Cognitive dysfunction in psychiatric disorders: characteristics, causes and the quest for improved therapy

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Abstract | Studies of psychiatric disorders have traditionally focused on emotional symptoms such as depression, anxiety and hallucinations. However, poorly controlled cognitive deficits are equally prominent and severely compromise quality of life, including social and professional integration. Consequently, intensive efforts are being made to characterize the cellular and cerebral circuits underpinning cognitive function, define the nature and causes of cognitive impairment in psychiatric disorders and identify more effective treatments. Successful development will depend on rigorous validation in animal models as well as in patients, including measures of real-world cognitive functioning. This article critically discusses these issues, highlighting the challenges and opportunities for improving cognition in individuals suffering from psychiatric disorders.

Cognition
A suite of interrelated conscious (and unconscious) mental activities, including: pre-attentional sensory gating; attention; learning and memory; problem solving, planning, reasoning and judgment; understanding, knowing and representing; creativity, intuition and insight; 'spontaneous' thought; introspection; as well as mental time travel, self-awareness and meta-cognition (thinking and knowledge about cognition).

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Historically, philosophers have subdivided the study of the human mind and behaviour into two broad categories: the cognitive (how we know the world) and the affective (how we feel about it). This division is, however, arbitrary as cognition — a highly complex construct (FIG. 1) — and emotion interact; cognitive status can colour the processing of emotions, and changes in mood affect cognitive function[1,2].

It is therefore surprising that changes in emotion are universally recognized as being inherent to psychiatric disorders and their classification, whereas cognitive impairment — which has an equally disabling effect on patients — has been comparatively neglected. Despite this close interrelationship between cognition and mood, the cognitive deficits of psychiatric disorders are not just a secondary consequence of perturbed affect, and their underlying neurobiological substrates differ. Although certain symptoms of psychiatric disorders — such as depression, delusions and anxiety — are alleviated by current drugs, cognitive deficits are not usually improved, and may even be worsened[3,4]. Cognitive dysfunction is, therefore, a poorly controlled and highly relevant dimension of psychiatric disorders that cuts across traditional diagnostic boundaries, and improved treatment should be a major goal in efforts to enhance quality of life for patients.

Cognitive dysfunction in psychiatric disorders

Challenges of defining and characterizing cognitive deficits. Alzheimer's disease is characterized by poor learning and memory, Parkinson's disease by motor impairment, depression by melancholy, and schizophrenia by delusions; however, these and related diagnoses are also accompanied by a range of symptoms involving alterations in mood, motor behaviour, appetite, sleep, diurnal rhythms and, most pertinently, cognitive function. For example, psychosis is common in Alzheimer's disease, depression can be just as debilitating as motor deficits in Parkinson's disease, and perturbed cognition is a characteristic of both psychiatric and neurological disorders (TABLE 1).

Defining the precise nature of changes in cognition is challenging. Specificity relative to generalized changes in overall intelligence remains under discussion, in

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Learning
The active, experience- and/or training-driven acquisition of information or behaviour. The term 'conditioning' is usually used in an experimental context of associative learning. Learning necessitates complementary and distinct processes of encoding and acquisition that can be perturbed and modulated independently.

Memory
Partly separate mechanisms permitting consolidation, retention and retrieval of information from various sensory domains. Short-term memory relates to immediately available information maintained for ~30 seconds. Information retained for longer periods must be consolidated into mechanistically different long-term memory; in principle, this relates to the unlimited (in quantity and in time) capacity to store information.

particular for schizophrenia and autism spectrum disorders (ASDs), in which development is abnormal[5–8]. Furthermore, the precise interrelationship between alterations in cognition and changes in mood, reward, motor performance and effort can be difficult to establish[9,10]. Finally, apart from treatment, various other factors modify cognitive performance and its measurement in a patient- and disorder-dependent fashion, including: education and age; hormonal status; disease progression; co-morbidity (psychiatric and somatic); whether cognitive function is determined in crisis or in remission; motivation; the neuropsychological test used and practice effects; and the means of quantification (self-rating, semi-quantitative scales or informant assessment)[6,7,11]. Similarities and differences between various disorders are clearly complex — and still being delineated — but several general patterns can be discerned.

Contrasting patterns of cognitive deficits among distinct psychiatric disorders. Cognitive dysfunction does not just signify poor memory — the range of cognitive impairment is broader and more complex (TABLE 1). There are conditions in which a failure to forget or 'inhibit' is a characteristic symptom: for example, intrusive thoughts in obsessive compulsive disorder (OCD)[12] and recurrent, unwanted recall (flashbacks) in post-traumatic stress disorder (PTSD)[13,14]. The latter state represents a form of 'hyper-memory' resulting from defective processes of fear extinction — an active process for suppressing negative emotional memories — rather than just the decay of the mechanisms involved in storage and recall[14,15] (FIG. 2). Phobias and social anxiety disorder are likewise typified by blunted fear extinction[16,17]. Comparatively little cognitive disturbance has been documented for generalized anxiety disorder, despite some subtle changes and a negative cognitive bias to threatening stimuli[16,17] (TABLE 1). Cognitive dysfunction in panic disorders is mainly confined to excessive attention and hyperreactivity to threatening — but not emotionally neutral — stimuli. Interestingly, processing speed may actually be accelerated in panic disorders[16,18]. Schizophrenia is characterized by a broad pattern of cognitive deficits, from attention and working memory to social cognition and language[7,19–22] (BOX 1). Impairments in bipolar disorder, which shares certain genetic risk factors with schizophrenia (Supplementary information S1 (figure)), are similar but generally less severe[19,23,24] (TABLE 1).

Cognitive impairment is not traditionally associated with depression but it is common, broad-based and often debilitating[4,19,25,26]. Poor performance in certain tasks reflects reduced reward, low motivation and/or an incapacity for sustained effort — possibly owing to disruption of limbic dopaminergic signalling[4,10]. This does not, however, provide a satisfactory explanation for overall cognitive impairment. For example, the bias of patients suffering from depression towards affectively negative — and even ambiguous — stimuli (such as facial expressions) involves diminished top-down fronto-cortical cognitive control of emotional processing[2,27].

Deficits in attention deficit hyperactivity disorder (ADHD) are not restricted to attention; they affect several other cognitive domains, including an interrelated impairment in working memory and processing speed[28,29]. Among the deficits characterizing OCD, impairment of procedural learning is of particular note[12,30]. Finally, although disrupted social cognition is a cardinal symptom of ASD, several other domains are also affected[9,31,32] (TABLE 1).

Changes in specific cognitive domains seen across distinct diagnoses. Determining which cognitive domains are affected in diagnostically discrete disorders is complicated by co-morbidity. Nonetheless, certain cognitive domains can be perturbed in several distinct disorders (TABLE 1).

Most conspicuously, attention is affected in all disorders, varying from a cardinal loss of focused attention in ADHD[28] to hypervigilance to threatening stimuli in PTSD, panic disorder and even OCD[12,13,16–18] (TABLE 1). In ASD, attention to people and their emotions — as well as joint attention with others — is blunted; furthermore, attention towards objects and details is enhanced, while disregarding global aspects (central coherence)[8,31].

Perturbed executive function is an additional example of transnosological deficits; however, reflecting their contrasting integration (FIG. 2), subdimensions are affected

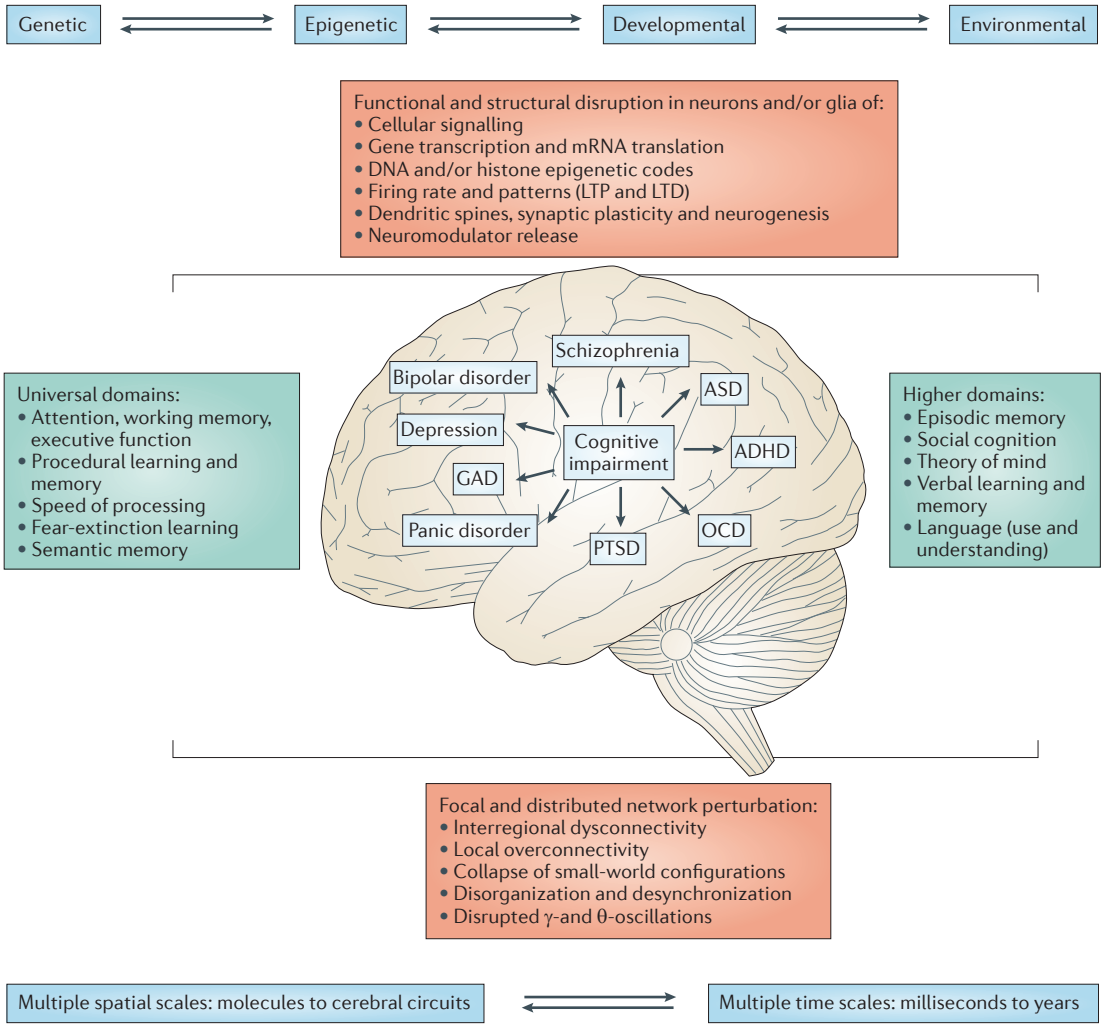

Figure 1 | **A global view of cognition and its disruption in psychiatric disorders.** Psychiatric disorders are associated with complex and disease-specific patterns of cognitive impairment (TABLE 1). Certain domains may be considered to be 'higher' in terms of their specialized and sophisticated nature. They are all well represented in humans compared with rodents, and some are prominent both in great apes and — reflecting evolutionary convergence — in higher birds, cetaceans and elephants (Supplementary information S3 (box); Supplementary information S5 (box)). Disruption of cognition is provoked — and countered — by various interacting genetic, epigenetic, developmental and environmental factors. Changes are expressed both at the level of neurons and glia (from altered gene transcription to shifts in neuronal firing) and at the level of neural networks (locally and among interlinked cerebral regions). Dysfunction underlying cognitive impairment is hierarchically and spatially diverse, and enacted over a temporal scale running from milliseconds (for example, cellular firing) to hours (for example, protein synthesis) to years (for example, synaptic architecture). Some susceptibility factors, such as germline and epigenetic factors, can be passed on to offspring. Certain causes of cognitive impairment can be rectified or compensated, but network shifts at the molecular to systems level are not necessarily reversible so prevention and early treatment is crucial. ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder: GAD, generalized anxiety disorder; LTD, long-term depression; LTP, long-term potentiation; OCD, obsessive compulsive disorder; PTSD, post-traumatic stress disorder.

Extinction
The progressive reduction of a response to a stimulus — for example, owing to discontinuation of reinforcement or loss of association between an unconditioned and conditioned stimulus. Extinction does not just refer to forgetting (a loss or weakening of memory) or 'un-learning' (a decay of the processes involved in retention and recall); rather, it refers to a special form of learning that involves active processes of suppression. The extinguished response may reappear following a change of context or exposure to stress.

Attention
The awareness and attendance to a stimulus or set of stimuli. It depends on the perception, selection and filtering of sensory input and information. Sustained attention (vigilance) is the capacity to maintain attention over an extended period. Selective (focused) attention is the ability to preferentially attend to a subset of stimuli, thus avoiding distraction. Divided attention is the capacity to respond to multiple stimuli simultaneously, and may involve executive shifts in focused attention according to the demands of the situation.

Processing speed
The rapidity with which a cognitive operation is undertaken successfully. Although this is usually related to the speed of information processing, it may also apply to the speed of retrieval. Processing speed affects performance in many tasks and is operationally related to reaction time.

Working memory
Permits the transient 'online' evaluation, manipulation and synthesis of newly acquired and/or stored information. Working memory operates in short-term memory but the two terms are not synonymous. Working memory is closely interrelated to, and interacts with, attention and executive function.

differently. Children with ADHD have a poor sense of planning[28]; autistic individuals are inflexible[8,31,32]; individuals suffering from depression have problems with decision-making and initiating actions[16,26]; patients with OCD or bipolar disorder display difficulties with response inhibition[12,23]; and patients with schizophrenia have generalized deficits in all these aspects[6,7,22]. Declarative memory is also affected in psychiatric disorders. Of its two basic forms, deficits in semantic memory are mainly restricted to schizophrenia, whereas impairment of episodic memory is common to several disorders as well as schizophrenia[9,13,22–24,31] (TABLE 1).

A severe disruption in social cognition, including an impaired theory of mind (BOX 1) and empathy, is prototypical for ASD[8,31,32], and deficient social cognition is also seen in bipolar disorder[24], major depression[25], ADHD[29] and OCD[30]. In schizophrenia, faulty social cognition is a crucial issue: first, it predicts conversion to full psychosis

Table 1 | **Main characteristics of cognitive impairment in psychiatric disorders, and a comparison with PD and AD***

	Attention and/or vigilance	Working memory	Executive function	Episodic memory	Semantic memory	Visual memory	Verbal memory	Fear extinction	Processing speed	Procedural memory	Social cognition (theory of mind)	Language	References
Major depression	+(+)	++	++	++	+	+	+(+)	0/+?	++(+)	+	+(+)	+	2,16,19,25,26,36
Bipolar disorder	++(+)	++	++	++	+	+	++	+?	++	0	++	++	19,23,24,37
Schizophrenia	+++ ^{M}	+++^{M}	+++^{M}	+++	++	+(+)^{M}	+++^{M}	++	++^{M}	+	+++^{M}	+++	6,9,19–22
ASD	+++	+	+++	++	+	+	+(+)	+(+)	+ ++	0/+	+++	+++	8,31,32
ADHD	+++	++	+++	0/+	+	++	++	+	++	+	+	0/+	28,29
OCD	+++(↑)	+(+)	++	+	0/+	+	0/+	++	++	++	+	0/+	12,30
PTSD	+++(↑)	+(+)	+(+)	++	+	+	++(+)	+++	+	0	0/+	0	14,16
Panic disorder	+++(↑)	+	0/+	+	0/+	0/+	+	++	++	0	0	0	16,18
GAD	+	+	0	0	+	+	+	+	0	0	0/+	0	16,17
Parkinson's disease	++	++(+)	++	+	0/+	+	+	0?	+++	+++	+(+)	+(+)	-
Alzheimer's disease	+(+)	+(+)	+(+)	+++	+++	+++	++(+)	0?	+	+	+	++	-

0, essentially absent; 0/+, poorly documented, ambiguous, mild and/or variable; +, consistently present but not pronounced; ++, a common, marked characteristic; +++, a core, severe and virtually universal characteristic of the disorder; ?, not clearly evaluated; ↑, increase; AD, Alzheimer's disease; ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; GAD, generalized anxiety disorder; OCD, obsessive compulsive disorder; PD, Parkinson's disease; PTSD, post-traumatic stress disorder; *Cognitive deficits in the absence of treatment are depicted. 'M' indicates a cognitive domain specified in the MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) programme (BOX 2), in which episodic and semantic memories are subsumed under 'visual or verbal learning and memory'. Social cognition encompasses theory of mind. In rare cases (such as Savant syndrome), autistic individuals display a remarkable increase in declarative memory and processing speed for selected domains of interest. ADHD observations refer to the young; similar symptoms usually persist into adulthood. Individuals with OCD, PTSD and panic disorders show hypervigilance to threatening (intrusive) stimuli, which can disrupt performance of goal-directed tasks. For AD, observations are for a modest degree of progression. Brackets around '+' symbols indicate an intermediate magnitude of deficit: for example, '+(+)' indicates between '+' and '++'.

Top-down cortical cognitive control
Related to executive function. Refers to cortically integrated (in the prefrontal cortex, cingulate cortex and parietal cortex) top-down processes that favour goal-directed behaviours by flexibly investing resources (such as sustained attention) that are needed for goal accomplishment. It also involves the suppression of interference from irrelevant information, habitual actions, negative emotions, and so on.

Procedural learning
The progressive assimilation (learnt association between a stimulus and a response), by practice, of an appropriate behaviour generally involving a motor skill, such as driving a car, which may become an automatic habit. It is closely related to non-declarative (implicit) memory — a form of long-term memory that involves non-conscious recollection of skills, behaviours, habits and preferences such as cycling or one's favourite colour.

in high-risk, asymptomatic individuals; second, the consequent social withdrawal exacerbates negative symptoms; and third, false attribution to others of harmful intentions aggravates paranoia and delusions[9,20] (positive symptoms). Although most studies of the theory of mind have focused on 'other' minds, the inability of patients suffering from psychosis and autism to grasp their 'own' minds is a major source of distress. Social cognition is related to social learning (from others), shared intentionality (BOX 1) and collective cognition (collaborative problem solving)[33], which may also be impaired in ASD and schizophrenia[8,9,20,31]. Finally, social cognition must be intact to appropriately decode verbal language[34,35] (BOX 1), which is also compromised in psychiatric disorders. Delayed verbal language acquisition as well as impaired prosody and pragmatics are inherent to ASD[8,31], whereas disorganization of language, perturbed verbal fluency and a poor grasp of semantics are core features of schizophrenia[9,21,22].

Cognitive dysfunction is broad-based and seriously affects real-world functioning. Several conclusions may be drawn from the above discussion. First, cognitive deficits are common in psychiatric disorders, and multiple domains are usually affected: this complicates the task of discovering effective treatments. Second, for certain disorders, impairments in social cognition and language are core features, yet such deficits are very hard to model experimentally. Third, assuming that similar mechanisms are involved, a drug that improves executive function, for example, could be active across several disorders in which this domain is impaired.

Given the panoply of cognitive deficits in schizophrenia, their deleterious effect on patients' quality of life is not surprising[9,22] (BOX 2), and cognitive dysfunction limits the professional and social options of autistic individuals[8,31]. In depression, cognitive impairment is persistent and strongly related to disability, with recovery inversely correlated with the severity of deficits. Even in ostensibly remitted patients, residual cognitive impairment compromises real-world functioning and socioprofessional efficacy[4,36]. Cognitive deficits are prominent in even the euthymic phase of bipolar disorder, and persistance during remission predicts poor long-term recovery[24,37]. Finally, the debilitating cognitive deficits observed in ADHD often continue into adulthood[28].

Given the clear need for improved treatment of cognitive dysfunction in psychiatric disorders, considerable efforts are being made to better understand the cerebral substrates of cognition, and to determine how their disruption leads to cognitive impairment in psychiatric disorders. These issues are discussed below.

Basis of cognitive impairment in disease

Cerebral circuits and cellular cascades controlling cognition. Cognition can be best understood in terms of complex networks operating over multiple temporal scales and incorporating diverse dimensions: from cellular

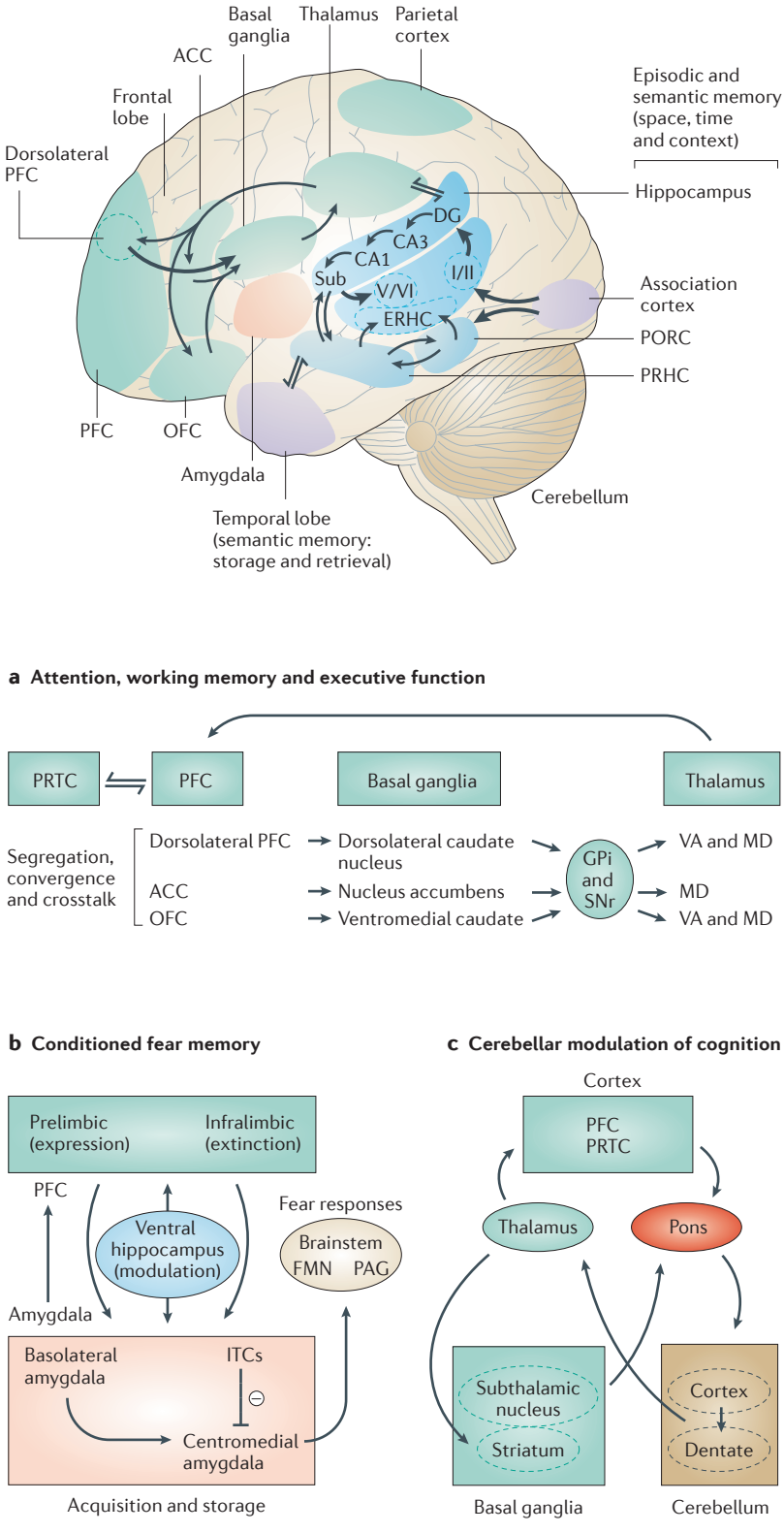

Figure 2 | **Schematic representation of major cerebral circuits underpinning core cognitive domains that are disrupted in psychiatric disorders.** Although individual cerebral structures fulfill distinctive roles in the control of core cognitive domains, they operate as coordinated and overlapping networks. **a** | The frontal lobe, basal ganglia and thalamus comprise loops that integrate attention, working memory and executive function[239]. The dorsolateral prefrontal cortex (PFC), anterior cingulate cortex (ACC) and orbitofrontal cortex (OFC) differentially contribute to programming and planning, decision-making and response inhibition, respectively[41,239]. Accordingly, they project to contrasting zones of the basal ganglia: the dorsolateral PFC projects to the dorsolateral caudate nucleus, the ACC projects to the nucleus accumbens and the OFC projects to the ventromedial caudate. Medium spiny neurons in these regions in turn converge onto the internal globus pallidus (GPi) and the substantia nigra pars reticulata (SNr), from which pathways diverge to the ventral anterior (VA) and medial dorsal (MD) thalamic nuclei[239]. The basal ganglia are also important for procedural learning and memory. The PFC is linked to the parietal cortex (PRTC), which exerts a modulatory influence on attention and working memory. Furthermore, the PFC and parietal cortex form the core of a circuit underpinning intelligence[240], and both structures exert a top-down modulatory influence (not shown) on subcortical regions. These include the hippocampal formation (the hippocampus and the entorhinal cortex (ERHC)) and the parahippocampus (the perirhinal cortex (PRHC) and the postrhinal cortex (PORC))[241]; see main panel. Hippocampal territories are themselves interconnected via several circuits: the perforant pathway projects from the superficial ERHC to the dentate gyrus (DG); Schaffer collaterals project from the DG to CA3 pyramidal neurons, and mossy fibres project from CA3 pyramidal neurons to CA1 pyramidal neurons[241]. The subiculum (Sub) is the major source of hippocampal output. The hippocampal formation integrates dimensions of space, time and context, and is crucial for declarative learning and memory, although long-term memory may be progressively transferred to regions such as the temporal lobes, PRTC and PFC[154,155,241]. **b** | The basolateral amygdala has a key role in conditioned fear learning and extinction[15,106]. It excites the centromedial amygdala, which in turn projects to the brainstem, periaqueductal grey (PAG) and facial motor nucleus (FMN), where fear responses are expressed. Conditioned stimuli also affect the PFC, which fulfils a dual role: its prelimbic division facilitates the expression of fear memories, whereas its infralimbic division promotes their extinction by recruiting inhibitory GABA (γ-aminobutyric acid)-ergic intercalated cells (ITCs)[15]. A context-dependent influence on fear learning and extinction is exerted by the ventral hippocampus, and by both the OFC and the MD thalamic nuclei, via the PFC (not shown)[15]. **c** | The cerebellum modulates cognition by reciprocal interconnections — mainly via the thalamus and the pons — with the basal ganglia and the cortex[242]. 'I/II' and 'V/VI' refer to layers of the entorhinal cortex.

cascades to cerebral circuits and, ultimately, society (FIG. 1). As shown in FIG. 2 and FIG. 3, specific domains such as executive function and social cognition are integrated across broad suites of interlinked and overlapping cerebral regions. Moreover, a diverse palette of neuromodulators — including acetylcholine[38], cytokines[39] and brain-derived neurotrophic factor (BDNF)[40] — influence cognitive performance. For example, the prefrontal cortex (PFC) and hippocampus receive a rich cholinergic input and are also heavily innervated by serotonergic, dopaminergic,

Box 1 | **Social cognition, theory of mind and verbal language**

Social cognition refers to processes that are used to acquire and interpret information about others, such as their character, intentions and behaviour. It necessitates: awareness, analysis, choice, sharing and/or avoidance of gaze, recognition of faces, interpretation of facial expressions, as well as scrutiny of head, whole-body and body-part motion[34,35,212,213]. Social cognition also refers to the understanding (and use) of the rules and concepts governing social interactions by means of gestures, etiquette, touch and proximity (personal space). Social cognition embraces the theory of mind (also known as mental attribution), which is the ability — partly by self-reflection — to infer and internally represent the mental states of others, and hence to attribute and interpret desires, beliefs, intentions and thoughts as determinants and predictors of behaviour[20,34,212,214].Cultural context can modify social cognition[214], which is indispensable for the full decoding and use of verbal language, especially prosody and pragmatics[34,35]. Reciprocally, language influences thoughts and feelings related to social cognition[215].

Both social cognition and language are disrupted in psychiatric disorders (TABLE 1), and the occurrence of autism spectrum disorder and schizophrenia in humans may be evolutionarily linked to selection for complex social cognition, verbal language, creativity, large brains, an expanded prefrontal cortex and cerebral asymmetry[9,20,21,35,216]. Sophisticated social cognition is seen in eusocial insects, cetaceans (Supplementary information S3 (box)), some rodents (Supplementary information S4 (box)), great apes, elephants and higher birds[102,217–219] (Supplementary information S5 (box)). However, the theory of mind in its fullest expression may be unique to humans, and its unequivocal demonstration in animals is therefore challenging[102,214,218]. Furthermore, although animals communicate in a sophisticated manner, they lack certain features of human language, such as genuine syntax, full recursion (an infinite palette of meanings generated from a finite set of elements or words) and meta-linguistics (thinking and talking about language)[35,103]. Hence, it is impossible to fully mimic human language in animals, and to adequately model its disruption in psychiatric disorders. Nonetheless, insights might be gained by studying the communicative role of vocal ultrasonic[220], olfactory[221] and tactile[222] exchanges in rodents and other species, and from both the learning of innate songs and the 'open-ended' use of verbal exchanges in birds[102,103] (Supplementary information S5 (box)).

Executive function
A purposeful, goal-directed operation such as planning, decision making, problem solving, reasoning, concept formation, self-monitoring or cognitive flexibility (adaptive alternation between different strategies, responses and behaviours). Executive function reciprocally interacts with attention and working memory. It includes both initiation of appropriate and suppression of inappropriate responses.

Declarative memory
A form of long-term memory that demands conscious learning. It is divided into episodic and semantic memory.

Semantic memory
A form of long-term memory that involves the learning and storing of immutable facts, information, ideas, and so on. In contrast to episodic memory, semantic memory cannot — in principle — be modified by questions and alternative accounts.

noradrenergic and histaminergic neurons. Like the amygdala, these key structures contain dense populations of GABA (γ-aminobutyric acid)-ergic interneurons and they communicate with each other — as well as with other territories controlling cognitive function — via glutamatergic projections[4,41,42] (FIG. 2).

Pharmacotherapy does not target cerebral circuits per se; rather, it targets G protein-coupled receptors (GPCRs), ion channels, transporters and other proteins involved in the actions of neuromodulators. These molecular substrates of cognition[43] constitute a vast repertoire of potential drug targets for countering cognitive impairment in psychiatric disorders (as discussed below). Mirroring the interlinking of cerebral regions controlling cognition, there is an intricate web of cross-talk among the cellular mediators influencing cognitive processes (Supplementary information S1,S2 (figures)) (FIG. 4), such as the core substrates of neuroplasticity, learning and memory, long-term potentiation (LTP) and long-term depression (LTD)[44,45] (BOX 3).

Finally, representing a level of integration that is intermediate between cells and cerebral circuits, neurons do not generally act in isolation; rather, they operate as synchronized and rhythmically active assemblies to encode, transmit and modulate information underpinning cognitive function[46,47] (BOX 4).

Disruption of cerebral networks as a cause of cognitive impairment. Networks that modulate cognition display considerable redundancy and pleiotropy at all levels of integration: from intracellular signals, to neurons, to cerebral nuclei[4,48,49]. The disruption of many elements (known as nodes) can be compensated by others with similar roles; in addition, each element itself has multiple functions (Supplementary information S2 (figure)) (FIG. 4). This organization affords considerable resilience to disruption[4,48,49]. However, the failure of functionally important, highly connected nodes (known as 'hubs') has a disruptive effect. For example, a dysfunction in NMDA (*N*-methyl-D-aspartate) receptors (at the cellular level) and a disruption in frontocortical GABAergic interneurons (at the circuit level) is implicated in the cognitive defects observed in schizophrenia[42,50].

Furthermore, multiple 'hits' to networks, such as a combination of genetic and developmental or environmental factors, are particularly hazardous. For example, when superimposed on a vulnerable genetic background, maternal infection or cannabis use during adolescence increases the risk of schizophrenia and cognitive impairment[7,11,51,52]. Importantly, certain changes in networks (known as phase shifts) may be irreversible, such as the aberrant developmental pruning of neurons in schizophrenia[7,42,49,53]. These network-related concepts can be formally handled by graph theory, which is useful for analysing the perturbation of cognitive circuits in psychiatric disorders[4,48,49]. For example, information-processing and cognitive performance are enhanced by the small-world features of circuits, which means that key structures are often directly linked to each other, rather than by intervening regions. This network attribute is compromised in schizophrenia and ASD[4,48,49].

Cognitive deficits observed in schizophrenia have long been ascribed to reduced activation of the dorsolateral PFC (known as hypofrontality) but many cortical and subcortical structures are also affected, with a complex pattern of region-dependent hypo- or hyperactivation[9,53–55]; increased activity may reflect an attempt to compensate for insufficient performance. Thus, it is arguably more pertinent to consider schizophrenia as a disconnection syndrome[55]. For example, a disturbance of frontocortical–striatal–thalamic loops (FIG. 2), together with impaired top-down cognitive control from the cortex, contributes to deficits in attention, working memory and executive function[54,55]. Furthermore, impaired verbal learning and language in schizophrenia can be related to diminished connectivity between the temporal–parietal zone (Wernicke's area) and frontal lobes (FIG. 3), as well as reduced left hemisphere lateralization of Broca's area and functionally related regions[56].

Altered laterality in language-processing regions is also apparent in ASD[57]. Altered structure and function of the corpus callosum has been reported in ASD. Although its generality is unclear, a large-scale disconnection among circuits such as frontostriatal, frontotemporal and prefrontal–parietal pathways is a consistent finding[58,59]. Interruption of coupling to the cerebellum has also been reported, together with a disruption of the corticolimbic circuits mediating social and emotional

Box 2 | **The MATRICS initiative**

The recognition that poorly treated cognitive deficits contribute to poor functional outcome in schizophrenia led to the establishment of the 'MATRICS' (Measurement and Treatment Research to Improve Cognition in Schizophrenia) initiative, which was sponsored by the National Institute of Mental Health (NIMH) in collaboration with the US Food and Drug Administration, academia and industry. The MATRICS initiative had three aims: first, to build a consensus regarding the nature of cognitive impairment in schizophrenia; second, to improve the evaluation of cognitive deficits; and third, to provide a framework for the formal recognition of treatments that specifically address the cognitive deficits associated with schizophrenia independently of an improvement in psychosis[6,69,98,178,179,223].

After identifying the cognitive domains that best characterized schizophrenia (TABLE 1), the MATRICS initiative devised a neuropsychological consensus cognitive battery to support the discovery, clinical assessment and registration of new agents[6,178,179]. Subsequently, the NIMH funded the selection of potential cognition-enhancing agents and set up a group of academic sites to evaluate their efficacy in proof-of-concept trials. Several compounds tested to date (including a $GABA_A$ (γ-aminobutyric acid type A) receptor α2 subunit agonist and a dopamine D1 receptor agonist) have not proven to be clearly efficacious (TABLE 2), despite having solid conceptual and preclinical support; this highlights the uncertain predictive utility of cognitive tests in animals[98,223]. Hence, another programme, titled 'CNTRICS' (Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia), was established[6,179] to build a consensus on two issues: first, the development of new, more reliable and practical translational paradigms for preclinical and early clinical assessment of drug effects on cognitive processes; and second, the development of imaging biomarkers for parallel use in cognitive trials. Particular efforts are being devoted to a more rigorous evaluation of the impact of therapies on real-world function in patients[180,181].

Episodic memory
The conscious recollection of experiences linked to times and places in the past — what happened, where and when. It may involve mental time-travel back into a situation (known as autobiographical re-experiencing), mirrored by projection into an imagined future (prospective envisioning). As such, it is related to the theory of mind ('travel into' or simulation of other minds). Fully-fledged episodic memory may be a uniquely human trait, but there is evidence for its presence in primates, corvids and even some rodents.

Prosody
The use (and interpretation) of features such as stress, intonation and rhythm that lend additional meaning and emotion to speech.

Pragmatics
The appropriate social use of spoken language.

Verbal fluency
The ability to use written and spoken language, to choose the right word at the right time and to make appropriate associations.

processing[58,59]. Some cortical regions may be more strongly linked, and — at least developmentally — local overconnection (that is, excess neurons and increased dendritic spine density) also exemplifies the brain of autistic individuals[59].

Somewhat reminiscent of ASD, poor attention in ADHD is related to a disruption of frontostriatal circuits, and networks interlinking temporal and parietal cortices with the cerebellum are also affected[60]. Although perturbed connectivity of the orbitofrontal cortex and subcortical regions has been consistently related to poor inhibitory control and reduced flexibility in OCD, both increases and decreases in connectivity have been observed depending on the experimental conditions[61]. Finally, PTSD is triggered by exposure to acute and intense stressors that disrupt PFC–amygdala connectivity, resulting in diminished fear-extinction learning[14,15] (FIG. 2). Conversely, the accompanying hypervigilance reflects enhanced coupling of the amygdala to structures modulating attention, such as the anterior cingulate cortex and adrenergic projections[62].

Thus, cognitive impairment in psychiatric disorders is characterized by a complex pattern of disconnection and overconnection. An important issue, therefore, is whether the circuits controlling cognition can be reconstituted once they are disrupted, as certain structural perturbations may be irreversible — as implied by the above-mentioned notion of phase shifts[4,63].

Genetic risk factors for cognitive deficits in psychiatric disorders. A full discussion of genetic susceptibility factors is beyond the scope of this article but several points that are relevant to cognitive dysfunction should be highlighted (Supplementary information S1 (figure)).

First, although psychiatric disorders have a moderate to high heritability, genetic risk factors are numerous and only have a small effect; they show low penetrance and epistasis, and they do not necessarily adhere to classical nosological boundaries. For example, schizophrenia and bipolar disorder share some susceptibility loci[7,11,52,64–66], and the same holds for schizophrenia and ASD (Supplementary information S1 (figure)). Hence, it is difficult to identify genetic risk factors for cognitive dysfunction in psychiatric disorders. Compounding the challenge, for specific psychiatric disorders cognitive impairment is heterogeneous among individuals, with regard to both its causes and characteristics[8,9,12,18,23,26,28].

Second, 'correlated' does not necessarily imply 'causal'. If a mutation, deletion or other genetic defect is associated with a psychiatric disorder, this does not necessarily indicate a role in the induction of cognitive impairment. Furthermore, the functional significance of single nucleotide polymorphisms is often uncertain, and some risk loci cover numerous genes[7,11,52,64–66].

Third, even if a genetic defect is implicated in the pathological mechanisms that lead to cognitive impairment, it is not necessarily an appropriate target for their alleviation, as it may trigger anomalous mechanisms that are no longer under its control. For example, mutations in the gene encoding neuregulin 1 contribute to aberrant patterns of neuronal migration and synaptogenesis in schizophrenia, but neuregulin 1 has a different functional role in the adult brain than in the developing brain, so targeting it is unlikely to reverse such anomalies[67].

Fourth, some plasticity-related genes predispose individuals to cognitive deficits under adverse developmental conditions but have the opposite effect in a favourable environment. This complicates analyses of their significance[64].

Last, the limited success of even genome-wide studies in finding genes that are major risk factors may also be ascribed to additional layers of epigenetic control that can mask the effects of genetic defects.

Despite these hurdles, with the aid of improved experimental models[7,11,68,69] several susceptibility genes for psychiatric disorders have been linked to cellular mechanisms that control cognitive processing (Supplementary information S1 (figure)). Furthermore, the future identification of genetic risk factors for cognitive deficits will be refined by: pathway analyses based on prior knowledge of protein networks[65]; multivariate statistics for simultaneous analysis of interacting genes[66]; and studies of gene associations with heritable, stable and co-segregating cognition-related endophenotypes that are likewise (although less markedly) impaired in healthy relatives[11]. Examples of such endophenotypes include: verbal learning and memory in bipolar disorder[70]; sensorimotor gating and social cognition in schizophrenia[71,72]; and cerebral circuit disruption in OCD and ASD[73,74]. Some cognitive endophenotypes may, reflecting similar pathological mechanisms, be common to disorders like schizophrenia, bipolar disorders or ASD.

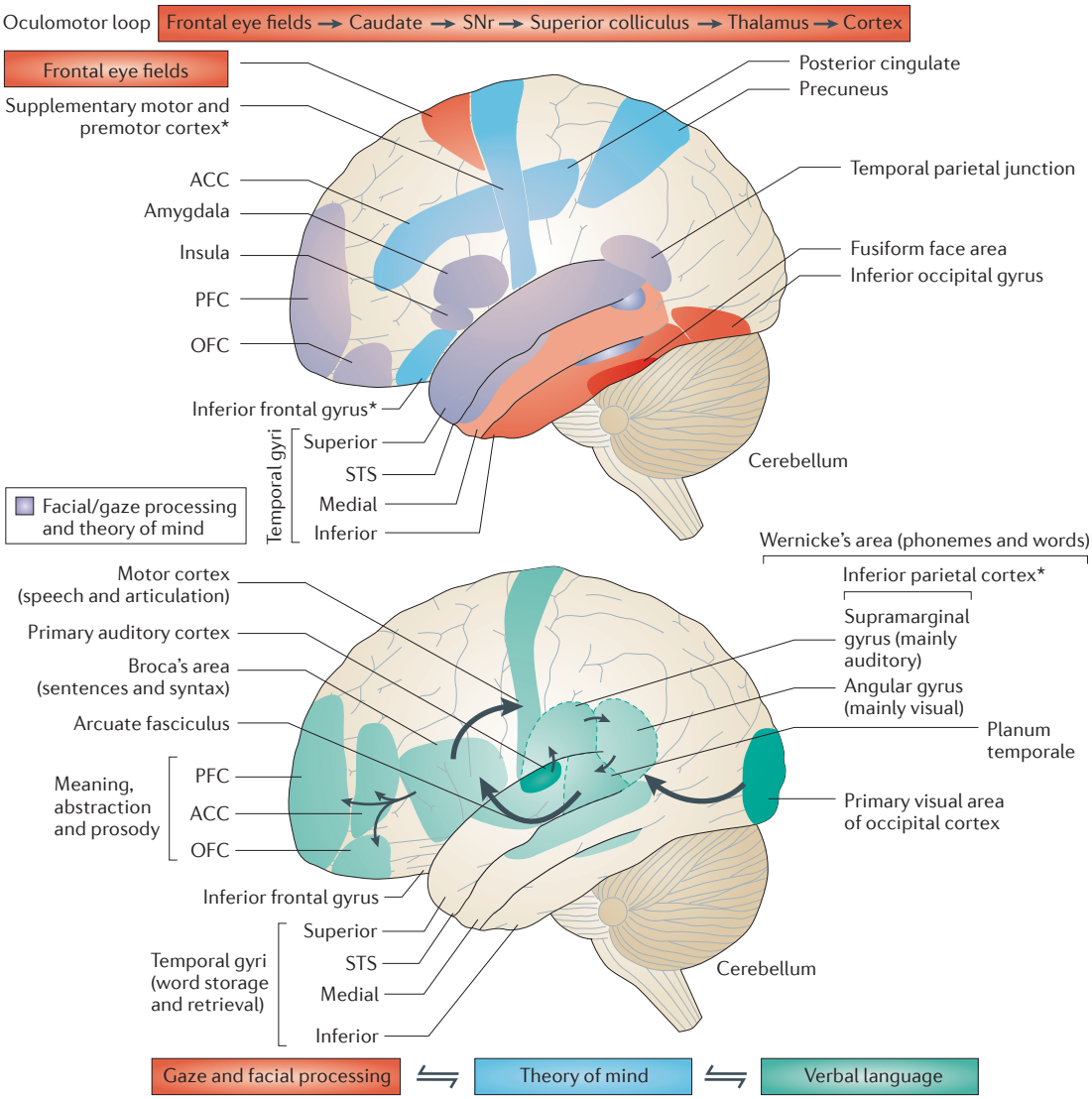

Figure 3 | **Schematic representation of the principal cerebral circuits integrating social cognition and verbal language, both of which are disrupted in psychiatric disorders.** A broad suite of interconnected and overlapping cerebral regions integrate and control social cognition (top panel) and verbal language (bottom panel). Verbal language is generally left-lateralized. However, prosody and the abstract features of language, as well as facial processing and the theory of mind (core elements of social cognition), have a marked implication of the right hemisphere: for example, the temporal–parietal junction[34,35,211,212,243,244]. The oculomotor loop is modulated by prefrontal and parietal inputs, and guides the direction and speed of voluntary eye movement[183–185]. Facial processing involves several interrelated dimensions of: facial perception (especially the fusiform face area and the adjacent inferior occipital gyrus); facial recognition and matching (the temporal–parietal junction); gaze tracking (the oculomotor loop, the region around the superior temporal sulcus (STS) and the temporal–parietal junction); and interpretation of facial emotion (the amygdala, the insula, the prefrontal cortex (PFC), the anterior cingulate cortex (ACC) and the orbitofrontal cortex (OFC))[183–185,245,246]. Some of these regions belong to a network underpinning the theory of mind, in which the medial PFC, the STS, the temporal–parietal junction and the precuneus have prominent roles. This circuit itself overlaps with the task-deactivated default-mode network located in the medial PFC, posterior cingulate, precuneus, angular gyrus and temporal lobes[203]. Certain structures contain mirror neurons that discharge when observing other people performing relevant behaviours; these neurons may be relevant to the theory of mind, imitation and other forms of social learning, and their dysfunction is possibly implicated in autism spectrum disorder and schizophrenia[33,34,212,247]. The main role of Wernicke's area is in the perception, recognition, representation and comprehension of phonemes and words from visual and auditory input[243,244]. Broca's area incorporates Brodman's areas 44 and 45 of the inferior frontal gyrus, as well as the contiguous zones of the frontal lobe and premotor cortex. It is involved in word matching and choice, formation and syntax of sentences, as well as preparation of speech, and has a broader role in motor action preparation, music and sign language[243,244,248]. The arrows on the figure indicate the principal flow of information involved in the processing and production of language, including the arcuate fasciculus, which projects from Wernicke's area to Broca's area. In addition to this dorsal stream, a ventral stream (not shown) runs from the middle temporal lobe to the medial PFC[244], which also integrates abstract features of language and prosody, together with the superior temporal gyri and amygdala. The cerebellum has a modulatory influence on social cognition, oculomotor function and language[249,250]. SNr, substantia nigra pars reticulata. *Contains mirror neurons.

Semantics
The meaning of what is said, written, read or heard.

Epigenetic control
A somatic and/or germline modification of chromatin (DNA plus nuclear proteins) that leads to long-lasting alterations in gene expression but not in the DNA sequence. DNA methylation silences genes and occurs mainly in CpG-rich promoter islands. Histone tails are subject to interacting processes of methylation (lysine and/or arginine residues), acetylation (lysine residues), phosphorylation, sumoylation, ubiquitylation and ADP ribosylation. Acetylation causes decondensation (unwinding), increased access for transcription factors and enhanced gene expression.

Default-mode network
A functionally interconnected network of cortical regions that is active under wakeful, resting conditions in functional magnetic resonance imaging paradigms, yet is consistently deactivated by goal-directed activity such as cognitive tasks. It includes the posterior cingulate cortex, precuneus, medial prefrontal cortex and inferior parietal cortex, and is characterized by synchronised, low-frequency oscillations of less than 1.0 Hz.

Linking risk genes to network disruption. As emphasized above, disturbed network synchrony and connectivity are implicated in the cognitive deficits observed in psychiatric disorders (BOX 4). From a therapeutic perspective, however, drugs target molecules, so it is crucial to link changes in network operation to events at the cellular and genetic level. Neuroimaging and electrophysiological techniques can help to achieve this goal, and they can be exploited both in humans and in animal models.

One example is the so-called Val158Met polymorphism (rs4680) in the gene encoding the enzyme catechol-*O*-methyltransferase (COMT), which catabolises dopamine; the Val and Met COMT variants are associated with high and low inactivation of dopamine, respectively[75,76]. In healthy individuals, the Val variant was associated with blunted coupling between hippocampal formation and the PFC during a recognition memory task[77]. This observation may be related to a role of hippocampal dopamine D1 receptors in gating hippocampal input to the PFC[77]. Furthermore, D1 receptor-mediated signalling is modulated by the dopamine- and cyclic AMP-regulated neuronal phosphoprotein (DARPP32; also known as PPP1R1B) (Supplementary information S2 (figure)), and a frequent *PPP1R1B* haplotype is associated with altered connectivity between the PFC and the striatum, as well as cognitive dysfunction and an increased risk of schizophrenia[78].

As a second example, a polymorphism (rs1344706) that is associated with the risk of developing schizophrenia is located in the gene that encodes zinc finger protein 804A, a transcription factor that affects cognitive function[72,79]. During a working memory procedure, healthy carriers of the polymorphism showed gene dosage-dependent alterations in PFC connectivity across hemispheres, and between the dorsolateral PFC and the hippocampus. Functional anomalies in networks underpinning theory of mind (FIG. 3) have also been observed[72]. Interestingly, in patients with schizophrenia this polymorphism also affects cognition and attention, as well as verbal and/or episodic learning and memory[80].

A third example is a rare but penetrant microdeletion in chromosome 22 (22q11.2) that is associated with learning disabilities, cognitive dysfunction and a 30-fold increased risk of schizophrenia[81]. Mice with an equivalent microdeletion have flawed working memory related to reduced hippocampal–prefrontal synchrony. This in turn reflects a failure of PFC neurons to phase-lock with hippocampal θ-oscillations as a result of aberrant firing of GABAergic interneurons — a deficit seen in psychotic states[82].

Stress as a risk factor for cognitive deficits and network disruption. Genetic factors do not fully account for the impaired cognition that is observed in psychiatric disorders. Especially in genetically predisposed individuals, exposure to excessive stress is a major risk factor for impaired cognitive function throughout life.

Stress is a familiar but imprecise term for the disruption of homeostasis that occurs following perceived or actual exposure to adverse events, and it harnesses a vast repertoire of neuromodulators that either promote or counter its effect[83,84]. An essential feature of pathological stress is hypothalamic–pituitary–adrenal (HPA) axis overdrive: this leads to poorly regulated, sustained and marked increases in levels of corticosterone downstream of the hypophyseal release of corticotropin-releasing hormone. Blockade of forebrain populations of corticotropin-releasing hormone receptor 1 counters the cognitive deficits and dendritic abnormalities elicited by acute stress and early-life adversity[85]. Nonetheless, most interest has focused on corticosterone. Mirroring the optimal cognitive performance seen at moderate levels of arousal, a well-regulated, modest and phasic recruitment of the HPA axis generally favours cognitive performance. However, excessive activation of the HPA axis is detrimental. In other words, there is a bell-shaped curve for the influence of corticosterone on cognition[83,84,86,87] (see below).

One explanation for this is that genomic mineralocorticoid receptors, which are recruited at rest, permit a positive influence over less sensitive glucocorticoid receptors. Conversely, when glucocorticoid receptor stimulation is disproportionate and persistent, cognition is compromised[83,88]. At least in the hippocampus, this occurs in association with a pronounced release of glutamate and the activation of NMDA receptors mediating LTD[45,83,89]. However, a diverse pattern of interactions among corticosterone, mineralocorticoid and glucocorticoid receptors, along with glutamatergic signalling, lead to a complex pattern of influence on cognition[83,84,86,90,91]. Thus, the notion of unitary beneficial and deleterious roles of mineralocorticoid versus glucocorticoid receptors, respectively, is an oversimplification that complicates their therapeutic exploitation.

Analogous to psychosocial stress in humans, the exposure of adult rodents to adverse events perturbs PFC-derived networks, leading to deficits in LTP, working memory and executive function[84,92,93]. Chronic stress-induced cognitive deficits are associated with structural remodelling, including dendritic spine retraction and neuronal atrophy in the PFC (BOX 3), reduced LTP and neurogenesis in the hippocampus, and an interference with PFC–hippocampus coupling[87,88,90,92,93]. Mirroring PTSD in patients[14,15], acute stress leads to over-intense encoding of negative emotional memories in PFC–amygdala circuits as well as blunted fear-extinction learning[94].

Prenatal and childhood stress triggers long-term changes in adolescents and adults, involving impaired cognitive function and an increased risk of depression and other psychiatric disorders[83,84]. These delayed effects of stress appear to reflect structural and functional changes in corticolimbic circuits. For example, in women suffering from major depression, cognitive impairment was related to a history of early childhood adversity and reduced hippocampal volume[84]. Correspondingly, early-life chronic stress in rats is associated with reductions in hippocampal LTP, dendritic spine complexity, neurogenesis and BDNF expression during adulthood[83,95]. However, early-life stress is not invariably associated with detrimental consequences. For instance, adult rats that had experienced early-life adversity performed poorly in non-stressful learning

Neurogenesis
The continuous generation of new neurons from neural precursor cells in humans and other mammals. It is seen mainly in two regions. First, the subventricular zone of the lateral ventricle gives rise to neurons that migrate to become granule neurons and periglomerular neurons mainly in the olfactory bulb. Second, neurogenesis in the subgranular zone of the hippocampal dentate gyrus yields neurons, some of which are integrated into local neural networks once they have matured.

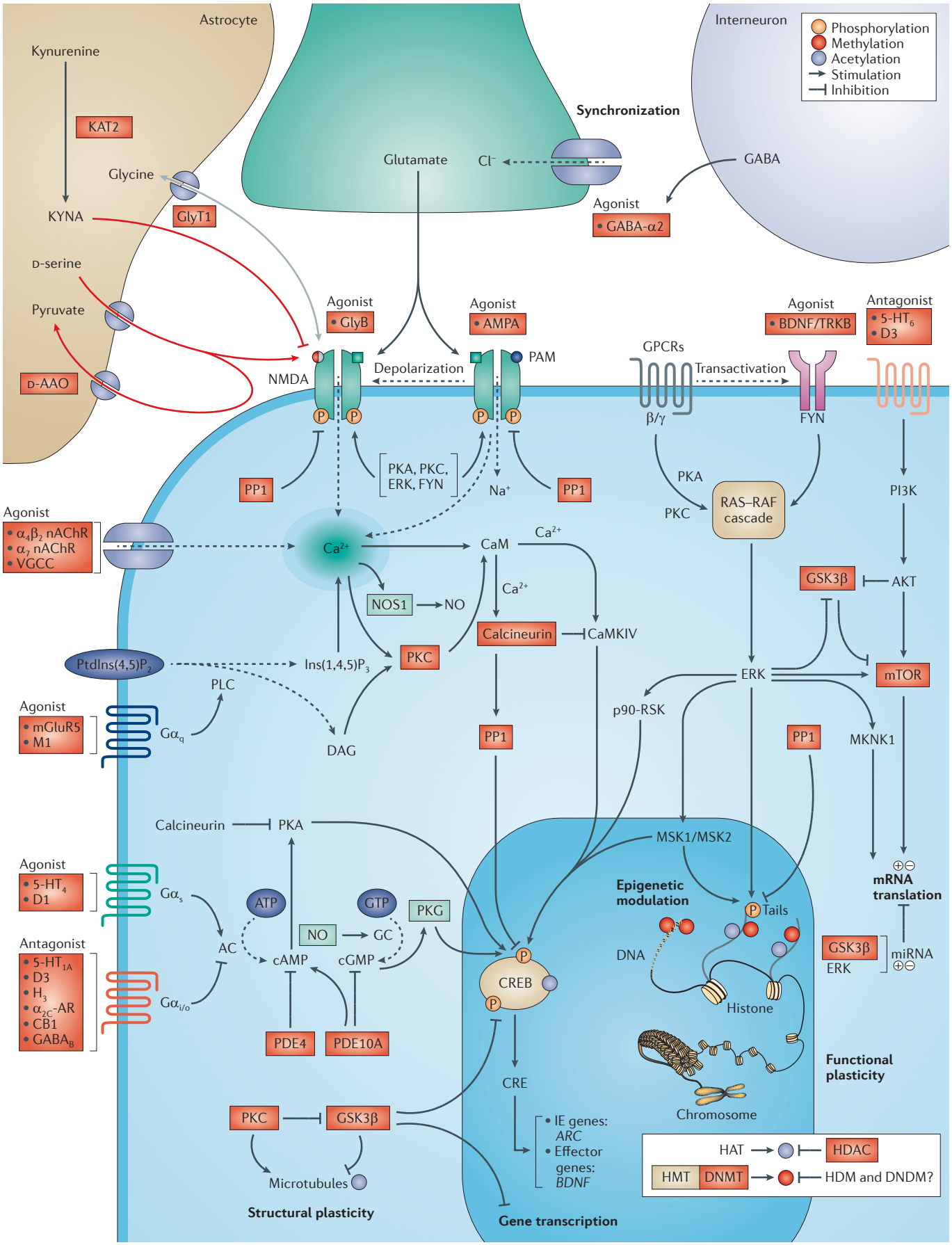

Figure 4 | **An overview of molecular substrates targeted by drugs that are designed to enhance cognitive performance in psychiatric disorders.** The figure illustrates the complex pattern of crosstalk among the cellular mechanisms influencing cognitive function, of which several (in red boxes and listed in TABLE 2) are potential targets for its improvement in psychiatric disorders. Most mechanisms are depicted for simplicity in a postsynaptic element. Although one specific cell type, such as a prefrontal cortex (PFC)-localized pyramidal projection neuron, might not express all elements, these signalling cascades are widespread. The cell is innervated by a glutamatergic terminal (shown in green) adjacent to an astrocyte (shown in beige) that releases the NMDA (*N*-methyl-D-aspartate) and glycine B receptor co-agonists D-serine and glycine as well as the antagonist kynurenic acid (KYNA), which is cleaved from kynurenine by kynurenine amino transferase II (KAT2). The GABA (γ-aminobutyric acid)-ergic interneuron synchronizes the activity of glutamatergic neurons and other components of neuronal networks controlling cognition (BOX 4). Notably, there is convergence and divergence in signalling pathways emanating from G protein-coupled receptors (GPCRs), ion channels and tyrosine receptor kinases (TRKs) that are either recruited (agonist properties) or blocked (antagonist properties) by pro-cognitive agents. Drugs may act on downstream intracellular targets: for example, kinases (phosphorylation), the phosphatases protein phosphatase 1 (PP1) and PP2B; also known as calcineurin) (dephosphorylation), and cyclic AMP-specific phosphodiesterase 4D (PDE4D) and PDE10A. They may also act through epigenetic mechanisms of DNA and histone methylation, acetylation and phosphorylation (TABLE 2). Moreover, pharmacotherapy may act upstream via the α2 subunit of $GABA_A$ receptors ($GABA_A$-α2), or it may control the availability of glycine (reuptake suppression), D-serine (breakdown inhibition) and kynurenine (synthesis suppression) to NMDA receptors located on pyramidal cells and GABAergic interneurons in the PFC. NMDA receptors mediate rapid changes in cellular excitability, and contribute to long-term potentiation (LTP) and long-term depression (LTD) — core substrates of synaptic plasticity (BOX 3). They are permeable to Ca^{2+}, which affects several mediators controlling cognition, including nitric oxide synthase 1 (NOS1). Changes in cognition are ultimately affected by alterations in: key signals such as extracellular-regulated kinase (ERK) and mammalian target of rapamycin (mTOR); transcription of genes pivotal to cognitive processing, such as cyclic AMP-responsive element binding protein (CREB); epigenetic programming of DNA and histones; microRNA (miRNA)-mediated regulation of mRNA translation; LTP, LTD and dendritic spine plasticity (BOX 3); synaptic architecture; and neurotransmitter release (not shown). CREB recruits CREB-responsive element (CRE) to activate immediate-early (IE) genes such as activity-regulated cytoskeleton-associated protein (ARC) and effector genes like brain-derived neurotrophic factor (BDNF). For a more comprehensive view, see Supplementary information S2 (figure). $5\text{-}HT_{1A}$, 5-hydroxytryptamine (serotonin) receptor 1A; α_{2C}-AR, α_{2C}-adrenergic receptor; α4β2 nAChR, α4β2 nicotinic acetylcholine receptor; AC, adenylyl cyclase; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; CaM, calmodulin; CaMKIV, calcium/calmodulin-dependent protein kinase IV; CB1, cannabinoid receptor 1; D1, dopamine D1 receptor; D-AAO, D-amino acid oxidase; DAG, diacylglycerol; DNDM, DNA demethylase; DNMT, DNA methyltransferase; $G\alpha_q$, guanine-nucleotide-binding protein $G\alpha_q$; GlyB, glycine B; GSK3β, glycogen synthase kinase 3β; H_3, histamine H_3 receptor; HAT, histone acetyltransferase; HDAC, histone deacetylase; HDM, histone demethylase; HMT, histone methyltransferase; $Ins(1,4,5)P_3$, inositol-1,4,5-trisphosphate; M1, muscarinic M1 receptor; mGluR5, metabotropic glutamate receptor 5; MKNK1, MAP kinase interacting serine/threonine kinase 1; MSK1, mitogen- and stress-activated protein kinase 1; NO, nitric oxide; p90-RSK, 90 kDa ribosomal protein S6 kinase; PAM, positive allosteric modulator; PI3K, phosphoinositide 3-kinase; $PtdIns(4,5)P_2$, phosphatidylinositol-4,5-bisphosphate; PKA, protein kinase A; PLC, phospholipase C; TRKB, neurotrophic tyrosine kinase receptor type 2; VGCC, voltage-gated calcium channel.

tasks yet performed well under stress, suggesting that the brain had been programmed to operate better under challenging conditions[64,96].

Nonetheless, uncontrolled stress and HPA axis overactivity can trigger cognitive dysfunction throughout life[84,85,90]. The risk of middle-age depression, cognitive impairment and metabolic disease followed by dementia is exacerbated by stress, possibly as corticosterone and corticotropin-releasing hormone aggravate glutamatergic neurotoxicity. In elderly patients these hormones worsen the harmful actions of β-amyloid and microtubule-associated protein tau — neurotoxic proteins that are implicated in Alzheimer's disease[84,87,90,92,93].

Modelling cognitive deficits. Modelling the genetic, developmental and environmental factors that lead to cognitive impairment in psychiatric disorders is clearly challenging. From the drug discovery perspective, the search for animal models of psychiatric disorders necessitates a compromise between fidelity to human pathology and efficient drug validation[8,11,52,68,69]. A related key issue is whether cognitive procedures in animal models can efficiently predict the efficacy of drugs in patients (BOX 2). This question is underscored by the concern that numerous pro-cognitive agents and mechanisms have been documented in rodents yet little positive feedback has been acquired in patients.

In fact, if one considers animal models to be for — rather than of — psychiatric disorders, and accepts that they can only reproduce specific aspects (such as individual causes, symptoms, responses, and so on) of a disease (not the psychiatric disorder itself), an array of genetic, developmental and environmental rodent models is available for studying cognitive impairment[7,52,68,97]. Nonetheless, the familiar adage that 'the best experimental model is man' is more applicable to psychiatric disorders than to any other field of medicine. Hence, animal models clearly need further refinement, and transgenic strategies only partially mimic human pathology and the attendant cognitive deficits[7,52,68]. Furthermore, no single procedure is adequate alone, gender and age are insufficiently studied, and inter-individual differences deserve greater attention in view of their prominence in humans and their relevance to personalized medicine[6,8,11].

Several other areas also require greater focus, particularly where there is a mismatch between the experimental evaluation of drugs and their ultimate use in patients. First, more studies should be undertaken with chronic drug administration to establish the delay to onset of action, long-term efficacy and lack of rebound deterioration in cognition following their discontinuation. Second, the pro-cognitive actions of drugs administered alone in rodents may not be reproduced in patients if they are masked by a deleterious cognitive impact of co-administered agents possessing, for example, antagonist properties at muscarinic receptors and histamine H_1 receptors[3,97,98]. Thus, mirroring their adjunctive use in humans, the effects of co-administration of pro-cognitive drugs with antipsychotics and antidepressants should be examined in rodents. Third, many studies examine drug effects on baseline cognition. This is very different to the clinical situation, so a greater focus on drug-induced reversal of cognitive deficits in models of psychiatric disorders is desirable[7,11,50,68]. Last, the influence of drugs on cognition-related parameters other than behavioural outputs should be studied more intensively, as such mechanisms can be translationally monitored in humans (see below).

Despite these potential advances, many problems will remain. Notably, clinical studies are focusing increasingly on real-world function rather than on

Box 3 | **LTP and LTD: key neuroplastic substrates of cognition**

Long-term potentiation (LTP) is the sustained (from hours to months) increase in synaptic strength elicited by a brief period (a few seconds) of patterned, high-frequency (~100 Hz) afferent stimulation. It is a flexible and diverse multiphase mechanism that is involved in many cognitive processes, from declarative learning in the hippocampus to fear-extinction learning in the prefrontal cortex (PFC)[15,44]. Conversely, long-term depression (LTD) refers to a long-lasting decrease in synaptic response, usually produced by a prolonged sequence (lasting a few minutes) of patterned, low-frequency (~20 Hz) stimulation[44,45,134,135]. A specific form of LTD (de-potentiation) follows LTP, but LTD does not just serve a homeostatic role as a balancing act for LTP or to improve the signal to noise ratio. Rather, it is also a core mechanism of cognitive plasticity and a legitimate drug target[44,45,135]. For example, LTD mediated by the NMDA (*N*-methyl-D-aspartate) receptors and muscarinic M1 receptors in the hippocampus may be implicated in learning[45,135]. Furthermore, impairment of metabotropic glutamate receptor 5 (mGluR5)-promoted, NMDA-dependent LTP in the PFC and hippocampus may be implicated in the cognitive impairment of schizophrenia[50,224–226]. Conversely, excessive mGluR5-mediated LTD in the amygdala and other structures contributes to cognitive deficits in fragile X syndrome[134,135]. The deleterious impact of stress on episodic memory has been related to excessive NMDA receptor-mediated LTD in the hippocampus, possibly as a result of AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptor endocytosis[45]. Conversely, stress also impairs cognition by disrupting LTP across a hippocampal–PFC-integrated network[88,92]. Thus, changes in both LTP and LTD are related to the cognitive deficits observed in psychiatric disorders, and numerous drug targets (such as NMDA receptors, M1 receptors and mGluR5) modulate both of these substrates of neuroplasticity[44,45,104,112,135,224,226] (TABLE 2).

Importantly, LTP and LTD are associated with the structural plasticity of dendritic spines — that is, their expansion and formation (LTP), and their contraction and loss (LTD)[128] — in several classes of neurons that are important for cognition, including pyramidal neurons in the PFC and medium spinal neurons in the basal ganglia (FIGS 2,4). Spines are regulated in an activity-dependent manner by local protein synthesis and mRNA translation, which is itself subject to modulation by microRNAs[168,170]. Structural spine plasticity is anomalous in disorders such as schizophrenia and autism spectrum disorder[128].

neurocognitive test procedures, raising the question of comparability to rodent data (BOX 2). Furthermore, verbal language and human-like social cognition (BOX 1) will presumably remain refractory to study in rodent models.

Non-rodent species may be useful in the search for improved pro-cognitive agents; notable examples include fruitfly models for studying genetics[99], *Aplysia californica* (sea hares)[101] for studying synaptic plasticity and *Danio rerio* (zebrafish)[100] for studying developmental processes and behaviour. Moreover, fruitflies and zebrafish are amenable to studies of stress, and to the use of high-throughput protocols[99,100]. In addition, certain other mammalian species may illuminate the nature and disruption of episodic memory, advanced social cognition and language. These include great apes, elephants, dolphins (Supplementary information S3 (box)), prairie voles (Supplementary information S4 (box)) and higher birds[102] (Supplementary information S5 (box)).

Most strikingly, convergent evolution in corvids and parrots has led to alternative neural solutions (including a non-laminar cortex) underpinning genuine episodic memory, sophisticated social cognition and complex vocal communication[102]. Furthermore, the acquisition of birdsong displays striking parallels to the learning of human language[103]. Obviously, great apes, elephants and dolphins are unsuitable models for pharmacological studies, and it remains to be seen whether higher birds will prove to be useful; however, as outlined in Supplementary information S4 (box), prairie voles are instructive for characterizing the roles of potential drug targets in the control of social cognition.

Strategies to counter cognitive impairment

Direct and indirect modulation of cognitive performance by pharmacotherapy. Increasing awareness of the seriousness of cognitive dysfunction in psychiatric disorders, and recent insights into its potential causes, have triggered substantial efforts to discover drugs for restoring cognitive function[104]. Studies have focused both on specific domains (such as attention[105] and extinction learning[106]) and on disorders (such as schizophrenia[98] and ASD[63]). The array of concepts under investigation, listed in TABLE 2, is based both on behavioural readouts and on surrogate indexes of cognitive performance, such as cellular signals, LTP and LTD, network synchrony, transmitter release and dendrite spine formation.

As TABLE 2 is limited to targets that directly affect cognition, the significance of drug-induced changes in mechanisms that indirectly modulate cognitive function should be briefly discussed. Agents that enhance sleep quality and architecture, especially slow-wave sleep, should improve hippocampal–cortical mechanisms of consolidation and other components of cognitive processing[107]. Drugs that normalize disrupted circadian rhythms may favourably affect cognitive performance[108]. Importantly, sleep and diurnal scheduling are often perturbed in psychiatric disorders[4,108]. The potential significance of drug-induced changes in appetite and energy balance should also be noted, as glucose is transformed into glutamate and GABA via astrocytes, and diabetes is a risk factor for depression and cognitive impairment[90,109]. An impact of drugs on immune elements such as cytokines may similarly affect cognitive performance[39].

Limited clinical feedback. There has been limited positive clinical feedback so far for many of the putative pro-cognitive drug targets mentioned in TABLE 2. For example, D1 receptor agonists have never been shown to exert pro-cognitive actions in humans[98,110], and $GABA_A$ receptor α2 subunit agonists have yielded mixed findings[98,111]. Nonetheless, there are some exceptions. Initial clinical studies suggest that α4β2 nicotinic acetylcholine receptor agonists[38,112] and 5-hydroxytryptamine (serotonin) receptor 6 ($5\text{-}HT_6$) antagonists[113,114] have positive effects, and substantial data have underscored the role of oxytocin in emotional processing and social cognition[115–117]. Although its effects may not be entirely unitary, oxytocin consistently improves social cognition in volunteers as well as in individuals with ASD or schizophrenia (TABLE 2).

The noradrenaline reuptake inhibitor atomoxetine improves focused attention and executive function in ADHD[118]. However, noradrenaline reuptake inhibitors have not shown substantial benefits in schizophrenia, and their putative beneficial actions in depression await confirmation[2,4,98]. Experimental studies have demonstrated that PFC-localized, pyramidal α_{2A}-adrenergic receptors have a positive influence on working memory. However, the effects of agonists are less robust than those of atomoxetine in ADHD. Furthermore, a genuine improvement

Box 4 | **Network synchrony: disruption in psychiatric disorders**

Network-coordinated rhythmic activity within and between the regions of the brain controlling cognition is associated with electroencephalographical (EEG) activity that can be quantified non-invasively[46,47,88,192,193]. Theta (θ; 4–7 Hz) frequencies are related to episodic memory and they are widely used to monitor oscillations driven by hippocampal regions in coordination with the prefrontal cortex (PFC)[46,47,88,192,193]. Conversely, the activity of GABA (γ-aminobutyric acid)-ergic interneurons in the PFC is reflected in the γ (30–80 Hz) range, which is linked to attention and working memory[47,193,195]. The synchronization of θ rhythms, γ rhythms and β (12–30 Hz) rhythms across regions of the brain represents a 'neural code' that modulates and drives cognitive processes such as top-down cortical control. Accordingly, disruption of EEG-monitored rhythms may reflect cognitive impairment[46,47,192,193,227].

Coordinated network activity in the PFC and hippocampus depends on GABAergic interneurons that impose a temporal signature on the firing patterns of neurons controlling cognition[42,193,195]. Thus, glutamatergic pyramidal cells in the PFC receive trains of fast, inhibitory postsynaptic potentials from parvalbumin-positive GABAergic interneurons that recruit the α2 subunits of $GABA_A$ receptors on their axon hillocks[42] (FIG. 4). In schizophrenia, a developmental deficit in excitatory NMDA (*N*-methyl-D-aspartate) receptors — and possibly AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptors — on these GABAergic interneurons leads to a decrease in their activity, anomalous patterns of pyramidal cell firing, perturbed PFC network synchronicity and cognitive impairment[42,50,192,228]. Frontocortical GABAergic interneurons and pyramidal cells integrate inputs from many modulators controlling cognitive function, including monoamines, acetylcholine and glutamate. Hence, they are a focal point of strategies for enhancing cognition both in schizophrenia and in other psychiatric disorders (FIG. 4). Finally, GABAergic mechanisms in the amygdala are important for fear memory, and a dysfunction of GABAergic intercalated cells (FIG. 2) is implicated in the weakened fear-extinction learning seen in post-traumatic stress disorder[15,106] (BOX 1).

in working memory has yet to be demonstrated and these agonists have a small therapeutic window. Long-term release forms of such agonists may therefore prove to be more useful[119,120].

Putative pro-cognitive actions of glycine transporter 1 inhibitors in schizophrenia are constrained by motor and autonomic side effects, and results with partial agonists at the glycine B co-agonist site on NMDA receptors have been variable[98,121]. Finally, a vigilance enhancer, modafinil, displayed encouraging effects on cognition (including facial processing and speed of processing) in patients with schizophrenia, thus supporting studies in volunteers, but the results of more recent, controlled studies have been less compelling[98,122,123].

Complex effects on cognition: bell-shaped dose–response curves. Clearly, considerable progress is needed with regard to the clinical profiles of pro-cognitive agents. Their experimental and therapeutic evaluation is complicated by the fact that the doses needed to improve cognition depend on several variables, including baseline performance, genotype, test sensitivity and end point. Furthermore, similarly to corticosterone (see above), many agents have 'inverted U' dose–response curves in behavioural and mechanistic procedures[124–126] (TABLE 2). Biphasic dose–response curves imply a 'set point' for optimal performance, such that under- or overactivation of the drug target has a deleterious effect. This is perhaps not surprising, as both deficient and excessive LTP, LTD, 'plasticity gene' activity, neurogenesis and dendritic spine generation have a deleterious effect on cognitive processing[43–45,64,87,127,128] (BOX 3).

Clinical studies of COMT inhibitors illustrate the significance of this phenonemon[75,76]. COMT inhibitors enhance extracellular levels of dopamine in the PFC, which improves cognition when basal levels of dopamine are low. This has been observed in volunteers and in patients with schizophrenia possessing a Val/Val phenotype associated with high dopamine metabolism, and also in pathologies in which dopamine levels are reduced in the PFC, such as depression and late-stage Parkinson's disease. Conversely, cognition deteriorates when basal levels of dopamine are high, as observed in some volunteers and in patients with schizophrenia possessing a Met/Met genotype[75,76].

Other than off-target, low-potency actions (like muscarinic receptor antagonism) of drugs that perturb cognition, there are several other non-exclusive explanations for complex and inverted-U dose–response curves. First, reflecting the homeostatic control of cognition, overactivation of any one mechanism (such as phosphorylation) by a drug may provoke the over-compensatory response of another (such as dephosphorylation)[129] (FIG. 4). Second, a drug may be highly selective for its target but the target itself may exert a complex influence on cognition via spatially distinct receptor populations. For example, activation of post-synaptic α_2-adrenergic receptors on PFC pyramidal neurons favours working memory[41,119]. Conversely, activation of α_2-adrenergic receptors that are inhibitory to frontocortical adrenergic, dopaminergic and cholinergic projections is detrimental for working memory and executive function[130,131] (TABLE 2). Third, even a single population of sites can mediate a biphasic dose–response curve. Induction of GPCR endocytosis with high concentrations of agonists offers one explanation for this (Supplementary information S2 (figure)), but a more widespread explanation comes from the coupling of GPCRs to functionally distinct transduction pathways. For example, 5-HT_6 receptors exert a dose-dependent positive and negative effect on cognition via recruitment of cAMP-responsive element binding protein (CREB) and mammalian target of rapamycin (mTOR), respectively[114]. Accordingly, monotonic, pro-cognitive dose–response relationships could be generated using biased ligands that only recruit specific cellular pathways favouring cognition. A complementary approach would be the exploitation of GPCR-modulatory proteins to direct signalling down specific transduction routes[132].

More generally, a prudent approach for enhancing cognition over a broad dose range would be to prioritize partial rather than full agonists; allosteric modulators may also be an option. For intracellular targets such as kinases, partial inhibition is also preferable for safety reasons.

Normalization of pathological processes versus symptomatic strategies. There are two complementary ways to restore cognitive performance: first, by countering pathological changes underlying deficits; and second, by recruiting pro-cognitive mechanisms that are independent of disease aetiology.

Fragile X syndrome
A disease that is usually caused by the expansion of a trinucleotide sequence in the 5′-untranslated region of the fragile X mental retardation 1 (*FMR1*) gene. This leads to *FMR1* promoter hypermethylation, transcriptional silencing and loss of the RNA-binding protein FMR1. Abnormal translation of mRNAs, including those regulated by metabotropic glutamate receptor 5, results in excessive long-term depression. Affected individuals have defects in speech, language, attention, working memory and social cognition.

Table 2 | **Overview of drug classes proposed for the treatment of cognitive impairments in psychiatric disorders***

Drug target and molecular action	Disorders to treat	Cellular substrates (sites of action)	Other useful functional properties	Possible MOA-related drawbacks	Clinical feedback on cognitive actions	Other useful tools	Refs
Dopamine D1 receptor agonist (PAG)	SCZ, PD	• ↑PKA, DARPP32, CREB • ↑ARC • ↑NMDA signalling • ↑LTP and LTD (PFC) • ↑ACh (PFC)	• Antiparkinsonian • ↓Drug-seeking behaviour	• IUDR • Dyskinesia • Desensitization • Hypotension	• Dihydrexidine • ↑PFC activity, inactive on WM (SCZ)	• SKF81297 • ABT-431 • A-77636	98,110, 126,198
Dopamine D3 receptor antagonist	SCZ, BPD, PD, ASD, ADHD, AD, NF, FXS, TSC	• ↓mTOR (PFC) • ↑NMDA signalling (PFC, NACC) • ↑ACh, D-serine (PFC)	• ↑SMG • Antiparkinsonian • Antipsychotic • ↓Drug-seeking behaviour • Nephroprotective	• Uncertain	• Unavailable	• ABT-614 • S33138 • S33084 • SB-277011	97,251, 252
COMT inhibitor	SCZ, PD, ADHD, depression	• ↑Dopamine, noradrenaline (PFC) • ↑PFC–subcortical connectivity	• ↑SMG • Antiparkinsonian	• IUDR • Genotype (Val/Met)-dependent • ↑Sympathetic output	• Tolcapone: ↑WM and PPI (HV) • ↑ or ↓EXF (Val or Met genotype, HV) • ↑Cognition (PD)	• Entacapone	75,76
α_{2A}-AR agonist (PAG)	ADHD, SCZ, Tic disorders	• ↑ERK • ↓HCN activity (Pyram., PFC) • ↑Connectivity (PFC)	• ↓Hyperactivity • ↓Impulsivity (ADHD) • Analgesic • ↓Opioid withdrawal	• IUDR • ↓LTP (HIPP) • ↓ACh, noradrenaline, dopamine (PFC, HIPP) • Mild ↓ in AP/HR • Somnolence	• Guanfacine XR, Clonidine: ↑attention (ADHD) • Inactive in SCZ	• Guanabenz	119,120
$\alpha_{2A/2C}$-AR antagonist	SCZ, PD, depression, PTSD, phobias	• ↑ARC, ACh noradrenaline, dopamine, histamine (PFC, HIPP) • ↑Neurogenesis (HIPP)	• Antidepressant • Antiparkinsonian • ↑Libido • ↓Erectile dysfunction	• ↓WM (PFC) • Nervousness • Panicogenic • ↑Sympathetic output • Over-arousal	• Idazoxan: ↑cognition. (modest) (HV, SCZ) • Yohimbine: ↑CFE (claustrophobia)	• Atipamezole • BRL-44408 (α_{2A}-AR) • JP-1302 (α_{2C}-AR)	104,130, 131
Noradrenaline transporter blocker	ADHD, depression, SCZ, OCD, PD, Korsakoff's syndrome	• ↑Dopamine, noradrenaline (PFC) • ↑Noradrenaline (HIPP) • ↑θ (HIPP) ↑BDNF and neurogenesis (HIPP)	• Antidepressant • Anti-impulsive?	• ↓Sleep • Hypertension or ↑HR • Over-arousal	• Atomoxetine: ↑attention, WM and EXF (ADHD); inactive in SCZ, ↑cognition in PD • Reboxetine: ↑attention and SOP, ↓negative bias in depression	• Maprotiline	98,118
5-HT_{1A} antagonist (PAG)	Depression, SCZ, AD, ASD	• ↑ERK • ↑Pyram. (PFC, HIPP) • ↑ACh, Glu (PFC, HIPP)	• Anxiolytic • Antidepressant (PAG) • ↑Sleep (antagonist)	• IUDR • Poor cardiovascular tolerance (PAG)	• Tandospirone: modest ↑WM and VLM (SCZ) • Buspirone: inactive in SCZ	• S-15535 (PAG) • Lecozotan • WAY-100635 (antagonists)	104,113
5-HT_4 agonist (PAG)	Depression, AD, OCD, SCZ	• ↑PKA, CREB • ↑BDNF, BCL-2, LTP (HIPP) • ↑ACh (HIPP)	• Antidepressant • Neuroprotective • ↓Aβ accumulation	• Gastrointestinal and cardiac side effects	• Unavailable	• PF-4995274 • RS-67333 • VRX-03011 • PRX-03140	104,113, 145
5-HT_6 antagonist	SCZ, BPD, AD, ASD, FXS, TSC	• ↓mTOR (PFC) • ↑NCAM-PSA • ↑γ (PFC) • ↑ACh, Glu, dopamine (PFC, HIPP)	• Anxiolytic • Antidepressant • ↓Obesity	• Interference with cognition (via ↓CREB and ERK activity)	• SGS518: ↑cognition (SCZ) • SB742457: ↑cognition (AD) • PRX07034: ↑cognition (HV)	• SYN-114 • SAM-531 • R-1485	104,113, 114

Table 2 (cont.) | **Overview of drug classes proposed for the treatment of cognitive impairments in psychiatric disorders***

Drug target and molecular action	Disorders to treat	Cellular substrates (sites of action)	Other useful functional properties	Possible MOA-related drawbacks	Clinical feedback on cognitive actions	Other useful tools	Refs
H_3 receptor antagonist or inverse agonist	ADHD, SCZ, AD, depression, EDS, narcolepsy	• ↑PKA, CREB • ↑NCAM-PSA • ↑θ (HIPP) • ↑ACh, histamine, noradrenaline (PFC, HIPP)	• ↑SMG • Analgesic • ↓Obesity	• Nervousness • Over-arousal • Poor sleep • Immune and gastrointestinal side effects	• MK0249: inactive (SCZ) • JNJ-17216498, PF-03654746: ↑attention, inactive in ADHD	• BF2.649 • GSK189254 • Ciproxifan	139,253
Muscarinic M_1 receptor agonist (PAM)	SCZ, BPD, AD	• ↓GSK3β • ↑NMDA signalling • ↑LTP and LTD (PFC, HIPP) • ↑Pyram. (PFC) • ↑ACh, dopamine (PFC)	• Antipsychotic • Neuroprotective • ↓Tau hyper-phosphorylation • ↓Aβ production and aggregation	• Gastrointestinal side effects • Depressogenic? • Sweating • Salivation	• Xanomeline: modest ↑WM and VLM (SCZ) • Sabcomeline: mild ↑attention, VLM and SOP (SCZ)	• TBPB • BQCA • AC-42 • ML-169	98,112, 254,255
α7 nAChR (PAG or PAM)	SCZ, AD, PD, ADHD	• ↑ERK • ↓GSK3β • ↑γ, θ (PFC, HIPP) • ↑ACh, Glu, noradrenaline (PFC, HIPP) • ↑BCL-2	• ↑SMG • Antidepressant • Neuroprotective • ↓Tau hyper-phosphorylation; Aβ neurotoxicity • Anti-inflammatory	• IUDR • Tachyphylaxis • Dependence? • Gastrointestinal side effects, especially nausea	• CP810123: inactive (HV) • DMXB: weak ↑attention, WM, EPM and SOP (HV) • DMXB/MEM3454/ EVP6124: ↑SMG, mild ↑cognition (SCZ) • MEM3454: ↑cognition (AD)	• TC-5619 • AZD0328 • SEN34625 • SSR180711	38,98, 112,140
α4β2 nAChR agonist (PAM)	ADHD, SCZ, AD, PD	• ↑LTP • ↑θ (HIPP) • ↑ACh, Glu, histamine (PFC, HIPP)	• ↑SMG • ↓Drug-seeking behaviour • Analgesic • Neuroprotective?	• IUDR • Depressogenic? • Nausea • Tachyphylaxis	• TC1734: ↑attention, EPM, PPI (HV) • Ispronicline: ↑attention, EPM (elderly patients) ABT418: ↑attention, WM (ADHD) • ABT089: inactive (ADHD) • Varenicline: ↑attention, WM (nicotine withdrawal)	• S38232 • A-85380	38,112
NMDA and/ or glycine B receptor agonist (PAG)	Phobias, SAD; panic disorder, PTSD, OCD, SCZ, BPD, ASD	• ↑ARC • ↑NOS1, PKG • ↑PKC • ↑LTP (PFC, HIPP, STM) • ↑LTD (HIPP, PFC, BLA)	• ↓Drug-seeking behaviour (for cocaine) • ↓Deficit symptoms (SCZ)	• IUDR • Tachyphylaxis • Excitotoxicity	• Glycine, D-cycloserine, D-serine: weak ↑cognition or inactive (HV, AD, SCZ) • D-cycloserine: ↑CFE (SAD, phobias, OCD, panic disorder)	• GLYX-13 • S-18841	98,125, 176,256
Glycine reuptake inhibitor	SCZ, BPD, phobias, PTSD?	• ↑Glycine (PFC, HIPP, STM) • ↑LTP (HIPP)	• ↑SMG • ↓Deficit symptoms (SCZ)	• IUDR • Motor and respiratory side-effects (cerebellum, medulla)	• Sarcosine: weak ↑cognition or inactive (SCZ) • R213129: inactive (HV)	• RF1678 • ALX5407 • SSR504734	98,121, 244,256
D-amino acid oxidase blocker	As for glycine B agonists?	• ↑D-serine (PFC, HIPP, CBM) • ↑LTP (PFC, HIPP)	• As for glycine B agonists?	• As for glycine B agonists?	• Unavailable	• AS057278 • CBIO • SEP-227900	257,258
AMPA receptor (PAM)	Depression, ADHD, AD, SCZ, PTSD, FXS	• ↑ARC • ↑NMDA signalling • ↑LTP, BDNF (HIPP, PFC) • ↑Noradrenaline (HIPP)	• Antidepressant • Neuroprotective	• LRS • Sensory dysfunction • Proconvulsant • Excitotoxicity	• CX516/CX717: weak ↑cognition or inactive (HV, SCZ, ADHD, FXS, elderly patients) • Farampator (NS): ↑EPM (HV) • LY451395: inactive (AD)	• S-18986 • Org-24448 • LY392098	98,104, 259,260

Table 2 (cont.) | **Overview of drug classes proposed for the treatment of cognitive impairments in psychiatric disorders***

Drug target and molecular action	Disorders to treat	Cellular substrates (sites of action)	Other useful functional properties	Possible MOA-related drawbacks	Clinical feedback on cognitive actions	Other useful tools	Refs
mGluR5 (PAM and/or PAG)	SCZ, BPD, PD, PTSD, phobias, OCD	• ↑PKC, CREB • ↑ARC • ↑NMDA signalling • ↑LTP (HIPP, PFC) • ↑LTD (BLA, HIPP)	• ↑SMG • Antipsychotic? • ↓Drug seeking behaviour	• IUDR • Excessive LTD (HIPP, CBM) • Epileptogenic • Excitotoxic	• Unavailable	• CDPPB • ADX-47273 • VU1545	225,226
mGluR5 antagonist	FXS, depression, PD	• ↓Excessive LTD • Normalization of dendrite morphology	• Anxiolytic • Antidepressant • Antidyskinetic • ↓GORD	• ↓NMDA signalling, LTP • ↓CFE • Pro-psychotic	• Fenobam (NS), AFQ056, acamprosate (NS): inactive, modest ↑attention, SOP and PPI (FXS)	• MPEP • MTEP	134,135, 261
$GABA_AR$ α5 subunit inverse agonist	Depression, AD, SCZ, NF, Down syndrome	• ↑LTP • ↑θ (HIPP) • ↑ACh (HIPP)	• ↑Neurogenesis?	• ↓CFE and spatial memory • Proconvulsant?	• α5IA: ↓ethanol-induced amnesia (HV), inactive in AD	• L-655708 • PWZ-029 • RO4938581 • MRK-016	42,133
$GABA_AR$ α2 subunit agonist (PAG)	SCZ, BPD, NF, OCD, ASD, depression	• ↑Synchrony of pyramidal cells • ↑γ (PFC)	• ↑SMG • Anxiolytic • Anticonvulsant	• Desensitization	• MK0777: ↑VLM, ↑γ but inactive in MATRICS battery (SCZ)	• TPA023B	42,111, 133,262
Adenosine A_{2A} receptor antagonist	ADHD, PD, AD, depression	• ↓p38 MAPK • ↑D1 and D2 signalling (STM) • ↑Motivation • ↑dopamine (NACC)	• Antiparkinsonian • Antidepressant • Neuroprotective • ↓Aβ neurotoxicity	• ↓BDNF and LTP (HIPP) • Insomnia • Nervousness • Psychostimulant	• Caffeine (NS): ↑arousal, attention and SOP (HV); inactive or modest ↑attention in ADHD	• Preladenant • SCH-58261 • ZM241685 • Istradefylline	263,264
Cannabinoid receptor 1 (CB1) antagonist	SCZ, BPD, AD	• ↓mTOR (HIPP) • ↑LTP (HIPP, PFC) • ↑ACh,Glu (PFC, HIPP)	• ↑SMG • Antipsychotic? • ↓Obesity	• IUDR • ↓LTD (HIPP) • ↓Extinction • Depressogenic • Anxiogenic	• Rimonabant: inactive (SCZ)	• SLV330 • AVE1625 • AM-251	51,104, 146,265
Oxytocin receptor agonist	ASD, SAD, ADHD, SCZ, BPD, phobias	• ↓Coupling of medial amygdala to brainstem (↓social fear and aversion) • ↑Dopamine release in nucleus accumbens (↑approach and reward)	• ↑SMG • Pro-social • ↑Pair-bonding, parental behaviour • ↓Anxiety • ↓Aggression • Antidepressant? • ↓HPA stress activation	• ↓VLM? • Gender-dependent prosocial actions • ↑Envy • ↓Trust (borderline personality disorder?) • Endocrine side effects	• Oxytocin (intranasal): ↑attention, trust, TOM, facial expression analysis, positive social memory, gaze to eye region, empathy, affective speech comprehension (HV, ASD, SCZ)	• Carbetocin • WAY-267464 (non-peptidergic)	115–117, 201,219
Vasopressin V_{1A} receptor agonist	ASD, SCZ, BPD, phobias	• Lateral septum • Centromedial amygdala • PFC • ↑Noradrenaline (HIPP)	• ↑SMG • ↓Sexual dysfunction • ↑Pair-bonding • ↑Partner preference	• Gender-dependent actions • ↑Anxiety • ↑Avoidance • ↑Aggression (male) • Endocrine and cardiovascular side effects	• Vasopressin (intranasal): ↑ability to encode happy and angry faces (males); ↑agonistic versus females (males); ↑friendly attributions (HV)	• NC-1900 • VP 4-9 • VP 4-8	115,266
BDNF receptor (PAG)	Depression, BPD, PD, AD, PTSD, phobias	• ↑CREB • ↑AMPA and NMDA signalling • ↑LTP and LTD • ↑Glu • ↑Neurogenesis (HIPP)	• Antidepressant • Neuroprotective	• IUDR • LRS	• Unavailable	• BDNF mimic, 7,8-dihydroxy-flavone	40,104, 158,159
PDE4D inhibitor	SCZ, depression, AD, RTS	• ↑PKA • ↑CREB • ↑LTP and LTD • ↑BDNF (HIPP)	• ↑SMG • Antidepressant • Neuroprotective?	• LRS • Emesis • Vasculitis • Immune side effects	• HT0712: inactive on WM; ↑VLM (elderly patients) • MK0952: ↑cognition (AD)	• Rolipram • MEM1091 • RO 20-1724	141–143, 145

Table 2 (cont.) | **Overview of drug classes proposed for the treatment of cognitive impairments in psychiatric disorders***

Drug target and molecular action	Disorders to treat	Cellular substrates (sites of action)	Other useful functional properties	Possible MOA-related drawbacks	Clinical feedback on cognitive actions	Other useful tools	Refs
PDE10A inhibitor	SCZ, BPD, PD	• ↑PKA and PKG • ↑CREB (STM) • ↑LTP and LTD	• Antipsychotic? • Anti-obesity	• Anxiety • Sedation • Dyskinesia • Side effects in testes	• Unavailable	• Papaverine • TP-10 • PQ-10 • MP-10	141,142
Protein kinase Cε activator	Depression, AD, stroke	• ↓GSK3β • ↑NMDA signalling • ↑GAP43 • ↑ACh and Glu • ↑Synaptogenesis	• ↓Tau and soluble Aβ levels • Anti-tumorigenic	• LRS • Desensitization • Pro-manic • ↑Stress-induced damage (PFC) • Myalgia	• Unavailable	• Bryostatin 1c • DCP-LA	144,267
mTOR1 inhibitor	BPD, SCZ, HD, AD, PD, TSC, FXS, NF	• ↓Excessive NMDA signalling, LTP and mGluR5-mediated LTD • ↓5-HT_6, D3 and CB1 overstimulation	• ↓Dyskinesia (PD) • ↓Tau hyperphosphorylation and Aβ production • Neuroprotective • Antitumorigenic	• LRS • IUDR • ↓LTP and LTD • Oncogenic • Immunosuppression	• Unavailable	• Rapamycin • Everolimus • Temsirolimus	136,146, 147
GSK3β inhibitor	BPD, SCZ, AD, depression, PD, stroke	• ↑CREB • ↑NMDA and AMPA signalling • ↑LTP (HIPP)	• Antimanic • Antidepressant • Neuroprotective (PD, stroke) • ↓Tau hyperphosphorylation and ↓Aβ aggregation	• LRS • ↓LTD • Oncogenesis ↑β-catenin activity	• Lithium (NS): inactive or ↓ cognition (BPD)	• AR014418 • SB415286 • NP031115 • NP12	148,149
Calcineurin (protein phosphatase 2B) inhibitor	SCZ, AD, BPD	• ↑D1 signalling • ↑CREB • ↑LTP, ↓LTD (HIPP/PFC)	• ↑SMG • Anti-apoptotic • Neuroprotective • ↓Aβ deposition and neurotoxicity	• LRS • ↓CFE • Pro-psychotic • Depressogenic	• Unavailable	• FK306 • Cyclosporin A • Tacrolimus	129,150, 151,166
Class I histone deacetylase 2 inhibitor	BPD, AD, PD, HD, PTSD, RTS, ASD, FXS,	• ↑CREB, BDNF and LTP (HIPP) • ↑BCL-2 • ↑Synaptogenesis	• Antimanic • Antidepressant • Neuroprotective • Anti-oncogenic	• LRS • Cytoxicity	• Valproate (NS): ↑social cognition (FXS)	• Vorinostat • Trichostatin A • Sodium butyrate • EVP0334	137,138, 165,167
Microtubule stabilizer	SCZ, BPD, AD, PD, ASD, cerebral palsy	• ↑LTP (HIPP) • ↑Neurite growth • ↑Neurogenesis	• Neuroprotective • ↓Tau hyperphosphorylation	• LRS • Cytoxicity	• Davunetide: ↑cognition (SCZ, elderly patients)	• Epothilone D • Darbepoetin α	268

*Major potential domains of therapeutic exploitation are indicated. Several possible neuronal and cellular substrates of pro-cognitive properties are shown but owing to limited data and differences between various cognitive domains, this information is inevitably incomplete; 'absence of evidence' must not be misconstrued as 'evidence of absence'. Many studies have focused on the prefrontal cortex, hippocampus, and as concerns fear-extinction learning, the basolateral amygdala. Some have investigated the cerebellum, striatum and nucleus accumbens. For transmitters like glutamate, changes refer to release *in vivo*. In most cases sensorimotor gating signifies prepulse inhibition. Apart from cognition, other potential beneficial and undesirable actions related to mechanism of action are summarized. For schizophrenia, cognitive testing in humans has invariably been in association with established antipsychotics, yet the opposite is true for rodents. As clinical data are limited, comparative data for Alzheimer's disease are provided in some cases. Cognition is indicated when details on cognitive domains tested are unclear. Amyloid-β and tau refer to the load of toxic and/or phosphorylated forms of the proteins. 'Pyram.' implies increased firing rate of pyramidal cells. The drugs shown are described as selective for their respective targets, although some agents of limited selectivity are included where clinical data are available. 5-HT_{1A}, 5-hydroxytryptamine (serotonin) receptor 1A; α_{2A}-AR, α_{2A}-adrenergic receptor; γ, increased γ power; θ, increased θ power; Aβ, amyloid-β; ACh, acetylcholine; AD, Alzheimer's disease; ADHD, attention-deficit hyperactivity disorder; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; AP/HR, arterial pressure and/or heart rate; ARC, activity-regulated cytoskeleton-associated protein; ASD, autistic spectrum disorder; BCL-2, anti-apoptotic protein B cell lymphoma 2; BDNF, brain-derived neurotrophic factor; BLA, basolateral amygdala; BPD, bipolar disorder; BQCA, benzylquinolone carboxylic acid; CBIO, 5-chlorobenzo[d]isoxazol-3-ol; CBM, cerebellum; CBT, cognitive behavioural therapy; CDPPB, 3-cyano-*N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)benzamide; CFE, conditioned fear extinction; COMT, catechol-*O*-methyltransferase; CREB, cyclic AMP-responsive element binding protein; CV, cardiovascular; DA, dopamine; DARPP32, cyclic AMP-regulated neuronal phosphoprotein; DCP-LA, 8-[2-(2-pentyl-cyclopropylmethyl)-cyclopropyl]-octanoic acid; DMXB, 3-2,4-dimethoxy-benzylidene anabaseine; EDS, excessive daytime sleep; EPM, episodic memory; ERK, extracellular signal-regulated kinase; EXF, executive function; FXS, fragile X syndrome; $GABA_A$R, γ-aminobutyric acid type A receptor; Glu, glutamate; GORD, gastroesophageal reflux disease; GSK3β, glycogen synthase kinase 3β; HCN, hyperpolarization-activated cyclic nucleotide-gated channel; HD, Huntington's disease; HIPP, hippocampus; HPA, hypothalamic–pituitary–adrenal axis; HV, human volunteers; IUDR, inverse 'U'-shaped dose–response curve; LRS, lack of regional selectivity; LTD, long-term depression; LTP, long-term potentiation; MAPK, mitogen-activated protein kinase; MATRICS, Measurement and Treatment Research to Improve Cognition in Schizophrenia; mGluR5, metabotropic glutamate receptor 5; MOA, mechanism of action; MPEP, 2-methyl-6-(phenylethynyl)pyridine; MTEP, 3-((2-methyl-4-thiazolyl)ethynyl)pyridine; mTOR, mammalian target of rapamycin; NA, noradrenaline; NACC, nucleus accumbens; nAChR, nicotinic acetylcholine receptor; NCAM-PSA, polysialylated form of neuronal cell adhesion molecule; NF, neurofibromatosis; NMDA, *N*-methyl-D-aspartate; NOS1, nitric oxide synthase 1; NS, not selective; OCD, obsessive compulsive disorder; PAG, partial agonist; PAM, positive allosteric modulator; PD, Parkinson's disease; PDE4, cyclic AMP-specific phosphodiesterase 4; PFC, prefrontal cortex; PPI, prepulse inhibition; PKA, protein kinase A; PTSD, post-traumatic stress disorder; RTS, Rubinstein–Taybi syndrome; SAD, social anxiety disorder; SCZ, schizophrenia; SMG, sensorimotor gating; SOP, speed of processing; STM, striatum; TBPB, 1-[1′-(2-methylbenzyl)-1,4′-bipiperidin-4-yl]-1,3-dihydro-2*H*-benzimidazol-2-one; TOM, theory of mind; TRKB, neurotrophic tyrosine kinase receptor type 2; TSC, tuberous sclerosis; VLM, verbal learning memory; WM, working memory; XR, extended release.

As an example of the former strategy, glycine B agonists are designed to treat schizophrenia by stimulating hypoactive NMDA receptors localized on GABAergic interneurons in the PFC[42,50,98]. PFC-integrated cognition can also be restored by agonists acting downstream at the α2 subunit of $GABA_A$ receptors[42,98,133] (FIG. 4). Another example of this strategy is provided by the mechanism of action of COMT inhibitors, which compensate for low levels of dopamine in depression[75,76]. The epigenetic developmental disorder fragile X syndrome is characterized by excessive metabotropic glutamate receptor 5 (mGluR5)-mediated LTD, which leads to cognitive deficits that can be countered by mGluR5 antagonists at these sites[134,135]. Similarly, cognitive deficits associated with the ASD-related disorder tuberous sclerosis are provoked by mutations in the genes encoding tuberous sclerosis protein 1 and tuberous sclerosis protein 2, which interact with mTOR (Supplementary information S2 (figure)); cognitive impairment may therefore be reversed by the mTOR inhibitor rapamycin[63,136]. More generally, epigenetic reprogramming raises the hope of reversing the cognitive impairment accompanying monogenic ASD and caused by early-life stress (see below)[63,137,138].

Although they are conceptually attractive, pathology-driven approaches have limitations. First — as exemplified by rare, genetic forms of ASD — they may only be applicable to a subpopulation of patients. Second, molecular substrates underlying cognitive deficits are still not generally well understood. Third, it may be impossible to retrospectively normalize certain pathological events, such as neonatal insults that trigger alterations in synaptic architecture, and neural circuits that lead to schizophrenia[63,67].

Complementary strategies for symptomatic treatment do not attempt to normalize a pathological change, such as NMDA receptor hypofunction. Rather, they engage compensatory pro-cognitive mechanisms spared by the disorder in question. For example, there is no evidence for 5-HT_6 or histamine H_3 receptor hyperactivation in schizophrenia, yet antagonists hold promise for correcting a range of cognitive deficits in schizophrenia as well as in other disorders such as depression[113,114,139]. Pathology-decoupled mechanisms may actually have a broader application than pathology-driven strategies. In addition, some drugs should have beneficial actions not only against cognitive impairment but also against other symptoms (TABLE 2).

Domain-specific and generalized improvements in cognitive performance. A crucial issue is whether drugs will primarily correct one specific cognitive domain or improve several simultaneously. This obviously depends on the drug's mechanism of action. If a treatment completely reversed the underlying pathology it might — in theory — correct all deficits: one example, as further evoked below, is the blockade of mTOR overactivation in the monogenic disorder tuberous sclerosis[63,136]. Conversely, for a complex, multifactorial and heterogeneous disease like schizophrenia, aiming to normalize cognitive performance across all domains and in all patients appears to be overambitious.

There may be greater hope of finding a mechanism that could improve one specific cognitive domain in a transnosological manner across numerous diseases. Examples include oxytocin agonists for promoting social cognition[115–117], and α7 nicotinic acetylcholine receptor agonists for reinforcing attention and working memory[38,112,140] (Supplementary information S4 (box)) (TABLE 2). Clearly, a balance must be sought between the holy grail of 'one drug, all domains, all disorders' versus 'a separate drug for each domain and each disorder'. Although a pan-cognitive agent that can restore all domains may be unobtainable, multitarget drugs uniting complementary mechanisms of action appear to be the most promising route towards achieving a broad-based improvement in cognition[4,104].

Intracellular targets. Intracellular targets are attracting increasing interest as substrates for improving cognitive deficits in psychiatric disorders (FIG. 4) but they are not easy to exploit[43,45,57–60,63,212]. Such agents do not necessarily sidestep the issue of biphasic dose–response relationships, and they raise serious issues of tolerance and regional specificity because of the ubiquity and the multiple roles of most cellular targets. This is illustrated by the contrast between the restricted cerebral localization of 5-HT_6 receptors and the broad organismal distribution of phosphodiesterases catalysing cAMP degradation[114,141,142] (FIG. 4).

One solution may be to develop drugs that are selective for protein isoforms such as phosphodiesterase 4D or protein kinase Cε. Although achieving selectivity is a formidable challenge, exploitation of allosteric rather than catalytic sites may help drug design[141,143,144]. The influence of an inhibitor should be most prominent where and when the activity of its target is aberrantly high. Hence, another approach involves 'vectoring' drugs using dual-acting molecules that act on an intracellular protein and an upstream mechanism. For example, coupling inhibition of phosphodiesterase 4D to 5-HT_4 receptor agonism may restrict the facilitation of cAMP-dependent transmission to regions where 5-HT receptors control cognition[145]. Association of 5-HT_6 receptor antagonism with mTOR inhibition could yield similar benefits[114,136]. However, the design of drugs acting at two or more useful sites is challenging, and it is important to demonstrate an improved therapeutic window of beneficial versus deleterious actions as well as advantages of these drugs compared with selective drugs used in combination.

mTOR is involved in both LTP and LTD; furthermore, it favours and — when hyperactive — counters cognitive processes, so it is a particularly interesting intracellular target[136]. For example, tuberous sclerosis involves loss of the mTOR inhibitory protein partner tuberculosis sclerosis protein, leading to its overstimulation (Supplementary information S2 (figure)). Accordingly, the mTOR inhibitor rapamycin attenuated excessive hippocampal LTP and relieved cognitive deficits in a mouse model of tuberous sclerosis, and it may also be effective in other forms of ASD[136]. Rapamycin antagonises cognitive deficits elicited by the stimulation of cannabinoid receptor 1 on inhibitory GABAergic

Tuberous sclerosis
An autosomal dominant disorder, usually caused by sporadic mutations, leading to inactivation of the tumour suppressor genes tuberous sclerosis 1 (*TSC1*;also known as hamartin) and *TSC2* (also known as tuberin), which normally inhibit RHEB (a GTPase that is an activator of mammalian target of rapamycin). Loss of *TSC1* or *TSC2* leads to disinhibition of cell growth, cortical tubers and giant astrocytomas in the brain. Patients have deficits in attention, executive function and memory, as well as symptoms resembling autism spectrum disorder and attention deficit hyperactivity disorder.

interneurons in the hippocampus[146], and by the activation of 5-HT_6 and D3 receptors in the PFC[14] (TABLE 2), which suggests that mTOR overactivation may be relevant in schizophrenia. mTOR is also implicated in hippocampal processes sustaining abnormal fear memory[147]. Despite these indications that mTOR inhibitors might improve cognitive deficits, their therapeutic use could interfere with physiological LTP, and therefore raises issues of safety and specificity. Such concerns also apply to glycogen synthase kinase-3β inhibitors for promoting LTP and long-term memory in depression and bipolar disorder[148,149] (TABLE 2).

Protein phosphatase 1 and protein phosphatase 2B (also known as calcineurin) are targets for improving long-term memory as they interfere with the activation of *CREB* and downstream cognition-related genes such as *BDNF*[129] (FIG. 4). Accordingly, calcineurin inhibitors normalize the biphasic dose–response curves of drugs that enhance CREB activity by phosphorylation, and they promote LTP and learning in the hippocampus[129,150]. However, inhibition of calcineurin strengthens the formation of aversive memories in the amygdala, underscoring the multiple effects of phosphatases on CREB activity and cognition[129,151] (Supplementary information S2 (figure)). As with kinases, the question of specificity must be addressed before phosphatase inhibitors could be therapeutically exploited for treating cognitive impairment[129].

Neurogenesis. In recent years, considerable attention has been devoted to hippocampal neurogenesis, as its suppression is implicated in the impaired episodic memory associated with depression[4,127,152]. Adult-born, maturing dentate gyrus cells are especially excitable and plastic, sustain prolonged LTP and are rapidly incorporated into and coordinate neural networks, suggesting that increased neurogenesis favours cognition[127]. This explains the role of these cells in learning, consolidation and updating of new memories, differentiating separate memories in the dentate gyrus, transferring hippocampal-dependent memories to extra-hippocampal regions and coupling cognition to external context[127,153–155]. However, neurogenesis is no exception to the inverted-U dose–response rule, as both the generation and suppression of new neurons is required to optimize cognitive function[127]. Moreover, although antidepressants consistently enhance neurogenesis in rodents, they do not generally favour cognitive performance[4,156]. On balance, therefore, facilitation of neurogenesis is not yet a compelling target for improving cognition in psychiatric disorders.

Further insights may be gained by studying the cellular signals mediating the influence of neurogenesis on mood and cognition, such as activity-regulated cytoskeleton-associated protein[157] and the upstream driver of neurogenesis, BDNF, which acts via neurotrophic tyrosine kinase receptor type 2 (NTRK2; also known as TRKB)[40,158] (FIG. 4). The decreased expression of BDNF seen in chronic stress may be related to the cognitive deficits associated with depression, as BDNF mediates several forms of hippocampal and PFC plasticity, including LTP[40,152]. Interest in BDNF has been enhanced by reports showing that TRKB activators block the disruptive influence of stress on hippocampus-integrated long-term memory[40,158], and that BDNF promotes extinction learning[159].

Epigenetics. Stress-induced epigenetic changes in germline cells can be passed on to and alter cognition in offspring, suggesting that environmental risks for cognitive deficits might be relevant even before conception[63,137,138,160–162]. Some changes can be sex-specific. For example, epigenetic imprinting of the maternal allele of genes in the 15q11–13 region is implicated in the aetiology of ASD[160].

Of perhaps broader relevance to pharmacotherapy, gene-specific alterations in DNA methylation and histone acetylation (FIG. 4) may contribute to long-term impairments in cognition resulting from exposure to stress during early life[84,137,138]. For example, DNA hypomethylation (leading to enhanced expression) of the gene encoding corticotropin-releasing hormone may account for HPA axis overdrive in adults who have undergone early-life stress[137,138,162]. Conversely, perinatal stress leads to hypermethylation-induced silencing of the gene encoding BDNF[138]. Another example is ASD, in which hypermethylation-induced suppression of the oxytocin receptor gene has been reported[161].

Although decreases in DNA methylation are hard to counter pharmacologically, increases could be countered by DNA-*N*-methyltransferase (DNMT) inhibitors. Apart from their potential utility for correcting epigenetic changes provoked by early-life stress, DNMT inhibitors may also be useful in other disorders: for example, for counteracting the consolidation of fear memories seen in PTSD[137,138]. Furthermore, DNMT inhibitors may improve cognition in Rett's syndrome, an X-linked ASD characterized by gene hypermethylation[138]. In addition, in schizophrenia DNMT inhibitors may normalize cognitive deficits resulting from hypermethylation-induced suppression of PFC-localized genes synthesizing GABA and reelin (a developmental glycoprotein that controls synaptic plasticity)[163,164].

Reflecting interactions between DNMTs and histone deacetylases (HDACs), certain effects of DNMT inhibitors can be mimicked by suppressors of overactive HDACs, such as valproate[137,138]. Valproate is not selective for HDAC isoforms but selective inhibition of HDAC2 could be especially useful as this isoform negatively regulates hippocampal LTP, dendritic spine density and visual learning, as well as *BDNF* and *CREB* gene expression. HDAC2 inhibitors could therefore enhance these pro-cognitive processes and also promote fear-extinction learning, suggesting utility in PTSD[137,138,165,166]. Turning to ASDs, fragile X syndrome is characterized both by the loss of the mRNA translation regulator fragile X mental retardation 1 protein and by hypoacetylation of several functionally interacting classes of histones[134,138]. Valproate and a class III HDAC inhibitor increased histone acetylation and reactivated silenced fragile X mental retardation 1 protein in lymphoblastoid cells of patients with fragile X syndrome. Furthermore, valproate also improved social cognition and attention[167].

Rett's syndrome
An X-linked developmental disorder, mainly seen in females, caused by *de novo* mutations in the gene encoding methyl CpG binding protein 2 (MECP2). MECP2 normally binds to methylated DNA to transcriptionally repress genes, although some are activated. MECP2 also interacts with histone deacetylases, so its loss leads to gene-dependent histone hypo- and hyperacetylation. Patients with Rett's syndrome suffer from retardation, loss of verbal learning and speech, and impaired social cognition.

Rubinstein–Taybi syndrome is an epigenetic ASD-related disorder caused by mutations in CREB-binding proteins that act as histone acetyltransferases (Supplementary information S2 (figure)). Hence, HDAC inhibitors are being studied for the correction of cognitive deficits associated with this syndrome[137,138].

Finally, blockade of nuclear protein phosphatase 1 (FIG. 4) should, by promoting histone phosphorylation, favour hippocampal-dependent LTP and memory[137,166].

Epigenetic control of gene transcription operates around a set point: DNA hyper- or hypomethylation and histone hypo- or hyperacetylation disrupts cognition. Hence, pharmacotherapy must restore the balanced integration of multiple modes of epigenetic control that are requisite for appropriate cognitive performance. Specificity and safety are also vital issues. A particular concern is the risk of tumorigenic side effects, for example, resulting from hypermethylation-induced inactivation of tumour suppressor genes. Nonetheless, the targeting of methylation, acetylation and other epigenetic markers offers a potentially unique route for the correction of cognitive deficits in disorders such as ASD and schizophrenia.

Modulation of miRNA-controlled neural circuits. Further potential opportunities for restoring cognitive function are emerging from studies on brain-enriched microRNAs (miRNAs) that fine-tune cellular networks controlling synaptic plasticity and cognition, both developmentally and in adults[168]. For example, miR-134 inhibits hippocampal LTP and synaptic plasticity in mice by repressing CREB and BDNF synthesis[169]. The relevance to cognitive deficits in psychiatric disorders is supported by the observation that schizophrenia is associated with the abnormal biogenesis of miRNAs[170]. More specifically, decreased levels of miR-219 may be due to NMDA receptor hypoactivity[171]. Furthermore, in fragile X syndrome altered miRNA processing is implicated in the excessive mGluR5 signalling that contributes to cognitive impairment[134,135,170].

With regard to the therapeutic exploitation of miRNAs, one possibility could be to modify their biogenesis via cellular signals that phosphorylate the proteins involved in their maturation[81] (Supplementary information S2 (figure)) (FIG. 4). Another approach could be to recruit HDACs that suppress the synthesis of miR-134, thereby promoting cognition by preventing the inhibition of CREB and BDNF generation[169]; furthermore, various classes of modified and stabilized oligonucleotides, and of mRNA analogues, have been designed to directly interfere with (or mimic) the activity of specific miRNAs[170]. Even if miRNA-targeted therapy appears to be a distant prospect at present, miRNA profiling may serve as a biomarker both of cognitive dysfunction and of the actions of pro-cognitive agents[170].

Coupling pharmacotherapy with alternative strategies. As mentioned above, highly selective agents acting at a single target may be insufficient for the broad-based correction of cognitive deficits across pathogenetically distinct psychiatric disorders; this has encouraged interest in the development of multifunctional agents[4]. More generally, it might be questioned whether the administration of pro-cognitive agents (even in combinations) will always be adequate. Rather, a combination of pharmacotherapy with alternative strategies (BOX 5) may sometimes be a more effective strategy for palliating cognitive deficits in psychiatric disorders, similarly to the combination of cognitive behavioural therapy and pharmacotherapy for improving the treatment of depression[7,172–175].

For example, although they are only modestly active when administered alone, the α_2-adrenergic receptor antagonist yohimbine and the NMDA receptor partial agonist D-cycloserine enhance the efficacy of behavioural extinction techniques for countering cognitive deficits associated with phobias, panic disorder and OCD[106,176]. Furthermore, D-cycloserine and oxytocin might be especially effective for treating social cognitive deficits in ASD when coupled with behavioural therapies that likewise reinforce social learning[176,177] (Supplementary information S4 (box)). It may be instructive to extend such studies to cognitive remediation therapy[173] (BOX 5), as the effects of novel agents for relieving cognitive impairments in schizophrenia could best be expressed in synergy with this approach, rather than on top of antipsychotics that even interfere with their actions[3,97,98,174].

Clinical development of pro-cognitive agents

As highlighted above, many concepts are under exploration for countering cognitive dysfunction in psychiatric disorders. Their successful development depends on the careful translation of information acquired in animal and cellular models into clinical research[6,8,11,68,69,97]. Clinical studies of pro-cognitive agents can now use various techniques with experimental counterparts (FIG. 5) for: estimating optimal drug doses for efficacy; tracking cognitive actions in a manner complementary to behavioural rating scales; improving stratification (choice of subpopulations) of patients for drug trials; and exploring cerebral mechanisms of pro-cognitive properties.

Neuropsychological tests for evaluating cognitive function in volunteers and patients. Many procedures are available for characterizing the influence of drugs on cognitive performance, and several test batteries have been proposed[7,9,11,68,69,98,178,179] (BOX 2). Although these test batteries are instructive, one drawback is the potential loss of a large domain-specific effect in an overall (average) non-effect. Furthermore, patient performance and test sensitivity can be compromised by poor engagement during long, tiring and stressful clinical trials[6,9,10]. Another issue is that separate cognitive domains may not be genuinely independent, as they interact with and depend on common neuronal substrates[5,6,178,179] (FIGS 2,3). Notably, sustained, focused attention — together with high processing speed — is important for success in many procedures. These observations — and a common interrelationship with intelligence — explain why measures of cognitive performance are often correlated[5,6,97,178,179]. It might even be suggested that a single

Rubinstein–Taybi syndrome
A rare disorder characterized by autistic features, learning difficulties and poor attention. In approximately 50% of cases, it is caused by *de novo* mutations or deletions in the genes encoding CREB-binding protein or, rarely, histone acetyltransferase p300. These CREB-binding proteins and transcriptional co-activators are also histone acetylases, so patients display histone hypoacetylation and reduced gene transcription.

MicroRNAs
(miRNAs). Small, non-protein-coding sequences (22–24 nucleotides) of RNA, mostly derived from intergenic regions, although some are found in introns. An individual species of miRNA can bind to the 3′-untranslated regions of up to hundreds of different species of mRNA. Translation is usually suppressed but it is sometimes enhanced, and in certain cases mRNA may even be degraded.

Box 5 | **Alternative therapeutic strategies to address cognitive impairment**

Conventional psychotropic drugs were not specifically designed to target cognitive dysfunction in psychiatric disorders, and they display a range of (usually modest) beneficial, deleterious and neutral actions on cognition (see table). Non-pharmacotherapeutic strategies can be compared in terms of their differential impact on cognitive impairment versus emotional symptoms.

Despite showing efficacy in refractory depression, neither electroconvulsive therapy (which provokes transient retrograde amnesia) nor deep-brain stimulation of the subgenual cortex exerts a long-term, beneficial influence on cognition[229,230]. Conversely, despite having a less robust influence on depression, repetitive transcranial magnetic stimulation (rTMS) over the left dorsolateral prefrontal cortex (PFC) appears to promote attention, working memory and procedural learning. It probably acts by enhancing GABA (γ-aminobutyric acid)-ergic interneuron activity, γ-oscillations and PFC-driven top-down cognitive control[227,230–233]. Intriguingly, rTMS of the PFC enhanced γ-activity and cognitive processing in autism spectrum disorder, and elicited Savant syndrome-like cognitive feats in normal individuals[233,234]. In schizophrenia, enhanced cognition and suppression of auditory hallucinations has been reported[230]. Beneficial effects are not restricted to the PFC. Application of rTMS to the right parietal cortex favours focused attention, whereas rTMS over Broca's or Wernickes's areas improves verbal fluency and language learning; these effects mimic direct transcranial current stimulation — a technique that is used for rehabilitating patients with language and cognitive deficits following brain damage[230,235].

Psychotherapy encompasses techniques such as problem solving, behavioural activation and cognitive behavioural therapy (CBT), which encourages patients to shed their negative views on themselves and their life. CBT for depression and anxiety can lead to durable improvements in mood (outlasting treatment), possibly by strengthening PFC-controlled top-down control of emotional processing in dysfunctional limbic structures like the amygdala and the hippocampus[172,236]. However, CBT has not yet been demonstrated to improve cognitive function. Conversely, cognitive remediation therapy (CRT), which adopts an approach that is broadly similar to cognitive training in elderly patients, can improve cognitive function in schizophrenia[173,237] and possibly also in depression[238]. As for CBT, it is labour-intensive and treatment outcome depends on the therapist, methodology, content and intensity of the programme. Furthermore, CRT cannot be used for all patients and requires a regular commitment despite the low motivation of many patients with schizophrenia. Nonetheless, CRT is instructive as improvement is measured in terms of community functioning, such as salary, time spent at work and normalized social interactions.

Finally, exposure therapy is a cognitive approach for treating post-traumatic stress disorder, phobias, social anxiety disorder and obsessive compulsive disorders. Its application involves repeated contact with an aversive situation or stimulus to encourage desensitization (extinction)[106,176,177].

Ideally, a novel pharmacotherapy should target both the emotional and cognitive impairments in psychiatric disorders. Moreover, agents should be developed and evaluated alone, in combination with other pro-cognitive mechanisms as well as in association with alternative therapies as a function of the symptom and patient population concerned. The combination of pharmacotherapy with CBT, CRT or similar approaches may be particularly effective for improving the cognitive impairments associated with psychiatric disorders[174,175].

Therapeutic approach	Influence on emotional symptoms*	Influence on cognitive impairment*	Psychiatric disorders targeted
Currently available pharmacotherapy	+	–/0/+	Schizophrenia, depression, bipolar disorder, anxiety disorders
Deep-brain stimulation or electroconvulsive therapy	+	0/–	Major depression
Repetitive transcranial magnetic stimulation	0/+	0/+	Mainly depression (autism, schizophrenia)
Cognitive behavioural therapy	+	0	Mainly depression (anxiety disorders)
Cognitive remediation therapy	0/+	+	Mainly schizophrenia (depression)
Exposure therapy for desensitization	0/+	+	Post-traumatic stress disorder, obsessive compulsive disorder, phobias, social anxiety disorders
Improved drugs (alone and in combination with above strategies)	+	+	Dependent on mechanism of action

*The '+' symbol corresponds to improvement; the '–' symbol corresponds to worsening; and '0' corresponds to no marked change.

Savant syndrome
A rare syndrome that is closely associated with high-functioning autism spectrum disorder but also found in other developmental disorders and following damage to or disease of the central nervous system. It alludes to 'islands of genius' in one or a few cognitive domains such as mathematics despite broader deficits in others, and is usually associated with prodigious memory. Savant-like abilities can partially be reproduced by transcranial magnetic stimulation over the cortex.

dimension, such as working memory, would suffice to predict the overall effect of the drug on cognitive function. However, this is both risky and contentious, so it is best to use multiple procedures to monitor the influence of drugs on baseline cognition and deficits in patients.

The importance of optimizing measurements of cognitive performance in volunteers and patients, and of optimizing comparability between preclinical and clinical procedures, is exemplified by the establishment of the MATRICS (Measurement and Treatment Research

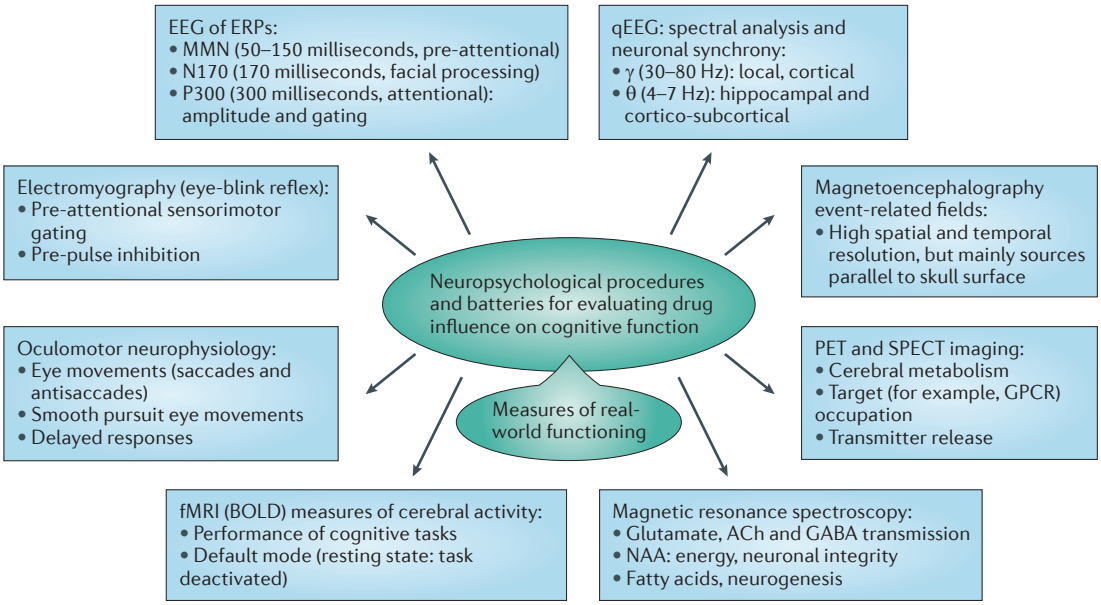

Figure 5 | **Overview of translational models for characterizing and predicting the influence of pharmacological agents on cognitive function in humans.** Numerous procedures are available for assessing cognitive domains ranging from attention to social cognition, and several test batteries have been designed, such as the CANTAB (Cambridge Neuropsychological Test Automated Battery) core cognition test and the BACS (Brief Assessment of Cognition in Schizophrenia) test for schizophrenia, as well as the MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia)-derived consensus cognitive battery (BOX 2). Currently, efforts are being directed towards measures that are more closely linked to real-world cognitive functioning. Complementary approaches for exploring the actions of putative pro-cognitive agents in humans, most of which have translational counterparts in rodents, may be broadly classified as follows: quantitative electroencephalographical (qEEG) analysis coupled to spectral analysis of neural circuits, and EEG quantification of auditory event-related potentials (ERPs); magnetoencephalography, which monitors magnetic fields emitted by synchronized neurons with millisecond precision; sensorimotor paradigms, which include measures of eye movement; functional magnetic resonance imaging (fMRI) to estimate neuronal activity in defined brain regions; positron emission tomography (PET) and single-photon emission computed tomography (SPECT) to visualize radioligand binding; and magnetic resonance spectroscopy to quantify the levels of neuromediators. Many informative ERP-based signals can be translationally exploited. Notably, prepulse inhibition refers to the blunting of the startle reflex to an intense auditory stimulus following pre-exposure 100 milliseconds earlier to a subthreshold stimulus. Mismatch negativity (MMN) is a response to an (auditory or visual) oddball stimulus deviating from a regular sequence. Negative deflection (N170) is a 170-millisecond EEG signal that is associated with facial processing, whereas a positive 300-millisecond (P300) signal is associated with attention to a task-relevant, infrequent stimulus. ACh, acetylcholine; BOLD, blood oxygenation level-dependent; GABA, γ-aminobutyric acid; GPCR, G protein-coupled receptor; NAA, *N*-acetylaspartate.

to Improve Cognition in Schizophrenia) initiative for schizophrenia[6,69,98,178,179] (BOX 2). The insights gained from this initiative could be exploited to set up comparable programmes dedicated to improving cognition in depression. In an effort to better relate drug actions to everyday living, for both MATRICS and other programmes, co-primary measures of functional capacity are being developed, including patient competence to undertake tasks such as shopping[180,181]. Improved prediction of the social and vocational outcomes of treatment is crucial, as relief of functional disability — not superior performance in test batteries — is the real goal. Notably, however, one tricky question is whether improved real-world functioning can be attributed to the cognitive and/or emotional actions of a specific treatment.

With regard to measures, patient self-assessment is desirable but can be misleading. Furthermore, although informants can reliably assess cognitive abilities of patients, this is not usually practical for drug trials[6,180,181]. Finally, the design of long-term studies — for example, from the prodrome to diagnosis in schizophrenia — is far from simple. Shifts from baseline performance rather than changes versus placebo may be preferable, but practice effects following repeated testing must be considered[6,182].

All clinical studies in the psychiatric domain commence with human volunteers. This population can deliver early feedback on how drugs potentially affect specific cognitive domains, how their effects may best be monitored in subsequent studies, and which underlying cerebral substrates they possibly engage — especially when neurocognitive tests are coupled to electroencephalography (EEG) and neuroimaging (FIG. 5). Some observations may also be of more direct relevance to patient populations. For example, oxytocin consistently enhances social cognition in healthy probands as well as in autistic or schizophrenic individuals[115–117]. Acute administration of the NMDA receptor antagonist

ketamine to volunteers mimics the NMDA receptor hypoactivity observed in schizophrenia, so this procedure is useful for characterizing the influence of putative pro-cognitive antipsychotics on sensorimotor gating (see below) and cognition[50,71,98]. Furthermore, abnormalities in cognitive function and its underlying neural substrates can be probed in healthy individuals displaying variants of susceptibility genes for psychiatric disorders, such as zinc finger protein 804A (see above)[72,79,80].

Nonetheless, several important limitations of Phase I studies should be mentioned. The influence of acute drug administration on baseline cognitive function in volunteers — and even its disruption by risk genes or pharmacological agents — may differ from its actions following chronic administration to patients with more complex pathologies. For example, drugs that are designed to normalize the aberrant epigenetic programming that causes cognitive dysfunction in ASD would be hard to evaluate in volunteers. Furthermore, many drugs developed for schizophrenia are intended for use in combinations, yet studies with other classes of agents cannot be undertaken in Phase I trials. More generally, the influence of drugs on cognitive performance in patients will reflect not only their direct impact on cognitive mechanisms but also their ability to relieve emotional symptoms, a facet largely inaccessible in volunteers. Finally, studies in healthy individuals are inevitably restricted to neurocognitive procedures rather than genuine measures of real-world function. Without neglecting the importance of early-stage clinical studies, these points illustrate the risk of drawing premature conclusions, and highlight that proof of concept can only come from studies in patients.

Oculomotor studies of the control of cognition. Eye-movement studies (FIG. 5) can be exploited to evaluate the influence of drugs on neural processes related to cognition[183–186]. As few preclinical models of social cognition are recognized, oculomotor-tracking studies of eye gaze in primates as well as in humans — including attention to (and avoidance of) the gaze of others — are of particular interest[184]. Oculomotor paradigms have also been proposed for evaluating the effect of drugs on neural bases involved in sensorimotor gating, attention, working memory, executive function and procedural memory[185]. For example, oculomotor techniques in primates have been used to explore the influence of PFC populations of D1 receptors on working memory and top-down control of visual processing[185,186]. Such observations provide a translational platform for clinical studies showing that oculomotor measures are sensitive to both the favourable and unfavourable effects of drugs such as antipsychotics and benzodiazepines on cognition[183,185].

Underpinning interest in eye-moment studies in patients, oculomotor deficits have been reported in schizophrenia and several other psychiatric disorders[183–185]. Eye-movement paradigms can also be coupled to neuroimaging to characterize the influence of potential pro-cognitive drugs on cerebral circuits[187]. Although further work is needed to clarify the relationship between eye-movement measures and cognitive mechanisms, they deserve further characterization as a distinctive translational approach for exploring the actions of putative pro-cognitive drugs, especially with respect to social cognition.

Sensorimotor gating in relation to cognitive performance. Information processing and sensory gating — pre-attentional and attentional processes that are required for effective cognitive performance — can be monitored by various procedures[7,71,98,188,189] (FIG. 5). These include prepulse inhibition (FIG. 5), which has marked dopaminergic, serotonergic and glutamatergic components. Accordingly, deficits in prepulse inhibition in patients with schizophrenia, and its disruption by psychotomimetic agents in volunteers, can be countered by antipsychotics[7,68,71,189]. Evaluation of new drugs, such as nicotinic acetylcholine receptor agonists and histamine H_3 receptor antagonists, can be guided by their influence on the perturbation of prepulse inhibition in humans and rodents by psychotomimetics and (in the latter) by genetic and developmental models of schizophrenia[52,71,97,98,139,140,189] (TABLE 2).

An additional pre-attentional response, 'mismatch negativity' (BOX 5), has a marked glutamatergic and NMDA receptor component, and deficits have so far been mainly seen in schizophrenia; moreover, impairment in high-risk individuals predicts onset of the disease[7,71,190]. In patients with schizophrenia mismatch negativity was enhanced by *N*-acetylcysteine, which elevates extracellular levels of glutamate in the PFC[191]. These observations highlight the interest in sensorimotor gating paradigms for exploring the effects of pro-cognitive drugs on pre-attentional and attentional function in both animals and in humans (FIG. 5).

Quantitative EEG for probing cognitive circuits. By directly probing large-scale electrical activity in the brain with high temporal resolution, quantitative EEG (qEEG) coupled to spectral analysis provides unique insights into the cortical processes underlying cognitive function and affected both in psychiatric disorders and by pharmacotherapy[46,47,188] (FIG. 5). EEG monitoring of cortical–subcortical networks in humans and animals is of particular interest because alterations in neural synchronization and connectivity are strongly related to cognitive deficits and their pharmacotherapeutic modulation[46,47,192,193] (BOX 4). For example, oxytocin can shift cortical resources in volunteers to regions involved in social cognition and emotional processing[194]. EEG studies are also instructive for characterizing the influence of drugs on arousal, sleep–wake cycles and sleep architecture, which can affect memory consolidation and other cognitive processes[107].

The related technique of magnetoencephalography picks up magnetic fields generated by intraneuronal currents to provide fine-grained (millisecond) temporal and spatial (superior to EEG) information on coordinated neuronal activity. It can also be used to characterize the relationship of cortical networks to cognition in psychiatric disorders[188]. Supporting its use for drug characterization, diazepam modifies θ- and γ-oscillations with a profile that is consistent with its negative influence on

cognition[195]. Low-resolution brain electromagnetic tomography provides three-dimensional information on electrical activity, affording further insights into the actions of pro-cognitive drugs and the allocation of resources to cognitive operations. It revealed a positive influence of modafinil on processing speed, and of psychotropic agents on network oscillations in relation to cognition[123,196].

Functional magnetic resonance imaging: cognitive task-related and default modes. An important difference between functional magnetic resonance imaging (fMRI) and qEEG is the high spatial (but lower temporal) resolution of fMRI, emphasizing complementary roles in drug characterization[48,49,53,188,197]. Although it is challenging to perform in animals (which must be anesthetized)[7], fMRI is widely used in humans, and there is increasing interest in pharmacological fMRI to explore the actions of new drugs. It has, for example, been used to probe the influence of antipsychotics and D1 receptor agonists on PFC connectivity in relation to cognition in schizophrenia[198,199]. Furthermore, α7 nicotinic acetylcholine receptor agonists have been shown to recruit hippocampal GABAergic interneurons[200]. Recent fMRI studies of the influence of oxytocin on social cognition suggest that it suppresses fear responses in the amygdala while enhancing insular mediation of empathy[201]. Interestingly, fMRI has shown that oxytocin and vasopressin influence cognitive and emotional processing via contrasting mechanisms of action, yet in each case involving the amygdala[115,202]. Despite its limitations[7,197], pharmacological fMRI holds considerable promise for the prediction of therapeutic (and undesirable) effects of pro-cognitive drugs, exploration of mechanisms of action and estimation of active doses, particularly when used in parallel with qEEG.

Although drug actions can be instructively evaluated while performing cognitive procedures, the human brain has an fMRI-accessible default mode of resting-state operation that is deactivated by goal-directed tasks involving attention and executive function[203]. This default network includes the medial PFC, posterior cingulate, precuneus, angular gyrus and temporal lobes (FIG. 3), although other related circuits may also be involved[203]. Default-mode networks mirror introspection, mind-wandering and the theory of mind, as well as social and emotional processing, and are related to episodic memory and prospective cognition (Supplementary information S5 (box)). Default-mode network function is disrupted in ASD, schizophrenia and other psychiatric disorders. In pharmacological fMRI studies, an α7 nicotinic acetylcholine receptor agonist enhanced default-mode function in schizophrenia, acting differently to the antipsychotic olanzapine[204,205]. Furthermore, modafinil enhanced task-related deactivation in volunteers, which was consistent with enhanced processing speed and PFC-mediated cognitive control[206].

Proton magnetic resonance spectroscopy. Paralleling neurochemical dialysis studies in rodents, proton magnetic resonance spectroscopy probes glutamatergic, GABAergic and cholinergic transmission in humans, and also evaluates levels of *N*-acetylasparate, which is an index of neuronal integrity[7,53,207] (FIG. 5). Three examples illustrate its relevance to cognitive dysfunction in psychiatric disorders and pro-cognitive drug characterization. First, in patients with schizophrenia, decreased levels of glutamate and *N*-acetylaspartate were correlated with cognitive deficits[207,208]. Second, the influence of antipsychotics on glutamate levels could be related to their modulation of cognition, such as a modest beneficial effect of clozapine on verbal memory[208,209]. Third, a distinctive spectral peak of fatty acids that is characteristic of progenitor neuronal cells may reflect neurogenetic processes. This offers a parameter for clarifying the relationship of neurogenesis with the influence of drugs on cognition[210].

PET and single-photon emission computed tomography. Like fMRI, positron emission tomography (PET) can be used to indirectly evaluate, with high (from seconds to minutes) temporal resolution, the influence of drugs on neuronal activity (glucose and/or oxygen utilization) in the PFC and other structures controlling cognition[7,53,211]. Although challenging to perform in animals[7], PET is widely used in clinical trials to study the dose- and time-dependent occupation of regionally defined populations of GPCRs and other targets by drugs in relation to their influence on cognition. Appropriate radioligands are available for many sites controlling cognition, including dopamine D3 receptors, noradrenaline transporters and α4β2 nicotinic acetylcholine receptors[211]. The related technique of single-photon emission computed tomography generates three-dimensional images of the brain, although spatial resolution is usually less impressive[7,53]. It has, for example, been used to evaluate the influence of clozapine on cortico–striatal–thalamic pathways in relation to its influence on cognition[209].

Translating translational research. Clearly, there is a panoply of techniques for guiding the clinical development of pro-cognitive agents and for optimizing the translational link from animals to the clinic. Time, expense and risk are key factors and it is impossible to perform all conceivable studies for any individual drug. Choosing the most appropriate and informative studies should help to reduce attrition by refining the choice of clinical indication, cognitive domain and drug doses, thereby enhancing the success rate of clinical trials. However, despite the sophistication of techniques — including PET, magnetoencephalography, the insights from fMRI and EEG analyses, and the vital role of neurocognitive batteries — these are all essentially surrogate parameters. As noted above, it is crucial to show that pro-cognitive treatments lead to a functionally relevant enhancement of cognitive performance and an improved quality of life. That is, we must rise to the challenge of 'translating translational research' for the more effective development and clinical exploitation of improved drugs to treat the cognitive deficits associated with psychiatric disorders.

Concluding comments

Although historically there has been an emphasis on the motivational, affective and emotional symptoms of psychiatric disorders, cognitive impairment is just as prominent, persistent and disabling. In recent years we

Functional magnetic resonance imaging
(fMRI). A technique that exploits the differential paramagnetic properties of oxy- and deoxyhaemoglobin to estimate local cerebral blood oxygenation level-dependent (BOLD) activity. Increased oxygen supply compensates for (and transiently exceeds) energy needs, so the BOLD signal is proportional to neuronal activity. Interpretation of data is challenging as BOLD integrates changes both in neurons and in glia, pre- and postsynaptic changes in excitability, as well as local and upstream effects of drugs. Furthermore, BOLD signals can be affected by energy balance and haemodynamic parameters.

Graph theory
A mathematical approach for modelling complex networks whereby individual elements, like cerebral regions, neurons or cellular proteins, are considered as 'nodes' linked by 'edges'. Brain graphs (derived from neuroimaging data) and cellular graphs (derived from studies of protein networks) reveal non-random topological properties such as modularity (clusters of nodes highly connected to each other) and hubs (nodes with numerous connections). These properties help to optimize network function, including cognitive processing.

have witnessed major advances in our understanding of the cellular and neuronal circuits controlling cognition, and of the causes of their perturbation in psychiatric disorders. In this regard, the notion of functional–structural networks and their disruption has emerged to be of particular importance. These insights, along with the improved linking of events integrated at the molecular versus neural level, studies of epigenetic programming, identification of novel drug concepts and other advances underpin the hope that it should ultimately be possible to improve the poor cognitive performance in patients with psychiatric disorders. However, rigorous experimental validation of concepts and targets will be required, as well as the imaginative use of translational procedures to maximize the chances of successful drug development and therapeutic exploitation.

As there is no unitary cause of cognitive impairment, and no single solution for its control, many promising lines of research should be pursued. Furthermore, improved treatment should be articulated around the notions of: uniting complementary mechanisms of pro-cognitive action (for example, with multitarget drugs); combining the benefits of pharmacotherapy with alternative strategies; and addressing both the emotional and interrelated cognitive deficits associated with psychiatric disorders. Irrespective of the mode of therapy, a focus on genuine improvements in the real-world functioning of patients is essential.

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Competing interests statement

The authors declare competing financial interests: see Web version for details.

SUPPLEMENTARY INFORMATION

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