Cognitive deficits caused by prefrontal cortical and hippocampal neural disinhibition

Short title: Prefrontal and hippocampal GABA and cognition

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Abstract

We review recent evidence concerning the significance of inhibitory GABA transmission and of neural disinhibition, i.e. deficient GABA transmission, within prefrontal cortex and hippocampus for clinically relevant cognitive functions. Both regions support important cognitive functions, including attention and memory, and their dysfunction has been implicated in cognitive deficits characterizing neuropsychiatric disorders. GABAergic inhibition shapes cortico-hippocampal neural activity and, recently, prefrontal and hippocampal neural disinhibition has emerged as a pathophysiological feature of major neuropsychiatric disorders, especially schizophrenia and age-related cognitive decline. Regional neural disinhibition, disrupting spatio-temporal control of neural activity and causing aberrant drive of projections, may disrupt processing within the disinhibited region and efferent regions. Recent studies in rats showed that prefrontal and hippocampal neural disinhibition (by local GABA antagonist microinfusion) dysregulates burst firing, which has been associated with important aspects of neural information processing. Using translational tests of clinically-relevant cognitive functions, these studies showed that prefrontal and hippocampal neural disinhibition disrupts regional cognitive functions (including prefrontal attention and hippocampal memory function); moreover, hippocampal neural disinhibition disrupted attentional performance, which does not require the hippocampus, but requires prefrontal-striatal circuits modulated by the hippocampus. However, some prefrontal and hippocampal functions (including inhibitory response control) are spared by regional disinhibition. We consider conceptual implications of these findings, regarding the distinct relationships of distinct cognitive functions to prefrontal and hippocampal GABA tone and neural activity. Moreover, the findings support that prefrontal and hippocampal neural disinhibition contributes to clinically relevant cognitive deficits, and we consider pharmacological strategies for ameliorating cognitive deficits by rebalancing disinhibition-induced aberrant neural activity.

Non-approved abbreviations

AHP, afterhyperpolarization

5-CSRT, 5-choice-serial-reaction-time

DMTP, delayed-matching-to-place

mGluR, metabotropic glutamate receptor

PAM, positive allosteric modulator

Introduction

Cognitive deficits, including attentional and memory deficits, are a cross-diagnostic symptom of many neuropsychiatric disorders that causes substantial functional disability and is a major treatment challenge; a prominent idea is that dysfunction within the prefrontal cortex and hippocampus causes such cognitive deficits (Millan *et al.*, 2012). In this review, we will begin by highlighting evidence that hippocampal and prefrontal neural disinhibition, i.e. deficient inhibitory GABA function, is a key neuropathological feature of important neuropsychiatric disorders characterized by cognitive deficits, including schizophrenia and age-related cognitive decline (**Table 1**). Although inhibitory GABA neurotransmission has emerged as a key factor in shaping neural activity in neocortex, including prefrontal cortex, and hippocampus (Buzsaki and Wang, 2012; Isaacson and Scanziani, 2011; Mann and Paulsen, 2007), direct evidence for a causal contribution of prefrontal and hippocampal neural disinhibition to clinically relevant cognitive deficits has been lacking until recently. We will highlight that neural disinhibition within prefrontal cortex or hippocampus has the potential to disrupt cognitive processing mediated by these regions and efferent sites, because regional inhibitory GABA transmission may be important to maintain balanced levels of neural activity within these respective regions, as well as in their projection sites. The review will, then, focus on recent studies examining the neural and cognitive impact of prefrontal and hippocampal reductions in inhibitory GABA tone by acute intra-cerebral microinfusions of GABA antagonists in rats, using in vivo electrophysiology and translational behavioural assays of clinically relevant cognitive functions. These studies revealed that prefrontal and hippocampal neural disinhibition causes aberrant neural activity within the disinhibited regions and impairs key cognitive functions, including attention and memory, in a way that is consistent with regional neural disinhibition disrupting cognitive processing of the disinhibited regions and their projection sites. We will consider the theoretical implications of these findings, concerning the distinct relationships of regional inhibitory GABA tone and neural activity to distinct cognitive functions, their clinical implications, as well as potential pharmacological strategies to rebalance disinhibition-induced aberrant neural activity in order to ameliorate cognitive impairments.

Prefrontal and hippocampal neural disinhibition in neuropsychiatric disorders characterized by cognitive deficits

Prefrontal cortex and hippocampus play key roles in important cognitive functions, including attention and everyday memory (Bast, 2007; Bast, 2011; Chudasama and Robbins, 2006). Over the past 20 years, neural disinhibition, i.e. reduced inhibitory GABA function, within these regions has emerged as a common feature of major neuropsychiatric disorders characterized by impairments in these important cognitive functions **(Table 1)**.

The most compelling evidence comes from studies on the neurobiological mechanisms underlying schizophrenia. Alterations in GABA-related post-mortem markers consistent with reduced prefrontal and hippocampal inhibitory GABA neuron function are a key neuropathological feature of schizophrenia, and many rodent models of schizophrenia show similar evidence for such neural disinhibition (Benes and Berretta, 2001; Heckers and Konradi, 2015; Lewis and Moghaddam, 2006; Lisman *et al.*, 2008; O'Donnell, 2011; Ruzicka *et al.*, 2015). The well-characterized schizophrenia-related cognitive and behavioural changes caused by NMDA receptor antagonists in humans and animal models have also been linked to neural disinhibition, with reduced GABAergic inhibition in hippocampus and neocortex being a key effect of NMDA receptor antagonists, possibly reflecting a blockade of NMDA receptor-mediated excitation of inhibitory GABA neurons (Anticevic *et al.*, 2012; Lisman *et al.*, 2008; Moghaddam and Krystal, 2012). Given that inhibitory GABA neurons play a key role in shaping hippocampal and neocortical neural oscillations (Buzsaki and Wang, 2012; Mann and Paulsen, 2007), neural disinhibition may also, at least partly, explain the aberrant oscillatory brain activity revealed by EEG and MEG measures in patients with schizophrenia (Lisman *et al.*, 2008; Uhlhaas and Singer, 2012). Finally, neural disinhibition may underlie regional brain hyperactivity reported by clinical imaging studies of early-stage schizophrenia (Anticevic *et al.*, 2015; Heckers and Konradi, 2015; Schobel *et al.*, 2013; Schobel *et al.*, 2009). More recently, consistent evidence for cortico-hippocampal neural hyperactivity due to neural disinhibition has also emerged in cognitive aging and early stages of Alzheimer's disease, with clinical and animal model studies showing a compromised inhibitory GABA system and aberrant increases in neural activity (Bakker *et al.*, 2012; Busche and Konnerth, 2016; Haberman *et al.*, 2017; Huang and Mucke, 2012; Robitsek *et al.*, 2015; Sanchez *et al.*,

2012; Schwab *et al.*, 2013; Sperling *et al.*, 2010; Spiegel *et al.*, 2013; Stanley *et al.*, 2012; Thomé *et al.*, 2016; Verret *et al.*, 2012; Wilson *et al*., 2006)[1].

In the long term, aberrant neural activity due to GABA dysfunction may lead to compensatory adjustments and excitotoxicity that could underlie the regional brain hypoactivity and atrophy characterising later stages of schizophrenia and age-related cognitive disorders (Anticevic *et al.*, 2015; Heckers and Konradi, 2015; Huang and Mucke, 2012; Krystal and Anticevic, 2015). Direct evidence for this possibility comes from longitudinal functional and structural imaging studies in schizophrenia patients and in a rodent model of schizophrenia, in which hippocampal metabolic overactivity in the prodrome or at early stages of the mouse model predicted hippocampal atrophy in patients who had progressed to schizophrenia or at later stages of the mouse model, respectively (Schobel *et al.*, 2013). However, as described in the following, independent of the induction of atrophy, aberrant prefrontal and hippocampal neural activity caused by reduced GABA function may cause clinically relevant cognitive deficits, and recent studies in rodent models support this.

Regional neural disinhibition may disrupt processing within the disinhibited region and in efferent sites

Inhibitory neurotransmission by GABA, which balances and controls excitatory neurotransmission, is important for shaping neural activity in hippocampus and neocortex, including prefrontal cortex (Buzsaki and Wang, 2012; Isaacson and Scanziani, 2011; Mann and Paulsen, 2007). Tightly controlled, spatio-temporally specific neuronal disinhibition, i.e. temporary reductions in the GABAergic inhibition of specific synaptic pathways, may open windows for enhanced processing of relevant stimuli, thereby facilitating learning and memory and, potentially, other cognitive processes (Letzkus *et al.*, 2015). However, tonic

[1] Increased hippocampal neural activity may, at first glance, appear at odds with another hippocampal biomarker of cognitive ageing: in vitro electrophysiological recordings from hippocampal slices of aged rabbits and rats consistently reveal an enhanced post-burst afterhyperpolarization (AHP) in pyramidal neurons of the hippocampal CA1 subregion, which results in hypoexcitability of these neurons (Oh *et al.*, 2010). However, contrasting such hypoexcitability in CA1, the CA3 subregion of the aged rat hippocampus shows hyperexcitability in vitro (Simkin *et al.*, 2015). These regional differences reported in vitro chime with some in vivo studies indicating that CA3 is the main locus of hippocampal neural hyperactivity associated with cognitive ageing in humans and rats (Bakker *et al.*, 2012; Wilson *et al.*, 2006). In light of the emerging evidence of hippocampal neural hyperactivity in aging, it has been suggested that the hypoexcitability in CA1 neurons may be a compensatory response to increased activity at CA3-CA1 synapses due to CA3 hyperexcitability (Simkin *et al.*, 2015).

neural disinhibition[2] within a brain region that is not restricted to specific synapses may disrupt both regional function and distal function in efferent brain sites (**Fig. 1**). First, by interfering with spatio-temporal control of regional neural activity, neural disinhibition within a brain region is likely to disrupt normal regional function. For example, single-neuron recording studies in animal models show that stimulus-selective, task-appropriate tuning of neurons in the sensory cortices (Isaacson and Scanziani, 2011) and in the prefrontal cortex (Rao *et al.*, 2000) requires intact GABA transmission. Second, by causing aberrant drive of projections, regional disinhibition may disrupt normal neural activity in efferent sites, thereby disrupting the normal function of these efferent sites. These two general hypotheses support two specific hypotheses concerning the cognitive impact of prefrontal and hippocampal neural disinhibition. First, given the importance of prefrontal cortex for attention (Chudasama and Robbins, 2006) and of hippocampus for everyday types of memory, such as episodic and place memory (Bast, 2007; Bast, 2011), prefrontal and hippocampal disinhibition may impair attention and everyday memory tasks, respectively. Second, considering strong hippocampo-prefrontal projections, hippocampal disinhibition may disrupt prefrontal-dependent cognitive function, such as attention, by disrupting prefrontal processing (Bast, 2011).

To test these hypotheses, we began investigating the neuro-cognitive impact of prefrontal and hippocampal neural disinhibition in rats. We induced temporary prefrontal and hippocampal neural disinhibition, using acute microinfusion of subconvulsive doses of the selective GABA-A receptor antagonist picrotoxin into the medial prefrontal cortex (Pezze *et al.*, 2014) or hippocampus (McGarrity *et al.*, 2016) and examined the impact on translational behavioural tests of attention and everyday-type place learning. The hippocampal infusions targeted temporal (also referred to as ventral) to intermediate hippocampus, because this part of the hippocampus features strong hippocampo-prefrontal connectivity and corresponds to human anterior hippocampus, dysfunction of which has been implicated in schizophrenia (Bast, 2011). To link any cognitive effects to specific neural changes within prefrontal cortex or hippocampus, we measured how picrotoxin infusions affected neural activity in the vicinity of the infusion site, using in vivo electrophysiological recordings in anaesthetised rats.

[2] Note that tonic, i.e. long-lasting, neural disinhibition (such as resulting from reduced GABA neuron function in neuropsychiatric disorders or from intra-cerebral microinfusions of GABA-A antagonists in rat models) would be expected to interfere with both phasic inhibition, caused by transient increases in synaptic GABA following firing of GABA neurons, and with tonic inhibition, caused by ambient GABA (Farrant and Nusser, 2005).

Neural disinhibition in prefrontal cortex and hippocampus enhances burst firing of neurons within these regions

In both the medial prefrontal cortex (Pezze *et al.*, 2014) and the hippocampus (McGarrity *et al.*, 2016), disinhibition by picrotoxin markedly enhanced firing of neurons in bursts, particularly increasing within-burst firing rate and prevalence of burst firing (e.g., as reflected by increased percentage of spikes in burst) within the prefrontal cortex and increasing prevalence of burst firing, accompanied by a moderate increase in overall firing rate, in the hippocampus (**Fig. 2**). Bursts are periods of relatively high firing that are separated by periods of comparatively little firing (Lisman, 1997). Our findings converge with the enhanced hippocampal burst firing reported following pharmaco- or optogenetic silencing of hippocampal inhibitory GABA interneurons in vitro (Lovett-Barron *et al.*, 2012) and in awake mice (Royer *et al.*, 2012) and suggest a key role of GABAergic inhibition in the regulation of prefrontal and hippocampal burst firing.

Aberrant burst firing is likely to be detrimental for cognitive functions of both the disinhibited region and their projection sites. Bursts have been suggested to be key units of neural information processing, increasing the reliability and selectivity of neural communication, and burst firing is particularly effective in driving post-synaptic targets (Cooper, 2002; Izhikevich *et al.*, 2003; Larkum, 2013; Lisman, 1997). In the visual cortex, short periods of vigorous firing in response to task-relevant stimuli, separated by relatively quiescent periods, have recently been associated with task-appropriate behavioural responding on a visual attention test, and it was proposed that such fine tuning of neural responses is widespread within cortical areas and important for a wide range of cognitive functions (Engel *et al.*, 2016). Moreover, in the hippocampus, burst firing has been implicated in the encoding and readout of hippocampal memory (Takahashi and Magee, 2009; Xu *et al.*, 2012). Our electrophysiological findings, in conjunction with the behavioural findings we outline below, support that dysregulation of burst firing within the prefrontal cortex and hippocampus, by disruption of local GABA function, can disrupt both regional cognitive function, as well as the cognitive function of projection sites.

Neural disinhibition within the prefrontal cortex or hippocampus causes clinically relevant cognitive deficits

Disruption of prefrontal-mediated cognitive function by prefrontal or hippocampal neural disinhibition

To test for attentional deficits, we used the five-choice-serial-reaction-time (5CSRT) task. This task requires rats to sustain and divide attention across a row of five apertures to detect brief light flashes occurring randomly in one of the apertures and to respond to these flashes to receive food reward. The 5CSRT task resembles human continuous performance tests, and its validity for assessing prefrontal-mediated attentional mechanisms as impaired in schizophrenia and early age-related cognitive decline has been well established (Chudasama and Robbins, 2006; Lustig *et al.*, 2013; Romberg *et al.*, 2013). Acute prefrontal (Pezze *et al.*, 2014) or hippocampal (McGarrity *et al.*, 2016) neural disinhibition by picrotoxin both caused attentional deficits on the 5CSRT test (**Fig. 3A, B**).

Attention as measured on the 5CSRT test requires neural activity within the medial prefrontal cortex, with both neurotoxic lesions (Chudasama *et al.*, 2012; Chudasama and Muir, 2001; Passetti *et al.*, 2002; Pezze *et al.*, 2009) and functional inhibition of this region by the GABA agonist muscimol (Pezze *et al.*, 2014) markedly impairing attentional performance. Therefore, the attentional deficits caused by prefrontal picrotoxin, which are consistent with attentional impairments reported by others with medial prefrontal infusions of GABA-A antagonists in rats (Paine *et al.*, 2011; Pehrson *et al.*, 2013) and, recently, with optogenetic inactivation of parvalbumin-positive prefrontal GABA neurons in mice (Kim *et al.*, 2016), suggest that sustained attention depends on appropriately tuned prefrontal neural activity, with both too little and too much causing attentional impairments (Pezze *et al.*, 2014). Similar to attention, aspects of cognitive flexibility, such as extra-dimensional response shifts, are disrupted by neurotoxic lesions of the medial prefrontal cortex (Birrell and Brown, 2000) or functional inactivation by the sodium channel blocker bupivacaine (Floresco *et al.*, 2008), as well as by neural disinhibition of the medial prefrontal cortex (Enomoto *et al.*, 2011; Gruber *et al.*, 2010), also suggesting a requirement for appropriately tuned medial prefrontal neural activity. However, not all cognitive functions requiring the prefrontal cortex are disrupted by prefrontal neural disinhibition. Response inhibition, as measured by the ability to withhold premature responses on the 5CSRT task, is impaired by prefrontal functional inhibition (Murphy *et al.*, 2012; Paine *et al.*, 2011; Pezze *et al.*, 2014) or lesions (Chudasama *et al.*, 2012; Chudasama and Muir, 2001; Passetti *et al.*, 2002; Pezze *et*

al., 2009), whereas prefrontal neural disinhibition does not change (Paine *et al.*, 2011; Pezze *et al.*, 2014) or, if more ventral portions of the medial prefrontal cortex are affected, may even improve response control (Murphy *et al.*, 2012). This suggests that response inhibition requires prefrontal neural activity, but not the appropriate tuning of such activity.

The selective attentional deficit on the 5CSRT test following hippocampal neural disinhibition (**Fig. 3B**), indicated by reduced accuracy without changes in any other performance measures, probably reflects disruption of extrahippocampal processing, most likely in prefrontal cortex or ventral striatum by way of strong hippocampal functional connectivity to these sites (Bast, 2011). Previous lesion studies suggest that the hippocampus itself plays, if at all, only a minor role in mediating sustained attention on the 5CSRT task and related tests (see discussion in McGarrity *et al.*, 2016). In contrast, as discussed in the preceding paragraph, sustained attention requires balanced prefrontal neural activity. Sustained attention on the 5CSRT test also requires an optimal level of prefrontal (Granon *et al.*, 2000) and ventral striatal (Pezze *et al.*, 2007) dopamine receptor stimulation, which may be disrupted by hippocampal neural disinhibition, given that hippocampal stimulation activates the meso-prefrontal-ventral striatal dopamine system (Bast, 2007; Bast, 2011; Floresco *et al.*, 2001; Lodge and Grace, 2011; Mitchell *et al.*, 2000; Peleg-Raibstein *et al.*, 2005). The attentional deficits following hippocampal neural disinhibition highlight that regional neural disinhibition can affect cognitive functions beyond those normally depending on the disinhibited region and result in impairments of cognitive functions mediated by projection sites of the disinhibited region.

The attentional deficits following hippocampal neural disinhibition, reflected by decreased response accuracy without changes in omissions on the 5CSRT test, are less pronounced than the attentional deficits following lesions (Chudasama *et al.*, 2012; Chudasama and Muir, 2001; Passetti *et al.*, 2002; Pezze *et al.*, 2009) or functional inhibition and disinhibition (Paine *et al.*, 2011; Pezze *et al.*, 2014) of the medial prefrontal cortex, which all manifest as decreases in accuracy alongside increases in omissions (additionally, lesions and functional inhibition reduce inhibitory response control, as reflected by increased premature responses). However, other experimental manipulations primarily targeting the afferent modulation of the prefrontal cortex cause selective reductions in accuracy without increasing omissions, including selective manipulations of the cholinergic (McGaughy *et al.*, 2002) or dopaminergic (Granon *et al.*, 2000) modulation of the prefrontal cortex. Selective reductions in accuracy, without increases in omissions, have also been reported in the triple transgenic mouse model of Alzheimer's disease (Romberg *et al.*, 2011) and the pilocarpine rat model of

temporal lobe epilepsy (Faure *et al.*, 2014), where the primary pathology is not within the prefrontal cortex, but in medial temporal lobe regions, including the hippocampus. Interestingly, both the pilocarpine rat model (Kumar and Buckmaster, 2006) and the triple transgenic mouse model of Alzheimer's disease (Davis *et al.*, 2014) show hippocampal hyperexcitability. The finding that hippocampal neural disinhibition causes attentional impairments suggests that hippocampal hyperexcitability may contribute to the attentional deficits in these rodent models.

Disruption of hippocampus-mediated memory function by hippocampal neural disinhibition

To test for everyday-type memory deficits, we used the watermaze delayed-matching-to-place (DMTP) task. This highly hippocampus-dependent test requires rats to learn within one trial the daily changing place of a hidden platform that offers escape from water (Bast *et al.*, 2009; Pezze and Bast, 2012; Steele and Morris, 1999), resembling the everyday task of remembering new places and routes. Similar place memory tests can be run in humans using virtual or real-space analogues of the watermaze, and such tests have revealed marked deficits in schizophrenia and age-related cognitive decline (Fajnerova *et al.*, 2014; Hort *et al.*, 2007). Hippocampal neural disinhibition by picrotoxin markedly disrupted rapid place learning performance on the watermaze DMTP test, as reflected by a marked reduction of search preference for the new location, which rats had to learn within the first trial of the day (McGarrity *et al.*, 2016) (**Fig. 3C**). Neural disinhibition within the medial prefrontal cortex did not impair such place learning performance, although it modulated behaviour on the DMTP task, biasing rats towards focused searching; experiments using functional inhibition of the medial prefrontal cortex by muscimol indicated that the prefrontal cortex is not required for this task (McGarrity *et al.*, 2014). Previous studies suggest that performance on the watermaze DMTP test requires the hippocampus for the rapid encoding of new places and for the translation of such rapid place learning into behavioural performance. DMTP performance is disrupted by pharmacological manipulations targeting synaptic plasticity mechanisms mediated by NMDA (Steele and Morris, 1999) and dopamine receptors (Pezze and Bast, 2012) and by partial hippocampal lesions, including lesions restricted to temporal and intermediate hippocampus (Bast *et al.*, 2009), which were targeted by the infusions in the study involving hippocampal neural disinhibition (McGarrity *et al.*, 2016). Functional inhibition by the GABA agonist muscimol, targeting the intermediate hippocampus, also disrupts task performance (McGarrity *et al.*, 2014). The requirement of temporal to

intermediate hippocampus probably reflects that these regions feature functional connectivity to frontal and subcortical sites necessary to translate hippocampal learning into performance, although the specific relevant brain sites remain to be determined (Bast, 2007; Bast, 2011; Bast *et al.*, 2009; McGarrity *et al.*, 2014). Overall, neural disinhibition, causing aberrant neuronal bursting, may disrupt everyday-type memory performance, as assessed on the watermaze DMTP task, by interfering with hippocampal encoding or readout of relevant place information or with passing on such information to hippocampal projection sites.

The finding that hippocampal neural disinhibition disrupts hippocampus-dependent performance on the watermaze DMTP task (McGarrity *et al.*, 2016) is consistent with other recent rodent studies reporting a learning-related increase of hippocampal inhibitory synapses (Ruediger *et al.*, 2012) and impaired memory performance following disruption of hippocampal GABA neuron function by molecular-, opto- or pharmacogenetic approaches (Andrews-Zwilling *et al.*, 2012; Caputi *et al.*, 2012; Donato *et al.*, 2013; Engin *et al.*, 2015; Gilani *et al.*, 2014; Lee *et al.*, 2016; Lovett-Barron *et al.*, 2014; Murray *et al.*, 2011). Moreover, our findings support recent studies in humans and rodent models linking hippocampal overactivity and hyperexcitability to age-related memory deficits (Bakker *et al.*, 2012; Davis *et al.*, 2014; Koh *et al.*, 2010) and are consistent with the correlation of hippocampal overactivity with memory deficits in schizophrenia (Tregellas *et al.*, 2014). However, hippocampal neural disinhibition may facilitate hippocampal synaptic plasticity (Martin *et al.*, 2010; Wigstrom and Gustafsson, 1983). Such facilitation of hippocampal synaptic plasticity by neural disinhibition may under some circumstances be beneficial for memory, for example, if the neural disinhibition is spatio-temporally regulated by endogenous plasticity (Donato *et al.*, 2013) or if there is a pre-existing deficit due to increased neural inhibition (Fernandez *et al.*, 2007). Moreover, systemic injection of a selective inverse agonist to negatively modulate GABA-A receptors containing the alpha5 subunit, which are predominantly expressed in hippocampus and constitute about 20% of hippocampal GABA-A receptors, has been reported to facilitate hippocampal plasticity and performance on the watermaze DMTP test (Dawson *et al.*, 2006), although other studies reported that transgenic reduction of hippocampal alpha5 subunit-containing GABA-A receptor expression disrupts aspects of hippocampus-dependent memory (Engin *et al.*, 2015; Prut *et al.*, 2010). Interestingly, the selective inverse agonist at alpha5-subunit containing GABA receptors that was reported to enhance watermaze DMTP performance enhanced induction of long-term potentiation at hippocampal (Schaffer collateral) synapses in vitro, without affecting the number of stimulation-evoked population spikes, which may indicate

that stimulation-evoked neural burst firing was unchanged (Dawson *et al.*, 2006). In contrast, hippocampal neural disinhibition caused by picrotoxin, which disrupted hippocampus-dependent DMTP performance, altered the temporal organization of hippocampal neural activity, markedly enhancing burst-pattern firing (McGarrity *et al.*, 2016). Overall, hippocampus-dependent memory performance appears to require hippocampal neural activity that is appropriately balanced by GABAergic inhibition, resembling the requirement of appropriately tuned prefrontal activity for prefrontal-dependent cognitive functions (Pezze *et al.*, 2014).

Significance of prefrontal and hippocampal inhibitory GABA transmission for distinct cognitive functions: distinct causal relationships linking regional neural activity to distinct cognitive functions

The recent studies discussed above show that inhibitory GABA transmission within prefrontal cortex and hippocampus is required to regulate neuronal firing, especially burst-pattern firing, and to sustain aspects of the cognitive functions supported by these regions and projection sites. Prefrontal neural disinhibition disrupts aspects of prefrontal-dependent attentional performance and of cognitive flexibility, similar to prefrontal lesions and functional inhibition/inactivation (Enomoto *et al.*, 2011; Gruber *et al.*, 2010; Pezze *et al.*, 2014), and hippocampal neural disinhibition disrupts hippocampus-dependent memory performance, similar to hippocampal lesions and functional inhibition[3] (McGarrity *et al.*, 2016). This suggests that neural activity within the prefrontal cortex or hippocampus, respectively, relates to these cognitive functions via an inverted-U shaped function, with both too much and too little neural activity causing disruptions (**Fig. 4A**). Moreover, the finding that hippocampal neural disinhibition impairs attentional performance, which does not require hippocampal neural activity, but is mediated by prefrontal-striatal circuits, shows that the regulation of neural activity by GABAergic inhibition within a particular brain region can also be important for aspects of cognitive function that require balanced levels of neural activity within this region's projection sites (McGarrity *et al.*, 2016). In other words, attention

[3] It should be noted that permanent lesions and temporary functional inhibition or inactivation do not necessarily have the same cognitive and behavioural impact. Depending on the cognitive or behavioural function, lesions and temporary inhibition or inactivation may even have opposite effects, probably reflecting compensatory responses to permanent neural damage or lesion-induced changes going beyond the target region of the lesion (Wang *et al.*, 2015).

is largely insensitive to reductions of hippocampal neuron activity, but is dirupted by aberrant tonic increases in hippocampal neural activity (**Fig. 4B**).

However, other hippocampal and prefrontal functions may be less dependent on the regulation of regional neural firing by inhibitory GABA transmission. In contrast to prefrontal and hippocampal lesions or functional inhibition, neither medial prefrontal nor hippocampal neural disinhibition disrupt inhibitory response control on the 5CSRT test (as reflected by premature or perseverative responses; McGarrity *et al.*, 2016; Pezze *et al.*, 2014). This suggests that such response control requires neural activity within the hippocampo-prefrontal circuit, but not the appropriate tuning of such activity. In other words, response control can be sustained as long as neural activity within the hippocampo-prefrontal circuit is above a minimal level (**Fig. 4C**).

Finally, there are also behavioural processes that are supported by prefrontal or hippocampal neural activity that may be enhanced by tonic reductions of local GABA transmission. Neural disinhibition of the (temporal) hippocampus (similar to direct chemical or electrical stimulation; Bast and Feldon, 2003) enhances locomotor activity (Bast *et al.*, 2001a; McGarrity *et al.*, 2016), which depends on neural activity within the temporal hippocampus and is reduced by temporary functional inhibition or inactivation of this region by muscimol or the sodium channel blocker tetrodotoxin (Bast *et al.*, 2001b). Similarly, prefrontal neural disinhibition increases, whereas prefrontal functional inhibition decreases locomotor activity (Pezze *et al.*, 2014). These findings suggest that hippocampal and prefrontal neural activity drives locomotor activity, with a monotonic positive relation between regional neural activity and locomotion (**Fig. 4D**). These locomotor effects may reflect a positive modulation of ventral striatal dopamine transmission by neural activity within the hippocampo-prefrontal circuit (Bast and Feldon, 2003; Floresco *et al.*, 2001; Karreman and Moghaddam, 1996; Lodge and Grace, 2011; Mitchell *et al.*, 2000).

In summary, regulation of prefrontal and hippocampal neural activty by GABAergic inhibition is important for cognitive and behavioral functions supported by these regions and by distal brain sites functionally connected to these regions. Neural disinhibition in prefrontal cortex and hippocampus may have distinct effects on distinct cognitive or behavioural functions supported by these regions, reflecting distinct relationships of inhbitory GABA tone and neural activity to distinct functions: some functions require an intact inhibitory GABA tone and appropriately balanced neural activity levels, wheras other functions do not require the tuning of neural acitivy by GABAergic inhibition (as long as neural activity remains subconvulsive).

Prefrontal and hippocampal GABA dysfunction in neuropsychiatric disorders may account for important cognitive deficits characterizing these disorders

Prefrontal and hippocampal GABA dysfunction has been implicated in schizophrenia and age-related cognitive decline, including early Alzheimer's disease (Benes and Berretta, 2001; Busche and Konnerth, 2016; Heckers and Konradi, 2015; Huang and Mucke, 2012; Nava-Mesa *et al.*, 2014; Ruzicka *et al.*, 2015; Stanley *et al.*, 2012). The neuro-cognitive effects of acute pharmacological prefrontal and hippocampal neural disinhbition discussed above are mainly relevant to early stages of these disorders, before chronic disinhibition-induced neural hyperactivity may lead to compensatory or excitotoxic effects, resulting in regional brain hypofunction and atrophy characteristic of later disease stages (Heckers and Konradi, 2015; Huang and Mucke, 2012; Krystal and Anticevic, 2015; Schobel *et al.*, 2013). Given the close link between neural activity and metabolic activation (Sokoloff, 1981), the enhanced hippocampal neural activity, especially of burst-pattern firing, caused by acute hippocampal GABA antagonism (McGarrity *et al.*, 2016) is consistent with the hippocampal metabolic overactivity at rest reported by functional imaging studies in early stages of both schizophrenia and age-related cognitive decline (Bakker *et al.*, 2012; Schobel *et al.*, 2013; Schobel *et al.*, 2009; Sperling *et al.*, 2010).

The rodent 5CSRT and watermaze DMTP tests have high validity to measure deficits in attention and memory relevant to clinical disorders, with related human paradigms – continuous performance tests and place learning tests in virtual and real-space analogues of the watermaze, respectively – revealing marked deficits in schizophrenia and age-related cognitive decline (Chudasama and Robbins, 2006; Fajnerova *et al.*, 2014; Hort *et al.*, 2007; Lustig *et al.*, 2013; Romberg *et al.*, 2013). Therefore, the findings that prefrontal and hippocampal neural disinhbition in rats causes impairments on these tests supports that prefrontal and hippocampal GABA dysfunction contributes to clinically relevant attentional and memory deficits. The memory and attentional deficits caused by hippocampal neural disinhibition (McGarrity *et al.*, 2016) also support that causal relationships underly the recently reported correlations of hippocampal overactivity with both memory and attentional deficits in schizophrenia patients (Tregellas *et al.*, 2014) and the association of hippocampal overactivity with memory deficits in amnestic mild cognitive impairment (Bakker *et al.*, 2012).

Implications for pharmacological strategies to treat cognitive deficits

Drugs targeting neural network disruptions resulting from prefrontal and hippocampal neural disinhibition may offer much-needed new treatment opportunities for cognitive deficits. As discussed above, recent findings show that key cognitive functions, including attention and memory, depend on balanced neural activity within prefrontal cortex or hippocampus, with both too little and too much activity being detrimental. This has important implications for drug treatments targeting the adverse neuro-cognitive effects of GABA dysfunction: Drugs simply suppressing neural activity will be of limited suitability to treat cognitive deficits. Instead, it is critical to rebalance aberrant neural activity – that is, to curb excessive excitation and burst firing, without suppressing normal firing, as required for cognitive function.

Several candidate drugs are available that may achieve such rebalancing of aberrant neural activity induced by neural disinhibition. Of particular interest are second generation antiepileptics, including levetiracetam and lamotrigine, and positive allosteric modulators (PAMs) acting at the metabotropic glutamate receptor 2 (mGluR2). The second-generation antiepileptics lamotrigine and levetiracetam block excessive hippocampal burst firing in vitro, while leaving basal neural activity largely unaffected, an effect suggested to reflect effects on state-dependent cation currents that mainly contribute to high-frequency firing (De Smedt *et al.*, 2007; Kuo and Lu, 1997). Levetiracetam has been shown to ameliorate aberrant cortico-hippocampal neural activity and improve cognitive deficits in rodent models of age-related cognitive decline (Haberman *et al.*, 2017; Koh *et al.*, 2010; Robitsek *et al.*, 2015; Sanchez *et al.*, 2012) and in human cognitive aging (Bakker *et al.*, 2012). Lamotrigine has been under consideration for repurposing to ameliorate schizophrenia-related cognitive deficits associated with cortico-hippocampal neural disinhibition, and has shown some promise in pre-clinical schizophrenia models, with limited benefits in clinical trials (Large *et al.*, 2011). The failure in clinical trials may reflect that the proposed rebalancing mechanism of lamotrigine would mainly benefit early-stage schizophrenia patients, characterised by aberrant regional brain hyperactivity, but be of limited benefit in long-standing patients, as typically included in clinical trials, who show regional brain hypoactivity (Anticevic *et al.*, 2015; Krystal and Anticevic, 2015). PAMs at the mGluR2 may rebalance activity by selectively curbing excessive glutamate release through activity-dependent stimulation of mGluR2, a presynaptic autoreceptor controlling glutamate release at forebrain terminals (Fell *et al.*, 2012). The mGluR2 has received much interest as a schizophrenia drug target, fuelled by findings that an orthosteric agonist improved cognitive deficits and psychosis-related changes in rat models of schizophrenia, as well as positive and negative symptoms in an

initial phase 2 clinical trial, although subsequent larger and longer clinical trials failed to support effectiveness against schizophrenia symptoms (Curley, 2012) and, more recently, an mGluR2 PAM also failed a phase 2 clinical trial (Litman *et al.*, 2016). Importantly, as considered above with respect to lamotrigine, the proposed rebalancing mechanism of mGluR2 stimulation would mainly benefit early-stage schizophrenia patients, characterised by aberrant regional brain hyperactivity, but be of limited benefit in long-standing patients, as typically included in clinical trials, who show regional brain hypoactivity (Anticevic *et al.*, 2015; Krystal and Anticevic, 2015). Consistent with this possibility, a recent re-analysis of the clinical trials with the mGluR2 orthosteric agonist indicated beneficial effects in early-stage, but not chronic, schizophrenia patients (Krystal and Anticevic, 2015).

What about drugs directly targeting GABA receptor function? Interestingly, substantial drug discovery efforts to improve cognitive function by targeting GABA receptors have focused on a negative modulation of GABA receptors, such as by inverse agonists selective for alpha 5-containing GABA receptors (Ballard *et al.*, 2009; Dawson *et al.*, 2006). However, the more recent findings reviewed here, highlighting the requirement of appropriate GABA tone in prefrontal cortex and hippocampus for important cognitive functions, including attention and memory, as well as the emergence of neural disinhibition as a feature of many disorders characterized by cognitive deficits, suggest a different approach. Drugs positively modulating GABA receptor function may have potential for ameliorating the neuro-cognitive effects in disorders associated with neural disinhibition, as long as overstimulation of inhibitory GABA receptor function can be avoided, as this would interfere with cognitive function. GABA receptor modulators selective for receptor subunits with preferentially prefrontal and hippocampal expression, such as alpha 2 and 5, have received particular interest as they may minimise sedation (Rudolph and Knoflach, 2011; Vinkers *et al.*, 2010). Recent studies in rats showed that a PAM selective for alpha 5-containing GABA receptors reduces hippocampal hyperexcitability in the methylazoxymethanol acetate (MAM) developmental model of schizophrenia (although the drug also reduced baseline hippocampal excitability in control rats, which may interfere with some hippocampus-dependent functions) (Gill and Grace, 2011) and ameliorates age-related memory impairments linked to hippocampal GABA dysfunction and hyperexcitability (Koh *et al.*, 2013). However, an alpha 2-selective partial agonist failed to improve cognition in schizophrenia patients, with potential reasons discussed by the authors including insufficient receptor activity and sedative side effects due to insufficient subunit selectivity (Buchanan *et al.*, 2011). As discussed above for the other drug candidates, long-standing, chronic patients, as typically included in clinical

trials, who show regional brain hypoactivity may show little benefit from any treatment targeting aberrant neural activity (Anticevic *et al.*, 2015; Krystal and Anticevic, 2015). Moreover, the effectiveness of GABAergic approaches in treating prefrontal and hippocampal disinhibition in schizophrenia may be limited because the GABA system may be compromised beyond repair - indeed, GABA-A receptors are already upregulated in schizophrenia patients, presumably as a compensatory response to presynaptic dysfunction (Benes and Berretta, 2001; Guidotti *et al.*, 2005; Heckers and Konradi, 2015; Lewis and Moghaddam, 2006).

Conclusions and future directions

Prefrontal and hippocampal neural disinhibition causes aberrant regional neuron firing, characterized by enhanced bursting, and disrupts some clinically relevant cognitive functions of these regions, including attention and memory, whereas some cognitive and behavioural functions supported by these regions (e.g., inhibitory response) are spared. This highlights that distinct cognitive and behavioural functions supported by a brain region can show distinct dependencies on regional inhibitory GABA transmission, reflecting distinct relationships to regional neural activity: some functions require an appropriate inhibitory GABA tone and balanced levels of neural activity, whereas other functions may not (as long as the disinhibition remains subconvulsive). To characterize the distinct causal relationships of prefrontal and hippocampal GABA tone and neural activity to specific cognitive functions, future studies will have to compare systematically the impact of both functional inhibition and functional disinhibition on tests of such cognitive functions. Acknowledging the diversity of the various receptor and neuron types making up the inhibitory GABA system (Ascoli *et al.*, 2008; Rudolph and Knoflach, 2011), studies using intra-cerebral microinfusions of broadly acting GABA agonists and antagonists may be complemented by studies using more selective ligands, to target specific GABA receptors subtypes (Rudolph and Knoflach, 2011), and opto- and pharmacogenetic methods, to modulate GABA transmission presynaptically with some specificity for different interneuron types (Lovett-Barron *et al.*, 2014; Nguyen *et al.*, 2014; Royer *et al.*, 2012).

Consistent with the idea that regional neural disinhibition can disrupt cognitive processing in distal sites, hippocampal neural disinhibition disrupts attentional performance that does not require the hippocampus, but is mediated by prefrontal-striatal mechanisms (McGarrity *et al.*, 2016). This supports that hippocampal dysfunction can partly manifest through deficits in

prefrontal function, consistent with strong hippocampo-prefrontal functional connectivity (Bast, 2011; Meyer-Lindenberg *et al.*, 2005). Future studies combining regional neural disinhibition with additional behavioural tests will be required to characterize further the 'distal cognitive impact', i.e. the significance for cognitive functions mediated by efferent sites, of regional GABA tone and neural disinhibition (e.g., does hippocampal neural disinhibition also disrupt other prefrontal cognitive processes, such as aspects of cognitive flexibility?). Moreover, neurophysiological measurements in projection sites will be required to characterize the brain-wide effects of regional neural disinhibition. Using translational imaging methods (e.g., metabolic radiological imaging or EEG measurements) for such measurements would make it possible to examine the role of hippocampo-prefrontal neural disinhibition in generating important clinical biomarkers (e.g., regional metabolic hyperactivity and aberrant EEG oscillations) of some of the disorders associated with neural disinhibition (see section on 'Prefrontal and hippocampal neural disinhibition in neuropsychiatric disorders characterized by cognitive deficits').

The reviewed findings suggest that prefrontal and hippocampal neural disinhibition contributes to important cognitive deficits, including attentional and memory deficits, in neuropsychiatric disorders characterized by such neural disinhibition, including schizophrenia and age-related cognitive decline (**Table 1**). Therefore, aberrant neural activity caused by neural disinhibition is a promising target for treatments aimed at restoring important cognitive functions in these disorders, especially at early disease stages, when disinhibition-induced prefrontal and hippocampal hyperactivity is prevalent, rather than hypoactivity and atrophy that characterize later disease stages (Anticevic *et al.*, 2015; Huang and Mucke, 2012; Krystal and Anticevic, 2015). Suitable pharmacological treatments will have to rebalance the disinhibition-induced aberrant neural activity by curbing excessive excitation and burst firing, while leaving intact normal firing, as required for cognitive function. Candidate drugs include second generation antiepileptics, including lamotrigine and levetiracetam, and mGluR2 PAMs. Pre-clinical studies in rodent models of prefrontal and hippocampal neural disinhibition can provide proof-of-concept for the suggested rebalancing actions of these candidate drugs, using a two-step approach, involving i) electrophysiological studies to determine if a candidate drug rebalances aberrant neural activity and ii) translational behavioural assays to determine if the drug ameliorates impairments of clinically relevant cognitive functions. Such studies could pave the way for clinical trials, where the challenge will be to include patients at early disease stages who are most likely to benefit from treatments rebalancing aberrant neural activity.

Nomenclature of Targets and Ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Southan *et al.*, 2016), and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 (Alexander *et al.*, 2015).

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Conflict of interest

TB currently holds a BBSRC iCASE Award in partnership with Boehringer Ingelheim.

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Table 1

Some important neuropsychiatric disorders that have been associated with cortico-hippocampal GABA dysfunction. All of these disorders show cognitive impairments (Millan *et al*., 2012).

Disorder	References supporting GABA dysfunction
Schizophrenia	Benes and Berretta, 2001; Fung *et al.*, 2010; Guidotti *et al.*, 2005; Heckers and Konradi, 2015; Lewis and Moghaddam, 2006; Lisman *et al.*, 2008; O'Donnell, 2011; Ruzicka *et al.*, 2015
Cognitive ageing and Alzheimer's	Busche and Konnerth, 2016; Huang and Mucke, 2012; Nava-Mesa *et al.*, 2014; Spiegel *et al.*, 2013; Stanley *et al.*, 2012; Thomé et al., 2016
Autism	Han *et al.*, 2014; Rubenstein and Merzenich, 2003
Depression	Luscher *et al.*, 2011; Rajkowska *et al.*, 2007
Bipolar disorder	Konradi *et al.*, 2011

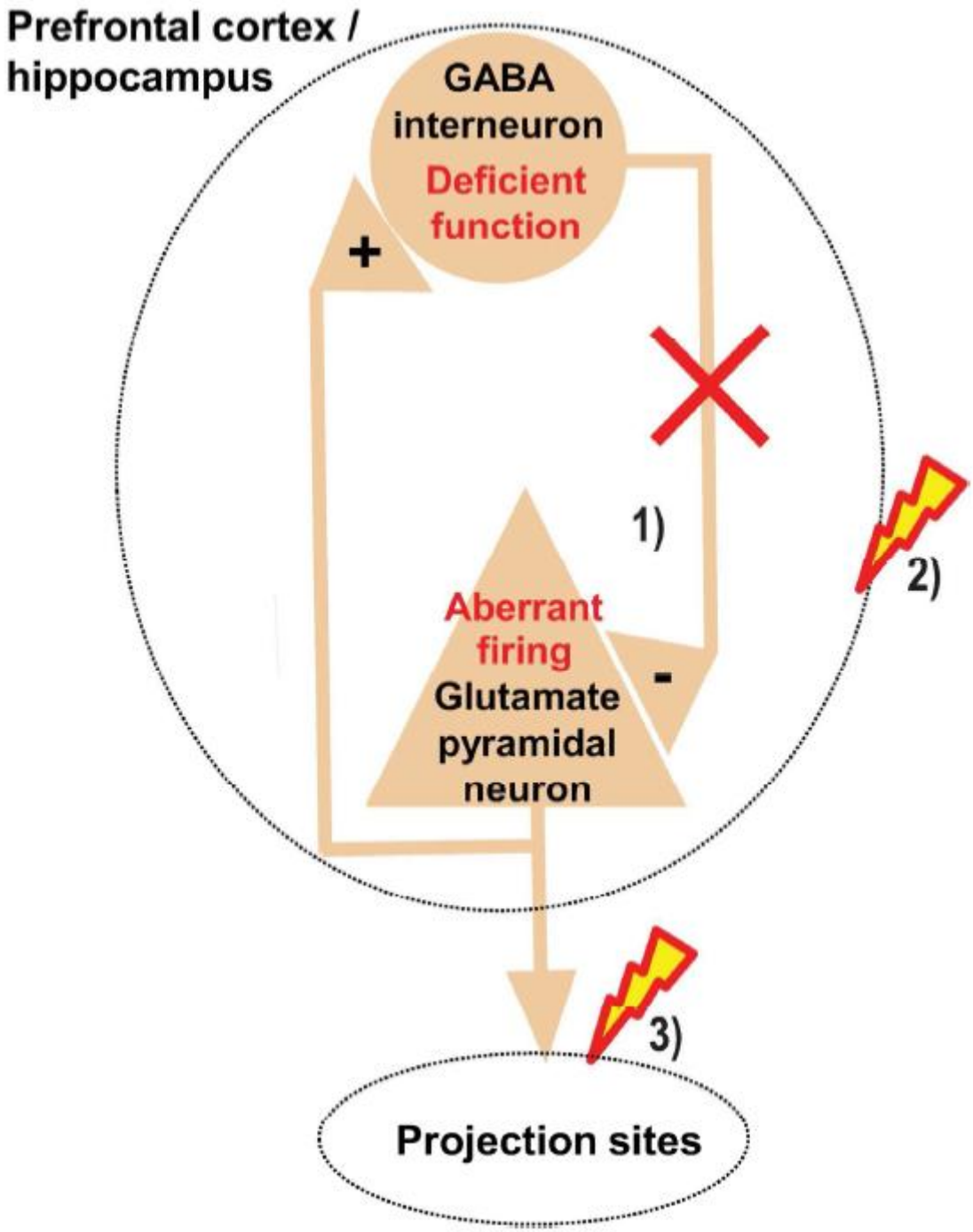

Fig. 1 *Regional GABA dysfunction may disrupt regional function and the function of projection sites*. Deficient function of inhibitory GABA interneurons within the prefrontal cortex or hippocampus disrupts the spatio-temporal control of excitatory glutamatergic neurons within these regions, causing aberrant firing of these neurons (1), which may disrupt the cognitive functions normally mediated by these regions (2). In addition, such aberrant firing may cause aberrant drive of neurons in projection sites, which may disrupt the functions normally mediated by these projection sites (3).

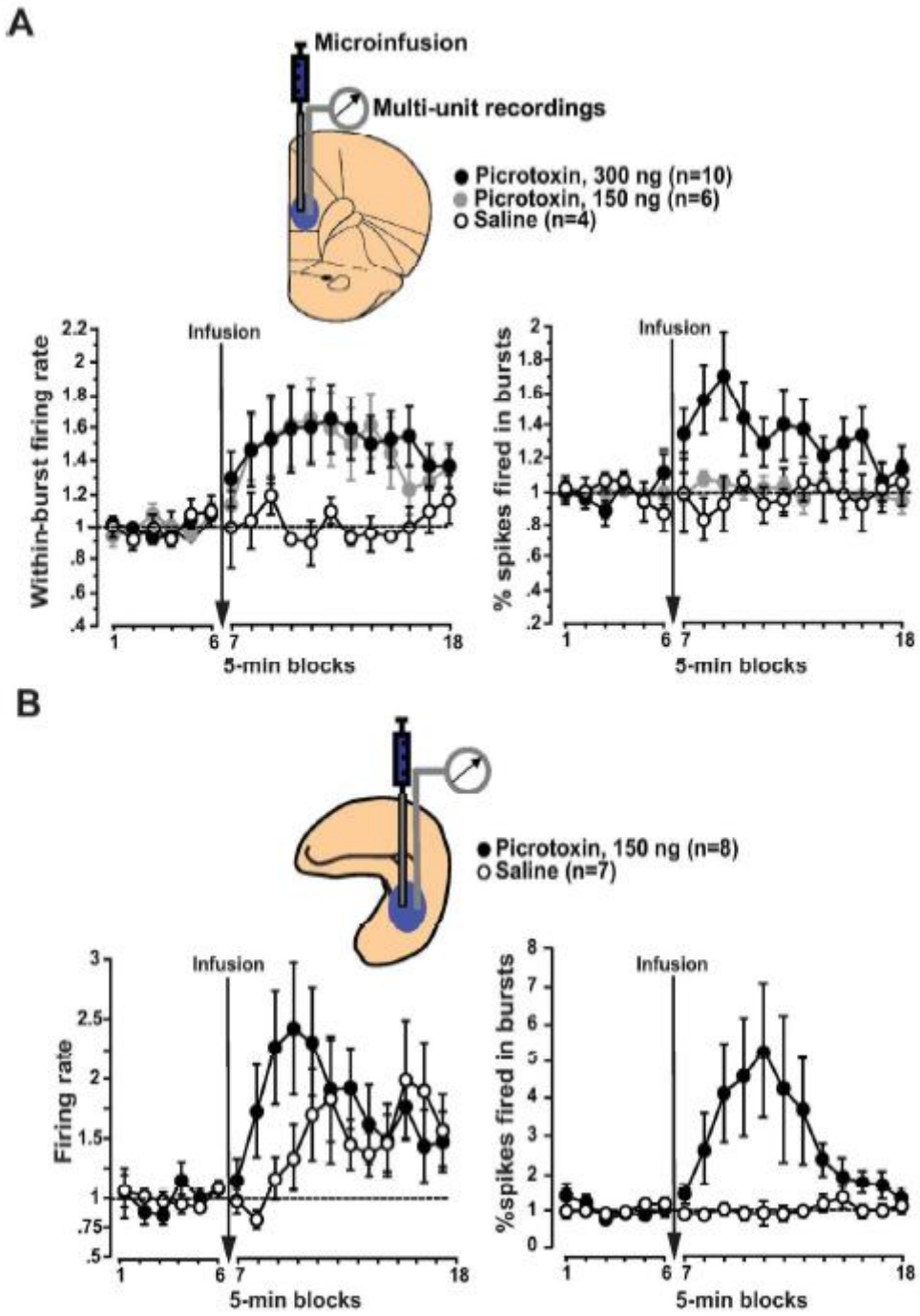

Fig. 2 *Neural disinhibition in prefrontal cortex and hippocampus enhances burst firing of neurons within these regions*. Following local microinfusions of the GABA antagonist picrotoxin into the medial prefrontal cortex (**A**) or hippocampus (**B**) of anaesthetised rats, the most marked effect revealed by in vivo electrophysiological recordings of multi-unit activity in the vicinity of the infusion sites is enhanced neuronal burst firing. **A** In the medial prefrontal cortex, regional neural disinhibition by picrotoxin primarily increases within-burst firing rate and, at the higher picrotoxin dose, also increases the prevalence of bursts, as reflected by an increased percentage of spikes fired in bursts. **B** In the hippocampus, local

picrotoxin infusion markedly increases the prevalence of bursts, as reflected, for example, by an increased percentage of spikes fired in bursts, accompanied by a comparatively moderate increase in overall firing rate. All values show multi-unit recording data normalized to baseline (average across the six 5-min blocks before infusion) and show mean±SEM; prefrontal data graphs are adapted from Pezze *et al*. (2014) and hippocampal data from McGarrity *et al*. (2016).

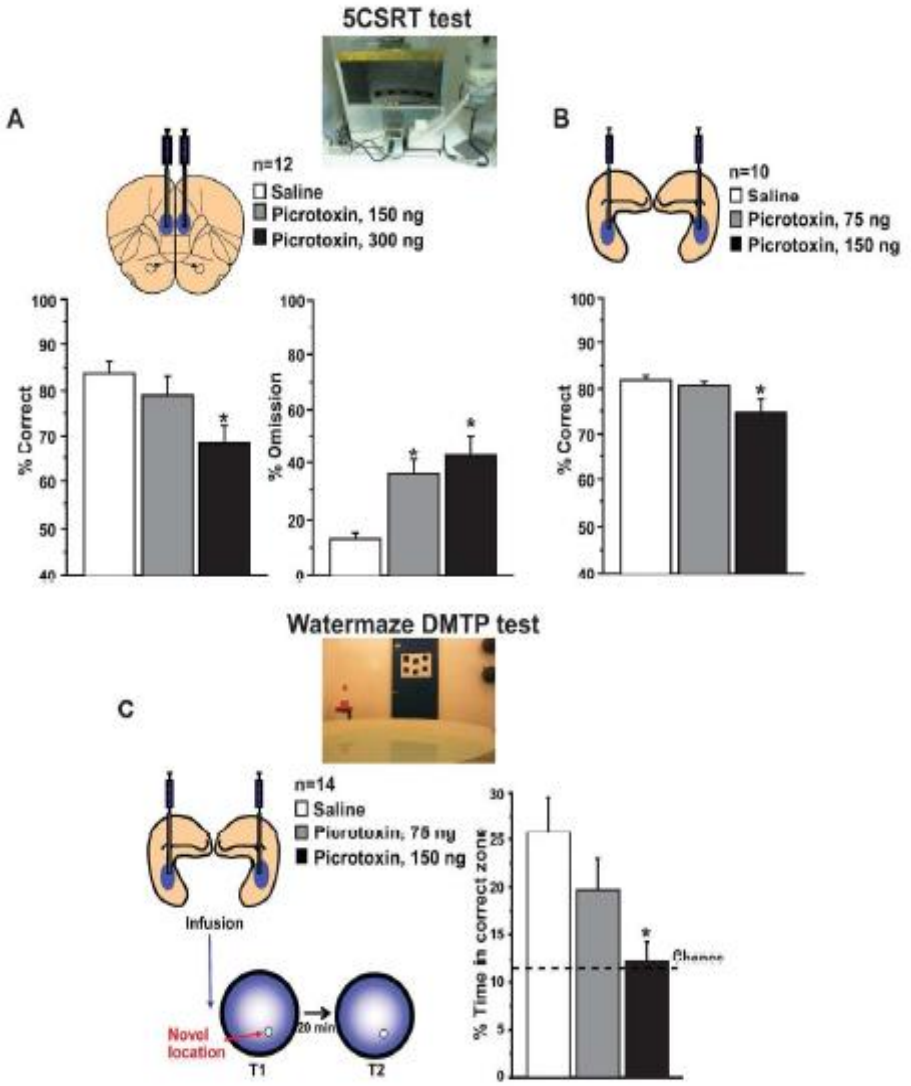

Fig. 3 *Neural disinhibition within medial prefrontal cortex and hippocampus causes clinically relevant attentional and memory deficits.* **A, B** Attentional deficits: Neural disinhibition in the medial prefrontal cortex or hippocampus disrupts attentional performance on the five-choice-serial-reaction-time (5CSRT) task. The 5CSRT task requires rats to sustain and divide attention across a row of five apertures to detect brief light flashes occurring randomly in one of the apertures and to respond to these flashes to receive food reward. Following local microinfusions of the GABA antagonist picrotoxin into the medial prefrontal cortex (**A**) or hippocampus (**B**), rats show reduced attentional performance, as reflected by a reduced percentage of correct responses and, in case of the prefrontal disinhibition, also an increase in omitted trials. **C** Memory deficits: Neural disinhibition in the hippocampus disrupts rapid place learning performance on the watermaze delayed-matching-to-place (DMTP) test. This highly hippocampus-dependent test requires rats to learn within one trial

the daily changing place of a hidden platform that offers escape from water, resembling the everyday task of remembering new places and routes. Following hippocampal picrotoxin microinfusion, rats show reduced one-trial place learning performance, as reflected by a marked reduction in search preference for the correct location. Prefrontal data graphs are adapted from Pezze *et al.* (2014) and hippocampal data graphs from McGarrity *et al*. (2016).

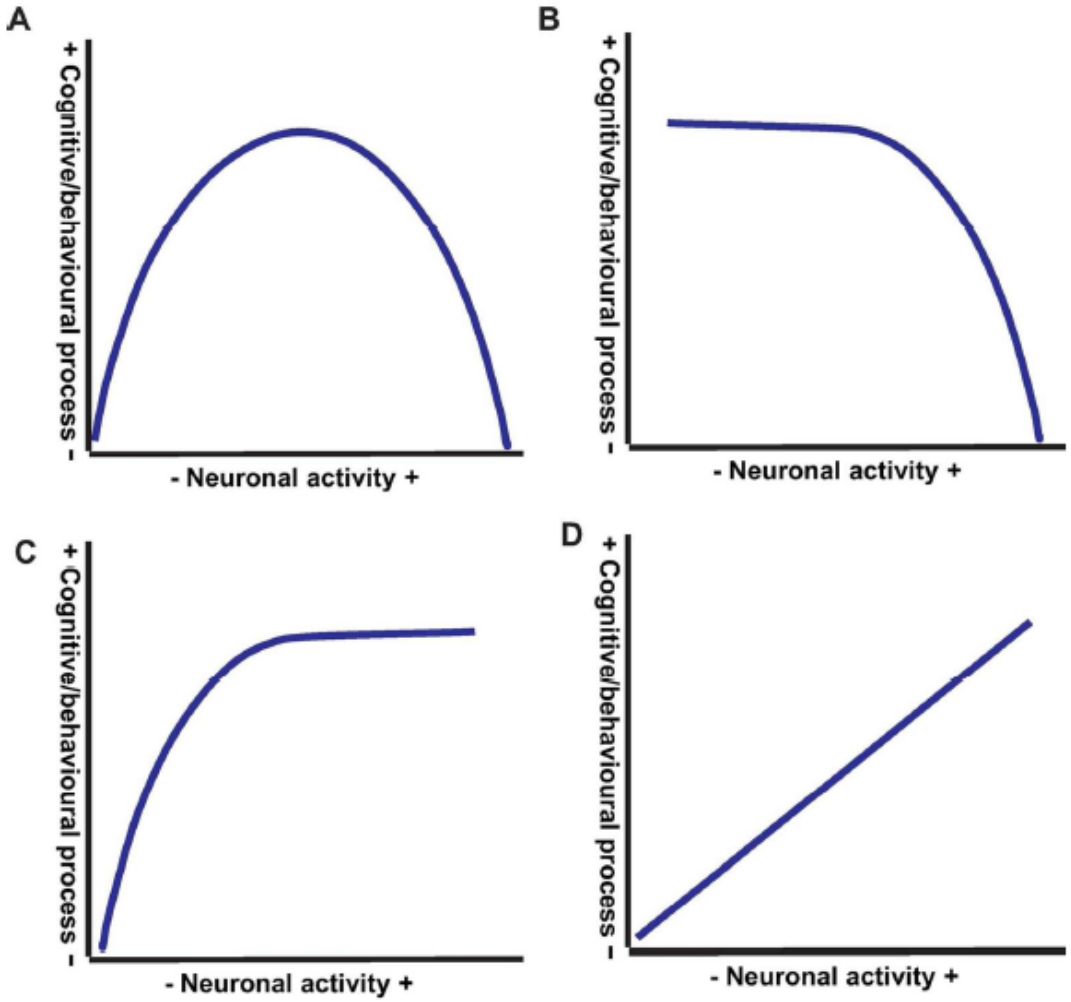

Fig. 4 *Distinct causal relationships link neural activity within medial prefrontal cortex and hippocampus to distinct cognitive and behavioural processes.* Studies examining the cognitive and behavioural impact of bidirectional changes of neural activity within the medial prefrontal cortex or hippocampus, including by local infusions of GABA agonists and antagonists, show that neural activity within these regions can be linked to distinct cognitive and behavioural processes by distinct causal relationships. **A** Inverted U-shaped relationship, with cognitive or behavioural process requiring a balanced level of neural activity and both too little and too much neural activity causing impairments; example: relationship between prefrontal neural activity and attentional performance and between hippocampal neural activity and rapid place learning performance. **B** Cognitive or behavioural process is not affected by reductions in neural activity, but impaired by increases in neural activity; example: relationship between hippocampal neural activity and attentional performance. **C** Cognitive or behavioural process can be sustained as long as neural activity is above a minimal level; example: relationship between hippocampal and prefrontal neural activity and

response control. **D** Monotonic positive relationship between neural activity and cognitive or behavioural process, with decreases in neural activity reducing the process and increases in neural activity increasing the process; example: relationship between hippocampal and prefrontal neural activity and locomotor activity.