later after patients have been seizure-free for extended periods of time (Simasathien et al., 2013).

The complexity of the findings, as well as the implications for planning resection in younger brains, are considerable. While all brains are capable of plasticity to some degree, we generally think of the greatest potential for plasticity as being in the first few years of life, with plasticity dropping off steeply in adolescence and early adulthood. Given that the average age at surgery was 13, this raises questions about whether the findings might have implications for older surgical patients, many of whom also have epilepsy of early childhood onset.

Perhaps most importantly, the findings of Skirrow and colleagues highlight the urgent need for earlier intervention and the importance of considering developmental plasticity and reorganization as part of efforts to spare and maximize post-surgical cognitive function.

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**References**


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**A mouse model of autoimmune encephalitis**

This scientific commentary refers to ‘Human N-methyl D-aspartate receptor antibodies alter memory and behaviour in mice’ by Planagumà et al. (doi: 10.1093/brain/awu310). Anti-N-methyl D-aspartate receptor (NMDAR) encephalitis is a severe autoimmune neuropsychiatric disorder accompanied by prominent memory and behavioural deficits (Titulaer et al., 2013). The disorder is characterized by circulating anti-NMDAR autoantibodies (NMDAR-Abs), which cause a selective and reversible internalization of cell-surface NMDARs in cultured neurons (Mikasova et al., 2012). This suggests an antibody-mediated pathogenesis, as does the frequent response of patients to immunotherapy (Titulaer et al., 2013), but to date there has been no animal model available to test this. In the current issue of *Brain*, Josep Dalmau and colleagues present robust evidence that continuous ventricular infusion of NMDAR-Abs induces memory and behavioural deficits in mice (Planagumà et al., 2014).

Experiments revealed that infusion of CSF from patients with anti-NMDAR encephalitis, but not from controls, causes mice to develop progressive memory impairments (Fig. 1) as well as anhedonic and depressive-like behaviours, while leaving their performance on other behavioural and locomotor tasks unchanged. Immunoblot and confocal microscopy revealed a progressive decrease in total hippocampal NMDAR protein, as well as total and synaptic receptor clustering, further implicating the NMDAR in the observed symptoms.

NMDARs are heterotetrameric calcium-permeable ion channels that are essential for brain plasticity and for the long-term synaptic modifications thought to underlie cognitive functions. NMDARs are composed of two constitutive NR1 subunits and two variable subunits from among GluN2A, GluN2B, GluN2C, GluN2D, GluN3A and GluN3B (Paoletti et al., 2013). Animal models based on genetically modified NMDARs have already confirmed the critical role of NMDARs in memory and learning (Cui et al., 2004), but with their mouse model, Planagumà et al. not only reveal a direct pathogenicity of NMDAR-Abs, but also validate a method for investigating mechanisms of synaptic dysfunction. A number of other neuropsychiatric diseases featuring altered NMDAR-mediated synaptic plasticity will benefit from this innovative approach of using antibodies from patients with autoimmune synaptopathies.

The demonstration that NMDAR-Abs affect learning and memory...
complements recent in vitro observations that NMDAR-Abs decrease NMDAR-mediated synaptic currents (Hughes et al., 2010), and provoke crosslinking of NMDARs that alters long-term potentiation (Zhang et al., 2012; Dupuis et al., 2014), the cellular correlate of memory. However, many other aspects remain to be addressed, including the long-term effects of NMDAR-Abs on AMPAR synaptic composition. While total AMPAR concentration in the hippocampus does not seem to be affected by NMDAR-Abs based on the experiences of Planagumà et al., the receptor distribution at synapses might be altered, leading to impaired synaptic plasticity. Another point still to be explained is the preferential binding of NMDAR-Abs to the hippocampus compared to cortex and other structures that express high levels of NMDARs. Even within the hippocampus, the location of the NMDARs targeted in encephalitis remains to be precisely determined. It is possible, for example, that NMDAR-Abs mainly target NMDAR subtypes preferentially expressed on certain interneuron or excitatory neuron populations.

Similarly, we do not know whether NMDAR-Abs mainly target presynaptic or postsynaptic NMDARs (Fig. 1). Previous in vivo experiments have shown that blockade of GABA-A receptors enhances the effect of NMDAR-Abs on glutamate release, suggesting that NMDAR-Abs might target cells other than pyramidal neurons (Manto et al., 2010). A decrease in the activity of inhibitory pathways in anti-NMDAR encephalitis could result in a hyperglutamatergic state, which could explain positive symptoms such as seizures, abnormal movements or hallucinations. The animal model developed by Planagumà et al. will help with deciphering the molecular effects of NMDAR-Abs in autoimmune encephalitis; however, addressing these

![Figure 1 NMDAR-Abs impair cognition in mice. Left: A mouse exposed to a novel object will spend time exploring it. In the presence of two novel objects, the animal will spend an equal amount of time exploring each (top left: habituation). However, a mouse exposed to a previously encountered object and a novel one will spend more time exploring the novel object. The mouse will then have a high novel object recognition (NOR) index (the ratio of time spent exploring the novel object: time spent exploring both objects) (bottom left: high NOR index). The extent to which the mouse prefers the novel object is assumed to reflect the strength of its memory for the previously encountered object. At the cellular level (magnified synapse), this behaviour is thought to reflect long-term potentiation, a form of synaptic plasticity. Long-term potentiation relies on the activation of NMDA receptors and on intracellular signalling that leads to an increased surface expression of AMPA receptors at the synapse. Right: In the experiments of Planagumà et al., mice infused with NMDAR-Abs show normal exploratory behaviour when presented with two novel objects (top right: habituation). However, when exposed to a previously encountered object and a novel one, the mice again spend the same amount of time exploring each of the two objects, indicating an impairment in memory. The animals thus have a low NOR index (bottom right: low NOR index). Although Planagumà et al. demonstrated a clear effect of NMDAR-Abs on cognition in vivo, the mechanisms by which these autoantibodies act at the synaptic level remain to be deciphered. In particular, efforts are required to identify the cellular and subcellular location of the NMDARs targeted, and the synaptic modifications leading to the alteration of long-term potentiation.]}
points will also improve understanding of the mechanisms by which NMDAR-Abs affect cognition, as well as the mechanisms underlying other diseases with NMDAR signalling dysfunction. This includes psychiatric and neurological disorders such as schizophrenia and Alzheimer’s disease (Huang et al., 2012).

In Alzheimer’s disease, little is known about how soluble amyloid-β oligomers exert their deleterious effects on synapses. One possibility is that amyloid-β oligomers induce NMDAR depletion via binding to ephrin type-B receptor 2 (EPHB2), a synaptic protein that forms a complex with NMDAR subunits and regulates their trafficking and function. In a transgenic mouse model of Alzheimer’s disease, upregulating EPHB2 receptor expression increased NMDAR-mediated synaptic plasticity and rescued memory impairments (Cissé et al., 2011). In vitro data provide evidence in favour of similar mechanisms involving NMDAR-Abs. Indeed, NMDAR-Abs directly modify NMDAR lateral diffusion at the membrane by disrupting the interaction between NMDARs and EPHB2 receptors (Mikasova et al., 2012). This might alter the imbalance between extrasynaptic and synaptic NMDARs that appears to be a central trigger for synaptic dysfunction in some neurodegenerative diseases, and in particular in Alzheimer’s disease (Parsons et al., 2014). Altogether, these data suggest that the effects of NMDAR-Abs on synapses may share common mechanisms with Alzheimer’s disease synaptopathy.

An emerging concept is that studying the impact of NMDAR-Abs at the synapse might shed new light on the molecular mechanisms of NMDAR-mediated brain disorders. The work of Planagumà et al. illustrates how the nature of these ‘ubiquitous’ synaptic dysfunctions can be addressed through the development of in vivo animal models, in which antibodies from patients are used as tools to induce synaptic dysfunction. Another question remaining is the impact on the brain at the morphological and cellular level of chronic antibody exposure. In particular, the morphology of dendritic spines, which form the postsynaptic component of synapses, is thought to undergo changes during synaptic plasticity (Araya et al., 2014); however, this process is highly compromised in Alzheimer’s disease and other NMDAR-mediated brain disorders. In the present study, NMDAR-Abs did not seem to affect either NMDAR-Abs did not seem to affect either PSD95 or AMPA receptors.

Although anti-NMDAR encephalitis reflects an initial isolated perturbation of NMDAR transmission, further neuronal and synaptic changes are suspected to play a part. Supporting this idea, cognitive recovery after immunosuppressive treatment occurs over months to years, which is not really compatible with the fast dynamics of the NMDAR and strongly suggests prolonged cellular and synaptic changes. Further studies are needed to understand how in vivo exposure to NMDAR-Abs might shape synapse structure, and to establish the link between these synaptic changes and the functional defects revealed by this first animal model of anti-NMDAR encephalitis. One hypothesis regarding the prolonged clinical recovery is that neurons may engage homeostatic synaptic plasticity mechanisms to compensate for the effects of NMDAR-Abs, as reported in an in vitro model of the acute effects of NMDAR-Abs (Moscat et al., 2014). Understanding the biological basis of this synaptic rescue will offer precious clues to aid the development of experimental therapies for neurological diseases involving the NMDAR.

This study by Planagumà et al. provides the first proof of concept for the use of auto-antibodies from patients with autoimmune encephalitis to generate mouse models, which can then provide insights into the underlying pathophysiology at the cellular, synaptic and neuronal network levels. A similar approach could be used to study other forms of encephalitis associated with antibodies that target synaptic receptors and proteins. Such studies will have direct implications for the many brain disorders in which synapses are affected through a variety of regulatory pathways and mechanisms.

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A new TRAIL in Alzheimer’s disease therapy

This scientific commentary refers to ‘Neutralization of TNFSF10 ameliorates functional outcome in a murine model of Alzheimer’s disease’ by Cantarella et al. (doi: 10.1093/brain/awu318).

Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), now known as TNFSF10, is a member of the TNF superfamily identified by Wiley and colleagues (1995). There are five known subtypes of TNFSF10 receptor, and binding of TNFSF10 to DR4 (TNFRSF10A) and DR5 (TNFRSF10B) receptors, for example, can trigger cell death through activation of caspases leading to apoptosis (Ashkenazi et al., 2008). Activation of TNFSF10 receptors has been suggested to have anti-tumour efficacy; however, variable levels of TNFSF10 receptor expression on tumour cells may limit the usefulness of this approach (Ashkenazi et al., 2008). Whereas TNFSF10 is not detectable in healthy human brain, its expression is upregulated in several neurodegenerative diseases including Alzheimer’s disease (Uberti et al., 2004). In this issue of Brain, Cantarella and colleagues report that an anti-TNFSF10 antibody can reduce brain amyloid-β load and activation of TNFSF10 apoptotic receptors, as well as improve cognition, in a triple transgenic mouse model of Alzheimer’s disease (Cantarella et al., 2014).

Much of the neuronal death in Alzheimer’s disease occurs in brain regions linked to the processing of memory (Walsh and Selkoe, 2004). The pathological hallmarks of the disease are the accumulation of neurotoxic oligomers of amyloid-β, and the formation of neurofibrillary tangles—intraneuronal aggregates of hyperphosphorylated tau protein—both of which lead to neuronal death (Walsh and Selkoe, 2004). The inflammatory process may also have a role in Alzheimer’s disease: an increase in inflammation has been linked to progression of the disease (Wyss-Coray, 2006), while polymorphisms in the TNFSF10 DR4 receptor gene (TNFRSF10A) may influence Alzheimer’s disease susceptibility (Edgunlu et al., 2013). Moreover, amyloid-β deposition has been suggested to activate TNFSF10 apoptotic pathways in neurons, whereas blockade of this cascade via a TNFSF10-neutralizing monoclonal antibody appears to prevent neurotoxicity in vitro (Cantarella et al., 2003). While epidemiology research suggests that non-steroidal anti-inflammatory drugs may have therapeutic efficacy in Alzheimer’s disease, clinical trials in patients failed to show a direct effect (Heneka et al., 2011). Nevertheless, therapies targeting specific inflammatory compounds may hold promise. Here, Cantarella and colleagues demonstrate that intraperitoneal injection of an anti-TNFSF10 antibody for 6 months improves cognition in an Alzheimer’s disease animal model. They also report a reduction in inflammatory markers such as interleukin 1, inducible nitric oxide synthase—which may increase oxidative stress in neurons—and cyclooxygenase, which has previously been linked to Alzheimer’s disease pathology. Furthermore, the results suggest mechanisms of neurotoxicity that may be relevant to a variety of neurodegenerative diseases, including stroke (Cui et al., 2010).

TNFSF10 is thought to be expressed by peripheral immune cells, glial cells and neurons. However, serum levels of TNFSF10 are not consistently increased in patients with Alzheimer’s disease relative to healthy controls (Genc et al., 2009). This suggests that, if TNFSF10 plays a pathogenic role it is secreted within the CNS. One possibility is that, in response to either autocrine or paracrine signalling, neurons secrete TNFSF10 to induce apoptosis of cells affected by amyloid-β and neurofibrillary tangle pathology. Consistent with this, amyloid-β has been shown to mediate neuronal death through TNFSF10 death pathways (Cantarella et al., 2003). Furthermore, while there is clear evidence for increased numbers of astrocytes and activated microglia in the vicinity of amyloid plaques, there is less consensus on their role in pathology (Wyss-Coray, 2006). Some argue that an increase in these cells leads to further neuronal stress, which might be associated with increased activation of...