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## **Stress and the risk of Alzheimer dementia: Can deconstructed engrams be rebuilt?**

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**The exact neuropathological mechanism by which dementia process unfolds is under intense scrutiny. The disease affects about 38 million people worldwide, 70% of which are clinically diagnosed with Alzheimer's disease (AD). If the destruction of synapses essential for learning, planning and decision-making is part of the problem, must the restoration of previously lost synapses be part of the solution? It is plausible that neuronal capacity to reconstitute information corresponds with the adaptive capacity of its connectivity reserve. A challenge will be to promote the functional connectivity that can compensate for the lost one. This will require better clarification of the remodeling of functional connectivity during the progression of AD dementia and its reversal upon experimental treatment. A major difficulty is to promote the neural pathways that are atrophied in AD dementia while suppressing others that are bolstered. Therapeutic strategies shall aim at scaling functional connectivity to a just balance between the atrophic and hypertrophic systems. However, the exact factors that can help reach this objective are still unclear. Similarities between the effects of chronic stress and some neuropathological mechanisms underlying AD dementia support the idea that common components deserve prime attention as therapeutic targets.**

### **Introduction**

Despite tremendous efforts, few useful predictive indicators of dementia have been identified (1). The few that have been characterized explain 5% of cases usually associated with early familial onset (2, 3). Most common forms of dementia develop in Alzheimer's disease (AD). The majority of AD is sporadic, cannot be ascribed to a single genetic or environmental cause, and therefore most likely arises from a complex interplay of genetics and environment (4).

Stress plays a role in dementia development from mild cognitive impairment but it is unlikely the only contributing factor (for reviews see (5, 6)). Lifestyle choices (*e.g.* sleep-wake cycle, nutrition, work balance, physical exercise...) and the uncertain environment (*e.g.* pollution, climate change, economic and social pressure...) influence dementia progression by acting as systemic stressors on the body and converging on brain functions through the regulation of neuroendocrine systems (for reviews see (7-11)). Stress, especially when it is chronic can trigger conditions such as depression and anxiety that are often comorbid with dementia (12). The adversity that activates the neuroendocrine stress

response beyond its physiological homeostatic limits at any time across development and aging should be admitted as major risk factor but not as causal factor of sporadic AD (13). For instance, people with post-traumatic stress disorders (PTSD) have about twice the risk of developing dementia (14). Yet having PTSD isn't predictive of cognitive progression into dementia.

The effects of stress *must* cumulate with pathogenic factors to accelerate dementia progression from mild cognitive impairment. It is believed that such risk factors that are stress-sensitive only become pathogenic when organismal physiology chronically derails from homeostasis also coined *allostasis* (15, 16). Therefore, McEwen and colleagues (17) proposed that an overload of systemic allostatic factors consisting of circulating steroids, inflammatory, immune and metabolic hormones must cumulate with dementia risk factors to damage health in the long term. Control of allostasis erodes in the elderly in accordance with the slow progression of AD during aging that is its most prominent risk factor (18).

Recently, several biomarkers of the allostatic overload (*e.g.* brain atrophy, loss of functional connectivity, grey-white matter ratio...) predicted the impairment of cognitive, executive and emotional functions in patients with frontotemporal dementia (19). More markers of the allostatic overload have already been validated in several preclinical models of AD dementia (20). Neuroinflammation, permeability of the blood brain barrier (21, 22), hyperglycemia and insulin resistance (23), synaptic loss and steroid hormones (24), disrupted circadian rhythms (25), mitochondrial dysfunction (26), DNA methylation (27), amyloid- $\beta$  deposition and Tau hyperphosphorylation (28), are some of the markers building up more quickly in preclinical models of chronic stress than might have been expected in absence of stress exposure. Therefore, the people most at risk of *early onset* dementia could be the ones featuring abnormal physiological reactivity to stressors (29).

Here, we review some of the facts presenting the temporal and anatomical restrictions of glucocorticoid signaling, a major adaptive hormonal response to stressors, in neuronal networks as pivot of allostasis control in preclinical models of cognitive impairment and AD. One corollary is to exploit such pivot as opportunities to leverage the risk of dementia through prevention and treatment. Surprisingly, it might be more efficient to influence functional neuronal network connectivity in AD using non-neuronal strategies.

## **1. The facts**

### **The ligand**

Glucocorticoids are robust enhancers of emotional memory but *only if* exposure arises at the right time of the learning phase (30). Experimental applications of this knowledge permitted the alleviation of traumatic phobia in humans by focusing glucocorticoid administration during the extinction-learning phase (31). Naturally, glucocorticoid secretion follows ultradian and circadian rhythms with temporal peaks and troughs that are partly disrupted along with sleep patterns in subjects with cognitive impairment, resulting in abnormally high and flat basal levels in plasma during the active period of the day (32). Changes in rapid-eye-movement (REM) sleep, brain theta oscillation and glucocorticoid signaling all predicted cognitive dysfunctions triggered by chronic stress exposure in mice (33). In particular, brain markers correlate strongly with the gradual loss of glucocorticoid sensitivity measured in the dexamethasone-suppression test. Low responders to this test typically fail to control the allostatic load under duress (34) and in AD patients (35). It is due to a reduction of glucocorticoid signaling efficacy in the

hypothalamo-pituitary-adrenal axis that causes an imbalance between the activation and termination signals commanding glucocorticoid release.

Excessive awakening levels of glucocorticoids are linked to poorer cognitive abilities developing within 5 years in healthy aged subjects and also linked to dementia in AD patients (36, 37). De Quervain and colleagues identified several polymorphisms in glucocorticoid-related genes like 11 $\beta$ -hydroxysteroid dehydrogenase type-1 (11 $\beta$ HSD1), the enzyme that generates glucocorticoids directly in the brain, associated with an elevated risk for sporadic AD (38). Excess of glucocorticoids by chronic administration also increases amyloidosis, TAU phosphorylation associated with cognitive impairment, neuronal atrophy and synaptic loss in animal models (23, 39, 40). In contrast, acute rise of glucocorticoids do *not* promote amyloidosis and behavioral impairments (41). These findings posit glucocorticoids as major endocrine effector of chronic stress that can fast track cognitive dysfunctions into dementia progression.

### **The receptors**

The mechanisms underlying these effects might be *counterintuitive*. Indeed, the allostatic overload of chronic stress modifies the expression of glucocorticoid receptors (GR) that could compensate for the elevated levels of the ligand. For instance, some chronic stressors decrease GR levels in the prefrontal cortex and hippocampus, while others increase GR in the amygdala and ventral tegmental area (42-45). These alterations of GR levels are variable across brain regions, and usually long-lasting if adversity was experienced early in life whereas expression returns to normality on cessation of stress in the adults (46). This could explain how chronic stress during prenatal periods (47) or early postnatal (13) or in adolescence (48) enhances later in life the vulnerability to cognitive impairment and AD dementia. But in the adults, other factors than GR expression might better explain the impact of glucocorticoids on neuropathology.

A systemic reduction of tissue sensitivity and responsiveness to glucocorticoids despite its heightened circulating levels is typical in aging, with the allostatic overload and reported in patients with depression and AD dementia (49, 50). In the brain after chronic stress, GR signaling becomes less responsive despite abundant glucocorticoid concentration and normal GR expression. GR desensitization is consistent with aberrant phosphorylation of its N-terminal domain (51). By assisting the structural folding of the N-terminal domain from intrinsic entropy to acquired order, phosphorylation acts as prerequisite for docking signaling effectors (52). The numerous GR phosphorylation sites classified according to glucocorticoid dependency, kinases and phosphatases specificity form a code linking post-translational modifications with 3D structures that GR can adopt reversibly, in various cellular environments (53). The most characterized are the: (i) neurotrophin-dependent sites that are brain specific and neurocentric, and (ii) glucocorticoid-dependent sites that are widespread across organs and cell types (54). Both types are detectable in the cortex of preclinical models and AD subjects but in opposite proportion compared to age-matched healthy controls (24). Such a misrepresentation of GR phosphorylation status is associated with the age-dependent cognitive impairment, Braak staging and synaptic pathology. The sole genetic invalidation of the neurotrophic-dependent sites impaired long-term potentiation (LTP), learning-induced synapse consolidation and memory performance but failed to modify the build up of amyloid- $\beta$  and cerebrovascular pathology (24). Given the role of stress hormones on the physiology of the neurogliovascular unit (55, 56), it will be

essential to determine factors that can dissociate between the neurocentric and the vascular signaling defects underlying glucocorticoids mixed sensitivity in various brain regions, cell types, states of activity, and allostatic loads.

### **The signaling**

Although the genomic effects of glucocorticoids are well described in multiple cell types (57), the coordinated responses among various cell types and across functional networks has been overlooked, and a subject for speculation (58). Single cell transcriptomic helped advance this question by revealing that chronic stress triggers coordinated effects across cell types and brain microcircuits through changes in the expression of components of the inhibitory and excitatory systems (59). Fluorescence deconvolution tomography in postmortem human cortex revealed significant pro-excitatory perturbation of the balance of inhibition and excitation in early-onset AD patients compared to age-matched controls (60). However, others reported that early onset hyperexcitability of interneurons in the hippocampus may also exacerbate functional impairment induced by amyloid- $\beta$  with consequences on the quality of spatial memory (61). Recently, Lesuis and colleagues reported that glucocorticoids increase the number of hippocampal neurons allocated to the acquisition of fear conditioning in a time sensitive manner, by increasing the excitability of *active* neurons contrary to the *silent* neighboring cells that also contain GR (62).

The pairing of glucocorticoid exposure with neural activity triggers a *synergistic* response distinct from the additive effects of both stimuli (63). For example, the synergy between norepinephrine and glucocorticoids on memory consolidation is explained by the neuromodulation at the pre- and post-synaptic sides of an active neural network (64). The synergy spreads across the rapid and slow temporal domains of glucocorticoid actions (**Figure 1**). Indeed, glucocorticoids use a yet to be identified membrane-bound receptor to promote endocannabinoid secretion that suppresses neurotransmitter release from the presynaptic terminals (65). This way, the rapid effects could transform the slow effects compared to what might have been expected in absence of neural activity and neurotransmitter release. For instance, the synergy between glutamate release and glucocorticoid exposure facilitates the consolidation of newly formed dendritic spines by stabilizing the actin cytoskeleton whereas it does *not* in absence of glutamate stimulation, and new dendritic spines disappear spontaneously (66).

GR antagonists, mutations of GR phosphorylation sites, and the BDNFval66met polymorphism that impairs activity-dependent secretion of BDNF all blocked the rapid non-genomic effects of glucocorticoids on spine formation and consolidation (67). Local injection of membrane-impermeable glucocorticoid-BSA conjugates also promoted the formation of dendritic spines within minutes independently of gene transcription, further pointing at the implication of a fast acting membrane-bound GR (66). These findings establish that glucocorticoids do *not* act alone but rather in combination with activity-dependent trans-synaptic messengers like the retrograde endocannabinoids and the anterograde BDNF to modify engram cells network function and plasticity (see **box 1** for definitions) (68). Both systems are impaired onwards from the early stages of cognitive decline, and in carriers of polymorphisms in relevant risk genes (*e.g.* BDNFval66met, NTRK2) (69-71).

### **Collective cell response**

*Engram synapses* that fire together during learning, link the cells ensemble allocated at the same time to the memorable experience (72). But new synapses formed and consolidated posterior to learning also integrate into the engram network to enhance the functional connectivity that likely retains the memory trace (73). The more engram synapses the stronger the memory performance despite the number of allocated cells remained constant. Pre- and post-synaptic mechanisms that involved more neurotransmitter release and AMPA receptor mobilization in spines increased the strength of engram synapses but it did *not* in synapses between non-engram cells (74). Neurons receiving engram synapses are already potentiated *in vivo* before serial tetanus stimulations *ex vivo*, causing an occlusion of experimental LTP induction (75). This phenomenon is absent in non-engram neurons and when lacking BDNF-dependent GR phosphorylation sites because it impairs AMPA receptor mobilization in new dendritic spines, which prevents their stabilization, maturation and survival (67).

Amnesia results when dendritic spines newly formed at the time of learning are destroyed artificially with optical tools (76), and upon chronic stress or chronic glucocorticoid administration (67, 77). The clustering of 2 or more dynamic dendritic spines measured within a short distance and time window is *not* random, and creates hotspots of plasticity where memories are scripted, retained and retrieved (78). Spine clustering is impaired in preclinical models of AD (24). Neighboring spines that cluster usually respond to distinct stimuli (79), and may retain the functional connectivity from interregional inputs signaling the associative contents of memory (80). Maintenance of these clusters depends on the local mitochondria metabolism influenced by chronic stress, glucocorticoids and BDNF levels in healthy mice (81), in animal models of AD (82) and in the human AD brain (83). At the molecular level, chronic stress down-regulates gap junctions that *astrocytes* normally use to shuttle glucose and lactate into neurons and synapses thereby altering their maintenance (84).

Maintenance of collective synapses between engram neurons contributes to the retrieval of an excitable network (85). Yet, misfolding of the APP metabolite amyloid- $\beta$  curtails the excitability of such networks in the earliest stages of AD (86, 87). As amyloid- $\beta$  accumulates in the brain, a significant reorganization of the inhibitory-excitatory balance develops (88), along with an aberrant turnover of engram synapses that could underlie memory inaccuracy (89). For instance, the closer to amyloid plaques, the lesser dendritic spines form and survive; but away from plaques, dendritic spine formation increases while spine survival prevails (24). Amyloid deposits are often surrounded by a halo of soluble amyloid- $\beta$  oligomers (90). This gradient from insoluble to soluble forms of amyloid- $\beta$  also promotes region-specific differentiation of *microglial cells* and *astrocytes* into reactive species in preclinical models and in the human AD brain (91, 92). By influencing neuronal and non-neuronal cells, such a distribution of amyloid- $\beta$  as plaques and oligomers alters interregional neuronal connectivity in ways that could transform how the memory trace form and evolve with time (**Figure 2**). Indeed, there are abnormally high proportions of silent neurons proximal to plaques and hyperactive neurons in its surroundings (93). This is consistent with the increased excitation-inhibition ratio in cortex of middle-aged AD patients (60). These findings point toward converging effects of chronic stress and AD neuropathology that provide useful and compelling information about functional neuronal circuitry.

## 2. The opportunities

Based on the facts and technological innovation, some of the recurrent outstanding questions in the field (see **box 2**) are now being addressed experimentally. With new developments come new opportunities for translation in human clinical trials.

### Target the ligand

Strategies to block glucocorticoids synthesis have been a therapeutic focus. A major issue remains to retain pulsating release that is required for multiple peripheral and brain functions including learning and memory (94). Inhibitors of 11 $\beta$ -HSD1 either showed no effects (95), failed to clear the amyloid- $\beta$  load and produced unwanted side effects on emotional memories despite the amelioration of cognitive abilities in animal models (96, 97). Several clinical trials are either ongoing (NCT03823404, NCT04601038) or stopped due to futility (NCT01137526). A newer generation of these inhibitors (98) shows very promising results for ameliorating age-related cognitive impairment (99). Advance in neuroimaging confirmed penetration and stability of these ligands in the brain despite the regional differences (100). A new PET ligand revealed that the higher expression of HSD1 protein in the brain, the lower the symptoms in PTSD patients, indicating that complete inhibition of HSD1 might be counterproductive (101). A recent meta-analysis in AD subjects indicated that extra-adrenal blockade of glucocorticoid regeneration using this class of molecules has *not* met the primary endpoints of clinical trials (102). Development of inhibitors targeting other conjugating enzymes for the metabolism of neurosteroids such as hydroxysteroid dehydrogenases (17 $\beta$ HSD10), sulfotransferases (SULT) and uridine diphosphate glucuronosyl transferases (UGT) is attracting more attention given some neurosteroids (*e.g.* dehydroepiandrosterone, progesterone and allopregnanolone) act as cognitive enhancers directly targeting ionotropic and metabotropic receptors for neurotransmitters (103).

### Target the receptors

Twenty years ago, two clinical trials reported moderate effects of the non-selective GR full antagonist Mifepristone on cognitive performance in AD (104) and in major depression (105). Despite the benefits, research halted because Mifepristone also antagonizes receptors for progesterone and androgens. Gonadal hormones are neuroprotective, and inhibiting their receptors might exacerbate AD neuropathology (106). Future research with more selective antagonists warrants interesting prospects in the field of behavioral and psychological neuroscience (107).

More recently, reverse translation from human to preclinical models confirmed that full antagonists of GR reduced AD neuropathology and amnesia (108). Subchronic GR blockage with Mifepristone rescued early deficits of episodic memory and synaptic plasticity in preclinical mouse models of amyloidosis (109). But completely blocking GR in the body even for short periods of time might be risky, and evoke side effects given the pleiotropic effects of glucocorticoids on adaptive physiology. For example, systemic administration of Mifepristone at the time of learning prevented AMPA receptors mobilization into learning-induced new dendritic spines, promoted their destabilization and impaired memory retention (67). Additionally, the conditional knockout of GR in the amygdala prevented anxiety-like behavior induced by chronic stress (110), and GR antagonism in the mesolimbic pathway impeded stress-induced drug sensitization (111,

112). In contrast, GR agonists prevented stress-induced behavioral despair when injected in corticolimbic areas (113). Despite the region-specific effect of GR activation, a brief systemic administration of Mifepristone for 3 days, one year after exposure to early life stress was sufficient to alleviate cognitive impairment and ameliorate neuropathological features of AD in mouse models (114). Therefore, glucocorticoids have robust mnemonic effects, and strategies to limit their actions shall be carefully planned according to the memory phases using behavioral therapy (30).

With glucocorticoids on board all the time at naturally occurring oscillating levels (94, 115), *allosteric* modulators should in theory be safer to use than molecules with full agonistic or antagonistic activities given that GR signaling can be paired with neural activity (52). Selective GR modulators like CORT108297 and CORT113176 that can act as partial antagonists and inverse agonists in distinct tissues or brain regions prevented the persistent rise of plasma glucocorticoid concentration and behavioral deficits induced by intracerebrovascular injection of amyloid- $\beta$  oligomers (116). Switching between positive and negative allosteric modulation does not necessarily require that the interactions between glucocorticoids and its pharmacophore differ (117). It is the cooperativity between domains that sets the response evoked by structural transduction from the glucocorticoid-binding pocket where most GR ligands bind including agonists, antagonists and modulators (52). New structural studies of GR interaction with select coactivators better defined the allosteric cavities to target in future high throughput screening for dissociative modulators (118-120). Future ligands will be directed toward the unmet needs, that is not only the tissue or cellular specificity but also the dissociation between the non-genomic and the genomic glucocorticoid effects (121, 122).

Glucocorticoid actions in the limbic brain also involve the mineralocorticoid receptor (MR) (123). MR displays higher affinity for cortisol than GR. MR also binds selectively to aldosterone if cortisol is converted by 11 $\beta$ -hydroxy steroid dehydrogenase Type 2. This occurs, for instance, in the kidney and in the nucleus tractus solitarius where aldosterone enhances salt retention and appetite, respectively (124). Selective MR antagonists are currently tested in phase 4 clinical trial of early onset AD (NCT04522739) with the objective to lower blood pressure and subsequent neurological effects following conclusive preclinical studies (125, 126).

### **Target the signaling**

Separation of GR trans-repression from trans-activation activities resulted in synthetic ligands with lesser side effects that can profile the expression of pro-inflammatory gene targets (127). Clinical applications are limited because trans-activation of anti-inflammatory genes is also needed for full efficacy (128, 129). Synthetic ligands designed to favor trans-activation of target genes also produced mixed results as the desired response often composes with a mixture of activated and suppressed genes in target tissues (130, 131). Other strategies targeting GR downstream gene substrates in mice provided promising preclinical results. For example, *(i)* the GR-regulated gene *Dusp1* that acts as phosphatase against TAU kinases is under-expressed upon chronic glucocorticoid exposure, resulting in uncontrolled TAU phosphorylation. The expression of DUSP1 is lower in the brain of AD subjects compared age-matched controls, and gene therapy restoring DUSP1 levels with a Tetracycline-inducible vector decreased TAU phosphorylation in mice (40); *(ii)* the GR-regulated gene *Nr4a1* that adjusts mitochondrial functions with synapse



number escapes proteasomal degradation upon chronic stress, causing mitochondrial uncoupling and dendritic spine elimination. The expression of NR4A1 is higher in the brain of AD subjects compared age-matched controls, and gene therapy expressing a dominant-negative mutant of NR4A1 with a Tetracycline-inducible promoter prevented stress-induced elimination of dendritic spines in mice (81, 132); (iii) the GR-regulated gene *Sgk1* that can act as TAU kinase is upregulated in the brain of AD subjects compared to age-match controls, and inhibition of SGK1 decreased TAU neuropathology and cognitive decline in a preclinical mouse model (23); (iv) the GR-regulated gene *Fkbp51* that blocks GR nuclear import also decreases GR sensitivity during aging and AD progression. The levels of FKBP51 are higher in the brains of AD subjects compared to age-matched controls, suggesting that inhibitors of FKBP51 are desirable to restore GR functions in aging (133); (v) the GR-regulated gene *Klf9* that acts as transcription factor reduces glucocorticoid efficacy under duress in mice, and genome editing-based silencing of KLF9 prevented the effects of chronic stress on brain and behavior (134); and (vi) GR signaling through the BDNF-dependent phosphorylation pathway deleted in knockin mice impaired the expression of specific target genes including *Nr4a1*, *Dusp1* and *Sgk1* contrary to *Fkbp51* and *Gilz* that remained unchanged (40, 135). These finding covering a non-exhaustive list of GR-regulated genes indicate that some targets are upregulated and others downregulated in AD, suggesting that GR ligands promoting biased signaling properties (*e.g.* rapid non-genomic versus slow genomic) are desirable to restore GR functions with lesser side effects (52). Structural cooperativity between GR pharmacophore and allosteric sites modifiable by phosphorylation sets the basis for promoting signaling pathway specificity expected to vary between different tissues and cell types (136). For instance, GR phosphorylation at glucocorticoid-dependent sites compared to BDNF-dependent sites permitted the dissociation between beneficial and deleterious effects of glucocorticoids on brain and behavior in response to chronic stress and during AD progression (68, 137).

Given the etiology of major depression in patients with AD, treatment with antidepressant therapies has been a major focus (138). For instance, Escitalopram improved neuropathology but not behavior in animal models of Tauopathy (139). In contrast, Fluoxetine (140) and Agomelatine (141) reduced behavioral deficits and neuropathological features in animal models of amyloidosis. The effects of Fluoxetine depended on GR signaling via the BDNF pathway (54). In humans, Escitalopram reduced the build up of amyloid- $\beta$  although cognition was *not* reported (142). A phase 3 clinical trial (NCT03108846) is ongoing in AD subjects. What's more, sertraline, venlafaxine and desipramine ameliorated depressive and cognitive symptoms of AD patients (143). So far, the clinical trials with antidepressants and cognitive enhancers have demonstrated modest efficacy in AD patients. More phase 3 clinical trials targeting prodromal cases in the earlier phase of AD with serotonergic reuptake inhibitors (NCT02817906, NCT02586909, NCT02006641, NCT01955161, NCT02006654), dopamine reuptake inhibitors (NCT03811847), noradrenergic reuptake inhibitors (NCT03031184), multitarget-directed neuromodulators (NCT01832350, NCT01922258, NCT03226522, NCT02168920, NCT03393520, NCT02446132) are ongoing. Other strategies aimed at clearing the build up of glutamate excess levels under duress with Riluzole, which decreased amyloid build up, LTP deficits and cognitive impairment in mice (144), and ameliorated glucose metabolism in AD patients (145). A clinical trial testing the effects of a prodrug formulation of Riluzole, Troriluzole on cognitive abilities and neuropathology is ongoing in AD subjects

(NCT03605667). Together, these studies present the ability of antidepressant drugs to safely decrease amyloid- $\beta$  concentrations despite harmful side effects typical of antidepressants and cognitive enhancers. More importantly, this research indicates that a substantial fraction of dementia cases might be *preventable*. Beyond medication, behavioral and psychological alternatives that increase wellbeing and decrease depression such as physical exercise, meditation, enrichment living can also slow the progression of AD dementia (146, 147).

### **Target the cells**

The effects of stress follow an inverted U-shaped response characterized by moderate levels of glucocorticoids as optimal for brain and behavior compared to too low or too high levels that are deleterious (148). We have recently integrated this model across large-scale brain networks to better explain the mechanisms underlying biological functions (68). The types of cells (*e.g.* parvalbumin (PV), somatostatin (SST), cholecystinin (CCK), vasoactive intestinal peptide (VIP) or principal neurons (PN)) and synapses (*e.g.* inhibitory versus excitatory, apical versus basal dendrites) targeted by glucocorticoids and the state of neuronal activity (*e.g.* depolarized versus resting state) are expected to transform the response (**Figure 3**). First of all, the ratio of GR and MR is different between cell types and brain regions (*e.g.* in cortex GR>MR in excitatory neurons, GR<MR in VIP and CCK inhibitory neurons whereas in hippocampal CA2/CA3 subfields GR<MR in excitatory neurons in human and rodent tissues according to the transcriptomic atlas of the Allen Brain Atlas at the Allen Institute for Brain Science and (149)), which restricts the programs available for the adaptive response to stressors. Second, inhibitory neurons have non-overlapping innervation territories (*e.g.* PV cells innervate PN's basal dendrites, SST cells innervate PN's apical dendrites, CCK cells innervate PN's primary dendrite, VIP cells innervate mostly SST cells), which dictates the flow of information. Third, trans-synaptic messengers that rapid glucocorticoid signaling relies on are expressed at some but *not* all types of synapses (*e.g.* endocannabinoid system enriched at the VIP $\leftarrow$ SST, CCK $\leftarrow$ PN and PN $\leftarrow$ PN synapses, and BDNF system enriched at PN $\rightarrow$ inhibitory cells and PN $\rightarrow$ PN synapses). Fourth, neuromodulation by rapid glucocorticoid signaling is only accessible to the engram network at play.

Although complex, the glucocorticoid system presents an opportunity to elaborate strategies that would alter the neural bases of behavior during the progression of AD dementia. For example, systemic therapeutic strategies are rather crude considering that GR signaling triggers effects that can oppose between brain regions, types of cells and synapses (68). In preclinical models of chronic stress, GR become hypoactive in corticolimbic areas while hyperactive in the amygdala and the mesolimbic areas, which demanded local interventions with either agonists or antagonists to reduce stress-induced depressive-like phenotypes and promote motivated behaviors. Brain regions where GR is hyporesponsive are also expressing lower BDNF levels whereas the regions where GR is hypersensitive are also expressing more BDNF signaling, which demanded local interventions with BDNF mimetics or NTRK2 receptor antagonist to reduce stress-induced depressive-like phenotypes and promote motivated behaviors (46, 150). In preclinical models of AD, recombinant BDNF infusion reverted cognitive decline without altering the amyloid- $\beta$  load (151). In contrast, inhibitors of endocannabinoid synthesis reduced amyloid- $\beta$  load and neuroinflammation but failed to improve cognition (152). In the clinic,

ligands of Cannabinoid receptors are currently tested as neuromodulators to influence the behavioral and psychological symptoms in subjects with AD (NCT02351882). Additionally, gene therapy with recombinant BDNF is currently assessed in phase 1 trial including people affected with AD and mild cognitive impairment to reduce neurodegeneration and rebuild synapses (NCT05040217). The fact that BDNF can also be increased with non-invasive protocols (*e.g.* electroconvulsive therapy, transcranial magnetic stimulation, behavioral therapy, physical exercise, environmental enrichment) and drugs (*e.g.* antidepressant drugs...) makes it attractive for human therapies.

At the *network* level, optogenetic stimulation of engram cells restored memories lost in aged amnesic mouse models of AD (89, 153). So, memory is not destroyed but hidden in the symptomatic stages of AD in preclinical models. Strategies that promote the survival of collective synapses between engram neurons as well as their excitability should help reconstitute memories. For instance, inhibitory interneurons gate the excitability of neuronal network, and have been manipulated to prevent the reactivation of non-relevant quiescent memory engram cells (154). Therefore, inhibitory engrams can make memories quiescent, but available through disinhibition (155). The proportion of inhibitory neurons among all neurons is specific of brain regions and remains fixed throughout the lifetime (15-30%). An exception is chronic stress under which the number of PV cells decreases in some regions (*e.g.* orbitofrontal cortex) but increases in others (*e.g.* amygdala). As a result, optogenetic silencing of PV cells in the amygdala restored emotional memories unlike in the orbitofrontal cortex (156, 157). In fact, changes of inhibitory transmission can modify functional connectivity across large-scale brain networks (59). In humans, stress modulates the coherence between striatal GABA levels and hippocampal activation during motor learning because inhibitory transmission in one brain region affects activity of connected regions (158). In rodents, activation of GABA-A receptors with muscimol injected in the infralimbic cortex reduced glutamate outflow in projection areas of the posterior hypothalamic nucleus where inhibitory neurons normally suppress excitatory neurons projecting onto CRH neurons in the paraventricular nucleus causing an excessive response of the HPA axis to chronic stress (159). Silencing the vesicular transporter of glutamate (vGLUT1) in the infralimbic cortex caused a phenotype similar to muscimol injection because reduced expression of vGluT1 decreases glutamate packaging and release in projection areas of the posterior hypothalamic nucleus (160). Both studies elegantly described a complex macrocircuit made of excitatory and inhibitory neurons for controlling an ON-switch onto CRH neurons and downstream HPA axis. Consequently, the manipulation of interneuron functions in the stressed brain came into focus with for example, the chemogenetic stimulation of cortical PV cells that prevented the loss of excitatory engram synapses and behavioral deficits (161).

Targeting *synapses* for sustaining memory engrams relies on the core idea that engram synapses express specific molecules at the time of learning, and during replay of memories. Such synaptic tags are labile, respond to trans-synaptic messengers and initiate signaling that must go to the nucleus-and-back for self-maintenance of the synapses. The BDNF-CREB and glucocorticoid-GR-cofilin pathways have been proposed as such synaptic tags (73, 162). Remarkably, the pool of dendritic spines lost to chronic glucocorticoid exposure can be functionally restored with antidepressant treatment (77), which is consistent with a modification of the inhibition-excitation ratio in animal models and patients (163, 164).

*Microglial cells* promote the forgetting of memories by pruning engram synapses via the complement-phagocytosis signaling pathway (165). Specifically, the complement factor C1q mobilizing into dendritic spines serves as synaptic tag for phagocytosis by activated microglia in a mouse model of AD, which could be alleviated by a silent allosteric modulator of mGLUR5 (166). C1q deletion diminished physical contact between microglial cells and synapses and also between *reactive astrocytes* and dendritic spines, causing a reduction of phagocytic activity that preserved synapse density in preclinical models of AD. Remarkably, lysosomes of reactive astrocytes contained more material derived from excitatory synapses compared to lysosomes of microglial cells that contained more material derived from inhibitory synapses (167). Therefore, both microglial cells and reactive astrocytes mobilize in the peri-plaque domain to phagocytose dystrophic dendrites and synapses in the brains of animal models of AD and patients. However, the high levels of soluble amyloid- $\beta$  oligomers in the halo surrounding plaques reduces the expression of the phagocytosis receptors Mertk and Megf10 in astrocytes (168), which explains the high proportion of restored lost dendritic spines in the halo surrounding amyloid- $\beta$  plaques of animal models of AD (24). Remarkably, reactive astrocytes and microglial cells are also central mediators of the stress response impacting on memory systems (169). GR in astrocytes is required to react to neuronal damage and prevent differentiation of nearby microglial cells. Deletion of GR in astrocytes impaired the neuroinflammatory response and microglial cells engagement (170). The exact role of GR in microglia has yet to be determined. Given the anatomical mobilization of astrocytes and microglia at sites of neuronal damage in chronic stress and AD, targeting the complement system, the differentiation and migration of glia represent an alternative strategy to protect the memory trace (171). Alternative strategies aimed at suppressing the downstream effects of reactive glia by limiting the neuroinflammatory response via the NPLR3 system using the inhibitor Mc950 to counteract the effects of high glucocorticoid levels in a preclinical model of AD (172). These findings indicate that targeting neuromodulation, synaptic tags, inhibitory microcircuits and glia to preserve the functional connectivity between neurons is very credible for AD research.

## **Conclusions**

Recent advances provided major clarifications of neuropathological mechanisms and responses to the outstanding questions aforementioned.

First, information isn't necessarily destroyed in neurodegenerative conditions but rendered inaccessible by changes in the excitability and connectivity between cells ensembles allocated to memory engrams. The amyloid and non-amyloid pathways contribute to these changes along side with stress-induced mechanisms that alter the expression of the very building blocks permitting the assembly, disassembly and maintenance of neuronal networks.

Second, optogenetic activation of engram cells in amnesic rodents permitted the retrieval of lost memories and facilitated the emergence of new synaptic connections. New discoveries inevitably come with new challenges. For instance, the number or type of engram neurons and synapses to loose beyond which memories become irretrievable remains to be determined. Moreover, it is plausible that each pool of engram synapses encodes a memory such that a lifetime of memories would constitute a reserve of silent synapses from which to download from. Each synapses of a pool would have to be retrieved together to replay the fidelity of the memory trace.

Third, several innovations are currently explored among which the synaptic tag hypothesis is one of the most attractive to combat anterograde amnesia (for review see (73, 173)). The most accessible strategies to maintain functional connectivity aim at competing with clearance mechanisms that are intrinsic (*e.g.* neuronal genome, epigenome, neuromodulators...) and extrinsic (*e.g.* inhibition, glia, hormones, immune and inflammatory factors...). Targeting both at once could help retrieve more accurate memories.

Fourth, a major difficulty will be to promote the neural pathways that are atrophied in AD dementia while suppressing others that are bolstered. To combat retrograde amnesia and retrieve forgotten remote memories, it will be necessary to unmask the remaining pool of silent engram synapses through Hebbian plasticity. Future strategies for neuroprotection and regeneration will assist self-generated Hebbian plasticity through combinations of behavioral, psychological treatment and pharmacotherapy. A good example is antidepressant therapy that is more efficient on brain and behavior when combined with behavioral and psychotherapies.

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#### **CReDiT**

FJ: Conceptualization, Writing – original draft

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**Memory engram** corresponds to an ensemble of neurons across multiple brain regions that manifest experience-induced changes in anatomical connections and physiological processes. Those persistent cellular and molecular traces experienced collectively are recognized to be substrates for memories.

**Engram network** is the ensemble of neurons initially excitatory then a mixture with inhibitory components as homeostatic scaling develops.

**Engram cell** takes part to the collective neural response specifically allocated to the experience.

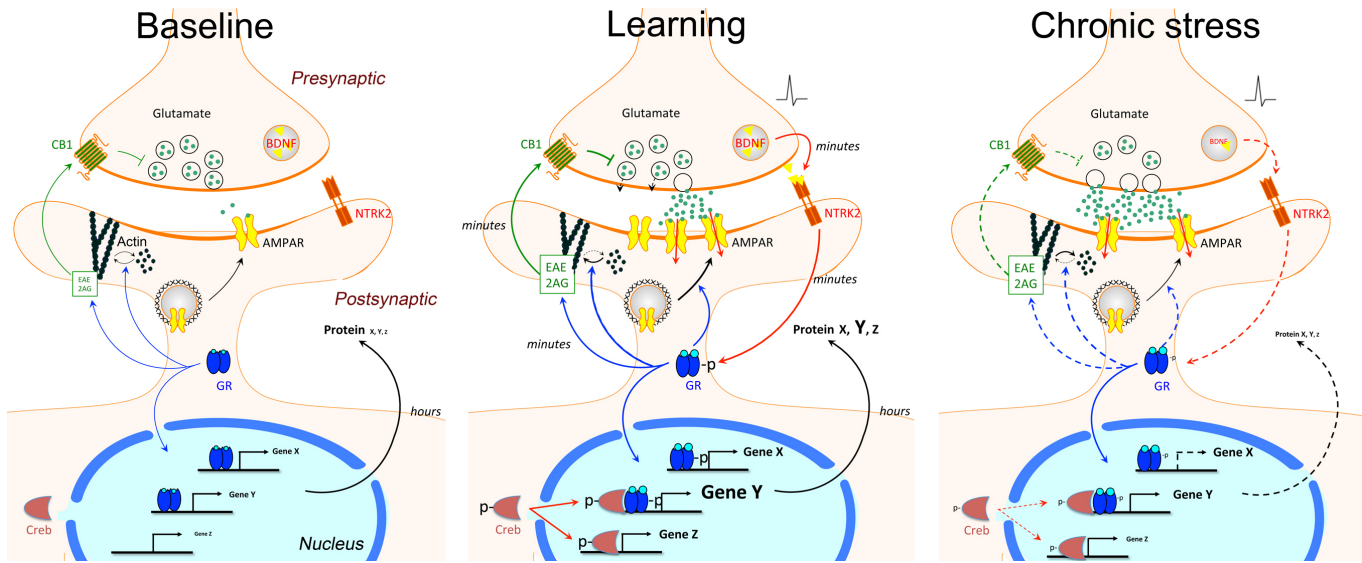
**Engram synapse** is made between engram cells whereas non-**engram synapses** are made with other cells not specifically allocated to the experience.

**Engram capture** is a genetic trap system using a neuronal immediate early gene as promoter to induce a transgene for identification. Several tools have now been constructed according to this principle using Arc, Egr1 or Fos as promoter for induction. Beyond memories, any experience that induces the expression of such immediate early genes would evoke an engram.

### **Box 1. Glossary.**

- Why information isn't reactivated after reaching a tipping point of ageing or pathophysiological progression?
- Must the restoration of previously lost synapses be necessary to retrieve information?
- Can non-neuronal mechanisms sensitive to stress be targeted for restoring neurocentric traces of memory?
- What combinations of treatments would best restore the memory traces partially degraded in advanced AD dementia?

### **Box 2. Outstanding questions.**

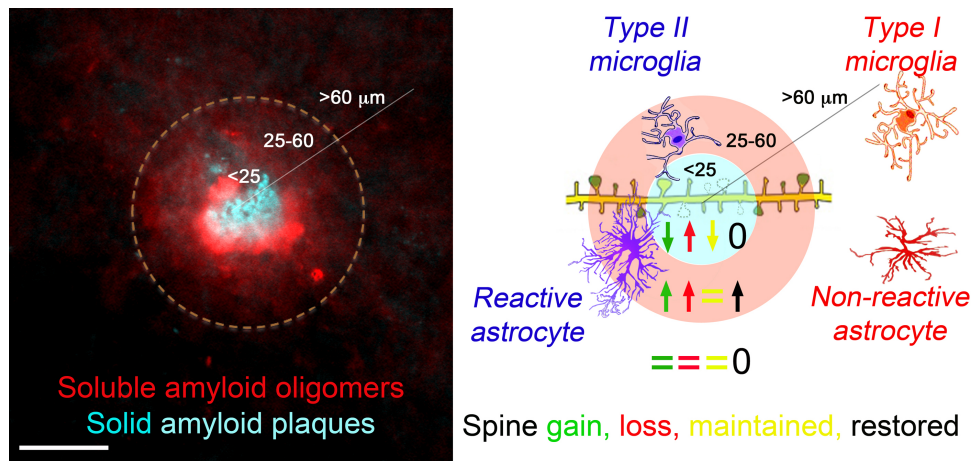


**Figure 1. Synergy of glucocorticoid actions with neuronal activity is distinct from additive effects**

**Left:** At baseline, the excitatory input on cortical neurons is not depolarized, synaptic activity is basal, trans-synaptic messengers are not being used, GR phosphorylation is low, the actin cytoskeleton in dendritic spines is at equilibrium, and a small pool of GR regulates gene transcription. Target gene X could be *Dusp1*, *Nr4a1*, *Bdnf* and others; gene Y could be *Sgk1*, *Gilz* and others, gene Z could be *Fkbp51* and others.

**Middle:** At learning, the excitatory input is depolarized, glutamate and BDNF are released, glucocorticoid levels rise, GR is phosphorylated at BDNF-responding sites, AMPA receptors are mobilized into the synapse, depolarization of the post-synapse initiates calcium signaling activating the transcription factor Creb, GR stimulates endocannabinoid release for suppressing neurotransmitter release, the actin cytoskeleton in dendritic spines is building up via the LIMK1-cofilin pathway, and gene transcription is regulated by a larger pool of transcription factors like GR and Creb that can have overlapping effects at selective loci.

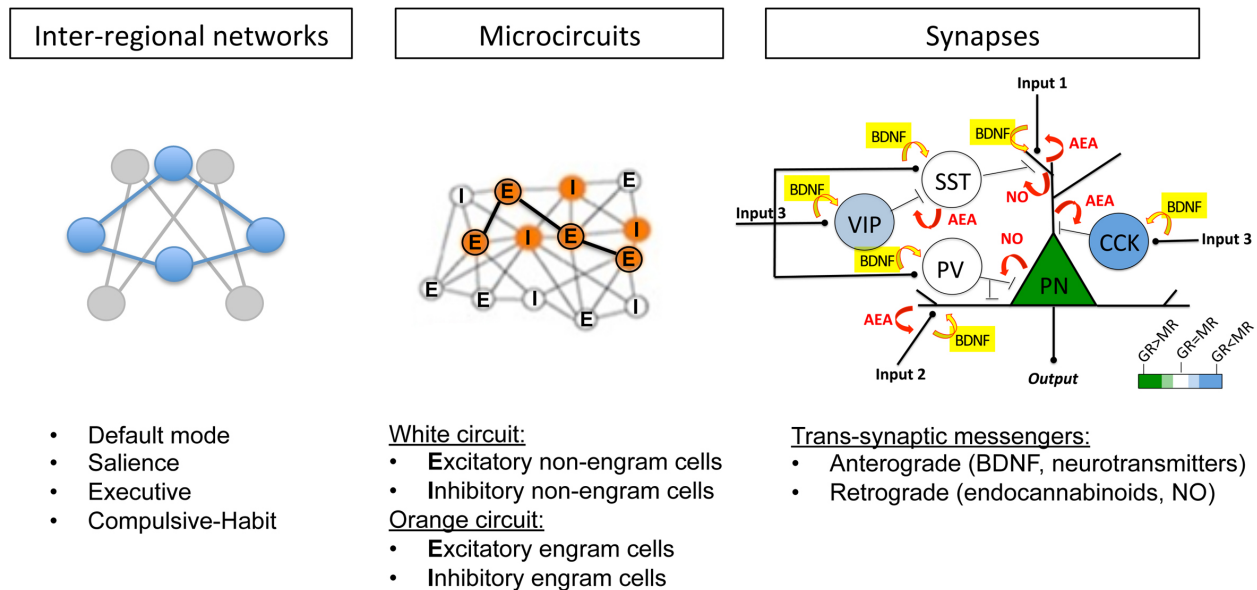
**Right:** At learning upon chronic stress exposure, the scenario is the same except that glucocorticoid levels may be disproportionate relative to the experience, BDNF levels have been downregulated, GR phosphorylation status is disproportionate, AMPA receptor trafficking diminished, endocannabinoid release by GR is reduced and neurotransmitter release excessive impairing synaptic potentiation, the actin cytoskeleton in dendritic spines is collapsing via the Slingshot-cofilin pathway that can spread throughout neighboring spine clusters, and gene transcription is regulated by a disproportionate selection of transcription factors.



**Figure 2. Distribution of soluble and solid amyloid- $\beta$  determines microglia reactivity and functional neuronal connectivity**

**Left:** Brain section of 6 months-old APP/PS1 mouse stained with A11 antibodies to detect small soluble amyloid- $\beta$  oligomers and methoxy-XO<sub>4</sub> to reveal plaques of solid amyloid- $\beta$ . The ring shows the peri-plaque gradient of soluble oligomers.

**Right:** Schematic representation of dendritic spine dynamic remodeling according to the peri-plaque topography determined by in vivo 2-photon microscopy in APP/PS1;thy1-YFP mouse between 3-9 months of age. A spine attrition focus at amyloid plaques is surrounded by a halo of spinogenesis where soluble amyloid- $\beta$  oligomers are enriched together with type II microglial cells and reactive astrocytes differentiated with a damage-response molecular arsenal established in AD dementia like *Trem2*, *chemokines receptors* and complement receptors *Mertk*, *Megf10*, respectively (24, 91, 168). Before detectable cognitive impairment, the relentless growing number of plaques surrounded by gradients of soluble amyloid oligomers could transform how the memory trace form and evolve with time. Arrows mean up/down regulated, = means unchanged, 0 means none.



### Figure 3. Glucocorticoid actions on large-scale neuronal networks

**Left:** Effects of glucocorticoids across brain regions depends on inter-regional networks playing at the time of exposure (color code not referring to specific anatomy). The *default mode* assembles large distributed regions of the association cortex that show reduced activity during attention-demanding tasks relative to steady state for integrating new information with existing knowledge. The *salience network* integrates internal and external sensory inputs via connections between cortical regions (cingulate, prefrontal, insular, temporal), the thalamus, amygdala, ventral striatum, thalamus, and specific brainstem nuclei for motivated reactive responses. The *executive network* is a fronto-parietal system playing a critical role in actively maintaining and manipulating information in working memory that are necessary for rule-based problem solving and for decision making in the context of goal-directed behavior. The *compulsive habit network* integrates dorsal striatum, cortical and subcortical projections forming an emotional-reward-habit system. Chronic stress switches the configuration of neural systems at play from a default cognitive executive state to a compulsive habit state. This is reverted by successful antidepressant treatment (174-176).

**Middle:** Pairing neuronal activity with glucocorticoid signaling elicits synergistic effects in engram cells that are absent in non-engram cells. The engram network in the cortex or hippocampus is often made of a mixture of excitatory and inhibitory neurons (177).

**Right:** The ratio of GR and MR levels and the availability of the synthesis enzymes and receptors for the trans-synaptic messengers influence rapid glucocorticoid signaling (EAE=endocannabinoids and NO=nitric oxide). Color codes are representative of the GR:MR ratio in cortex but difference exist other brain regions like the hippocampus (149). The configuration of the neural network at play determines output transmission and the effects of glucocorticoids because each type of synapse (e.g. PN→PN, PV→PN, SST→PN, CCK→PN, VIP→SST) is equipped with specific sets of trans-synaptic messengers (PN=principal neuron, PV=parvalbumin, SST=somatostatin, CCK=cholecystokinin, VIP=vasoactive intestinal peptide) (68).