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REVIEW

Of mice and men: modelling post-stroke depression experimentally

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At least one-third of stroke survivors suffer from depression. The development of comorbid depression after stroke is clinically highly significant because post-stroke depression is associated with increased mortality, slows recovery and leads to worse functional outcomes. Here, we review the evidence that post-stroke depression can be effectively modelled in experimental rodents via a variety of approaches. This opens an exciting new window onto the neurobiology of depression and permits probing potential underlying mechanisms such as disturbed cellular plasticity, neuroendocrine dysregulation, neuroinflammation, and neurodegeneration in a novel context. From the point of view of translational stroke research, extending the scope of experimental investigations beyond the study of short-term end points and, in particular, acute lesion size, may help improve the relevance of preclinical results to human disease. Furthermore, accumulating evidence from both clinical and experimental studies offers the tantalizing prospect of 5-hydroxytryptaminergic antidepressants as the first pharmacological therapy for stroke that would be available during the subacute and chronic phases of recovery. Interdisciplinary neuropsychiatric research will be called on to dissect the mechanisms underpinning the beneficial effects of antidepressants on stroke recovery.

LINKED ARTICLES

This article is part of a themed section on Animal Models in Psychiatry Research. To view the other articles in this section visit http://dx.doi.org/10.1111/bph.2014.171.issue-20

Abbreviations

BDNF, brain-derived neurotrophic factor; MCA, middle cerebral artery; MCAo, middle cerebral artery occlusion; SSRI, selective 5-HT re-uptake inhibitor

Unipolar major depression is projected by the World Health Organization to rank as the leading cause of disease burden worldwide by 2030 (Lépine and Briley, 2011). Depression is a debilitating mental disorder characterized by negative mood, diminished interest or pleasure in daily activities, fatigue, changes in appetite and sleep, a diminished ability to think or concentrate, feelings of worthlessness or guilt, and suicidal ideation. It is an important clinical observation that vascular diseases such as stroke or myocardial infarction frequently precipitate depression (e.g. Sher *et al.*, 2010). Conversely, major depression confers an increased risk of cardiac and cerebrovascular morbidity and mortality (e.g. Salaycik *et al.*, 2007; Majed *et al.*, 2012). With the dramatic aging of Western populations, the number of patients suffering from some combination of mood disorder and somatic illness is set to balloon in the years ahead.

Worldwide, stroke is the second most common cause of death with more than 6 million fatalities in 2010 (World Health Organization, 2013). In the clinical setting, stroke is generally defined as the acute onset of focal neurological symptoms related to cerebral or retinal ischaemia. As opposed to a transient ischaemic attack, the neurological syndrome in stroke persists beyond 24 h or is interrupted by death. The 24 h criterion is somewhat arbitrary, yet widely accepted

(Stroke, 1989). Conceptually, the main difference between a transient ischaemic attack and a stroke is that, in the former, neural tissue makes a full recovery, while in the latter, brain matter is permanently lost. The rapid development of new imaging techniques will probably lead to a refinement of diagnostic criteria for stroke in the future. The incidence of ischaemic stroke is roughly 10 times higher than the incidence of haemorrhagic stroke (Kolominsky-Rabas *et al.*, 1998). A narrow definition of stroke does not encompass brain injury due to global brain hypoxia such as may occur in cardiac arrest and in cyanide or carbon monoxide poisoning.

Psychiatric classifications typically strive for an atheoretical approach. As such, the term 'post-stroke depression' is used descriptively and does not imply causation. Therefore, any depression that has been diagnosed after a stroke has occurred should be termed post-stroke depression, irrespective of whether some or all depressive symptoms preceded the stroke (Williams, 2005). As is the case for depression in the general population, depression in stroke survivors often goes undetected. It is conservatively estimated that more than one-third of all stroke patients display signs and symptoms of depression at some point after the onset of stroke. Symptoms such as overt sadness and crying may be useful for the clinician working in a stroke unit setting to spot patients with incipient depression (Carota *et al.*, 2005). A recent meta-analysis suggests that the frequency of mood symptoms may even rise in the long-term phase of recovery (Hackett and Anderson, 2005). There are a number of established risk factors for the development of depression subsequent to brain ischaemia. Physical disability, stroke severity and cognitive impairment figure especially prominently in the clinical literature (Hackett and Anderson, 2005). Women are at a greater risk of post-stroke depression than men (Poynter *et al.*, 2009). Furthermore, individuals with a history of major depression are more likely to experience depression after suffering a stroke (Andersen *et al.*, 1995; Pohjasvaara *et al.*, 1998). A patient's personal circumstances such as family, home environment or the availability of informal care, may also have a major impact on psychological well-being and mental health after stroke (Eriksson *et al.*, 2004).

Psychiatric complications attendant to stroke can be devastating. Sustaining a stroke increases the risk of experiencing suicidal ideation and of dying from suicide (Pompili *et al.*, 2012). Depression after stroke is associated with an increase in all-cause mortality (Bartoli *et al.*, 2013). Furthermore, depression slows recovery and predicts poorer functional outcomes following stroke (Mayo *et al.*, 1991; van de Weg *et al.*, 1999; Wulsin *et al.*, 2012). Finally, depression in survivors adds significantly to hospitalization and health care costs (Ghose *et al.*, 2005; Husaini *et al.*, 2013). Given this state of affairs, it is quite remarkable that, to this day, post-stroke depression has remained relatively under-diagnosed, under-treated and under-researched (Kronenberg *et al.*, 2006; Loubinoux *et al.*, 2012).

A working group set up by the National Institute of Mental Health to make recommendations for research on mood disorders highlighted the development of novel hypothesis-driven animal models as a key area for future investment (Nestler *et al.*, 2002). Rodent models of stroke-induced depressive-like behaviours may offer an entirely new glimpse into the pathophysiology of depression. As is the case for major depression in general, the cellular and molecular basis of post-stroke depression is also poorly defined. Furthermore, the effects of antidepressant pharmacotherapy after stroke remain to be fully understood. Suitable animal models can therefore give a much-needed boost to research on depression in general and post-stroke depression in particular.

Translation in stroke research – roadblocks and detours

Translational stroke research has witnessed both great successes and failures in recent years. Experimental research played a decisive role in the development of intravenous thrombolysis (Matsuo *et al.*, 1981; Zivin *et al.*, 1985; Hacke *et al.*, 2008) and in bringing the concept of the ischaemic penumbra to fruition (Endres *et al.*, 2008). On the downside, thrombolysis may benefit only a subset of patients, and, notwithstanding billions of dollars allocated to stroke research, not a single pharmacological agent with a site of action within the brain parenchyma has made it to the bedside (Dirnagl and Macleod, 2009). From the point of view of experimental stroke research, it is particularly disappointing that scores of neuroprotectants, which demonstrated efficacy in laboratory animals, fell through in subsequent clinical trials. This discrepancy between preclinical efficacy and ultimate clinical failure is probably best illustrated by the SAINT II trial (Shuaib *et al.*, 2007), which marked the worst in a string of setbacks for the field. This randomized, double-blind trial of free-radical-trapping agent NXY-059, which enrolled more than 3000 patients with acute ischaemic stroke, came out negative, despite clear and confirmed evidence that NXY-059 indeed exerts neuroprotective effects in experimental stroke models (Bath *et al.*, 2009). In response, the field has begun to draw up measures intended to reduce different forms of bias such as 'selection bias', 'performance bias' and 'publication bias' (Dirnagl and Macleod, 2009). It has also been argued that experimental animals should be better matched to stroke patients, for example, by testing aged animals or animals with baseline comorbidities such as hypertension, obesity and diabetes (Savitz, 2009). Finally, evaluation of functional outcomes over the course of several weeks after ischaemia has been proposed as a key element in improving the clinical validity of experimental stroke studies (Balkaya *et al.*, 2013).

Studying behavioural outcomes in rodent models of brain ischaemia

Clinical stroke trials typically measure the degree of disability or dependence in daily activities several months after the event. Scores on frequently used clinical stroke scales such as the modified Rankin Scale (van Swieten *et al.*, 1988) or the Barthel Index (Mahoney and Barthel, 1965) may be heavily influenced by psychiatric comorbidity. A major criticism of preclinical stroke studies is therefore that they tend to focus too narrowly on histological reduction of acute infarct

volume. Notably, a number of studies in human patients clearly demonstrated that lesion volume *per se* is of only subordinate importance to functional outcomes in the chronic phase after stroke (e.g. Mark *et al.*, 2008; Riley *et al.*, 2011; Page *et al.*, 2013). Experimental investigators are therefore beginning to extend their studies beyond short-term end points and, in particular, acute histological lesion size. Remarkably, similar to the results from clinical investigations, the association between lesion sizes and functional deficits is generally rather weak in experimental studies, especially during the subacute and chronic phases of recovery (Reglodi *et al.*, 2003; Freret *et al.*, 2006; Bouët *et al.*, 2007).

When rigorously assessed, replicability of behavioural results from mice across different laboratories is not always satisfactory (Crabbe *et al.*, 1999; Wahlsten *et al.*, 2003). Furthermore, behavioural end points are subject to larger variation than histological analyses, thus creating the need for increased sample sizes (Rosell *et al.*, 2013). Nevertheless, neurobehavioural outcomes at delayed recovery time points have increasingly been incorporated into the design of preclinical stroke studies. In principle, three kinds of behavioural tests of stroke-induced deficits can be distinguished: (i) tests measuring sensorimotor performance including locomotion, (ii) tests of cognitive skills including learning and memory, and (iii) tests reflecting mood changes such as anxiety or despair (DeVries *et al.*, 2001). Since a single behavioural measure is easily liable to misinterpretation, it is generally desirable that a comprehensive multi-tiered battery of tests be conducted (Crawley, 2007).

Simple sensorimotor tests such as rotarod, adhesive removal, pole test and the wire hanging procedure have already become quite commonplace in experimental stroke studies in mice (Balkaya *et al.*, 2013). Current research is aimed at defining which of these sensorimotor tests is best suited to which type of research design. For example, a recent study of 30 min middle cerebral artery occlusion (MCAo)/reperfusion found that the rotarod test detected stroke-related deficits only within the first week of stroke surgery. The pole test was reliable up to intermediate time points in that model. Finally, the corner test, adhesive removal test, catwalk and paw preference were sensitive to stroke-induced deficits for up to 4 weeks (Balkaya *et al.*, 2013). In a distal MCAo model, grip strength and the latency to move test have recently been reported to be particularly useful for the characterization of long-term stroke outcome (Rosell *et al.*, 2013). Gauging the utility of these and similar measures in the context of pharmacological manipulations will be a crucial task for future studies.

It is now more than three decades since Robinson published his landmark study on the lateralization of the behavioural response to cerebral infarction. He reported that rats subjected to right MCA ligation became transiently hyperactive (open field test, wheel running), whereas no such behavioural effect was observed in animals following ligation of the left MCA (Robinson, 1979). This early experimental report still nicely dovetails with an ongoing clinical controversy regarding lesion location and the emergence of certain post-stroke behavioural changes in humans (Carson *et al.*, 2000; Narushima *et al.*, 2003; Bhogal *et al.*, 2004). Interestingly, two recent studies in mice also found increased locomotor activity following right as compared with left transient brain ischaemia (Winter *et al.*, 2005; Kronenberg *et al.*, 2012). However, several other studies in rats failed to corroborate increased locomotion after ischaemic damage to the right hemisphere (permanent right MCAO: Grabowski *et al.*, 1988; Grabowski *et al.*, 1991; transient right MCAO: Sakai *et al.*, 1996).

In recent years, experimental researchers have steadily extended their scope to the neuropsychological and neuropsychiatric consequences of cerebral ischaemia. For example, our group has shown that mice subjected to mild focal brain ischaemia develop impairments in executive functioning, which are reminiscent of the dysexecutive syndromes associated with subcortical vascular disease (Winter *et al.*, 2004). Six weeks after 30 min left MCAo/reperfusion, 129/SV mice displayed only mild sensorimotor neurological deficits. Moreover, spatial learning in the Morris water maze was undisturbed (stroke mice and sham-operated mice had similar latencies and path lengths to find the hidden platform in a standard place task over 7 days). However, stroke mice displayed distinct deficits in the probe trial and visible platform task that indicated impaired cognitive flexibility and strategy switching after MCAo (Winter *et al.*, 2004).

Finally, anxiety- and depression-related behavioural tests such as the elevated plus maze, the shuttle box, Porsolt's forced swim test, sucrose consumption and the novelty-suppressed feeding paradigm are also gradually entering the stroke field (Table 1). The precise role of individual tests as measures of depression is under, at times, fierce debate in psychiatry and behavioural neuroscience. In particular, this is the case for Porsolt's forced swim test, which is probably the most widely used test of depression in rodents. Here, the experimental animal is forced to swim in a beaker of water from which it cannot escape. The latency to passively float (i.e. the time to 'give up') and the total time floating serve as indicators of behavioural despair. The test was developed primarily as a screening tool for antidepressants (Porsolt *et al.*, 1977) and the precise relevance of immobility in the test to human depression remains to be defined. Furthermore, antidepressant drugs elicit behavioural changes in the forced swim test within 24 h of treatment, whereas the recovery from clinical depression usually requires several weeks (Detke *et al.*, 1997). The tail suspension test is sometimes used as a 'dry' version of the forced swim test where immobility is induced by suspending the mouse from the tail (Porsolt *et al.*, 2001).

The novelty-suppressed feeding paradigm was originally developed as a test for anxiety, not depression (Britton and Britton, 1981; Bodnoff *et al.*, 1988). The novelty-suppressed feeding paradigm capitalizes on an approach-avoidance conflict where the food-deprived rodent is motivated both by the drive to ingest food and by the competing fear of moving into the centre of a brightly illuminated arena. The test is ethologically relevant. Furthermore, effects of antidepressants on latency to eat in the novelty-suppressed feeding paradigm are only observed after chronic treatment in mice and rats (Bodnoff *et al.*, 1988; Santarelli *et al.*, 2003).

Lastly, sucrose preference is frequently used as an additional measure of an altered hedonic state (Strekalova *et al.*, 2004). Chronic exposure to mild unpredictable stressors has been reported to reduce sucrose consumption, whereas antidepressant treatment reverses this effect (Monleon *et al.*,

Table 1

Structural and behavioural consequences of stroke models

	Ischaemia model	Details of behavioural methods	Results
Studies in mice			
Bouët *et al.*, 2007	60 min right MCAo/reperfusion	Sensorimotor and cognitive test battery; analyses up to 26 days after surgery	Long-lasting sensorimotor deficits (postural asymmetries on the corner test, bilateral skilled forepaw reaching deficits on the staircase test, contralateral sensorimotor impairment on the adhesive removal test). Normal spatial learning abilities on the Morris water maze test.
Craft & DeVries, 2006	60 min right MCAo/reperfusion	day 7 after surgery; sucrose consumption (as measure of hedonia)	Anhedonia; treatment with interleukin-1 receptor antagonist can reverse post-stroke anhedonia
Espinera *et al.*, 2013	Distal right MCAo	Subset of animals treated with citalopram; adhesive removal test (3 and 14 days post stroke)	Citalopram treatment has no effect on infarction formation and brain oedema 72 h after stroke; citalopram-treated mice show better functional recovery than saline-treated controls 3 and 14 days after stroke in the adhesive removal test; increased expression of BDNF in the peri-infarct region 7 days after stroke in citalopram-treated animals
Freret *et al.*, 2006	Transient (30 min or 60 min) occlusion of the right MCA	Sensorimotor behaviour was assessed using neurological score, limb-placing, adhesive removal, and staircase tests	Cortical damage correlated to all transient and long-lasting sensorimotor deficits, striatal lesion more consistently reflected by forelimb-placing reflexes and adhesive removal motor deficits.
Kronenberg *et al.*, 2012	30 min MCAo/reperfusion	14 weeks after surgery; comprehensive behavioural battery including spontaneous locomotor activity, elevated plus maze, sucrose consumption, Porsolt's forced swim test; subset of animals received delayed treatment with SSRI citalopram beginning 7 days after MCAo	rMCAo: hyperactivity lMCAO: anxious-depressive phenotype which could be reversed by treatment with citalopram
O'Keefe *et al.*, 2014	60 min of reversible right MCAo	Investigation of the sub-acute (2 weeks) and chronic (7 weeks) effects of social isolation on post-stroke functional and histological outcome; open field test, elevated zero maze, Porsolt's forced swim test	No effect of stroke on locomotor activity; no difference in anxiety-like behaviour between groups; however, worsened histological damage from ischaemic injury and an increase in depressive-like behaviour in isolated mice as compared with pair-housed mice. Mice isolated immediately after stroke show a decrease in the serum levels of BDNF.
Royl *et al.*, 2009	45 min left MCAo/reperfusion	Sucrose consumption, pole test, wire hanging test (during the third week after MCAo); subset of animals were treated with PDE5 inhibitor vardenafil	Sensorimotor and hedonic deficits after MCAO, no effect of vardenafil
Sun *et al.*, 2013	Distal left MCAo	Analysis approximately 8 weeks after surgery; Catwalk automated gait analysis; Barnes maze test; conditional ablation of neurogenesis using nestin-δ-HSV-TK-EGFP transgenic model and GCV treatment	Conditional ablation of NPCs exacerbates stroke-induced cognitive impairment
Winter *et al.*, 2004	30 min left MCAo/reperfusion	6 weeks after surgery; Bederson score, sensorimotor coordination (rotarod), spatial navigation (Morris water maze)	Dysexecutive syndrome with distinct deficits in the probe trial and visible platform task (Morris water maze)
Winter *et al.*, 2005	30 min MCAo/reperfusion	8 to 10 weeks after surgery; Bederson score, spontaneous locomotor activity, Porsolt's forced swim test	lMCAo: increased anxiety rMCAo: hyperactivity

Table 1

Continued

	Ischaemia model	Details of behavioural methods	Results
Studies in rats			
Boyko *et al.*, 2013	Permanent right MCAo	Analysis of young and old rats after MCAO; behavioural tests at 3 weeks after MCAO (sucrose preference test, two-way shuttle avoidance task, forced swimming test)	Reduced sucrose consumption as well as increased anxiety and despair-related behaviours in MCAO rats as compared with sham-operated rats with no additional effect of aging; however, old rats have larger infarcts.
Cheng *et al.*, 2013	90 min left MCAo	Ovariectomy (all animals); treatment with 17β-oestradiol in a subset of animals; open field test, sucrose consumption and Porsolt's forced swim test	Ischaemia causes reduced sucrose consumption, reduced locomotion and reduced rearing activity (from the end of the first week to the end of the third week after MCAo); treatment with 17β-oestradiol attenuates depressive-like behaviours (measured by sucrose consumption and Porsolt test); treatment with 17β-oestradiol does not influence infarct volume, but increases neurogenesis after MCAO
Kato *et al.*, 2000	2 h left MCAo	Shuttle box behaviour (day 15); subset of animals received monoamine re-uptake inhibitor T-794 after stroke	MCAO results in more escape failures, this is attenuated by T-794
Nemeth *et al.*, 2012	Microembolism model (micro-spheres are injected into the left internal carotid artery)	Short recovery (SR) time point (4–6 days) or long recovery (LR) time point (14–17 days post-surgery); open field test, sucrose consumption, social interaction; spatial memory in the Barnes Maze at the LR time point and beyond (35 days post-surgery).	Microembolism infarcts lead to an increase in anxiety- and depressive-like behaviours at the LR, but not the SR, time point. Impaired spatial memory at 33 days.
Robinson, 1979	Ligation of left or right MCA	4 to 17 days after surgery; spontaneous activity (running wheel activity and open field exploration)	Right hemispheric infarction results in generalized hyperactivity
Quinn *et al.*, 2005	90 min left MCAo	Homecage behaviour (LABORAS) and social interaction	Rats subjected to MCAO showed deficits in general home cage behaviours including locomotion, rearing, grooming and drinking for up to 7 weeks post-occlusion, as compared with sham-operated controls; significant decrease in the total duration of social interaction in occluded rats compared with shams.
Wang *et al.*, 2008	Permanent left MCAo	Additional chronic mild stress (CMS) procedure for 18 consecutive days after ischaemia; subset of animals received citalopram; open field test and sucrose consumption after approximately 3 weeks	Locomotor activity is reduced by combination of CMS and MCAO, citalopram reverses this effect; sucrose consumption is reduced by combination of CMS and MCAO, citalopram also reverses this effect
Wang *et al.*, 2009b	Permanent left MCAo	Additional CMS procedure for 18 consecutive days after ischaemia in a subset of animals; subset of animals received citalopram; open field test and sucrose consumption; analyses up to 6 weeks	MCAO + CMS decreases locomotor activity, citalopram reverses this effect; MCAO alone does not alter sucrose consumption; MCAO + CMS decreases sucrose consumption, citalopram reverses this effect
Wang *et al.*, 2009a	Permanent left MCAo	Additional CMS procedure for 18 consecutive days after ischaemia in a subset of animals; subset of animals received citalopram; open field test and sucrose consumption; analyses up to four weeks	MCAO + CMS decreases locomotor activity, citalopram reverses this effect (day 19); MCAO + CMS decreases sucrose consumption, citalopram reverses this effect; decreased protein expression and mRNA levels of 5-HT1A receptors in MCAO + CMS, reversed by citalopram treatment

Table 1

Continued

	Ischaemia model	Details of behavioural methods	Results
Wang *et al.*, 2010	Permanent left MCAo	Additional 14 day CMS protocol; subset of animals received citalopram and selective 5-HT1A antagonists WAY-100635; sucrose consumption; analyses up to 4 weeks	Combination of citalopram and WAY-100635 increases sucrose consumption in MCAO + CMS rats; combination of citalopram and WAY-100635 increases hippocampal neurogenesis in MCAO + CMS rats
Wang *et al.*, 2012	Permanent left MCAo	Additional CMS procedure for 18 consecutive days after ischaemia in a subset of animals; subset of animals received γ-secretase inhibitor DAPT; open field test and sucrose consumption; analyses up to 28 days	MCAO + CMS decreases locomotor activity and sucrose consumption; DAPT increases sucrose consumption in MCAO + CMS group; DAPT reduces apoptosis in dentate gyrus of MCAO + CMS group

1995). A combination of the three depression tests described above or of similar procedures is probably best suited to cover the whole spectrum of depressive-like behaviours in rodents (Strekalova *et al.*, 2004; Kronenberg *et al.*, 2012; Son *et al.*, 2012).

It is impossible to gloss over the fact that the currently existing body of experimental literature describing post-stroke 'affective syndromes' is still relatively paltry (please refer to Table 1 for a summary of relevant studies). In consequence, the investigations conducted so far vary widely according to key methodological characteristics including the stroke model used, the time of behavioural assessment, and the behavioural tests employed. In order to lay a solid foundation for future mechanistic studies, the field will have to place a high premium on repetition, replication and, ultimately, standardization. Notwithstanding, a number of groups have reported genuine 'depressive-like syndromes' characterized by varying degrees of anxiety, despair and anhedonia following diverse models of MCAo or microembolism-induced brain ischaemia (Kato *et al.*, 2000; Winter *et al.*, 2005; Craft and DeVries, 2006; Royl *et al.*, 2009; Kronenberg *et al.*, 2012; Nemeth *et al.*, 2012; Boyko *et al.*, 2013; see Table 1 for a brief summary of each study). Furthermore, some studies have even been able to demonstrate that stroke-induced mood changes are amenable to antidepressant medication (Kato *et al.*, 2000; Kronenberg *et al.*, 2012). In summary, neuropsychiatric sequelae of brain ischaemia are clearly accessible to experimental investigation. Hopefully, such complex behavioural end points will also improve the predictive validity of experimental stroke studies and thereby aid future research in finding a detour around the current translational 'roadblock' in the development of stroke therapeutics. Finally, although this is somewhat beyond the scope of our current review, it is interesting to note that global cerebral ischaemia may also induce mood symptoms. For example, cessation of cerebrovascular blood flow and subsequent reperfusion during the course of experimental cardiac arrest and cardiopulmonary resuscitation have recently been reported to lead to increased levels of anxiety (open field) as well as depressive-like behaviours (Porsolt's test; Norman *et al.*, 2010).

Neurobiology of post-stroke depression

The nature of post-stroke depression versus other forms of major depression remains under debate. Suffering and recovering from a stroke may constitute a life-changing and potentially catastrophic experience. It would therefore be foolish to deny that the attendant psychological distress plays a critical role in the development of post-stroke depression (Gainotti *et al.*, 1999). But it would be equally unconvincing to completely dismiss biological factors, the relevance of which is made particularly apparent by such clinical observations as the occurrence of depression in patients with anosognosia (i.e. patients lacking awareness of the stroke-related deficit; Starkstein *et al.*, 1992; Biran and Chatterjee, 2003) and the higher prevalence of affective symptoms in stroke survivors relative to orthopaedic patients with the same degree of functional impairment (Folstein *et al.*, 1977).

Current biological theories of major depressive disorder, which are partly interconnected, centre on dysregulation of the hypothalamus-pituitary-adrenal (HPA) axis, impaired neurogenesis and cellular plasticity (Kempermann and Kronenberg, 2003), altered neurotrophin signalling (Lang *et al.*, 2004; Duman and Voleti, 2012), neuroinflammation (Maes, 2008) and even downright neuronal loss (Sapolsky *et al.*, 1985). As preclinical stroke research is pivoting to the study of complex long-term end points, similar processes increasingly find themselves the cynosure of experimental neurology and psychiatry.

Stress and the brain

The one biological mechanism, if indeed it exists, underlying 'pure' major depression is unresolved, and depression remains a perplexing disorder in its particulars. However, the bidirectional relationship between depression and stress on the one hand and disturbed brain plasticity on the other hand has emerged as a common theme from both clinical research and basic neuroscience (Lupien *et al.*, 2009). Numer-

ous neuroimaging studies have documented structural brain changes during an episode of major depression, including volumetric alterations of hippocampus (Sheline *et al.*, 1996; Colla *et al.*, 2007), thalamus (Nugent *et al.*, 2013) and amygdala (Kronenberg *et al.*, 2009b; Burke *et al.*, 2011; Foland-Ross *et al.*, 2012; Saleh *et al.*, 2012). Dysregulation of the HPA axis is a hallmark of major depressive disorder (Carroll *et al.*, 1981; Rush *et al.*, 1996). Similarly, dysregulation of the HPA system has also been linked to hippocampal atrophy (Sheline *et al.*, 1999; Starkman *et al.*, 1999; Colla *et al.*, 2007). Furthermore, the stress hormone response has been connected with alterations in central 5-HT transporter levels, which also correlated with the severity of negative mood states (Reimold *et al.*, 2011).

Moving to the realm of stroke research, cortisol levels on the first day after stroke have been shown to predict 28 day mortality (Marklund *et al.*, 2004). Similarly, cortisol levels on admission have recently been reported to predict functional outcome after ischaemic stroke (Zi and Shuai, 2013). Furthermore, a recent meta-analysis in stroke patients yielded an association between depression and hyperactivity of the HPA system (higher post-dexamethasone cortisol levels in post-stroke depression; Noonan *et al.*, 2013). In summary, these clinical findings suggest that the established link between depression and stroke severity (Hackett and Anderson, 2005) may partly be mediated by HPA system overdrive.

This conclusion is also supported by quite a number of preclinical investigations demonstrating that different forms of stress such as repeated immobilizations, social isolation, social stress generated by intimidation or chronic exposure to various stressors may significantly worsen short-term stroke outcome in rodents. Table 2 provides a short overview of relevant experimental studies. For example, Balkaya and co-workers were able to show that the adverse effects of chronic pre-stroke stress in mice relate to impaired endothelium-dependent vasorelaxation, increased superoxide production, and reduced endothelial NOS levels. Importantly, stress-induced endothelial dysfunction and increases in infarct size could be attenuated by treatment with the glucocorticoid receptor (for receptor nomenclature see Alexander *et al.*, 2013) antagonist mifepristone (Balkaya *et al.*, 2011). Similarly, Sugo and colleagues found that social stress exacerbates acute stroke damage, which again could be reversed by mifepristone (Sugo *et al.*, 2002). Current experimental research is aimed at characterizing how the precise cellular and temporal context of glucocorticoid signalling shapes acute stroke outcome (Sorrells *et al.*, 2013). Furthermore, the effects of stress on potential mechanisms of recovery and on long-term stroke outcome still largely remain to be explored.

Brain plasticity and stroke recovery

In the last 20 years, a wealth of experimental research has revealed that the adult brain is a highly plastic organ that retains the capacity to make new glia and, under certain circumstances, even new neurons (Kaplan and Hinds, 1977; Kuhn *et al.*, 1996; Eriksson *et al.*, 1998; Kempermann and Kronenberg, 2003). Psychological stress and depressive-like behaviours have been linked to impairments of all major aspects of plasticity in the adult mammalian brain such as neurogenesis (Gould *et al.*, 1997; Czéh *et al.*, 2001; Kronenberg *et al.*, 2009a; Snyder *et al.*, 2011), gliogenesis (Gosselin *et al.*, 2009; Ye *et al.*, 2011), synaptogenesis (Liston and Gan, 2011) and, not least, angiogenesis (Ekstrand *et al.*, 2008; Czéh *et al.*, 2010). Conversely, even minor perturbations of brain structure such as glial ablation in the prefrontal cortex (Banasr and Duman, 2008) or reduced hippocampal volume and reduced neurogenesis in folate deficiency (Kronenberg *et al.*, 2008) have been shown to bring about depressive-like symptoms in experimental animals.

Neurogenesis and gliogenesis constitute an integral part of the adaptive response of the brain to ischaemia. Focal stroke has been shown to increase proliferation of neural precursor cells in the subgranular zone of the dentate gyrus and the rostral subventricular zone bilaterally (Jin *et al.*, 2001). Similarly, transient global ischaemia has been reported to enhance hippocampal neurogenesis in rats (Kee *et al.*, 2001). In most non-neurogenic regions of the adult brain, ischaemia strongly promotes proliferation of resident glial cells (Buffo *et al.*, 2005; Kronenberg *et al.*, 2010). So far, only few studies have addressed the role of cellular plasticity in the aetiopathogenesis of post-stroke depression. For example, unpredictable chronic mild stress after left MCAo was shown to result in depressive-like behaviours along with decreased levels of hippocampal neurogenesis in rats (Wang *et al.*, 2008; 2010). Furthermore, antidepressant treatment with citalopram reversed both the behavioural and the antineurogenic effects of chronic stress after brain ischaemia (Wang *et al.*, 2008). An exciting recent study using nestin-δ-HSV-TK-EGFP transgenic mice elegantly demonstrated the importance of neuroprogenitor cells for post-stroke cognitive recovery. Conditional ablation of neuroprogenitors did not affect lesion size or motor function in a model of distal MCAo; however, recovery from stroke-induced cognitive deficits was significantly impaired by genetic disruption of neurogenesis (Sun *et al.*, 2013). This finding is particularly notable in our context because cognitive impairments and depression after stroke frequently go hand in hand (Hackett and Anderson, 2005).

Neurotrophin signalling

Several neurotrophic and growth factors such as VEGF, fibroblast growth factor-2 and insulin-like growth factor-1 have been implicated in the pathobiology of major depressive disorder (Duman and Li, 2012). In particular, much research has been devoted to the brain-derived neurotrophic factor (BDNF). BDNF is a versatile molecule with a wide range of biological actions, including boosting synaptogenesis and neurogenesis and promoting neuronal survival (Young *et al.*, 1999; Seil and Drake-Baumann, 2000; Lee *et al.*, 2002; Chao, 2003). Numerous basic research studies have reported decreased hippocampal BDNF levels in response to diverse stress conditions (reviewed in Duman and Monteggia, 2006). Several analyses of human *post-mortem* brain have likewise yielded reduced BDNF concentrations in suicide victims and patients with mood disorders (Karege *et al.*, 2005; Thompson Ray *et al.*, 2011; Banerjee *et al.*, 2013). Conversely, antidepressant psychopharmacotherapy and electroconvulsive seizures

Table 2

Effects of psychological stress and glucocorticoids in experimental stroke models

	Stress and ischaemia model	Results
Studies in mice		
Balkaya *et al.*, 2011	Chronic stress paradigm over 28 days; treatment with glucocorticoid receptor antagonist mifepristone or vehicle; subsequently, mice are subjected to 30 min MCAo/reperfusion; assessment of histological stroke damage at 72 h after MCAo	Stress causes increase in heart rate, impaired endothelium-dependent vasorelaxation, increased superoxide production, and reduced aortic and brain endothelial nitric oxide synthase levels. Stress confers major increases in ischaemic lesion size. The negative effects of stress are reversed by mifepristone.
Caso *et al.*, 2008	Immobilization (1 h for 7 days) prior to permanent MCAO by electrocoagulation; assessment of histological stroke damage at 24 h after MCAO	Immobilization stress increases infarct size, lipid peroxidation and iNOS expression; these effects of stress on stroke outcome are attenuated in TLR4-deficient mice
Custodis *et al.*, 2011	Chronic stress paradigm over 28 days; treatment with I(f)-channel inhibitor ivabradine (10 $mg \cdot kg^{-1}$ per day) or vehicle; subsequently, mice are subjected to 30 min MCAo/reperfusion; assessment of histological stroke damage at 72 h after MCAo	Stress impairs endothelial function, exacerbates vascular and brain oxidative stress, and increases infarct size. Heart rate reduction with ivabradine restores endothelial function, reduces oxidative stress, and reduces lesion size.
DeVries *et al.*, 2001	Social stress paradigm over 3 days; last stress session approximately 1 h before induction of cerebral ischaemia by 60 min MCAo/reperfusion; assessment of histological stroke damage at 24 h after MCAo	Stress increases infarct size and reduces bcl-2 mRNA levels in the ischaemic hemisphere; significant inverse correlation between post-stroke corticosterone levels and bcl-2 mRNA levels
Karelina *et al.*, 2009	Social isolation or social housing for 2 weeks before surgery and throughout reperfusion period; 60 min MCAo/reperfusion.	Peri-ischaemic social isolation decreases post-stroke survival and exacerbates infarct size and oedema development; central IL-6 signalling is down-regulated and peripheral IL-6 is up-regulated in isolated mice.
O'Keefe *et al.*, 2014	60 min of reversible right MCAo; investigation of the subacute (2 weeks) and chronic (7 weeks) effects of social isolation on post-stroke functional and histological outcome; open field test, elevated zero maze, Porsolt's forced swim test	No effect of stroke on locomotor activity; no difference in anxiety-like behaviour between groups; however, worsened histological damage from ischaemic injury and an increase in depressive-like behaviour in isolated mice as compared with pair-housed mice. Mice isolated immediately after stroke show a decrease in the serum levels of BDNF.
Sorrells *et al.*, 2013	Implantation of s.c. corticosterone pellets; MCA permanently occluded by electrocoagulation; assessment of histological stroke damage at 24 h after MCAO	Pre-MCAO glucocorticoids worsen MCAO damage in wild-type mice; key role of glucocorticoid signalling in myeloid and endothelial cells in mediating this effect
Sugo *et al.*, 2002	Social stress (45 min) or injection with 1 $mg \cdot kg^{-1}$ corticosterone or vehicle for 7 days; mice subjected to social stress were injected with 1 $mg \cdot kg^{-1}$ mifepristone (glucocorticoid receptor antagonist) or vehicle; stroke induced by 60 min of intraluminal MCAo	Chronic social stress or exogenous corticosterone before MCAo result in larger infarcts at 72 h. Effect of social stress on infarct volume is reversed by pretreatment with mifepristone.
Venna *et al.*, 2012	Social isolation or social housing for 7 days before surgery and throughout reperfusion period; 90 min MCAo/reperfusion	Peri-ischaemic social isolation increases infarct size (72 h) and expression of NF-κB
Caso *et al.*, 2006	immobilization (1 h for 7 days) prior to permanent MCAO; assessment of infarct volume at 24 h after MCAO	Immobilization stress increases infarct size; this relates to increased iNOS expression and lipid peroxidation, and increased TNF-α levels
Madrigal *et al.*, 2003	Subacute (1 h for 7 days) or chronic (6 h for 21 days) immobilization stress 24 h before permanent MCAO; assessment of infarct volume at 48 h after MCAO	Subacute immobilization stress increases brain infarct volume; chronic immobilization stress reduces brain infarct volume

increase hippocampal BDNF (Nibuya *et al.*, 1995; 1996). However, BDNF has numerous functions in the brain and regulation in different brain areas may follow different principles. For example, chronic social-defeat stress has been shown to up-regulate BDNF levels in the nucleus accumbens (Berton *et al.*, 2006).

BDNF serum levels are reduced in depressed subjects relative to healthy controls. Furthermore, serum BDNF concentrations are significantly increased after antidepressant treatment (Sen *et al.*, 2008; Bocchio-Chiavetto *et al.*, 2010). Interestingly, the Framingham study identified low-serum BDNF levels as a risk factor for incident stroke (Pikula *et al.*, 2013), which may be part of the mechanistic explanation as to why depression constitutes an independent risk factor for cerebral ischaemia (Salaycik *et al.*, 2007). BDNF serum levels are elevated early after stroke (Yang *et al.*, 2011). In line with this finding, a number of experimental studies reported increased BDNF mRNA expression or increased BDNF protein levels in brain tissue after MCAo (Kokaia *et al.*, 1995; 1998; Kronenberg *et al.*, 2012). Importantly, our recent finding of increased BDNF protein concentrations in ischaemic murine striatum (including ventral striatum) fits well with earlier studies linking increased BDNF signalling specifically in the nucleus accumbens to depressive-like behaviours (Berton *et al.*, 2006; Kronenberg *et al.*, 2012). Interestingly, however, low-circulating BDNF levels after stroke have been linked with the emergence of post-stroke depression (Yang *et al.*, 2011).

Neuroinflammation

Immune dysregulation and, in particular, altered proinflammatory signalling have long been implicated in major depression. A recent meta-analysis concluded that concentrations of the pro-inflammatory cytokines TNF-α and IL-6 are higher in depressed subjects compared with controls (Dowlati *et al.*, 2010). Phenotypically, 'sickness behaviour' and depression share many of the same symptoms including withdrawal from the social and physical environment, decreased reactivity to reward as well as so-called 'vegetative' symptoms such as anorexia, fatigue and disordered sleep (Dantzer *et al.*, 2008). The relationship between immune activation and depressive symptoms is strongly illustrated by the fact that patients undergoing cytokine therapy frequently experience profound mood changes (Bonaccorso *et al.*, 2001; Capuron *et al.*, 2001). Conversely, acute psychological stress has been shown to increase IL-1β, IL-2 and soluble intercellular adhesion molecule-1 plasma concentrations, which may contribute to atherosclerosis and vascular disease (Heinz *et al.*, 2003). A number of studies have also documented increased circulating IL-1β (Owen *et al.*, 2001; Thomas *et al.*, 2005) and IL-18 (Kokai *et al.*, 2002; Merendino *et al.*, 2002) levels in major depression. Increased serum IL-18 levels were also suggested as a biomarker for depression after ischaemic stroke (Yang *et al.*, 2010). Furthermore, it has recently been shown that, in the acute phase of ischaemic stroke, increased serum levels of IL-6 play an important role in the onset of depressive psychopathology, apathy/amotivation and somatic symptoms of depression (Spalletta *et al.*, 2013).

Of late, experimental research has established a fascinating link between altered 5-hydroxytryptminergic signalling and neuroinflammation. Specifically, bacille Calmette-Guérin (BCG)-induced chronic depressive-like behaviours in mice were mechanistically linked to up-regulation of tryptophan-degrading enzyme indoleamine 2,3-dioxygenase (IDO) in microglia (O'Connor *et al.*, 2009a). Similarly, peripheral administration of LPS was shown to activate IDO and thereby culminate in a distinct depressive-like behavioural syndrome, probably mediated through tryptophan catabolites (O'Connor *et al.*, 2009b). Based on these and similar findings, a 'new 5-HT hypothesis of depression' revolving around up-regulation of IDO, subsequent depletion of 5-HT precursor tryptophan, and increased synthesis of detrimental tryptophan catabolites, has recently been formulated, particularly with respect to depression in somatic illness (Maes *et al.*, 2011). Increased production of pro-inflammatory cytokines after brain ischaemia may also set off and amplify this pathological cascade (Spalletta *et al.*, 2006). It has been hypothesized that activation of IDO, especially in limbic and paralimbic regions, would then result in physiological dysfunction and ultimately lead to post-stroke depression (Spalletta *et al.*, 2006). Importantly, altered IL-1 transmission in the brain has already been shown to contribute to post-stroke anhedonia following 60 min MCAo/reperfusion (Craft and DeVries, 2006).

Neurodegeneration

Finally, stroke entails neurodegeneration. The 'vascular depression' hypothesis posits that even small lesions disrupting critical neural pathways may precipitate depression. For example, ischaemic brain injury may directly interrupt the monoaminergic projections ascending from midbrain and brainstem. Furthermore, the gradual accumulation of multiple vascular lesions may eventually cross a critical threshold beyond which the risk of depression is also greatly increased (Alexopoulos *et al.*, 1997). In addition to pan-necrosis (i.e. necrosis of all brain cells as well as degeneration of neuropil and white matter), which usually occurs in the ischaemic infarct, selective neuronal loss represents a further important pathophysiological consequence of ischaemic stroke (Baron *et al.*, 2014). Selective neuronal loss may occur in the salvaged penumbra as well as in remote brain areas not directly impacted by the stroke (Baron *et al.*, 2014). Such secondary extrafocal neurodegeneration either in the midbrain or in the thalamus is a well-known feature of cerebral ischaemia (Nordborg and Johansson, 1996; Dihné *et al.*, 2002; Brecht *et al.*, 2009) and may also contribute to mood symptoms after stroke. In particular, alterations in the mesolimbic reward system can lead to anhedonia and depressive states (Praag *et al.*, 1975; Heinz *et al.*, 1994). Remarkably, delayed degeneration of dopaminergic neurons in ipsilateral midbrain along with reduced dopamine concentrations in ischaemic striatum and increased dynorphin messenger RNA expression in nucleus accumbens has recently been demonstrated in a mouse model of chronic post-stroke depression (Table 1; Kronenberg *et al.*, 2012).

Antidepressant treatment after stroke

If one views the evolution of neuropharmacology from a long-term perspective, the picture is sobering. Many important breakthroughs came about through almost sheer luck. For example, iproniazid, the first monoamine oxidase inhibitor, was initially developed as an antituberculosis drug. Similarly, imipramine, the first tricyclic antidepressant, was designed to act as a neuroleptic (Ban, 2006). These early serendipitous discoveries, which were both made in the 1950s, led to the formulation of the monoamine hypothesis of depression, which permitted the successful development of a rational approach to antidepressant drug design. Selective 5-HT re-uptake inhibitors (SSRI), the most tangible result of this line of research, were introduced in the 1980s (Judd, 1998). However, contrary to wide-held belief, the mechanism of antidepressant drug action remains far from clear. For example, tianeptine, which paradoxically acts as a selective 5-HT re-uptake enhancer, is a potent antidepressant (Mennini *et al.*, 1987; McEwen *et al.*, 2010). By the same token, the characteristic time lag between the start of antidepressant medication and the full-fledged therapeutic response strongly argues that biological targets far downstream of, and potentially even independent from, neurotransmitter turnover are ultimately responsible for antidepressant action.

Psychopharmacotherapy provides an effective treatment for depression after stroke (Hackett *et al.*, 2008). Exciting new clinical findings also suggest that subacute treatment with an SSRI may exert beneficial effects on various aspects of stroke recovery extending far beyond mood effects (Mead *et al.*, 2013). For example, the recently published multicentric 'FLAME study' demonstrated that, in non-depressed patients with ischaemic stroke and moderate to severe motor deficit, the early prescription of fluoxetine, starting 5 to 10 days after the onset of stroke, significantly enhanced motor recovery after 3 months (Chollet *et al.*, 2011). Furthermore, double-blind antidepressant treatment for 12 weeks during the early recovery period was reported to increase the survival of both depressed and non-depressed stroke patients (Jorge *et al.*, 2003). Experimental research on the actions of antidepressants after cerebral ischaemia, which has really only just begun, will have to define the precise cellular and molecular targets underlying these propitious effects.

An abundance of evidence from neuroimaging studies indicates that chronic treatment with antidepressants or the mood stabilizer lithium counteracts the deleterious interaction between affective disorders and brain structure (Moore *et al.*, 2000; Lavretsky *et al.*, 2005; Malykhin *et al.*, 2010; Arnone *et al.*, 2012). In parallel, preclinical psychiatric research has begun to uncover neurotrophic and neuroprotective mechanisms activated by long-term treatment with either antidepressants or lithium (Nibuya *et al.*, 1995; Chen *et al.*, 2000; Malberg *et al.*, 2000; Fukumoto *et al.*, 2001; Hellweg *et al.*, 2002; Santarelli *et al.*, 2003). In particular, up-regulation of cAMP response element-dependent gene transcription has been implicated in the salutary effects of chronic antidepressant treatment (Thome *et al.*, 2000). Of special interest in the context of stroke are studies demonstrating neuroprotection. For example, several *in vitro* investigations of oxygen-glucose deprivation yielded neuroprotective effects of lithium (Cimarosti *et al.*, 2001) and of heterocyclics (Stavrovskaya *et al.*, 2004). Similarly, administration of the SSRI fluoxetine within 9 h of MCAo resulted in a significant decrease in the size of the acute ischaemic lesion (Lim *et al.*, 2009). Moreover, delayed treatment with SSRI citalopram starting 7 days after 30 min MCAo/reperfusion not only prevented post-stroke depression, but also attenuated secondary extrafocal neurodegeneration in the midbrain and the attendant dopaminergic deficit (Kronenberg *et al.*, 2012; see Table 1).

Stroke outcome may also be improved by aiding neuronal plasticity and inducing cellular regeneration. In a seminal study of the recovery of visual functions in amblyopic rats, Maya Vetencourt and co-workers were able to demonstrate that chronic fluoxetine restores neuronal plasticity and increases BDNF expression in the adult visual cortex (Maya Vetencourt *et al.*, 2008). The finding that fluoxetine induces neuronal plasticity and thereby facilitates recovery of neural networks opens up the question as to whether facilitation of neuronal plasticity by SSRIs might also be useful not just for stroke recovery, but also other conditions in which there is a severe disruption to neuronal integrity. As regards cellular plasticity, citalopram has recently been reported to promote post-stroke sensorimotor recovery likely via enhancing neurogenesis, neural cell migration and the microvessel support in the peri-infarct region (Espinera *et al.*, 2013). Future research will have to set these findings in context by also studying the effects of other classes of antidepressant drugs (e.g. selective noradrenaline re-uptake inhibitors, tricyclic antidepressants, tianeptine) on chronic stroke outcome. Furthermore, it remains to be assessed to what extent the beneficial effects of SSRIs after stroke are indeed attributable to 5-hydroxytryptaminergic mechanisms. For example, an alternative hypothesis of antidepressant drug action proposes that the lowering of brain ceramide levels is central to antidepressant efficacy (Gulbins *et al.*, 2013). The sphingomyelin pathway represents a relatively new, yet ubiquitous signal-transduction system, which is initiated by the hydrolysis of sphingomyelin to the second messenger ceramide (Gulbins and Kolesnick, 2003). Therapeutic concentrations of the antidepressants amitriptyline and fluoxetine were recently shown to reduce acid sphingomyelinase activity and ceramide content in the hippocampus, which resulted in increased hippocampal neurogenesis and improved behaviour in murine models of stress-induced depression (Gulbins *et al.*, 2013). Importantly, cerebral ischaemia/reperfusion injury is known to result in elevated ceramide levels, which, in turn, may lead to mitochondrial dysfunction (Yu *et al.*, 2007), increased generation of reactive oxygen species and impaired cellular plasticity (Gulbins *et al.*, 2013).

In summary, the study of behavioural outcomes in rodent stroke models may be of great value for bridging the gap between clinical and experimental perspectives in stroke research. The experimental literature on 'affective syndromes' after brain ischaemia is still young and limited. In consequence, considerably more research will have to be undertaken to standardize experimental methodology and replicate findings across different laboratories. However, a number of experimental studies have already clearly established the emergence of genuine 'depressive-like syndromes' following brain ischaemia. These experimental models of post-stroke depression should lend themselves well to testing classical

and new theories of the neurobiology of major depression on a molecular and cellular level. At the same time, stroke research is increasingly pivoting to the study of long-term end points, which are heavily influenced by a complex array of intermingled and competing processes contributing, alternatively, to delayed neurodegeneration or recovery and repair. Today, accumulating evidence from clinical and experimental studies raises the tantalizing prospect of antidepressant therapy as the first pharmacological therapy for stroke that would be available during the subacute and chronic phases of recovery. It is heartening to see the field approaching this new concept in a truly translational manner. Now, experimental research, in particular, is called on to dissect the precise mechanisms underpinning the beneficial effects of antidepressants on stroke recovery.

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Conflict of interest

M. E. received grant support from AstraZeneca, Sanofi and Roche; participated in advisory board meetings of Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb, MSD, Pfizer, Sanofi; and received honoraria from Astra Zeneca, Bayer, Boston Scientific, Berlin Chemie, Bristol-Myers Squibb, Boehringer-Ingelheim, Desitin, Ever, Glaxo Smith Kline, MSD, Novartis, Pfizer, Sanofi, Servier and Takeda. G. K. received honoraria from Eli Lilly.

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