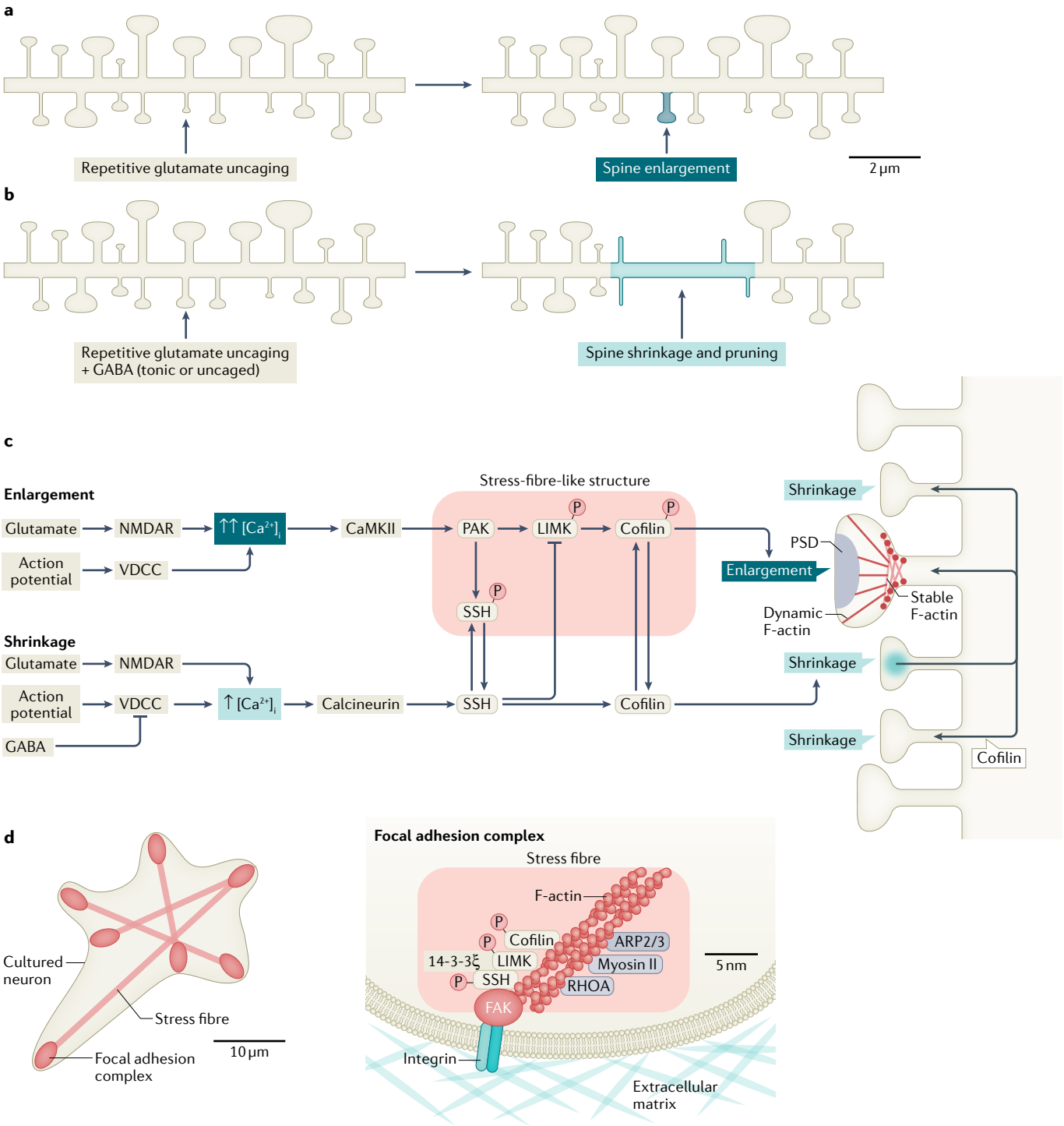


maximize cumulative rewards. In recent years, RL has been combined with ANN-based deep learning, giving rise to the field of deep RL. Here too, insights gained might offer new frameworks and hypotheses for understanding brain function[13]. Although AI has surpassed human performance in well-defined tasks[5], current AI falls short in realistic, complex situations in which human (and often animal) intelligence excels. Notably, unlike in AI, the goals and algorithms underlying information processing in the brain are not explicitly designed. Instead, they are embedded in the physical implementations of neural circuits and synapses ('nature') and in the way these circuits and synapses are tuned through interactions with the environment ('nurture'). It is thus likely that much of the algorithmic richness embedded in synapses and neural circuits remains to be discovered[14].

Here we attempt to provide a concise review of spine dynamics, their relationships with explicit and implicit brain 'algorithms', how these dynamics relate to key mental functions and certain mental disorders, and how these insights might further inform neuro-inspired AI. We first consider extrinsic dynamics — forms of spine enlargement and shrinkage that are dependent on

◀ Fig. 1 | **Enlargement and shrinkage of dendritic spines. a** | Two-photon-induced glutamate uncaging can be used to selectively stimulate long-term potentiation (LTP) at a single synapse (in the absence of Mg^{2+} or spike timing-dependent plasticity). This leads to enlargement and LTP of the stimulated synapse but not of nearby synapses. **b** | Two-photon-induced glutamate uncaging at a single spine in the presence of GABA (tonic or uncaged during a short time window) can be used to target a spine for shrinkage or elimination. However, shrinkage is not confined to the targeted spine and can 'spread' along the dendrite to affect neighbouring spines. **c** | Signalling cascades for spine enlargement and shrinkage. Large increases in intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) activate Ca^{2+}/calmodulin-dependent kinase II (CaMKII) (within about 1 second)[39,70], resulting in the activation of a serine/threonine-protein kinase, PAK, and the phosphorylation of many proteins, including LIM-domain kinase (LIMK), slingshot (SSH) and cofilin, which are responsible for the stable enlargement of filamentous actin (F-actin) networks, and are constituents of stress fibres (red shaded area). By contrast, moderate increases in intracellular Ca^{2+} concentration selectively activate calcineurin (in about 1 second)[70] but not CaMKII, leading to the dephosphorylation of SSH and cofilin. The encircled 'P' denotes protein phosphorylation. A lateral spread of cofilin induces shrinkage of neighbouring spines. In addition to the global increases in intracellular Ca^{2+} concentration, Ca^{2+} nanodomains beneath the cytosolic mass of synaptic NMDA receptors (NMDARs) are necessary for synaptic plasticity[37,58]. The involvement of a small, representative subset of molecules in spine remodelling is more fully described in the main text. **d** | Stress fibres and adhesion complexes in a cell (left). The right-hand schematic shows stress fibres and adhesion complexes whose molecular composition is similar to that of the enlarged, stable F-actin networks at the spine base. Many of the proteins activated or phosphorylated by CaMKII are components of stress fibres in cultured cells. SSH bundles F-actin, to which RHOA, phosphorylated LIMK, phosphorylated cofilin, myosin II, actin-related protein 2/3 complex (ARP2/3) and drebrin (not shown) bind. Protein 14-3-3ζ binds with these phosphoproteins. The fibres are anchored to the extracellular matrix via focal adhesion molecules, such as FAK and integrins. This supramolecular complex is referred to as a stress fibre and connects the extracellular matrix and the cytosol. Many of these proteins are requisite for LTP. PSD, postsynaptic density; VDCC, voltage-dependent calcium channel.

excitatory (and inhibitory) input or neuromodulation — and then consider intrinsic dynamics — activity-independent changes in spine sizes and numbers that are also amenable to neuromodulation. The cooperative actions of both extrinsic and intrinsic dynamics may enable functions that are still missing in contemporary AI, such as self-management of memory systems, deep adaptability and creativity. Moreover, a full appreciation of these dynamics is key to understanding brain dysfunction and psychiatric disorders. We apologize for not being able to cite all relevant literature or cover additional frameworks and molecular mechanisms owing to space limitations. For further reading on dendritic spines, we refer readers to several other reviews[15–21].

Spine enlargement

Studying the function of single spines requires the ability to selectively stimulate specific spines (FIG. 1a,b). Commonly used optogenetic methods are not suitable as they stimulate multiple targeted axons. Electrophysiological stimulation is even less specific as it excites multiple presynaptic fibre types, including glutamatergic (excitatory), GABAergic (inhibitory) and neuromodulatory fibres, creating complications addressed in later sections. By contrast, two-photon glutamate uncaging releases glutamate within a femtolitre volume and thus is particularly suited for stimulating spine synapses along dendritic shafts[22]. Such glutamate uncaging has demonstrated the tight correlation between the spine-head size and the functional expression of fast AMPA-type glutamate receptors (AMPARs), a major determinant of synaptic weight[22,23]. The results agree with electron microscopy studies showing that the spine-head sizes are proportional to PSD area[24] and AMPAR contents[25,26], while a recent study reported a direct correlation between synaptic strength and ultrastructure[27]. These findings imply that structural alterations are inevitably associated with functional modifications. Moreover, given their nature, structural alterations are probably the most likely means for implementing long-lasting functional modifications. These structure–function relationships also obviate painstaking and error-prone estimates of postsynaptic glutamate sensitivity (or functional AMPAR expression).

Dendritic spines have been demonstrated to undergo rapid enlargement within approximately 1 minute of repetitive glutamate uncaging[28] (FIG. 1a) or glutamate uncaging repeatedly followed by postsynaptic spikes[29–31] to induce spike timing-dependent plasticity (STDP)[32,33]. These protocols result in effective opening of Ca^{2+}-permeable NMDA-type glutamate receptors (NMDARs) and large increases in intracellular Ca^{2+} concentration. Importantly, spine enlargement induced by such protocols is associated with increased glutamate sensitivity[28,32–34]. Thus, spine enlargement presumptively constitutes the structural basis of LTP in spine synapses[10,28]. Consistent with many LTP studies, spine enlargement requires activation of Ca^{2+}/calmodulin-dependent kinase II (CaMKII)[35–39] and small GTPases[40,41], which through activation and phosphorylation of many proteins (partly listed in FIG. 1c) lead to the polymerization of filamentous actin (F-actin)[16,18,42–45] (FIG. 1c).

Confinement of spine enlargement. Uncaging studies indicate that spine enlargement and LTP are confined to stimulated spines, as neighbouring spines did not show enlargement or shrinkage (neither LTP nor LTD)[28,32,33,37] (FIG. 1a). This enables independent modification of synapses, similar to weight modification in ANNs. The ability to confine changes to single synapses is not trivial, given that hundreds of molecular species are involved in spine enlargement, and many of these have been shown to diffuse from spines to dendrites and among nearby spines[44,46–49]. Indeed, spine shrinkage readily spreads, as discussed below (FIG. 1b). Moreover, LTP leads to the selective activation of several key molecules, including CaMKII and small GTPases[37,40,41,48,50] (FIG. 1c). The degree to which these molecules spread is determined by their diffusion and inactivation rates, which for some key molecules (for example, CaMKII and CDC42) effectively confine their activation to within approximately 1 μm of stimulated spines. For others, such as RAS, RHOA and RAC1, the situation is less clear, as confinement of spine enlargement is not well explained by their diffusion and inactivation rates[18].

An alternative explanation for the confinement of spine enlargement relates to the presence of higher-order molecular assemblies within spines, in particular the dense F-actin networks that define and regulate spine morphology. As actin networks are primary targets of many LTP-activated molecules, it is plausible that their steric properties and polymerization–depolymerization dynamics confine the activities of LTP-activated

Spike timing-dependent plasticity
(STDP). Adjustments of connection strengths based on the relative timing of the output of a particular neuron and input spikes.

Filopodia
Thin transient protrusions that act as 'feelers' that allow cells to probe their surrounding environment. Can occasionally give rise to dendritic spines.

Integrins
Transmembrane molecules that facilitate cell–cell and cell–extracellular matrix adhesion by connecting stress fibres and other intracellular actin structures to the extracellular matrix.

Metaplasticity
The plasticity of synaptic plasticity.

Nanodomains
The cytosolic domains within about 10 nm of the open pore of Ca^{2+} channels or NMDA receptors where Ca^{2+} concentrations can readily exceed 10 μM.

Shunting inhibition
A predominant form of GABAergic inhibition that depends on increases in the membrane conductance but not necessarily on hyperpolarization.

molecules in space and time. Spine actin networks share many similarities with other actin-based structures, such as stress fibres, lamellipodia and filopodia, that shape and underlie motility in non-neuronal (and neuronal) cells[51–53]. Furthermore, integrins have also been shown to be involved in LTP[54] (FIG. 1d). Strikingly, many proteins that regulate spine enlargement (such as RAC1, CDC42 and RHOA) also regulate actin dynamics and actin-based cell motility in other settings on timescales of minutes[51–57] (FIG. 1c,d).

One key molecule in this respect is cofilin. Cofilin binds F-actin and severs F-actin polymers when cofilin is dephosphorylated. Conversely, phosphorylation of cofilin suppresses its binding and F-actin-severing activity (FIG. 1c), consequently allowing spine enlargement[48,58]. Although phosphorylated cofilin (p-cofilin) is highly diffusive in dendrites, p-cofilin generated during spine enlargement is observed to be trapped selectively in stimulated spines[48], indicating that p-cofilin is bound to higher-order molecular complexes (FIG. 1d). In support of this view, during spine enlargement, F-actin can rapidly (within approximately 1 minute) form a stable gel (the enlargement pool of F-actin)[44], which occasionally (in about 20% of enlarged spines) flows out en bloc into the dendritic shaft, followed by the reversal of spine growth[44], resulting in only transient enlargement. Conversely, if the F-actin gel remains in the spine head, enlargement is long-lasting, possibly because the gel clears space in the spine head, facilitating PSD growth and consolidation over the course of about 1 hour[33,59]. Thus, the rapid, independent and long-term modifiability of synaptic specializations relies on ubiquitous cellular mechanisms used by most living cells for shaping and rapidly modifying their structures (FIG. 1d).

Confined spine enlargement can last at least 3–6 hours in vitro, and a fraction of newly generated or enlarged spines can last more than 2 months in vivo[20,60]. Spine enlargement can be efficiently induced in most small spines (more than 90%), although the extent of enlargement is highly variable among spines, even in young hippocampal in vitro preparations[28,33,61]. The variability is more prominent in the adult cortex, where spine enlargement occurred in only 20% of small spines even though similar uncaging protocols were used[62]. An interesting possibility is that this heterogenic amenability to enlargement is a manifestation of the 'cascade model' of synaptic metaplasticity[63] in which each synapse exhibits a cascade of states with different levels of plasticity, connected by metaplastic transitions, thereby preventing overwriting of synaptic memory traces to make memory long-lasting. Regardless, in vivo experimental evidence points to the importance of cortical spine enlargement in motor memory, as selective optical 'undoing' of the enlargement of approximately 400,000 spines in the motor cortex associated with learning a specific motor task selectively erased learning acquired for that motor task[64].

Spine shrinkage and pruning

Prolonged, low-frequency stimulation of specific spines can lead to their shrinkage and pruning[48,58,65,66]. Here we discuss how and why such shrinkage spreads to other spines along the dendrite, the roles of inhibitory signalling in this shrinkage and implications of these extrinsic dynamics.

Spreading of spine shrinkage and pruning. Unlike spine enlargement, spine shrinkage and pruning can spread to neighbouring spines, as far as 15 μm from the stimulated spine[58] (FIG. 1b). This is consistent with many studies reporting the spread of LTD[31,62,67–69] and spine pruning[66] when an input fibre bundle is stimulated at a low frequency. Notably, neighbouring spines that are stimulated with a protocol that induces spine enlargement are 'protected' against the spine shrinkage that may otherwise spread from neighbouring synapses[58].

Spine shrinkage depends on Ca^{2+} flux through NMDARs (influx through dendritic voltage-gated channels is not sufficient), which leads to moderate increases in intracellular Ca^{2+} concentrations sufficient to activate the Ca^{2+}-dependent phosphatase calcineurin, but not CaMKII[70] (FIG. 1c). Activation of calcineurin depends on Ca^{2+} nanodomains underneath the cytosolic openings of NMDARs[58], as is the case with CaMKII in spine enlargement[37] for synaptic specificity. Calcineurin is thought to dephosphorylate p-cofilin, and by doing so, it activates the latter's F-actin-severing ability (FIG. 1c), resulting in spine shrinkage[48,58,71,72] (FIG. 1b). By diffusing to neighbouring spines, dephosphorylated cofilin acts as a spreading shrinkage factor[48] shown to be necessary[58,71] and sufficient for spine shrinkage[48]. Spreading of spine shrinkage has been observed in the visual cortex of adult mice[62], although it seems to be less common and more confined than spreading in hippocampal slices from young rats[48,58]. Notably, a form of spine shrinkage that depends on NMDARs, but not on ion flux through these receptors[73], occurs in young but not adult animals[74].

Whereas spine enlargement typically occurs within 1 minute[28,37,59,62] (FIG. 1b), spine shrinkage occurs on much longer timescales (for example, over 10–60 minutes)[58,62,66,68]. This difference probably reflects the rapid dynamics of actin polymerization involved in initial spine enlargement[43,44] as compared with the slow dismantling of PSD scaffolds[75].

Roles of inhibition in spine shrinkage and pruning. When postsynaptic spikes precede presynaptic stimulation, stimulated synapses will often undergo LTD[29,31] (FIG. 1b). As mentioned earlier, this depends on Ca^{2+} influx through NMDARs that elevate intracellular Ca^{2+} concentration to moderate levels only[9,31] (FIG. 1c). Precisely timed activation of postsynaptic GABA type A receptors ($GABA_A$Rs) could serve to restrict intracellular Ca^{2+} concentration elevations to such levels by shunting inhibition. Indeed, feedforward (and feedback) GABAergic neuron activity driven by glutamatergic fibre stimulation has been shown to be necessary for LTD induction[69]. In support of this finding, glutamate uncaging-mediated spine stimulation paired with postsynaptic stimulation induced spine shrinkage only when increases in spine intracellular Ca^{2+} concentration were dampened by GABAergic inhibition (or intracellular calcium chelation)[58] (FIG. 1c). By contrast, when intracellular Ca^{2+} concentration increases were not suppressed, CaMKII

was activated and competed with calcineurin, and the shrinkage was abated[58] (FIG. 1c). Thus, spine growth and shrinkage are determined by spine intracellular Ca^{2+} levels (FIG. 1c), and inhibitory neurons play a key role in determining these levels.

Extrinsic dynamics versus weight adjustments in ANNs. Extrinsic dynamics share similarities with synaptic weight adjustments in ANNs, but also differ from these substantially. In ANNs, weight adjustments are based on comparisons between computed network output and desired network output; errors at the output level are then 'backpropagated' and used to adjust synaptic weights in the entire network. Purely local rules, such as simple Hebbian learning, can enhance features in the input[9,10,31,76] but cannot be used to solve a general task that requires information (feedback in some form) as to the manner by which local synaptic changes affect network output and ultimately behaviour. This observation indicates that purely local rules might not suffice to explain the role of extrinsic dynamics in behavioural learning. Indeed, global error signals might play critical roles (see the section entitled Reinforcement learning)[11]. Alternatively, backpropagation might occur indirectly through feedback connections and circuit-level organization[11,77,78].

Other important differences between extrinsic dynamics in the brain and ANN synaptic weight adjustments also exist. 'Synapses' in ANNs can have positive or negative weights, whereas spine synapses are predominantly excitatory, hinting at the importance of inhibitory synapses[79]. Furthermore, extrinsic dynamics are asymmetric: spine growth is rapid and spatially confined, whereas shrinkage is slow, is non-local and can lead to pruning. Rapid, confined spine enlargement could help diversify downstream circuits (see the section entitled Reinforcement learning), whereas non-local pruning (as a form of heterosynaptic plasticity) may help to remove inactive synapses, which synapse-specific plasticity nor backpropagation enables[11]. These differences may be instrumental for circuit rewiring during critical periods in the course of development[80], and in the ANN domain for finding sparsely connected subnetworks (see the section entitled Pruning and rewiring)[81].

Reinforcement learning

RL is a machine learning approach in which agents explore interactive environments, receive feedback (reward) in response to selected actions and learn action models for maximizing cumulative rewards. RL[82] was inspired by concepts developed in behavioural experiments, in particular operant conditioning[83]. A key concept adopted in RL is the eligibility trace, with which agents (such as robots) involved in producing behaviours are sensitive to feedback for the effective detection of contingencies between actions and rewards for a certain period. Such learned associations are later used to predict rewards and estimate the reward prediction errors (RPEs), the differences between expected and actual rewards. Substantial experimental work suggests that RPE signals might be encoded in the brain by the firing of midbrain dopaminergic neurons[84–86] that densely innervate the striatum. In particular, these neurons innervate the nucleus accumbens (NAc; FIG. 2a) in the ventral striatum, which is considered to be a major 'reward centre' involved in classical conditioning and addiction[86–88].

Dendrites of NAc spiny projection neurons (SPNs; also called 'medium spiny neurons') are decorated with spines that receive inputs from both glutamatergic and dopaminergic fibres (FIG. 2a). Dopamine activities are mediated by dopamine receptors, members of a family of ~400 non-olfactory G-protein-coupled receptors (GPCRs) expressed in the brain and that also mediate activities of many additional, crucially important neuromodulators[89]. D1-like family receptors (D1Rs) and D2Rs stimulate and inhibit adenylate cyclases (ACs), thus increasing and decreasing levels of intracellular cyclic AMP (cAMP), respectively. Compounds that elevate dopamine concentrations can cause drug addiction, owing to excessive D1R activation[88].

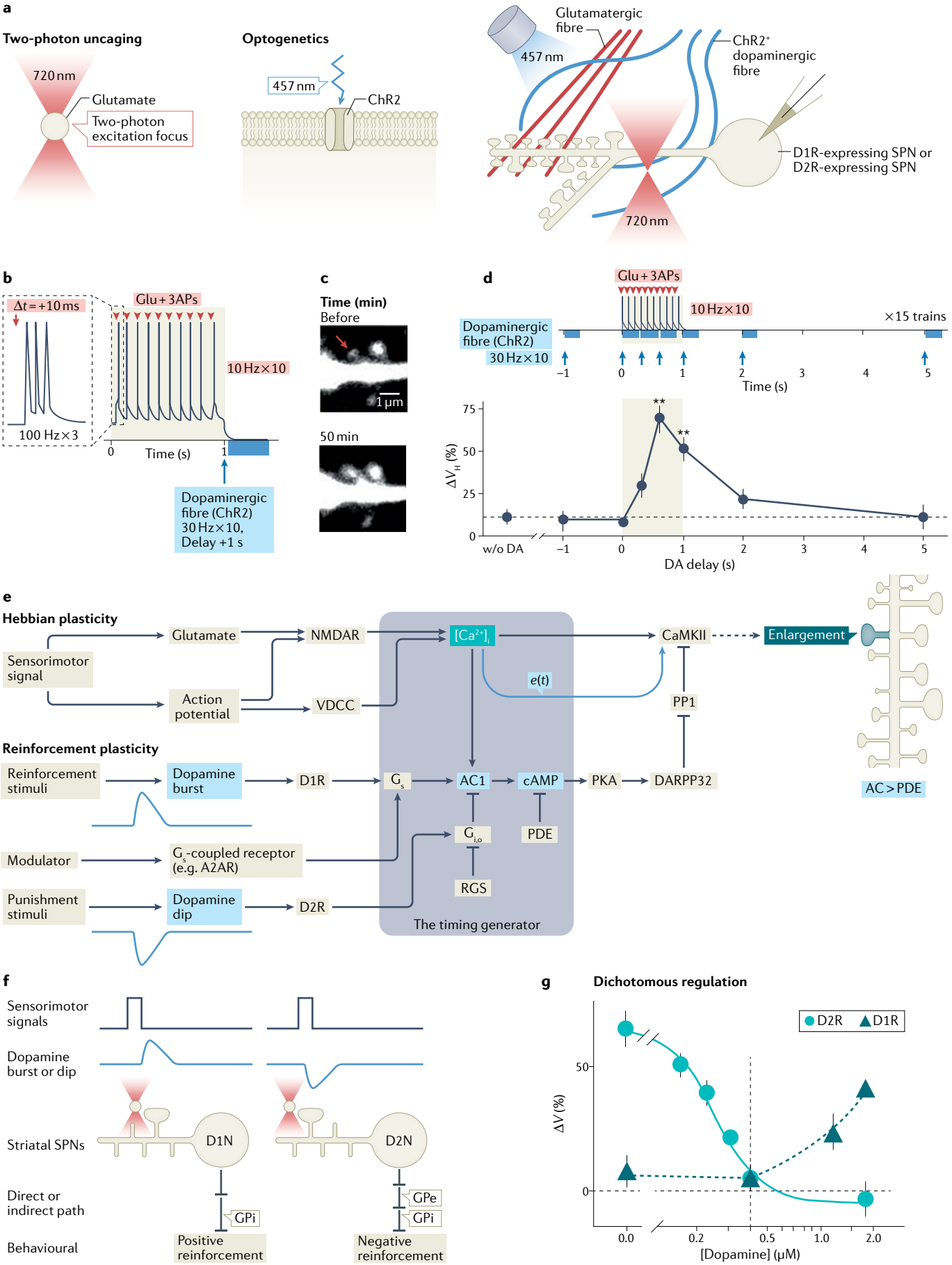
D1Rs and the eligibility trace. What might be the biological substrate of the eligibility trace? Although various mechanisms have been explored theoretically (for example, see REF.[90]), experimental validation has proved difficult, mainly because methods based on electrical stimulation inevitably recruit both glutamatergic and dopaminergic fibres[91]. This difficulty was solved by use of two-photon glutamate uncaging to selectively stimulate individual spines, and optogenetics to independently stimulate dopaminergic fibres[34]. In these experiments, performed in D1R-expressing SPNs in mice NAc slice preparations, STDP protocols and timed dopaminergic stimulation were used to assess the effects of dopaminergic input on spine enlargement (FIG. 2b). Dopamine was found to promote spine enlargement only when its release was triggered within a narrow time window (0.3–2 seconds) after the onset of glutamatergic input (FIG. 2c,d), which tracked the temporal profiles of intracellular cAMP levels. These results are interpreted to indicate that increases in intracellular Ca^{2+} concentration associated with STDP prime Ca^{2+}-dependent AC (AC1), such that D1R-induced activation of stimulatory G proteins at the delayed reward time efficiently triggers cAMP synthesis[92,93] (FIG. 2e). Increases in intracellular cAMP concentration lead to CaMKII disinhibition (via protein kinase A (PKA)), and thus repetitive conditioning summates to induce measurable spine enlargements within about 1 minute[34,93], according to the molecular cascade shown in FIG. 2e. Moreover, similar time windows were also observed to determine the effects of noradrenaline on spine size[94], suggesting that these timing dependences may reflect the kinetics of conformational changes of AC[95]. Importantly, the timing of the dopamine sensitivity of spines (FIG. 2d) is similar to the minimum behavioural time window needed for reward conditioning measured in behavioural experiments[96]. Thus, the temporal features of the eligibility trace are embedded in the molecular cascades within spine synapses (FIG. 2e).

D2Rs and psychosis. D2Rs are a second class of dopamine receptors of particular relevance to psychiatry, as they are the major targets of drugs used to treat psychosis (including symptoms such as delusions and

Critical periods
Periods during development in which a particular skill or characteristic is believed to be most readily acquired.

Operant conditioning
A form of learning that uses rewards and punishments for enforcing behaviour. Sometimes called 'instrumental conditioning'.

Eligibility trace
A temporary record of the occurrence of an event which marks the memory parameters associated with the event as eligible for undergoing learning changes.


a
Two-photon uncaging
720 nm
Glutamate
Two-photon excitation focus
Optogenetics
457 nm
ChR2
Glutamatergic fibre
457 nm
ChR2+ dopaminergic fibre
D1R-expressing SPN or D2R-expressing SPN
720 nm
b
Δt = +10 ms
Glu + 3APs
10 Hz×10
100 Hz×3
0
Time (s)
1
Dopaminergic fibre (ChR2) 30 Hz×10, Delay +1 s
c
Time (min)
Before
1 μm
50 min
d
Glu + 3APs
10 Hz×10
×15 trains
Dopaminergic fibre (ChR2)
30 Hz×10
−1
0
1
2
3
4
5
Time (s)
75
50
25
0
ΔV_H (%)
**
**
w/o DA
−1
0
1
2
3
4
5
DA delay (s)
e
Hebbian plasticity
Sensorimotor signal
Glutamate
NMDAR
Action potential
VDCC
[Ca2+]i
e(t)
CaMKII
Enlargement
PP1
Reinforcement plasticity
Reinforcement stimuli
Dopamine burst
D1R
Gs
AC1
cAMP
PKA
DARPP32
AC > PDE
Modulator
Gs-coupled receptor (e.g. A2AR)
Gi,o
PDE
RGS
Punishment stimuli
Dopamine dip
D2R
The timing generator
f
Sensorimotor signals
Dopamine burst or dip
Striatal SPNs
D1N
D2N
Direct or indirect path
GPi
GPe
GPi
Behavioural
Positive reinforcement
Negative reinforcement
g
Dichotomous regulation
D2R
D1R
50
0
ΔV (%)
0.0
0.2
0.5
1.0
2.0
[Dopamine] (μM)

◀ Fig. 2 | **Reinforcement plasticity of dendritic spines in D1 and D2 neurons.** **a–d** | Two-photon-mediated uncaging of glutamate combined with optogenetic stimulation of dopaminergic inputs to spiny projection neurons (SPNs) expressing dopamine 1 receptors (D1Rs) leads to spine enlargement only if the dopaminergic stimulation is performed 0.3–2 seconds after the onset of glutamatergic spike timing-dependent (STDP) stimulation. This time window can be considered the lifespan of the synaptic eligibility trace. **e** | The signalling cascades for the modulation of spine enlargement by dopamine. Adenylate cyclase 1 (AC1) in the grey shaded region dictates the time course of the eligibility trace ($e(t)$). Sensory stimuli (for classical conditioning) or motor command activity (for operant learning) are translated into elevations of intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$), which prime AC1 for subsequent activation by dopamine signalling. **f** | The optogenetically driven bursting and pausing (blue) of dopaminergic axons following STDP stimulation (red) of D1R-expressing SPNs and D2R-expressing SPNs for the control of behaviours. D1R-expressing SPNs project mainly to the globus pallidus interna (GPi), whereas D2R-expressing SPNs project indirectly to the GPi via the globus pallidus externa (GPe) and the subthalamic nucleus. All neurons in the direct and indirect pathways are inhibitory. **g** | Dichotomous regulation of spine enlargement at 50 minutes after induction by dopamine concentrations surrounding D1R-expressing SPNs and D2R-expressing SPNs. **Statistically significant. A2AR, adenosine A_{2A} receptor; AP, action potential; CAMKII, Ca^{2+}/calmodulin-dependent kinase II; cAMP, cyclic AMP; ChR2, channelrhodopsin 2; D1N, D1 neuron; D2N, D2 neuron; DA, dopamine; DARPP32, protein phosphatase 1 regulatory subunit 1B; Glu, glutamate; NMDAR, NMDA receptor; PDE, phosphodiesterase; PKA, protein kinase A; PP1, protein phosphatase 1; RGS, regulator of G protein signalling; VDCC, voltage-dependent calcium channel; w/o, without. Parts **a–d** are adapted with permission from REF.[34], AAAS. Part **g** is adapted from REF.[103], Springer Nature Limited.

hallucinations) in disorders such as schizophrenia, for example. Psychotic symptoms have been hypothesized to result from aberrant attribution of salience (the 'salience misattribution hypothesis')[97,98]. How dopamine causes salience misattribution, however, is largely unknown.

Several findings provide important pieces to this puzzle. First, as mentioned already, D2Rs inhibit AC (FIG. 2e). Second, dopaminergic neurons typically fire tonically at approximately 5 Hz and, following reward omission or punishment, cease firing for brief periods (0.4–2 seconds), resulting in transient 'dips' in extracellular dopamine levels[84,86,99,100]. Such dips would be expected to be detected by D2Rs and lead to transient increases in intracellular cAMP concentration. Third, about half of SPNs selectively express D1Rs, whereas the others express D2Rs[87,101,102]. These SPN populations belong to the direct and indirect basal ganglia pathways, which are used in positive and negative control of cortical activities (and behaviour), respectively (FIG. 2f). These three observations have led to the suggestion that the dopamine dip associated with reward omission (or punishment) suppresses behaviours due to D2R-expressing SPN-mediated negative reinforcement. Indeed, recent experiments, using two-photon uncaging and optogenetics, showed that D2Rs detect dopamine dips as short as 0.4 seconds, which are followed by PKA and CaMKII-dependent spine enlargement in D2R-SPNs[103] (FIG. 2e–g). These findings are further supported by in vivo measurements of dopaminergic neuron activity, extracellular dopamine levels and PKA activity in SPNs during learning[104] as well as a systems biology analyses of D2R signalling[93]. Collectively, they suggest that dopamine has dichotomous effects on D1R-expressing SPNs and D2R-expressing SPNs (FIG. 2g) such that they store memories of reward and reward omission (or punishment), respectively, through cell type-specific spine enlargement.

Salience
The quality of being particularly noticeable or important.

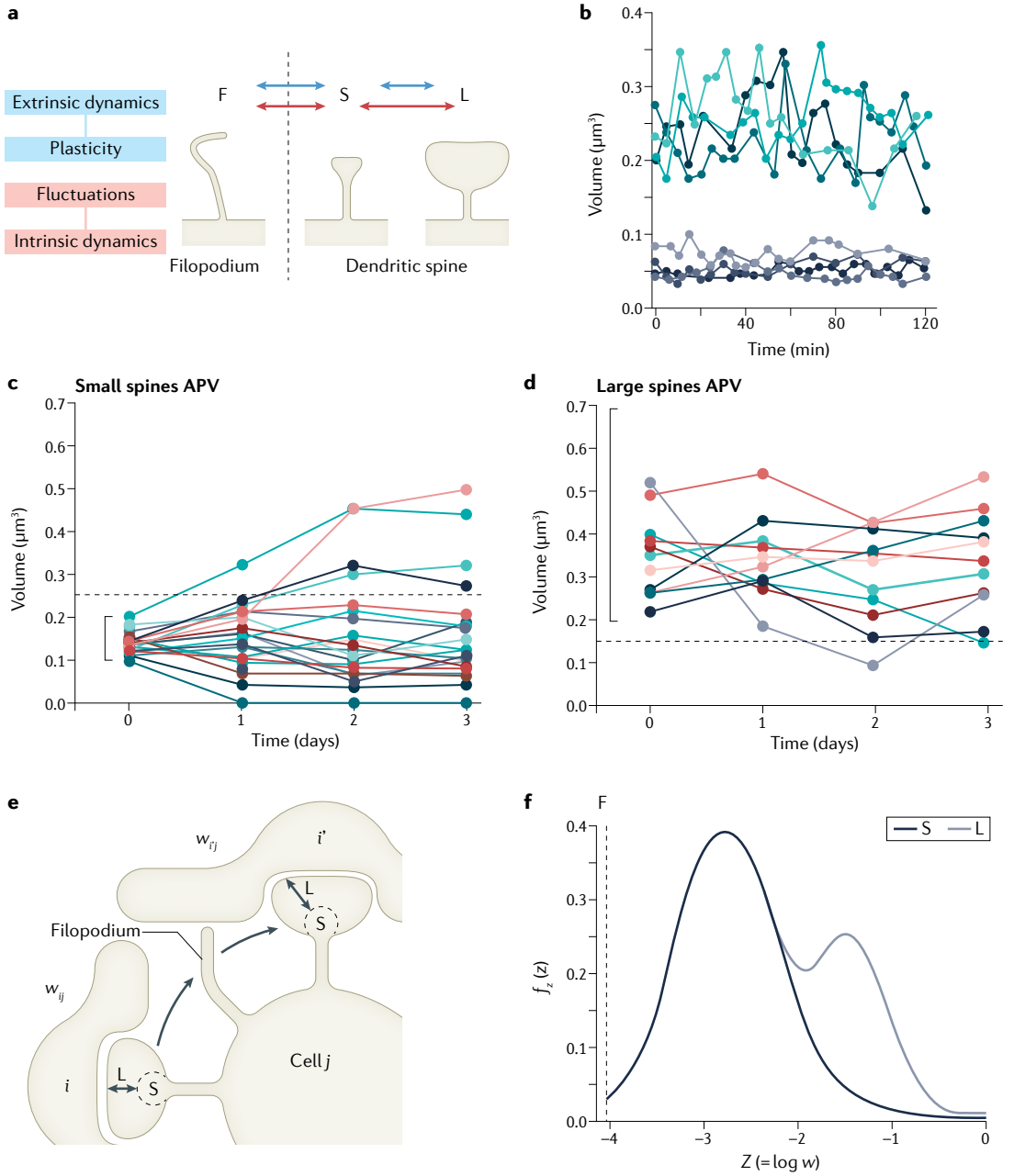
Reward conditioning via D1R-expressing SPNs exhibits an unexpectedly high degree of generalization[103,105]. Intriguingly, dopamine-dip detection by D2R-expressing SPNs seems to be particularly important for discrimination learning; that is, the ability to discriminate between similar conditioning stimuli[103]. Thus, D2R-expressing SPNs sculpt conditioning, tuning it to specific stimuli[103]. Consequently, impairment of discrimination learning might result in overgeneralized conditioning, giving rise to salience misattribution and misplaced emotional reactions. The dopamine generalization–discrimination hypothesis described here[103] naturally explains how salience can be misattributed and subsequently trigger psychotic symptoms[97,98]. Indeed, repetitive amphetamine treatment — which typically induces psychosis in humans and mice — impairs discrimination learning, whereas D2R antagonists can mitigate these impairments[103]. Collectively, these ideas and findings provide a physiological framework for understanding psychosis and antipsychotics, with the discrimination task representing a rational behavioural diagnostic for evaluating psychosis and potential treatments in both humans and animal models.

Neuromodulator-gated learning. Traditional RL typically involves a single RPE and a single target system. However, if traces engraved by reward and reward omission or punishment are stored separately, the possibility arises that they might also be activated differentially, in particular in different brain states shaped by neuromodulatory influences[89]. This multiplexing of multivariate storage[103] and complex readout modes might underlie the rich landscape of emotional influences characteristic of mammals[89,106]. The advantages of multivariate reward signals were demonstrated in dichotomous RL machines, which were able to flexibly modulate risk preference of the agent[107,108]. Intriguingly, disturbances that caused noisy generalization and impaired discrimination led to aberrant behaviour[108].

The coding of RPE by dopamine seems to apply only to part of the NAc and only in certain contexts[103]. Even though the same eligibility and dichotomous mechanisms probably hold in the dorsal striatum, dopamine may code internal, more subjective signals other than explicit sensory signals for reward and punishment[109,110]. In addition, GPCR agonists other than dopamine may work on other timescales, with their operation acting as a three-factor learning rule[77,111], in which change in synaptic weight is described by a product of a presynaptic factor, a postsynaptic factor and an additional third factor, such as a GPCR agonist. The three-factor learning framework may provide versatile bases for neuromodulator-gated learning in the brain and AI. Notably, more than one third of the 400 non-olfactory GPCRs are targets of authority-approved drugs, and a better understanding of neuromodulator-gated learning, in general, will be key to advancing psychiatry and neuroscience-inspired AI.

Intrinsic dynamics

So far we have described major features of extrinsic dendritic spine dynamics — that is, spine enlargement and shrinkage driven by activity, synaptic input and neuromodulation — and highlighted parallels and



differences between these and modifications to synaptic weights implemented in ANNs. Dendritic spines, however, unlike synaptic weights in ANNs, also change spontaneously, in manners independent of activity[61,112,113]. The definition of activity independence is somewhat nebulous and differs subtly among studies. Here we refer to intrinsic spine dynamics as forms of remodelling not driven directly by evoked synaptic transmission at the spines in question. Within this framework, however, characteristics of intrinsic dynamics are still amenable to the influences of global features such as background activity levels or neuromodulatory tone. Although these intrinsic dynamics (FIG. 3a–d) are in all likelihood associated with corresponding changes in synaptic strength[114], they were, until quite recently, mostly unheeded. We therefore describe these dynamics in some detail, and then consider their implications for the management of memory systems and their contributions to 'heuristic' algorithms.

Presence of intrinsic spine dynamics. Multiple studies have shown that blocking synaptic transmission and network activity only moderately suppresses the extent of spine-size fluctuations[61,115,116]. Similarly, rates of spine formation and elimination are only weakly affected when activity is fully suppressed in vivo[117]. Indeed, a complete gamut of dendritic spine sizes and shapes is observed even when networks develop in the complete absence of synaptic transmission[118,119]. Moreover, although blockade of key molecules that underlie extrinsic dynamics results in severe behavioural deficits[120,121], only subtle changes in spine-size distributions are observed[122,123]. The nearly universal shape of spine-size distributions — unimodal, skewed and heavy-tailed[124,125]

◀ Fig. 3 | **Intrinsic dynamics and rewiring of dendritic spines. a** | Transitions of spines among the three categories. Nascent spines without stable presynaptic partners are referred to here as 'filopodia' (F). Spines with small (S) or large (L) heads are connected to presynaptic partners. They may carry working memory and long-term memory, respectively (see the main text). Note that transition from F to S might involve a switch in the spines' presynaptic partner, further limiting the lifetime of specific connections[60,61]. **b** | Spontaneous fluctuations of spine-head sizes over a 2-hour period. Spine-size fluctuations are proportionally greater in larger spines. Over these short timescales, sizes fluctuate around their mean values due to filamentous actin (F-actin) dynamics. **c**,**d** | Spontaneous fluctuations over days in the presence of an NMDA receptor inhibitor, APV, for initially small spines (**c**) and large ones (**d**). Most small spines stay in the same category, whereas some become bigger or are eliminated. Large spines show proportionally large fluctuations. **e** | Rewiring of synaptic connections during spine pruning and generation, which occurs for 1–2% of spines per day even in the absence of spiking activity, as compared with 1–8% in active networks[60,117,210]. **f** | Semilogarithmic plot of spine-size distributions f_z with the logarithm of synaptic weight $z = \log w$. Most spines are small (black, S), but an additional large peak (grey, L) can be seen in certain preparations or in the artificial neural network simulation[141] only after learning that results in the formation of cell assemblies. We use the natural logarithm, and $z = -4$ corresponds to $w = 0.018\ \mu m^3$. The L peak (at $z = -1.4$) in the semilogarithmic plot is introduced by the coordinate transformation from w to z[182,193,194,211]. By the same token, the occurrence of the smallest spines and spine genesis or pruning (transition between S and F) may seem to occur less frequently than they actually do (see BOXES 1–3). Part **b** adapted from REF.[28], Springer Nature Limited. Parts **c**,**d** adapted with permission from REF.[61], Society for Neuroscience.

(BOXES 1–3) — emerges even in networks that never experienced any activity whatsoever[61,116]. Intrinsic spine-size fluctuations account for more than 50% of the size changes that individual spines undergo in active networks[115,126] and occur independently of neighbouring spine dynamics[61].

Mechanisms of intrinsic dynamics. Intrinsic dynamics have at least two components. The first is a rapid component (FIG. 3b) mediated mainly by continuous reorganization of the actin scaffold[28,127] that does not strongly affect PSD size but does seem to drive spine 'morphing' and glutamate receptor dynamics over timescales of minutes[75,128]. The second component involves changes in PSD sizes over timescales of many hours[75] and encompasses the entire range of spine sizes[115,129] (FIG. 3c,d). The latter dynamics seem to be driven by the continuous binding, unbinding and interchange of PSD molecules[116,130] (over a typical timescale of several hours)[47,75] and their metabolic turnover (over a timescale of many days[131]). These dynamics also depend on the extracellular matrix[15,117] and interactions with motile microglia and astrocytes[132]. Comparable molecular dynamics probably drive size fluctuations in presynaptic specializations[75], as well as postsynaptic specializations of GABAergic synapses[133]. Thus, it would seem that intrinsic dynamics are inevitable by-products of ongoing biological processes.

Quantification of intrinsic dynamics and weight distributions. Despite this complexity, multiple studies demonstrate that measurement of a single parameter — spine size — provides a good approximation of intrinsic dynamics, quantitative explanations of underlying phenomena and insights concerning their consequences. Moreover, these studies show that size dynamics can be captured surprisingly well by very low parametric processes that are essentially stochastic[61,116,129,134,135]. Details differ somewhat among studies, but they can be generally characterized as stochastic processes that have drift and diffusion terms (BOX 3 figure parts a–c). Importantly, these models account quite accurately for the experimentally observed stationary, unimodal, skewed and heavy-tailed distributions of synaptic sizes (BOX 3 figure part d), which peak at values lower than the population mean (BOX 3). This skewed shape can be attributed to the observation that the diffusion term (which describes the magnitude of size fluctuations) scales with synaptic size[61,134] (BOX 3 figure part b; FIG. 3c,d).

More quantitatively, the standard deviation of size fluctuations $\sigma(w)$ is approximately proportional to the momentary synaptic weight, w, or more precisely to spine surface or PSD area[116,135]. Thus, relatively large spines occasionally make large excursions in size such that they grow even larger (FIG. 3d), whereas small spines make smaller excursions, and consequently tend to change less and accumulate (BOX 3 figure part d). This dependence of size fluctuations on momentary size might be related to multiplicative synaptic change rules[134] or to continuous, noisy multiplicative downscaling of synaptic sizes[129]. At a more detailed level, it might be explained by the dependence of molecular dynamics on surface area[135] or the cooperative binding and unbinding kinetics of synaptic molecules[130].

The presence of a fixed point (FP) in the drift component of the aforementioned stochastic processes has important implications. First, it implies that newly formed spines, which tend to be particularly small[114,115,136,137] (that is, smaller than the FP; BOX 3 figure part c), will tend to grow larger. Second, it implies that synapses with sizes greater than the fixed point will tend to become smaller. Both tendencies are due to the negative slope of the drift component (BOX 3 figure part c) in the absence[116] and presence of ongoing activity[61,115,116,129,134,135,138,139]. Consequently, synaptic weight distributions are confined (in a quasi-lognormal manner; BOX 3) to mostly below about 1 μm^3, regardless of the details of the drift term. Thus, intrinsic dynamics can serve to normalize synaptic weights[61,116,135,140,141]. Notably, most cerebellar Purkinje cell spines are relatively large[24], suggesting that FP is large in Purkinje cells, while it is set to lower values in other neurons, possibly for reasons described later.

The stochastic models of size fluctuations described above also account for the rate of spine elimination observed in experiments[61,116], which can be calculated by counting changes in the number of spines that hit the detection threshold volume (for example, 0.02 μm^3; FIG. 3a) over a measurement interval[61,135,141]. Indeed, the life expectancy of small spines has been consistently reported to be shorter than that of large spines[61,137,142–144]. In this sense, small spines are less persistent than large spines simply because the former are closer to the pruning boundary[115,116].

Rewiring via dendritic filopodia. The elimination of (small) spines is continually matched by the formation of new (small) spines (FIG. 3e), at typical rates of a few percent per day in the cortex[20,145] and about 10% in the hippocampus[61,144,146]. Although these rates are affected by many forms of learning and external stimuli

Drift
The averaged change of a parameter in a certain period. In the general case, the drift, $\mu(w)$, is dependent on the current value of the parameter w.

Diffusion
The standard deviation of a parameter in a certain period. In the general case, the diffusion, $\sigma(w)$, is dependent on the current value of the parameter w.

Bit
A binary digit. The smallest unit of measurement used to quantify computer data.

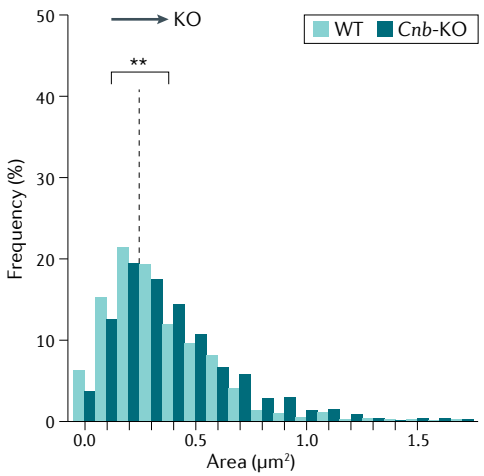
(for example, see REFS[60,64,117,147–150]), spine formation and elimination continue at surprisingly high rates even when action potentials and Ca^{2+} entry to neurons are blocked[117,137], suggesting that spine formation is mediated in part by intrinsic dynamics. New formations include dendritic filopodia and transient spines, (relatively) short-lived protrusions that extend and retract from dendrites, forming ephemeral contacts with nearby axons. A fraction of these formations occasionally evolve into bona fide synaptic connections within hours to days, facilitated by learning-associated stabilization and enlargement[20,148,151–153]. Filopodia and transient spines define overlapping 'capture volumes' around dendritic shafts[154,155] within which dendrites can potentially establish connections with three or four nearby axons within approximately 6 µm (REFS[156–158]). This mode of synapse formation undoubtedly contains an important random, exploratory component and thus a route for activity-independent 'rewiring' of neuronal circuitry (FIG. 3e). Note, however, that spinogenesis might also occur in a targeted fashion towards neurotransmitters or neurotrypsin secreted by active axons[159,160].

The formation of filopodia and spines is also regulated by broadly acting biological signals related to physiological and pathological processes. For example, spine genesis and pruning are affected by corticosteroid and sex steroid hormones[161–164], linking stress, circadian rhythms and reproductive cycles, among other factors, to spine dynamics. Likewise, the anaesthetic ketamine has been shown to drive spine genesis, possibly explaining its slow-onset, long-term antidepressant effects in the mouse prefrontal cortex[165]. Intrinsic spine dynamics are also affected by multiple neuromodulators, including canonical ones such as acetylcholine[166]. Moreover, mounting evidence points to the importance of spine generation in conferring resilience to Alzheimer disease[167]. Collectively, these findings highlight the importance of intrinsic and extrinsic dynamics to network rewiring (FIG. 3a,e), and, in turn, its importance for brain function, and potentially for novel ANN algorithms (see the section entitled Pruning and rewiring).

Box 1 | **Dendritic spines in schizophrenia**

Schizophrenia is characterized by positive symptoms (such as delusions and hallucinations), negative symptoms (such as anhedonia and lack of motivation) and cognitive symptoms[19,212]. Analysis of many mice lacking or harbouring mutations in genes implicated in schizophrenia has revealed that synaptic plasticity is often impaired[212]. Impairments in long-term potentiation may account for working memory deficits and therefore represent a possible underlying mechanism of schizophrenia cognitive symptoms[212,213]. Notably, spine loss reported in individuals with schizophrenia seems to apply mainly to small spines[173,174], in contrast to observations in individuals with autism spectrum disorder (BOX 2). The same tendency was found in mice harbouring mutations detected in people with schizophrenia[123,214], for example, in calcineurin B (*Cnb*)-knockout (KO) mice (see the figure)[123], which also show impairments in long-term depression and working memory[215]. These observations suggest that small spines may have key roles in working memory, which may be impaired by defective spine enlargement or reductions in small-spine numbers (see the figure). If so, the functional outcome of such mutations is probably severer than implied by the subtle effects on size distributions (in common with autism spectrum disorder models).

Both positive and negative symptoms of schizophrenia may reflect impairments in sensitivity to dopamine: positive symptoms (also called 'psychotic symptoms') may result from a disrupted ability to detect dopamine dips (see the main text), which is extremely sensitive to either increases in baseline dopamine concentrations or genetic mutations affecting spine enlargement[212], either of which can prevent discrimination learning. Impairments to spine enlargement may further contribute to the negative symptoms of schizophrenia by impairing reward-based learning via striatal dopamine 1 receptor-expressing spiny projection neurons[216]. Thus, both positive and negative symptoms might be attributable to the dichotomous regulation of spine enlargement by dopamine (FIG. 2f,g). **Statistically significant. WT, wild type. Figure reproduced with permission from REF.[123], Elsevier.



Spine dynamics and memory management

Humans can recall an enormous number of events that occurred in the preceding few days — places we visited, people we met and much of what was said. Such memories are essential for executive functions in daily life. Eventually, however, most of these memories are lost, and only a small fraction persists beyond a few days. Memories that do persist, however, tend to be retained for longer periods, such that forgetting is characterized by an ever-decreasing rate of memory decay[168], as originally observed more than a century ago[169]. To date, the roles of intrinsic spine dynamics in memory management and decay have rarely been considered. In the following sections, we point to potential ties between these phenomena.

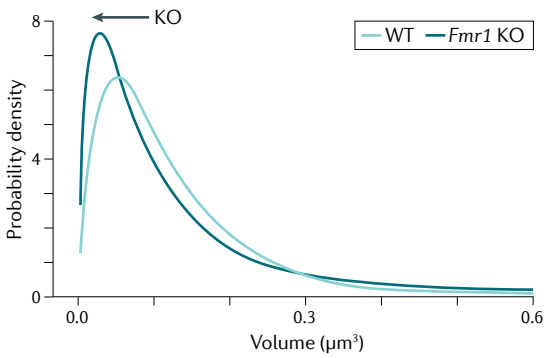
Storage of new and working memories in small spines. Extensive evidence indicates a central role of small spines in the storage of new memories[2,170]. First, small spines most frequently show rapid spine enlargement following glutamate uncaging[28,33,62], natural[61] and synchronous activity[115]. Even after their enlargement (by as much as 50%)[32,33,62], they tend to remain relatively small (FIG. 1a). The precise timing of the onset of enlargement is difficult to measure, but can be less than 10 seconds from uncaging[28]. Second, as evident from the skewed shape of spine-size distributions (BOX 3), most dendritic spines are small with potentially huge storage capacity. Small spines could account for about 10 TB of memory if we attribute one bit to one spine, because 80% of 100 trillion spines are small (FIG. 3f). Thus, intrinsic dynamics, by giving rise to these skewed distributions (BOX 3), produce extensive capacity for new memory storage. Third, because small spines are close to the pruning boundary, their life expectancies are short, congruent with the short lifetimes of most new memories[168].

Box 2 | **Dendritic spines in autism spectrum disorder**

Individuals with autism spectrum disorder (ASD) show early-onset abnormalities in communication and behaviour and often exhibit epileptic brain activity[19,217]. Although the causes of ASD remain a topic of intense research, a common co-morbidity is intellectual disability. Early studies reported particularly small spine sizes (spine dysgenesis) in the brains of individuals with various intellectual disabilities[172]. In *Fmr1*-knockout mice, a model of fragile X syndrome, which is often associated with ASD, spine dysgenesis is often less obvious (see the figure)[135]. By contrast, rates of spine turnover (genesis and pruning) are strikingly increased (twofold to threefold higher) compared with those in control animals[117,171,218–220]. These increases in spine-turnover rates are not affected by blockade of spikes and NMDA receptors in a fragile X syndrome mouse model[117], suggesting that they reflect exaggerated intrinsic spine dynamics. The fluctuations were directly measured in *Fmr1*-knockout mice, and the amplitudes were larger, in line with higher turnover rates and the smaller spine sizes[135]. This demonstrates that even subtle changes in spine-size distributions might reflect severe impairments in the selection of synapses.

Consistently, proteins crucial for spine structure and function, such as neuroligins, SHANK proteins (SH3 and multiple ankyrin repeat domains proteins; also known as proSAPs), fragile X mental retardation protein (FMRP), methyl-CpG-binding protein 2 (MECP2) and cell adhesion molecules are implicated in ASD[19], in line with the idea that ASD might stem in part from impaired synaptic tenacity[221]. The shorter lifetimes of spines would be expected to give rise to slower acquisition of long-term memory[141,222] and this may manifest itself as spine dysgenesis. Moreover, a compensatory increase in synaptic connections involved in memory functions may contribute to the epilepsy[141] often found in individuals with ASD[217]. Thus, schizophrenia (BOX 1) and ASD may be ascribed to preferential impairments in extrinsic and intrinsic synaptic dynamics, respectively[223] (FIG. 3a).

It is worth emphasizing that mental disorders are not discrete entities, and are better thought of as a spectrum[224]. In particular, owing to diagnostic criteria, many different early-onset communication disorders are often classified as ASD, irrespective of the cause. For example, symptoms related to mutations in plasticity-related molecules such as synaptic RAS GTPase-activating proteins[225] and Ca^{2+}/calmodulin-dependent kinase IIγ[226] are diagnosed as ASD because of their early onset. KO, knockout; WT, wild type. Figure adapted from REF.[135], CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).



Further evidence for this reasoning can be found in the observation that a shift towards small spine sizes in *Shank1*-knockout mice (an animal model of autism spectrum disorder) is associated with enhanced acquisition of working memories and new memories[171]. Strikingly, in these same animals, long-term memory preservation was impaired, in line with the predicted effects of reductions in the levels of SHANK1 (SH3 and multiple ankyrin repeat domains protein 1), a PSD molecule, on intrinsic spine dynamics and synaptic tenacity[116]. Indeed, small spines are prevalent in individuals with autism spectrum disorders[172] (BOX 2). By contrast, the numbers of small spines are reduced in individuals with schizophrenia[173,174], in aged rhesus monkeys[175] and in calcineurin B-knockout mice[123] (BOX 1), all of which tend to exhibit deficits in working memory.

Working memories
Information stored in an accessible state for use in complex mental tasks.

Memory persistence via multisynaptic connections. Intrinsic dynamics may seem to challenge the stability of spine-based memory encoding[79,113]. Their functional consequences, however, might be dampened by connections formed of multiple synapses[113]. More quantitatively, if a connection is based on N synapses, each with a weight of w and variance of σ^2, and given that the intrinsic fluctuations of individual synapses in the connection are uncorrelated[61], the total connection variance will be $N\sigma^2w^2$, as compared with $N^2\sigma^2w^2$ for a single synapse with the weight Nw (BOX 3 figure part b). In this sense, compound connections that are based on multiple (weak) synapses are stabler than connections based on single strong synapses. Moreover, the stability conferred by such compound connections might extend beyond connection strength to connection persistence, as suggested recently[176,177]. Compound synapses (involving two to six synapses) are commonly found among connected cortical neurons[178], seem to occur more than expected by chance[179] and, given spine-size distributions, are likely to be composed primarily of multiple small spines. As might be expected, synapse remodelling within compound connections is partially correlated[126] as are synaptic sizes within such connections[126,179–183]. Notably, new spines formed following task learning are frequently added to existing connections between neurons[136,149,184,185].

The advantage of multiple synapses might also apply for synapses from different presynaptic neurons whose activities are correlated[177]. Along this line, recent studies[186,187] reported the enrichment of synapses receiving inputs from co-active neurons, and the functional predominance of synapse multitude over synapse strength, indicating that populations of co-active synapses might be both very large and functionally important. Thus, N in the aforementioned description might be huge as well. Indirect support may also be found in an estimate of spine numbers affected by motor task learning, which are, as mentioned earlier, in the hundreds of thousands in the motor cortex alone[64].

Memory persistence through reliance on large spines. Large spines, owing to their remoteness from the pruning boundary, are likely to be more persistent. Moreover, it has been speculated that such spines, the heavy tail of spine-size distributions, are particularly important for network function[188–190] (but see REF.[187]). For example, the strongest 25% of connections are responsible for 75% of cortical ocular dominance[191]. This idea faces two challenges, however. First, owing to the positive-feedback nature of Hebbian-like synaptic plasticity, ongoing network activity would lead to runaway activity due to the synaptic strengthening it entails and, consequently, to a non-physiological excess of large synapses[192]. Second, as intrinsic dynamics scale with synaptic size, the largest and most functionally important synapses would also be expected to fluctuate the most. Both challenges might be partially resolved by intrinsic dynamics, however.

Box 3 | **Stochastic models of dendritic spines**

Assuming synaptic weight, w, fluctuates from $w(t)$ to $w(t+\Delta t)$, the fluctuation can be approximated by the normal distribution with a mean (μ) and a standard deviation (SD; σ) (see the figure, part **a**). The general case, in which the mean and SDs are functions of w (rather than constants), gives rise to a stochastic differential equation (SDE)[227]:

$$dw = \mu(w)dt + \sigma(w)dB_t,$$

where B_t is Brownian motion, $\mu(w)dt$ is the drift term and $\sigma(w)dB_t$ is the diffusion term. Note that both μ and σ depend on w (see the figure, parts **b**,**c**).

The dynamics of spines determine the stationary weight distributions, $f(w)$ (see the figure, part **d**). This dependency was explored independently by three groups (colour coded in figure parts **b–d**): dark blue[61], light blue[116,129] and red[134]. As can be seen in parts **b**,**c** of the figure, all studies point to the conclusions below. First, the SD, $\sigma(w)$, is approximately proportional to the spine size, yielding a multiplicative noise term ($\sigma w dB_t$) (part **b** of the figure), which gives rise to skewed and stationary weight distributions (part **d** of the figure). By way of contrast, if this term is constant (as in an Ornstein–Uhlenbeck process (OUP) in part **b** of the figure), the stationary distribution is normal and not skewed (not shown). Second, the drift term, $\mu(w)$, has a negative slope, crossing the w axis at FP (part **c** of the figure), which would be a stable fixed point in the absence of the diffusion term. Because of this drift term, the peak of the distribution is shifted from 0 to the positive weight of about 0.1 μm³, although not exactly at FP. A very similar picture emerges when the dynamics are modelled as a Kesten process, in which size changes are given by a drift term (as in part **c** of the figure, light blue line) with a stochastic slope and offset[129] (also described by an SDE as below)[116]. When the slope is negative, spine distributions are closer to lognormal (quasi-lognormal) distributions than to power-law distributions (the latter having heavier tails; not shown), and spine sizes are constrained to mostly below about 1 μm³ (part **d** of the figure). If the drift term instead has a positive slope (part **c** of the figure, grey line), the Black–Scholes model (used for modelling stock prices in financial markets, for example) emerges, predicting a power-law stationary distribution (not shown)[227]. All these distributions are heavy-tailed; that is, they decay more slowly than do exponential distributions. The three lines in parts **b–d** of the figure are based on theories from REFS[61,116,134]. In parts **b**,**c** of the figure, the theories have been expressed in the standard SDE formalism shown below for comparison. The parameters of the equations have been modified to emphasize similarities of the resulting stationary distributions in part **d** of the figure. The relevant equations are shown below:

Geometric OUP (dark blue): $dw = -(0.1w-0.02)dt+(0.2w+0.01)dB_t$.

Kesten (light blue): $dw = -(0.06w-0.011)dt+\sqrt{0.059w^2+0.0005}\,dB_t$.

Lognormal (red): $dw = -(0.11w+0.08w\,\log w)dt+0.29w dB_t$.

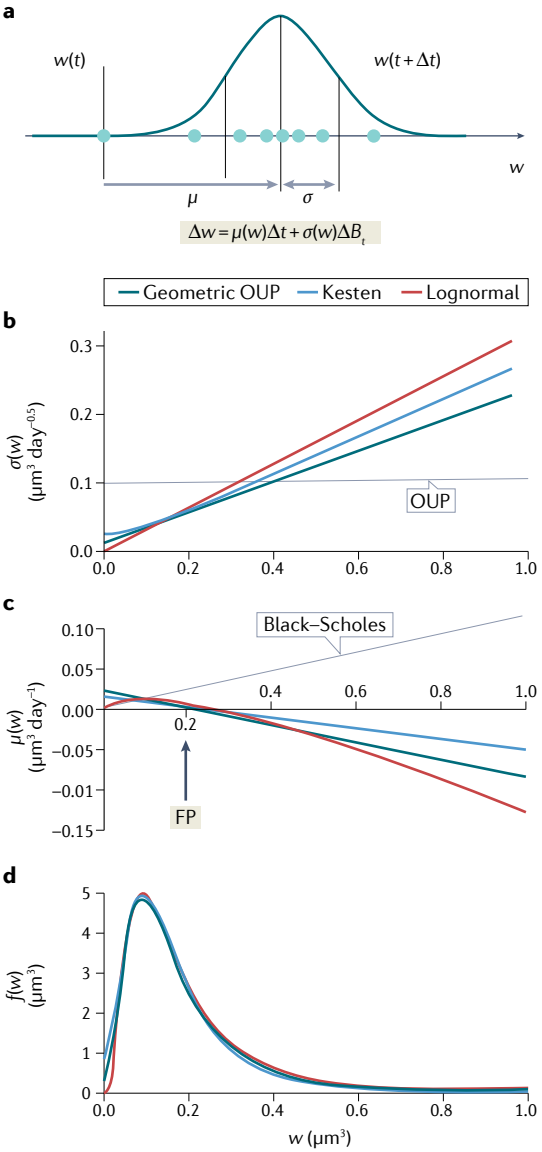


Figure adapted with permission from REF.[116], Society for Neuroscience.

Brownian motion
Random movement of microscopic particles suspended in liquids resulting from the effect of molecules of the surrounding medium.

Ornstein–Uhlenbeck process
A type of stochastic process whose stationary distribution is normal (Gaussian).

Black–Scholes model
The most popular stochastic differential equation in financial economics to estimate the changing value of an option over time.

First, as explained earlier, intrinsic dynamics confine synaptic size distributions, effectively normalizing them and preventing runaway plasticity[116,140,141]. Moreover, the normalization process can adjust these distributions according to global features such as overall activity levels or neuromodulatory tone[113,115,116,129,139]. This normalization process is effective only if extrinsic and intrinsic dynamics accumulate over time to a similar magnitude, irrespective of the kinetics of their elementary processes. Second, under certain assumptions, combined intrinsic and extrinsic dynamics can create a separation point between large and small synapses that minimizes their interconversion[141]. In this model, this division is predicted to manifest itself as a secondary peak in spine-size distributions, particularly in semilogarithmic plots[193] (FIG. 3f), as supported by several studies of synapse ultrastructure[182,194]. These findings hint that the brain might effectively use two 'representative' spine sizes, echoing older suggestions regarding binary synaptic states[195] and the utility of binary synapses in high-performance ANNs[196].

Synapses and learning algorithms

The preceding sections indicate that intrinsic dynamics effectively give rise to a 'self-managing' memory system. Synapses, however, are not merely memory elements or tuneable parameters that change neural network function: they also embody the 'learning algorithms' that drive the tuning, the processes that implement the brain's ability to learn from experience and handle new challenges. Extrinsic dynamics, which can be described as Hebbian learning, RL and three-factor learning, clearly constitute learning algorithms. Here we argue that intrinsic dynamics also give rise to important 'heuristic' learning algorithms that might confer organisms and possibly ANNs as well with significant adaptive properties.

Synaptic weight noise. The importance of synaptic weight 'noise' in the context of ANN training is well established, as explained below. ANNs are typically trained by minimizing a loss function that quantifies their performance. Specifically, in each training step, a change is calculated for each synapse such that in the next step the overall loss (effectively, the difference between the actual result and the desired result) will be lessened and performance will be increased. Consequently, with each step, synaptic weights move 'downhill' along the loss function gradient. In the stochastic gradient descent method[197], the loss function is evaluated using a subset of training samples. Consequently, synaptic weight changes do not strictly follow the gradient (which would be computed using all samples) but fluctuate according to the (randomly chosen) subset. The fluctuations improve learning by allowing synaptic weights to escape 'saddles' of the loss function in which learning slows down owing to shallow gradients[198]. The fluctuations also alleviate overfitting by regularizing networks (that is, imposing more-general solutions by focusing on global features of the loss function)[199]. Moreover, multiplicative weight noise (typical of intrinsic dynamics; BOX 3 figure part b) might further improve learning and generalization by narrowing the synaptic weight search space[200]. Weight noise might also provide a means to prepare for and cope with unforeseen challenges. For example, spine-size fluctuations might be used to sample synaptic weights from the posterior distribution (that is, the probability distribution of synaptic weights to reproduce observed sensory inputs) for Bayesian network inference[201]. Intrinsic dynamics can be combined with RL to obtain a distribution of changes in synaptic weights proportional to the expected reward[202]. More generally, by driving random weight changes and rewiring, intrinsic dynamics might produce new solutions where none existed before, giving rise to the elusive feature known as 'creativity'. Thus viewed, creativity may be considered an emergent feature of trial-and-error rewiring — a brain-specific instantiation of the ubiquitous biological principle of diversification and selection[115].

Continuous network initialization. Intrinsic dynamics mediate the continuous production of small spines and stochastic resetting of their sizes. This continual introduction of randomly weighted synapses into 'trained' networks might be viewed as a form of continual initialization. In this regard, biological networks differ greatly from ANNs, which are initialized once and then trained. This interleaving of initialization and training in the brain might be viewed as a necessary adaptation to a non-stationary world. How this might be done selectively, without impairing previously acquired knowledge or causing catastrophic forgetting[203] is currently an open question (for example, see REFS[204,205]).

Pruning and rewiring. Densely connected ANNs, first initialized and then trained, were recently shown to contain sparsely connected subnetworks comprising less than 10% of the original numbers of connections, referred to as 'winning ticket' (WTk) networks. These WTk subnetworks can be trained faster, perform and generalize better and are more robust to noise than their parent networks[81,206,207]. The biological principles of synaptic generation and rewiring can also be used in discovering such WTk networks[206,207]. WTk networks might be represented in biological networks that show spine formation within overlapping 'capture volumes' (see earlier)[154,155] during development, as well as spreading of spine shrinking (also described earlier) — processes that might find their way into AI as well.

Notably, human brains harness 100 trillion spines, a number generally maintained by balanced spine genesis and pruning. By contrast, contemporary AI networks contain up to 175 billion connections[4] and already require efforts to radically reduce these numbers to less than 10%[81,206,207]. As hardware limitations for AI are mitigated in the future, ANNs will also scale up and may adapt sparse information coding using spikes as in the brain[208,209] for energy efficiency. In such large and distributed networks, pruning can be of central importance. Consequently, using pruning and rewiring for discovering suitable sparse subnetworks within combinatorially huge possibilities will become of paramount importance, as they seem to be in the brain.

Conclusions

Evidently, dendritic spine dynamics are not merely passive manifestations of memory embedding processes: they are complex biological processes that give rise to implicit algorithms at cellular and system levels. Impairments in these processes can result in psychiatric symptoms, such as psychosis, impaired learning and possibly complex syndromes such as autism spectrum disorder. Synaptic dynamics — such as non-local pruning, regulation by inhibitory neurons, dichotomous and multivariate RL, management of memory systems and heuristic algorithms — might also inspire new machine learning algorithms. Our understanding of these dynamics and the algorithms they might give rise to is still primordial and crude, and obtaining a principled understanding is a challenge for the years ahead. Hopefully, such understanding will provide insights into our deep adaptability and creativity, enable future neuro-inspired AI that is more flexible and adaptable, and lay down the necessary groundwork for understanding mental disorders in physiological terms.

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Gradient descent
An optimization algorithm for finding a local minimum of a differentiable function.

Overfitting
The fitting that corresponds too closely to a particular set of data, and may therefore fail to fit additional data or predict future observations reliably.

Search space
The space of all feasible solutions, among which the desired solution resides.

Bayesian network inference
Use of a Bayesian network to estimate the probability that a hypothesis is true based on evidence.

Initialization
The assignment of initial values to parameters, such as synaptic weights in the context of artificial neural networks.

1. Fiala, J. C., Spacek, J. & Harris, K. M. Dendritic spine pathology: cause or consequence of neurological disorders? *Brain Res. Rev.* **39**, 29–54 (2002).
2. Kasai, H., Matsuzaki, M., Noguchi, J., Yasumatsu, N. & Nakahara, H. Structure-stability-function relationships of dendritic spines. *Trends Neurosci.* **26**, 360–368 (2003).
3. Yuste, R. *Dendritic Spines* (MIT Press, 2010).
4. Brown, T. et al. Language models are few-shot learners. *arXiv* https://arxiv.org/abs/2005.14165 (2020).
5. Sejnowski, T. J. The unreasonable effectiveness of deep learning in artificial intelligence. *Proc. Natl Acad. Sci. USA* **117**, 30033–30038 (2020).
6. Coss, R. G., Brandon, J. G. & Globus, A. Changes in morphology of dendritic spines on honeybee calycal interneurons associated with cumulative nursing and foraging experiences. *Brain Res.* **192**, 49–59 (1980).
7. Leiss, F. et al. Characterization of dendritic spines in the Drosophila central nervous system. *Dev. Neurobiol.* **69**, 221–234 (2009).
8. Cuentas-Condori, A. et al. *C. elegans* neurons have functional dendritic spines. *eLife* **8**, e47918 (2019).
9. Malenka, R. C. & Bear, M. F. LTP and LTD: an embarrassment of riches. *Neuron* **44**, 5–21 (2004).
10. Herring, B. E. & Nicoll, R. A. Long-term potentiation: from CaMKII to AMPA receptor trafficking. *Annu. Rev. Physiol.* **78**, 351–365 (2016).
11. Lillicrap, T. P., Santoro, A., Marris, L., Akerman, C. J. & Hinton, G. Backpropagation and the brain. *Nat. Rev. Neurosci.* **21**, 335–346 (2020).
12. Hasson, U., Nastase, S. A. & Goldstein, A. Direct fit to nature: an evolutionary perspective on biological and artificial neural networks. *Neuron* **105**, 416–434 (2020).
13. Botvinick, M., Wang, J. X., Dabney, W., Miller, K. J. & Kurth-Nelson, Z. Deep reinforcement learning and its neuroscientific implications. *Neuron* **107**, 603–616 (2020).
14. Hassabis, D., Kumaran, D., Summerfield, C. & Botvinick, M. Neuroscience-inspired artificial intelligence. *Neuron* **95**, 245–258 (2017).
15. Kasai, H. et al. Learning rules and persistence of dendritic spines. *Eur. J. Neurosci.* **32**, 241–249 (2010).
16. Bosch, M. & Hayashi, Y. Structural plasticity of dendritic spines. *Curr. Opin. Neurobiol.* **22**, 383–388 (2012).
17. Herms, J. & Dorostkar, M. M. Dendritic spine pathology in neurodegenerative diseases. *Annu. Rev. Pathol.* **11**, 221–250 (2016).
18. Yasuda, R. Biophysics of biochemical signaling in dendritic spines: implications in synaptic plasticity. *Biophys. J.* **113**, 2152–2159 (2017).
19. Forrest, M. P., Parnell, E. & Penzes, P. Dendritic structural plasticity and neuropsychiatric disease. *Nat. Rev. Neurosci.* **19**, 215–234 (2018).
20. Moyer, C. E. & Zuo, Y. Cortical dendritic spine development and plasticity: insights from in vivo imaging. *Curr. Opin. Neurobiol.* **53**, 76–82 (2018).
21. Okabe, S. Regulation of actin dynamics in dendritic spines: nanostructure, molecular mobility, and signaling mechanisms. *Mol. Cell. Neurosci.* **109**, 103564 (2020).
22. Matsuzaki, M. et al. Dendritic spine geometry is critical for AMPA receptor expression in hippocampal CA1 pyramidal neurons. *Nat. Neurosci.* **4**, 1086–1092 (2001).
23. Beique, J. C. et al. Synapse-specific regulation of AMPA receptor function by PSD-95. *Proc. Natl Acad. Sci. USA* **103**, 19535–19540 (2006).
24. Harris, K. M. & Stevens, J. K. Dendritic spines of CA 1 pyramidal cells in the rat hippocampus: serial electron microscopy with reference to their biophysical characteristics. *J. Neurosci.* **9**, 2982–2997 (1989).
25. Nusser, Z. et al. Cell type and pathway dependence of synaptic AMPA receptor number and variability in the hippocampus. *Neuron* **21**, 545–559 (1998).
26. Takumi, Y., Ramirez-Leon, V., Laake, P., Rinvik, E. & Ottersen, O. P. Different modes of expression of AMPA and NMDA receptors in hippocampal synapses. *Nat. Neurosci.* **2**, 618–624 (1999).
27. Holler, S., Kostinger, G., Martin, K. A. C., Schuhknecht, G. F. P. & Stratford, K. J. Structure and function of a neocortical synapse. *Nature* **591**, 111–116 (2021).
28. Matsuzaki, M., Honkura, N., Ellis-Davies, G. C. & Kasai, H. Structural basis of long-term potentiation in single dendritic spines. *Nature* **429**, 761–766 (2004).
29. Markram, H., Lubke, J., Frotscher, M. & Sakmann, B. Regulation of synaptic efficacy by coincidence of postsynaptic APs and EPSPs. *Science* **275**, 213–215 (1997).
30. Magee, J. C. J. D. A synaptically controlled, associative signal for Hebbian plasticity in hippocampal neurons. *Science* **275**, 209–213 (1997).
31. Dan, Y. & Poo, M. M. Spike timing-dependent plasticity: from synapse to perception. *Physiol. Rev.* **86**, 1033–1048 (2006).
32. Harvey, C. D. & Svoboda, K. Locally dynamic synaptic learning rules in pyramidal neuron dendrites. *Nature* **450**, 1195–1200 (2007).
33. Tanaka, J. et al. Protein synthesis and neurotrophin-dependent structural plasticity of single dendritic spines. *Science* **319**, 1683–1687 (2008).
34. Yagishita, S. et al. A critical time window for dopamine actions on the structural plasticity of dendritic spines. *Science* **345**, 1616–1620 (2014).
35. Takao, K. et al. Visualization of synaptic Ca^{2+}/calmodulin-dependent protein kinase II activity in living neurons. *J. Neurosci.* **25**, 3107–3112 (2005).
36. Okamoto, K., Narayanan, R., Lee, S. H., Murata, K. & Hayashi, Y. The role of CaMKII as an F-actin-bundling protein crucial for maintenance of dendritic spine structure. *Proc. Natl Acad. Sci. USA* **104**, 6418–6423 (2007).
37. Lee, S. J., Escobedo-Lozoya, Y., Szatmari, E. M. & Yasuda, R. Activation of CaMKII in single dendritic spines during long-term potentiation. *Nature* **458**, 299–304 (2009).
38. Pi, H. J. et al. CaMKII control of spine size and synaptic strength: role of phosphorylation states and nonenzymatic action. *Proc. Natl Acad. Sci. USA* **107**, 14437–14442 (2010).
39. Chang, J. Y. et al. CaMKII autophosphorylation is necessary for optimal integration of Ca^{2+} signals during LTP induction, but not maintenance. *Neuron* **94**, 800–808 e804 (2017).
40. Murakoshi, H., Wang, H. & Yasuda, R. Local, persistent activation of Rho GTPases during plasticity of single dendritic spines. *Nature* **472**, 100–104 (2011).
41. Hedrick, N. G. et al. Rho GTPase complementation underlies BDNF-dependent homo- and heterosynaptic plasticity. *Nature* **538**, 104–108 (2016).
42. Krucker, T., Siggins, G. R. & Halpain, S. Dynamic actin filaments are required for stable long-term potentiation (LTP) in area CA1 of the hippocampus. *Proc. Natl Acad. Sci. USA* **97**, 6856–6861 (2000).
43. Okamoto, K., Nagai, T., Miyawaki, A. & Hayashi, Y. Rapid and persistent modulation of actin dynamics regulates postsynaptic reorganization underlying bidirectional plasticity. *Nat. Neurosci.* **7**, 1104–1112 (2004).
44. Honkura, N., Matsuzaki, M., Noguchi, J., Ellis-Davies, G. C. & Kasai, H. The subspine organization of actin fibers regulates the structure and plasticity of dendritic spines. *Neuron* **57**, 719–729 (2008).
45. Kim, K. et al. A temporary gating of actin remodeling during synaptic plasticity consists of the interplay between the kinase and structural functions of CaMKII. *Neuron* **87**, 813–826 (2015).
46. Okabe, S., Urushido, T., Konno, D., Okado, H. & Sobue, K. Rapid redistribution of the postsynaptic density protein PSD-Zip45 (Homer 1c) and its differential regulation by NMDA receptors and calcium channels. *J. Neurosci.* **21**, 9561–9571 (2001).
47. Gray, N. W., Weimer, R. M., Bureau, I. & Svoboda, K. Rapid redistribution of synaptic PSD-95 in the neocortex in vivo. *PLoS Biol.* **4**, e370 (2006).
48. Noguchi, J. et al. State-dependent diffusion of actin-depolymerizing factor/cofilin underlies the enlargement and shrinkage of dendritic spines. *Sci. Rep.* **6**, 32897 (2016).
49. Tsuriel, S. et al. Local sharing as a predominant determinant of synaptic matrix molecular dynamics. *PLoS Biol.* **4**, e271 (2006).
50. Saneyoshi, T. et al. Reciprocal activation within a kinase-effector complex underlying persistence of structural LTP. *Neuron* **102**, 1199–1210 (2019).
51. Pellegrin, S. & Mellor, H. Actin stress fibres. *J. Cell Sci.* **120**, 3491–3499 (2007).
52. Kassianidou, E. & Kumar, S. A biomechanical perspective on stress fiber structure and function. *Biochim. Biophys. Acta* **1853**, 3065–3074 (2015).
53. Shirao, T. et al. The role of drebrin in neurons. *J. Neurochem.* **141**, 819–834 (2017).
54. Park, Y. K. & Goda, Y. Integrins in synapse regulation. *Nat. Rev. Neurosci.* **17**, 745–756 (2016).
55. Bamburg, J. R. & Wiggan, O. P. ADF/cofilin and actin dynamics in disease. *Trends Cell Biol.* **12**, 598–605 (2002).
56. Rex, C. S. et al. Myosin IIb regulates actin dynamics during synaptic plasticity and memory formation. *Neuron* **67**, 603–617 (2010).
57. Kim, I. H. et al. Disruption of Arp2/3 results in asymmetric structural plasticity of dendritic spines and progressive synaptic and behavioral abnormalities. *J. Neurosci.* **33**, 6081–6092 (2013).
58. Hayama, T. et al. GABA promotes the competitive selection of dendritic spines by controlling local Ca2+ signaling. *Nat. Neurosci.* **16**, 1409–1416 (2013).
59. Bosch, M. et al. Structural and molecular remodeling of dendritic spine substructures during long-term potentiation. *Neuron* **82**, 444–459 (2014).
60. Yang, G., Pan, F. & Gan, W. B. Stably maintained dendritic spines are associated with lifelong memories. *Nature* **462**, 920–924 (2009).
61. Yasumatsu, N., Matsuzaki, M., Miyazaki, T., Noguchi, J. & Kasai, H. Principles of long-term dynamics of dendritic spines. *J. Neurosci.* **28**, 13592–13608 (2008).
62. Noguchi, J. et al. Bidirectional in vivo structural dendritic spine plasticity revealed by two-photon glutamate uncaging in the mouse neocortex. *Sci. Rep.* **9**, 13922 (2019).
63. Fusi, S., Drew, P. J. & Abbott, L. F. Cascade models of synaptically stored memories. *Neuron* **45**, 599–611 (2005).
64. Hayashi-Takagi, A. et al. Labelling and optical erasure of synaptic memory traces in the motor cortex. *Nature* **525**, 333–338 (2015).
65. Oh, W. C., Hill, T. C. & Zito, K. Synapse-specific and size-dependent mechanisms of spine structural plasticity accompanying synaptic weakening. *Proc. Natl Acad. Sci. USA* **110**, E305–E312 (2013).
66. Wiegert, J. S. & Oertner, T. G. Long-term depression triggers the selective elimination of weakly integrated synapses. *Proc. Natl Acad. Sci. USA* **110**, E4510–E4519 (2013).
67. Abraham, W. C. & Goddard, G. V. Asymmetric relationships between homosynaptic long-term potentiation and heterosynaptic long-term depression. *Nature* **305**, 717–719 (1983).
68. Wang, S. S., Khiroug, L. & Augustine, G. J. Quantification of spread of cerebellar long-term depression with chemical two-photon uncaging of glutamate. *Proc. Natl Acad. Sci. USA* **97**, 8635–8640 (2000).
69. Nishiyama, M., Togashi, K., Aihara, T. & Hong, K. GABAergic activities control spike timing- and frequency-dependent long-term depression at hippocampal excitatory synapses. *Front. Synaptic Neurosci.* **2**, 22 (2010).
70. Fujii, H. et al. Nonlinear decoding and asymmetric representation of neuronal input information by CaMKIIalpha and calcineurin. *Cell Rep.* **3**, 978–987 (2013).
71. Zhou, Q., Homma, K. J. & Poo, M. M. Shrinkage of dendritic spines associated with long-term depression of hippocampal synapses. *Neuron* **44**, 749–757 (2004).
72. Bernstein, B. W. & Bamburg, J. R. ADF/cofilin: a functional node in cell biology. *Trends Cell Biol.* **20**, 187–195 (2010).
73. Stein, I. S., Park, D. K., Flores, J. C., Jahncke, J. N. & Zito, K. Molecular mechanisms of non-ionotropic NMDA receptor signaling in dendritic spine shrinkage. *J. Neurosci.* **40**, 3741–3750 (2020).
74. Dore, K. & Malinow, R. Elevated PSD-95 blocks ion-flux independent LTD: a potential new role for PSD-95 in synaptic plasticity. *Neuroscience* **456**, 43–49 (2021).
75. Ziv, N. E. & Fisher-Lavie, A. Presynaptic and postsynaptic scaffolds: dynamics fast and slow. *Neuroscientist* **20**, 439–452 (2014).
76. Toyoizumi, T., Pfister, J. P., Aihara, K. & Gerstner, W. Generalized Bienenstock–Cooper–Munro rule for spiking neurons that maximizes information transmission. *Proc. Natl Acad. Sci. USA* **102**, 5239–5244 (2005).
77. Kusmierz, L., Isomura, T. & Toyoizumi, T. Learning with three factors: modulating Hebbian plasticity with errors. *Curr. Opin. Neurobiol.* **46**, 170–177 (2017).
78. Whittington, J. C. R. & Bogacz, R. Theories of error back-propagation in the brain. *Trends Cognit. Sci.* **23**, 235–250 (2019).
79. Mongillo, G., Rumpel, S. & Loewenstein, Y. Inhibitory connectivity defines the realm of excitatory plasticity. *Nat. Neurosci.* **21**, 1463–1470 (2018).
80. Hensch, T. K. Critical period plasticity in local cortical circuits. *Nat. Rev. Neurosci.* **6**, 877–888 (2005).
81. Frankle, J. & Carbin, M. The lottery ticket hypothesis: finding sparse, trainable neural networks. *arXiv* https://arxiv.org/abs/1803.03635 (2019).

82. Sutton, R., Barto, A. *Reinforcement Learning, Second Edition: an Introduction* (Bradford Books, 2018).
83. Thorndike, E. L. *Animal Intelligence* (Macmillan, 1911).
84. Schultz, W., Dayan, P. & Montague, P. R. A neural substrate of prediction and reward. *Science* **275**, 1593–1599 (1997).
85. Reynolds, J. N., Hyland, B. I. & Wickens, J. R. A cellular mechanism of reward-related learning. *Nature* **413**, 67–70 (2001).
86. Gershman, S. J. & Uchida, N. Believing in dopamine. *Nat. Rev. Neurosci.* **20**, 703–714 (2019).
87. Soares-Cunha, C., Coimbra, B., Sousa, N. & Rodrigues, A. J. Reappraising striatal D1- and D2-neurons in reward and aversion. *Neurosci. Biobehav. Rev.* **68**, 370–386 (2016).
88. Luscher, C., Robbins, T. W. & Everitt, B. J. The transition to compulsion in addiction. *Nat. Rev. Neurosci.* **21**, 247–263 (2020).
89. Marder, E. Neuromodulation of neuronal circuits: back to the future. *Neuron* **76**, 1–11 (2012).
90. Izhikevich, E. M. Solving the distal reward problem through linkage of STDP and dopamine signaling. *Cereb. Cortex* **17**, 2443–2452 (2007).
91. Shen, W., Flajolet, M., Greengard, P. & Surmeier, D. J. Dichotomous dopaminergic control of striatal synaptic plasticity. *Science* **321**, 848–851 (2008).
92. Abrams, T. W. & Kandel, E. R. Is contiguity detection in classical conditioning a system or a cellular property? Learning in aplysia suggests a possible molecular site. *Trends Neurosci.* **11**, 128–135 (1988).
93. Urakubo, H., Yagishita, S., Kasai, H. & Ishii, S. Signaling models for dopamine-dependent temporal contiguity in striatal synaptic plasticity. *PLoS Comput. Biol.* **16**, e1008078 (2020).
94. He, K. et al. Distinct eligibility traces for LTP and LTD in cortical synapses. *Neuron* **88**, 528–538 (2015).
95. Ferguson, G. D. & Storm, D. R. Why calcium-stimulated adenylyl cyclases? *Physiology* **19**, 271–276 (2004).
96. Yamaguchi, K. M. Y. et al. The minimal behavioral time window for reward c 1 onditioning in the nucleus accumbens of mice. Preprint at *bioRxiv* https://doi.org/10.1101/641365 (2019).
97. Kapur, S. How antipsychotics become anti-"psychotic"–from dopamine to salience to psychosis. *Trends Pharmacol. Sci.* **25**, 402–406 (2004).
98. Winton-Brown, T. T., Fusar-Poli, P., Ungless, M. A. & Howes, O. D. Dopaminergic basis of salience dysregulation in psychosis. *Trends Neurosci.* **37**, 85–94 (2014).
99. Matsumoto, M. & Hikosaka, O. Two types of dopamine neuron distinctly convey positive and negative motivational signals. *Nature* **459**, 837–841 (2009).
100. Cohen, J. Y., Haesler, S., Vong, L., Lowell, B. B. & Uchida, N. Neuron-type-specific signals for reward and punishment in the ventral tegmental area. *Nature* **482**, 85–88 (2012).
101. Gerfen, C. R. & Surmeier, D. J. Modulation of striatal projection systems by dopamine. *Annu. Rev. Neurosci.* **34**, 441–466 (2011).
102. Kalivas, P. W. Deconstructing and reconstructing the dichotomy that is dopamine receptor-1- and dopamine receptor-2-expressing neurons. *Biol. Psychiatry* **84**, 862–864 (2018).
103. Iino, Y. et al. Dopamine D2 receptors in discrimination learning and spine enlargement. *Nature* **579**, 555–560 (2020).
104. Lee, S. J. et al. Cell-type-specific asynchronous modulation of PKA by dopamine in learning. *Nature* **590**, 451–456 (2021).
105. Waelti, P., Dickinson, A. & Schultz, W. Dopamine responses comply with basic assumptions of formal learning theory. *Nature* **412**, 43–48 (2001).
106. Nagai, T. et al. Phosphoproteomics of the dopamine pathway enables discovery of Rap1 activation as a reward signal in vivo. *Neuron* **89**, 550–565 (2016).
107. Mikhael, J. G. & Bogacz, R. Learning reward uncertainty in the basal ganglia. *PLoS Comput. Biol.* **12**, e1005062 (2016).
108. Fujita, Y., Yagishita, S., Kasai, H. & Ishii, S. Computational characteristics of the striatal dopamine system described by reinforcement learning with fast generalization. *Front. Comput. Neurosci.* **14**, 66 (2020).
109. Coddington, L. T. & Dudman, J. T. Learning from action: reconsidering movement signaling in midbrain dopamine neuron activity. *Neuron* **104**, 63–77 (2019).
110. Collins, A. L. & Saunders, B. T. Heterogeneity in striatal dopamine circuits: Form and function in dynamic reward seeking. *J. Neurosci. Res.* **98**, 1046–1069 (2020).
111. Gerstner, W., Lehmann, M., Liakoni, V., Corneil, D. & Brea, J. Eligibility traces and plasticity on behavioral time scales: experimental support of neoHebbian three-factor learning rules. *Front. Neural Circuits* **12**, 53 (2018).
112. Mongillo, G., Rumpel, S. & Loewenstein, Y. Intrinsic volatility of synaptic connections — a challenge to the synaptic trace theory of memory. *Curr. Opin. Neurobiol.* **46**, 7–13 (2017).
113. Ziv, N. E. & Brenner, N. Synaptic tenacity or lack thereof: spontaneous remodeling of synapses. *Trends Neurosci.* **41**, 89–99 (2018).
114. Cane, M., Maco, B., Knott, G. & Holtmaat, A. The relationship between PSD-95 clustering and spine stability in vivo. *J. Neurosci.* **34**, 2075–2086 (2014).
115. Minerbi, A. et al. Long-term relationships between synaptic tenacity, synaptic remodeling, and network activity. *PLoS Biol.* **7**, e1000136 (2009).
116. Hazan, L. & Ziv, N. E. Activity dependent and independent determinants of synaptic size diversity. *J. Neurosci.* **40**, 2828–2848 (2020).
117. Nagaoka, A. et al. Abnormal intrinsic dynamics of dendritic spines in a fragile X syndrome mouse model in vivo. *Sci. Rep.* **6**, 26651 (2016).
118. Sigler, A. et al. Formation and maintenance of functional spines in the absence of presynaptic glutamate release. *Neuron* **94**, 304–311 e304 (2017).
119. Sando, R. et al. Assembly of excitatory synapses in the absence of glutamatergic neurotransmission. *Neuron* **94**, 312–321 e313 (2017).
120. Robison, A. J. Emerging role of CaMKII in neuropsychiatric disease. *Trends Neurosci.* **37**, 653–662 (2014).
121. Zeng, H. et al. Forebrain-specific calcineurin knockout selectively impairs bidirectional synaptic plasticity and working/episodic-like memory. *Cell* **107**, 617–629 (2001).
122. Seaton, G. et al. Dual-component structural plasticity mediated by alphaCaMKII autophosphorylation on basal dendrites of cortical layer 2/3 neurones. *J. Neurosci.* **40**, 2228–2245 (2020).
123. Okazaki, H. et al. Calcineurin knockout mice show a selective loss of small spines. *Neurosci. Lett.* **671**, 99–102 (2018).
124. Benavides-Piccione, R., Ballesteros-Yanez, I., DeFelipe, J. & Yuste, R. Cortical area and species differences in dendritic spine morphology. *J. Neurocytol.* **31**, 337–346 (2002).
125. Montero-Crespo, M. et al. Three-dimensional synaptic organization of the human hippocampal CA1 field. *eLife* **9**, e57013 (2020).
126. Dvorkin, R. & Ziv, N. E. Relative contributions of specific activity histories and spontaneous processes to size remodeling of glutamatergic synapses. *PLoS Biol.* **14**, e1002572 (2016).
127. Fischer, M., Kaech, S., Knutti, D. & Matus, A. Rapid actin-based plasticity in dendritic spines. *Neuron* **20**, 847–854 (1998).
128. Choquet, D. & Triller, A. The dynamic synapse. *Neuron* **80**, 691–703 (2013).
129. Statman, A., Kaufman, M., Minerbi, A., Ziv, N. E. & Brenner, N. Synaptic size dynamics as an effectively stochastic process. *PLoS Comput. Biol.* **10**, e1003846 (2014).
130. Shomar, A., Geyrhofer, L., Ziv, N. E. & Brenner, N. Cooperative stochastic binding and unbinding explain synaptic size dynamics and statistics. *PLoS Comput. Biol.* **13**, e1005668 (2017).
131. Cohen, L. D. & Ziv, N. E. Neuronal and synaptic protein lifetimes. *Curr. Opin. Neurobiol.* **57**, 9–16 (2019).
132. Vainchtein, I. D. & Molofsky, A. V. Astrocytes and microglia: in sickness and in health. *Trends Neurosci.* **43**, 144–154 (2020).
133. Rubinski, A. & Ziv, N. E. Remodeling and tenacity of inhibitory synapses: relationships with network activity and neighboring excitatory synapses. *PLoS Comput. Biol.* **11**, e1004632 (2015).
134. Loewenstein, Y., Kuras, A. & Rumpel, S. Multiplicative dynamics underlie the emergence of the log-normal distribution of spine sizes in the neocortex in vivo. *J. Neurosci.* **31**, 9481–9488 (2011).
135. Ishii, K. et al. In vivo volume dynamics of dendritic spines in the neocortex of wild-type and Fmr1 KO mice. *eNeuro* **5**, 0282–18 (2018).
136. Knott, G. W., Holtmaat, A., Wilbrecht, L., Welker, E. & Svoboda, K. Spine growth precedes synapse formation in the adult neocortex in vivo. *Nat. Neurosci.* **9**, 1117–1124 (2006).
137. Quinn, D. P. et al. The stability of glutamatergic synapses is independent of activity level, but predicted by synapse size. *Front. Cell. Neurosci.* **13**, https://doi.org/10.3389/fncel.2019.00291 (2019).
138. van Rossum, M. C., Bi, G. Q. & Turrigiano, G. G. Stable Hebbian learning from spike timing-dependent plasticity. *J. Neurosci.* **20**, 8812–8821 (2000).
139. Kaufman, M., Corner, M. A. & Ziv, N. E. Long-term relationships between cholinergic tone, synchronous bursting and synaptic remodeling. *PLoS ONE* **7**, e40980 (2012).
140. Matsubara, T. U. K. Homeostatic plasticity achieved by incorporation of random fluctuations and soft-bounded Hebbian plasticity in excitatory synapses. *Front. Neurosci.* https://doi.org/10.3389/fncir.2016.00042 (2016).
141. Humble, J., Hiratsuka, K., Kasai, H. & Toyoizumi, T. Intrinsic spine dynamics are critical for recurrent network learning in models with and without autism spectrum disorder. *Front. Comput. Neurosci.* **13**, 38 (2019).
142. Holtmaat, A. J. et al. Transient and persistent dendritic spines in the neocortex in vivo. *Neuron* **45**, 279–291 (2005).
143. Loewenstein, Y., Yanover, U. & Rumpel, S. Predicting the dynamics of network connectivity in the neocortex. *J. Neurosci.* **35**, 12535–12544 (2015).
144. Pfeiffer, T. et al. Chronic 2P-STED imaging reveals high turnover of dendritic spines in the hippocampus in vivo. *eLife* **7**, e34700 (2018).
145. Berry, K. P. & Nedivi, E. Spine dynamics: are they all the same? *Neuron* **96**, 43–55 (2017).
146. Attardo, A., Fitzgerald, J. E. & Schnitzer, M. J. Impermanence of dendritic spines in live adult CA1 hippocampus. *Nature* **523**, 592–596 (2015).
147. Trachtenberg, J. T. et al. Long-term in vivo imaging of experience-dependent synaptic plasticity in adult cortex. *Nature* **420**, 788–794 (2002).
148. Xu, T. et al. Rapid formation and selective stabilization of synapses for enduring motor memories. *Nature* **462**, 915–919 (2009).
149. Yang, G. et al. Sleep promotes branch-specific formation of dendritic spines after learning. *Science* **344**, 1173–1178 (2014).
150. Yang, S., Santos, M. D., Tang, C. M., Kim, J. G. & Yang, S. A postsynaptic role for short-term neuronal facilitation in dendritic spines. *Front. Cell. Neurosci.* **10**, 224 (2016).
151. Fiala, J. C., Feinberg, M., Popov, V. & Harris, K. M. Synaptogenesis via dendritic filopodia in developing hippocampal area CA1. *J. Neurosci.* **18**, 8900–8911 (1998).
152. Konur, S. & Yuste, R. Imaging the motility of dendritic protrusions and axon terminals: roles in axon sampling and synaptic competition. *Mol. Cell. Neurosci.* **27**, 427–440 (2004).
153. Zito, K., Scheuss, V., Knott, G., Hill, T. & Svoboda, K. Rapid functional maturation of nascent dendritic spines. *Neuron* **61**, 247–258 (2009).
154. Ziv, N. E. & Smith, S. J. Evidence for a role of dendritic filopodia in synaptogenesis and spine formation. *Neuron* **17**, 91–102 (1996).
155. Mishchenko, Y. et al. Ultrastructural analysis of hippocampal neuropil from the connectomics perspective. *Neuron* **67**, 1009–1020 (2010).
156. Stepanyants, A., Hof, P. R. & Chklovskii, D. B. Geometry and structural plasticity of synaptic connectivity. *Neuron* **34**, 275–288 (2002).
157. Shepherd, G. M., Stepanyants, A., Bureau, I., Chklovskii, D. & Svoboda, K. Geometric and functional organization of cortical circuits. *Nat. Neurosci.* **8**, 782–790 (2005).
158. Kaiser, M., Hilgetag, C. C. & van Ooyen, A. A simple rule for axon outgrowth and synaptic competition generates realistic connection lengths and filling fractions. *Cereb. Cortex* **19**, 3001–3010 (2009).
159. Matsumoto-Miyai, K. et al. Coincident pre- and postsynaptic activation induces dendritic filopodia via neurotrypsin-dependent agrin cleavage. *Cell* **136**, 1161–1171 (2009).
160. Andreae, L. C. & Burrone, J. The role of neuronal activity and transmitter release on synapse formation. *Curr. Opin. Neurobiol.* **27**, 47–52 (2014).
161. Srivastava, D. P. et al. Rapid enhancement of two-step wiring plasticity by estrogen and NMDA receptor activity. *Proc. Natl Acad. Sci. USA* **105**, 14650–14655 (2008).
162. Liston, C. & Gan, W. B. Glucocorticoids are critical regulators of dendritic spine development and plasticity in vivo. *Proc. Natl Acad. Sci. USA* **108**, 16074–16079 (2011).
163. Liston, C. et al. Circadian glucocorticoid oscillations promote learning-dependent synapse formation and maintenance. *Nat. Neurosci.* **16**, 698–705 (2013).

164. Murakami, G. et al. Rapid nongenomic modulation by neurosteroids of dendritic spines in the hippocampus: androgen, oestrogen and corticosteroid. *J. Neuroendocrinol.* **30**, e12561 (2018).
165. Moda-Sava, R. N. et al. Sustained rescue of prefrontal circuit dysfunction by antidepressant-induced spine formation. *Science* **364**, eaat8078 (2019).
166. Schatzle, P. et al. Rapid and reversible formation of spine head filopodia in response to muscarinic receptor activation in CA1 pyramidal cells. *J. Physiol.* **589**, 4353–4364 (2011).
167. Walker, C. K. & Herskowitz, J. H. Dendritic spines: mediators of cognitive resilience in aging and Alzheimer's disease. *Neuroscientist* https://doi.org/10.1177/1073858420945964 (2020).
168. Wixted, J. T. The psychology and neuroscience of forgetting. *Annu. Rev. Psychol.* **55**, 235–269 (2004).
169. Ebbinghaus, H. *Uber das Gedachtnis* (Dunker & Humbolt, 1885).
170. Bourne, J. & Harris, K. M. Do thin spines learn to be mushroom spines that remember? *Curr. Opin. Neurobiol.* **17**, 381–386 (2007).
171. Hung, A. Y. et al. Smaller dendritic spines, weaker synaptic transmission, but enhanced spatial learning in mice lacking Shank1. *J. Neurosci.* **28**, 1697–1708 (2008).
172. Purpura, D. P. Dendritic spine "dysgenesis" and mental retardation. *Science* **186**, 1126–1128 (1974).
173. MacDonald, M. L. et al. Selective loss of smaller spines in schizophrenia. *Am. J. Psychiatry* **174**, 586–594 (2017).
174. McKinney, B. C. et al. Density of small dendritic spines and microtubule-associated-protein-2 immunoreactivity in the primary auditory cortex of subjects with schizophrenia. *Neuropsychopharmacology* **44**, 1055–1061 (2019).
175. Young, M. E., Ohm, D. T., Dumitriu, D., Rapp, P. R. & Morrison, J. H. Differential effects of aging on dendritic spines in visual cortex and prefrontal cortex of the rhesus monkey. *Neuroscience* **274**, 33–43 (2014).
176. Fauth, M., Worgotter, F. & Tetzlaff, C. Formation and maintenance of robust long-term information storage in the presence of synaptic turnover. *PLoS Comput. Biol.* **11**, e1004684 (2015).
177. Deger, M., Seeholzer, A. & Gerstner, W. Multicontact co-operativity in spike-timing-dependent structural plasticity stabilizes networks. *Cereb. Cortex* **28**, 1396–1415 (2018).
178. Branco, T. & Staras, K. The probability of neurotransmitter release: variability and feedback control at single synapses. *Nat. Rev. Neurosci.* **10**, 373–383 (2009).
179. Kasthuri, N. et al. Saturated reconstruction of a volume of neocortex. *Cell* **162**, 648–661 (2015).
180. Bartol, T. M. et al. Nanoconnectomic upper bound on the variability of synaptic plasticity. *eLife* **4**, e10778 (2015).
181. Bloss, E. B. et al. Single excitatory axons form clustered synapses onto CA1 pyramidal cell dendrites. *Nat. Neurosci.* **21**, 353–363 (2018).
182. Dorkenwald, S. T. et al. Binary and analog variation of synapses between cortical pyramidal neurons. Preprint at *bioRxiv* https://doi.org/10.1101/2019.12.29.890319 (2019).
183. Motta, A. et al. Dense connectomic reconstruction in layer 4 of the somatosensory cortex. *Science* **366**, aay3134 (2019).
184. Lee, K. J. et al. Motor skill training induces coordinated strengthening and weakening between neighboring synapses. *J. Neurosci.* **33**, 9794–9799 (2013).
185. Yang, Y. et al. Selective synaptic remodeling of amygdalocortical connections associated with fear memory. *Nat. Neurosci.* **19**, 1348–1355 (2016).
186. Choi, J. H. et al. Interregional synaptic maps among engram cells underlie memory formation. *Science* **360**, 430–435 (2018).
187. Scholl, B., Thomas, C. I., Ryan, M. A., Kamasawa, N. & Fitzpatrick, D. Cortical response selectivity derives from strength in numbers of synapses. *Nature* **590**, 111–114 (2021).
188. Ikegaya, Y. et al. Interpyramid spike transmission stabilizes the sparseness of recurrent network activity. *Cereb. Cortex* **23**, 293–304 (2013).
189. Chen, W., Hobbs, J. P., Tang, A. & Beggs, J. M. A few strong connections: optimizing information retention in neuronal avalanches. *BMC Neurosci.* **11**, 3 (2010).
190. Kusmierz, L., Ogawa, S. & Toyoizumi, T. Edge of chaos and avalanches in neural networks with heavy-tailed synaptic weight distribution. *Phys. Rev. Lett.* **125**, 028101 (2020).
191. Cossell, L. et al. Functional organization of excitatory synaptic strength in primary visual cortex. *Nature* **518**, 399–403 (2015).
192. Keck, T. et al. Integrating Hebbian and homeostatic plasticity: the current state of the field and future research directions. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* **372**, https://doi.org/10.1098/rstb.2016.0158 (2017).
193. Shimizu, G., Yoshida, K., Kasai, H. & Toyoizumi, T. Computational roles of intrinsic synaptic dynamics. Preprint at *bioRxiv* https://doi.org/10.1101/2021.04.22.441034 (2021).
194. Spano, G. M. et al. Sleep deprivation by exposure to novel objects increases synapse density and axon-spine interface in the hippocampal CA1 region of adolescent mice. *J. Neurosci.* **39**, 6613–6625 (2019).
195. Petersen, C. C., Malenka, R. C., Nicoll, R. A. & Hopfield, J. J. All-or-none potentiation at CA3-CA1 synapses. *Proc. Natl Acad. Sci. USA* **95**, 4732–4737 (1998).
196. Courbariaux, M. H., Hubara, I., Soudry, D., El-Yaniv, R. & Bengio, Y. Binarized neural networks: training deep neural networks with weights and activations constrained to +1 or -1. *arXiv* https://arxiv.org/abs/1602.02830 (2016).
197. Bottou, L. Large-scale machine learning with stochastic gradient descent. in *Proceedings of COMPSTAT'2010* (eds Lechevallier, Y., & Saporta, G.) 177-186 (Physica-Verlag, 2010).
198. Ge, R., Huang, F., Jin, C. & Yuan, Y. Escaping from saddle points – online stochastic gradient for tensor decomposition. *JMLR:WCP* **40**, 1–46 (2015).
199. Wan, L., Zeiler, M., Zhang, S., LeCun, Y. & Fergus, R. Regularization of neural networks using DropConnect. *JMLR:WCP* **28**, 1058–1066 (2013).
200. HaoChen, J. Z., Wei, C., Lee, J. & Ma, T. Shape matters: understanding the implicit bias of the noise covariance. *arXiv* https://arxiv.org/abs/2006.08680 (2020).
201. Kappel, D., Habenschuss, S., Legenstein, R. & Maass, W. Network plasticity as Bayesian inference. *PLoS Comput. Biol.* **11**, e1004485 (2015).
202. Kappel, D., Legenstein, R., Habenschuss, S., Hsieh, M. & Maass, W. A dynamic connectome supports the emergence of stable computational function of neural circuits through reward-based learning. *eNeuro* https://doi.org/10.1523/ENEURO.0301-17.2018 (2018).
203. French, R. M. Catastrophic forgetting in connectionist networks. *Trends Cognit. Sci.* **3**, 128–135 (1999).
204. Kirkpatrick, J. et al. Overcoming catastrophic forgetting in neural networks. *Proc. Natl Acad. Sci. USA* **114**, 3521–3526 (2017).
205. Zenke, F., Poode, B. & Ganguli, S. Continual learning through synaptic intelligence. *International Conference on Machine Learning* https://arxiv.org/abs/1703.04200 (2017).
206. Bellec, G., Kappel, D., Maass, W. & Legenstein, R. Deep rewiring: training very sparse deep networks. *ICLR* https://arxiv.org/abs/1711.05136 (2018).
207. Ding, X. D. G., Zhou, X., Guo, Y., Han, J. & Liu, J. Global sparse momentum SGD for pruning very deep neural networks. *NIPS* **32**, 8867 (2019).
208. Esser, S. K. et al. Convolutional networks for fast, energy-efficient neuromorphic computing. *Proc. Natl Acad. Sci. USA* **113**, 11441–11446 (2016).
209. Cao, Y., Chen, Y. & Khosla, D. Spiking deep convolutional neural networks for energy-efficient object recognition. *Int. J. Computer Vis.* **113**, 54–66 (2014).
210. Holtmaat, A., Wilbrecht, L., Knott, G. W., Welker, E. & Svoboda, K. Experience-dependent and cell-type-specific spine growth in the neocortex. *Nature* **441**, 979–983 (2006).
211. de Vivo, L. et al. Ultrastructural evidence for synaptic scaling across the wake/sleep cycle. *Science* **355**, 507–510 (2017).
212. Owen, M. J., Sawa, A. & Mortensen, P. B. Schizophrenia. *Lancet* **388**, 86–97 (2016).
213. Collins, A. G., Brown, J. K., Gold, J. M., Waltz, J. A. & Frank, M. J. Working memory contributions to reinforcement learning impairments in schizophrenia. *J. Neurosci.* **34**, 13747–13756 (2014).
214. Hayashi-Takagi, A. et al. PAKs inhibitors ameliorate schizophrenia-associated dendritic spine deterioration in vitro and in vivo during late adolescence. *Proc. Natl Acad. Sci. USA* **111**, 6461–6466 (2014).
215. Miyakawa, T. et al. Conditional calcineurin knockout mice exhibit multiple abnormal behaviors related to schizophrenia. *Proc. Natl Acad. Sci. USA* **100**, 8987–8992 (2003).
216. McCutcheon, R. A., Abi-Dargham, A. & Howes, O. D. Schizophrenia, dopamine and the striatum: from biology to symptoms. *Trends Neurosci.* **42**, 205–220 (2019).
217. Lin, Y. C., Frei, J. A., Kilander, M. B., Shen, W. & Blatt, G. J. A subset of autism-associated genes regulate the structural stability of neurons. *Front. Cell. Neurosci.* **10**, 263 (2016).
218. Pan, F., Aldridge, G. M., Greenough, W. T. & Gan, W. B. Dendritic spine instability and insensitivity to modulation by sensory experience in a mouse model of fragile X syndrome. *Proc. Natl Acad. Sci. USA* **107**, 17768–17773 (2010).
219. Jiang, M. et al. Dendritic arborization and spine dynamics are abnormal in the mouse model of MECP2 duplication syndrome. *J. Neurosci.* **33**, 19518–19533 (2013).
220. Isshiki, M. et al. Enhanced synapse remodelling as a common phenotype in mouse models of autism. *Nat. Commun.* **5**, 4742 (2014).
221. Zeidan, A. & Ziv, N. E. Neuroligin-1 loss is associated with reduced tenacity of excitatory synapses. *PLoS ONE* **7**, e42314 (2012).
222. Padmashri, R., Reiner, B. C., Suresh, A., Spartz, E. & Dunaevsky, A. Altered structural and functional synaptic plasticity with motor skill learning in a mouse model of fragile X syndrome. *J. Neurosci.* **33**, 19715–19723 (2013).
223. Kasai, H., Fukuda, M., Watanabe, S., Hayashi-Takagi, A. & Noguchi, J. Structural dynamics of dendritic spines in memory and cognition. *Trends Neurosci.* **33**, 121–129 (2010).
224. Adam, D. Mental health: on the spectrum. *Nature* **496**, 416–418 (2013).
225. Gamache, T. R., Araki, Y. & Huganir, R. L. Twenty years of SynGAP research: from synapses to cognition. *J. Neurosci.* **40**, 1596–1605 (2020).
226. Cohen, S. M. et al. Excitation-transcription coupling in parvalbumin-positive interneurons employs a novel CaM kinase-dependent pathway distinct from excitatory neurons. *Neuron* **90**, 292–307 (2016).
227. Tuckwell, H. C. *Introduction to Theoretical Neurobiology, vol. 2* (Cambridge University Press, 1988).

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All authors researched data for the article, contributed substantially to discussions concerning its contents and reviewed and/or edited the manuscript before submission. H.K., N.E.Z. and T.T. wrote the article.

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