

# Neural compensation in presymptomatic hAPP mouse models of Alzheimer's disease

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Largely inspired from clinical concepts like brain reserve, cognitive reserve, and neural compensation, here we review data showing how neural circuits reorganize in presymptomatic and early symptomatic hAPP mice to maintain memory intact. By informing on molecular alterations and compensatory adaptations which take place in the brain before mice show cognitive impairments, these data can help to identify ultra-early disease markers that could be targeted in a therapeutic perspective aimed at preventing rather than treating cognitive deterioration.

Since the beginning of their production and utilization, one critical issue with rodent models of neurodegenerative diseases has been that mutations, which cause disease-specific neuropathological hallmarks, do not necessarily produce phenotypic alterations (Crawley 2008). Despite the large consensus that no model can entirely recapitulate the peculiarities of human disorders (Kreiner 2015), models devoid of face validity have been systematically discarded for their inadequacy to unveil causal relationships between neural and clinical symptoms. The consequence of discarding such models has been to leave in the shadow the heuristic importance of understanding why disease-specific neural alterations were not triggering disease-specific phenotypes.

Meanwhile, clinical imaging investigations carried out in aging and Alzheimer's disease (AD) patients revealed that individuals could maintain intact cognitive abilities thanks to a redistribution of neural activity across brain regions unequally affected by amyloid load (Stern 2009, 2012). A large body of evidence then demonstrated that this redistribution basically occurs via overactivation of canonical circuits that compensates for their decreased efficiency, or recruitment of alternative regions with lower levels of neurodegeneration (Barulli and Stern 2011; Stern et al. 2019), these alternative pathways of reserve being simultaneously present in cognitively normal older adults (Oh et al. 2018). Although these findings demonstrate that neuronal networks rearrange to face cognitive demand, the synaptic mechanisms, which support these rearrangements, are still poorly understood due to limitations of *in vivo* subcellular imaging in human AD brains (Stern 2017).

By concurrently monitoring the activity of circuits and synapses in AD mice, Palop et al. (2007) provided the first evidence that the aberrant, epileptic-like, increase in hippocampal network activity was accompanied by a progressive compensatory increase of inhibitory activity at hippocampal synapses. This increase being observed in fully symptomatic AD mice prevented, however, to consider it as a potential cognitive reserve mechanism. Indeed, a paradox of studies carried out in hAPP mutant mice is that despite the age-related progression of AD-like symptoms is well-characterized (Middei et al. 2006; Ferguson et al. 2013) the functional status of their neural networks has been poorly examined at podromal stages, and mostly under naive conditions. Thus, exploring how circuits and synapses reorganize under cognitive challenge at the very onset of, or even before, the manifestation of

clinical symptoms offers the undisputable advantage of informing on the primary molecular alterations involved in neurodegeneration, and the compensatory neural adaptations which develop to contrast cognitive deterioration. Here we review data which demonstrate the presence of neural compensation phenomena in hAPP mice, and which shed light on the molecular alterations that play a role in brain circuits reorganization.

## Spatial learning produces overwiring of hippocampal circuits in early symptomatic APP23 mice

Memory formation requires changes in neuronal networks connectivity based on modifications in strength and number of synapses. Because dendritic spines host the majority of excitatory synapses, markers of memory-induced synaptic changes have been identified in the modification of dendritic spines (Leuner et al. 2003; Restivo et al. 2009) and of excitatory synaptic transmission (Sacchetti et al. 2002; Lange-Asschenfeldt et al. 2007) in healthy rodents. The study by Middei et al. (2010) provides the first evidence showing how memory reshapes of hippocampal circuits in heterozygous B6-Tg/Thy1APP23Sdz (APP23) mice before they exhibit AD-like neural alterations. Specifically, 7-mo-old APP23 mice were used in this study whereas they show amyloid plaques in the hippocampus (Sturchler-Pierrat et al. 1997) and deficits in hippocampal-dependent tasks (Lalonde et al. 2002; Vloeberghs et al. 2006) around 12 mo of age.

## APP 23 mice show a mild spatial learning impairment

APP23 mice at the preplaque stage and their wild-type age-matched controls were trained in a water maze for three daily sessions of four trials each. Results showed that the latencies and the distance traveled to find the submerged platform were globally higher in the mutant mice even though these two variables progressively decreased over training. The swimming speed did not vary between groups which excludes that the low performance of mutant mice can be ascribed to motor alterations. Confirming that the APP23 mutation does not trigger massive a cognitive

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deficit before amyloid plaques deposition, mutant and wild-type mice scored similarly on the last day of training. Following training, mice were sacrificed to evaluate the impact of spatial training on hippocampal dendritic spines and synaptic plasticity.

### APP23 mice show more training-induced spines in the hippocampus

Comparisons of Golgi-stained dendritic spines on CA1 neurons dendrites revealed no difference between genotypes in the resting and the pseudotraining conditions. In the training condition, all mice showed a posttraining increase in spines, which indicates that reactive plasticity was spared by the mutation. This increase was, however, stronger in the mutant mice thereby demonstrating that hippocampal circuits that are unaltered in nontraining conditions undergo compensatory stronger remodeling under cognitive challenge.

### Synaptic transmission and paired-pulse facilitation do not differ between genotypes

Indexes of synaptic transmission were measured to evaluate the functional state of synapses in these diversely remodeled hippocampi. The input–output (I–O) curves obtained in the training and the pseudotraining conditions were indistinguishable between genotypes. Of note, these curves showed that basal transmission was decreased in the training versus the pseudotraining condition in both mutant and wild-type mice, which confirms that associative spatial learning recruits a pool hippocampal synapses no longer available for basal transmission. Paired-pulse facilitation curves that depict presynaptic facilitation were also indistinguishable between genotypes, with less facilitation being observed in the training condition than the nontraining condition.

### CA1 LTP is regularly induced but decays more rapidly in APP23 mice

CA3–CA1 synaptic potentiation measured 50–60 min following high frequency stimulation (HFS) in hippocampal slices from trained and pseudotrained mice was regularly induced in both genotypes but decayed more rapidly in APP23 slices. These findings align with the report that the levels of BDNF, a regulator of LTP maintenance (Abraham and Williams 2008), are decreased in the hippocampus of APP23 mice upon spatial training (Hellweg et al. 2006). Of note, the deficit in LTP maintenance is a peculiarity of trained mutant mice which otherwise show the higher amount of learning-induced spines. Considering that neoformed spines host weak synapses (Trachtenberg et al. 2002; Holtmaat et al. 2005), it could be that LTP decays because it is induced in immature hippocampal circuits.

Altogether, these findings reveals that spatial training triggers a deficit in synaptic plasticity but a stronger increase in spine density in APP 23 mice. That structural plasticity can compensate for synaptic plasticity disruption is supported by data showing that the number of neocortical synaptic bouton is maintained in spite of robust amyloid deposition in APP23 transgenic mice (Boncristiano et al. 2005). Consistent with the idea that overformation of spines can be viewed as a compensatory mechanisms, mutant mice and wild-type mice achieve the same level the performance on the last day of training.

### Overactivation of regions spared by Ab load sustains intact memory in presymptomatic Tg2576 mice

Evidence that neuronal activity increases secretion of A $\beta$  peptides and depresses excitatory synaptic transmission in hippocampal neurons overexpressing APP (Kamenetz et al. 2003) or in the somatosensory cortex of aged hAPP mice (Bero et al. 2011) definitely demonstrates that intensification of synaptic activity contributes to the neurodegenerative process in these models. This explains, at least partly, why regions highly engaged in cognitive activity like the hippocampus and the neocortex are those where synaptic disruption and neurodegeneration firstly develop. It was therefore of primary importance determining at which age point learning-induced release of A $\beta$  starts to impact synapses and modifies the pattern of activation of brain regions in hAPP mutants (Pignataro et al. 2019).

### Tg2576 intact memory does not rely on hippocampus activation, but amygdala overactivation

Consistent with a previous report (D'Amelio et al. 2011), presymptomatic 2-mo-old Tg2576 trained for contextual fear conditioning (CFC encoding) show regular freezing when returned 24 h later to the safe training context (CFC recall). *c-fos* mapping of neuronal activity reveals that the hippocampus and the basolateral amygdala are concurrently activated 1 h after CFC encoding. Differently, no activation of the hippocampus but an overactivation of the amygdala which compensate for the hippocampus failure is detected 1 h following CFC recall.

### Tg2576 intact memory in presymptomatic Tg2576 mice does not rely on formation of dendritic spines in the hippocampus, but on more spines formed in the BLA

Upon CFC recall, trained WT mice, but not Tg2576 mice, show an increase in CA1 mushroom spines compared to their respective nontrained counterpart. In the BLA, mushroom spines are increased in trained mice of both genotypes but the additional increase in thin BLA spines found Tg2576 mice indicates more BLA rewiring in the mutant mice. Detection of immunostaining spots of the postsynaptic synaptic density 95 (PSD95) protein in both mushroom and thin spines, by informing on the presence active synapses (Béique and Andrade 2003) confirms that distinct synaptic rearrangements support regular memory in WT mice and presymptomatic Tg2576 mutants.

### CFC encoding triggers A $\beta$ release in the hippocampus, but not the amygdala, of Tg2576 mice

Dot blot quantification of A $\beta$  levels 24 h after CFC encoding in mice nonexposed to CFC recall reveals that Tg2576 mice showed a selective increase of A $\beta$ 42 oligomers in the hippocampus (CA1), but not in the amygdala (BLA). Complementary western blot analyses carried out using the amino-terminal specific-anti A $\beta$ 42 antibody AD54D2, and the carboxy-terminal specific anti-A $\beta$ 42 antibody (clone 295F2) confirmed that the A $\beta$  signal was selectively increased in the hippocampus of the trained mutants. In line with these immunoblot findings, immunofluorescent detection of A $\beta$  by means of the D54D2 and the carboxy-terminal specific antibody 12F4 confirmed the presence of an enhanced A $\beta$  signal in CA1 but not in BLA, following CFC encoding. Importantly, the hippocampal rise of A $\beta$ 42 returned to wild-type levels 48 h after the conditioning thereby showing its transitory nature as well as its suitability to be relaunched by further cognitive activity. In the WT mice, the A $\beta$ 42 signal was barely detectable in both regions at rest and no rise was observed following the conditioning.

### Pharmacological blockade of A $\beta$ release in the hippocampus of trained Tg2576 mice reverts CA1 defective, and BLA compensatory, spines rearrangements

Validation of the causal link between CFC-induced A $\beta$  rise and spine rearrangements in neural circuits comes from the demonstration that mushroom hippocampal spines were regularly formed in CFC-trained Tg2576 mice receiving intrahippocampus injections of DAPT, a gamma secretase inhibitor which reduced A $\beta$  levels. Notably, the same DAPT intrahippocampus injections eliminated the compensatory increase of thin spines the BLA. Thus, the blockade of A $\beta$  release in the hippocampus does not merely rescue the healthy pattern of CFC-induced hippocampal spines but also prevents the compensatory rearrangements, which takes place in the amygdala. The selective vulnerability of the hippocampus to activity-induced release of A $\beta$  oligomers is puzzling considering that the hippocampus and the amygdala both show strong levels of c-fos activation upon CFC. Indeed, local differences in A $\beta$  metabolism or network properties like variable densities of excitatory vs inhibitor neurons can play a role. For example, gamma oscillations, which favor microglia-mediated A $\beta$  elimination are more frequent in the amygdala (Randall et al. 2011), and are reduced in the hippocampus of AD 5xFAD mice (Iaccarino et al. 2016). Indeed, whether this pattern is specific to the presymptomatic stage remains to be investigated.

### Presymptomatic molecular changes

Anticipating the diagnosis at ever earlier stages of the disease constitutes one major challenge in AD clinical and preclinical research (Briggs et al. 2017; Völgyi et al. 2018; Schedin-Weiss et al. 2020). In this regard, the indisputable usefulness of AD mouse models lies in the possibility to detect molecular alterations before the onset of mild cognitive impairments (MCI). When detected, these alterations have the dual function to provide ultra-early disease markers and to unveil potential therapeutic targets for presymptomatic interventions oriented more toward prevention than healing patients. The overexpression of APP full length and the augmentation of calcium signaling detected in presymptomatic hAPP mice are relevant in both aspects

### Presymptomatic overexpression of APP full length in Tg2576 mice

Evidence that APP full length is overexpressed in several intellectually disabling pathologies including AD suggests that upstream to its abnormal proteolytic cleavage, APP overexpression per se is a disease pathogenic factor. To correlate APP levels with the severity of cognitive damage in mice, which overexpress mutant forms of hAPP, Borreca et al. (2016) measured the hippocampal levels of the protein and of its messenger in Tg2576 mice of 2, 3, and 6 mo of age with the hypothesis that these levels would have been maximal in the fully symptomatic phase. Results showed that APP and APP mRNA expression considerably fluctuate as a function of age but, unexpectedly, that the highest levels are observed in asymptomatic 1-mo-old mutants, that is, before circulating A $\beta$  oligomers can be detected in their brain. At every age, APP overexpression associates with variations in the levels of its translational regulators, the Fragile-X Mental Retardation Protein (FMRP) and the heteronuclear Ribonucleoprotein C (hnRNP C) which decreases and increases APP translation, respectively. Specifically, the stronger reduction of FMRP and the stronger augmentation of hnRNP C are observed in correspondence with the peak of APP expression (1 mo). Then, APP levels progressively decrease in association with the normalization of FMRP and hnRNP C levels, making it possible that reducing APP translation early in development

could be beneficial. Consistent with this view, recent data from the same group showed that overall translation is also prominently up-regulated at 1 and 3 mo of age (Borreca et al. 2020) and that its pharmacological down-regulation by i.p. injections of the drug salubrinal in 3-mo-old mutants normalizes hippocampal levels of APP, A $\beta$ , and BACE1, and prevents their memory deficit. Altogether, these findings demonstrate that overexpression of APP and alteration of its translational regulators are early-life events and, as such, can be seen as ultra-early disease markers. Second, the progressive diminution of FMRP and augmentation of hnRNP C observed in MCI (3 mo) and symptomatic (6 mo) hAPP mice show that compensatory mechanisms take place to contrast APP overexpression and reduce its accumulation. Third, the observation that salubrinal administered during the MCI phase normalizes translation and blocks the manifestation of neural and behavioral AD-like symptoms suggests that even stronger neuroprotective effects could be expected from translational blockers administered during the presymptomatic phase.

### Presymptomatic calcium signaling abnormalities as a compensatory mechanism which sustains synaptic plasticity in 3xTg-AD mice

There is evidence that presymptomatic 3xTg-AD mice show increased endoplasmic reticulum calcium release, and that this apparently pathogenic alteration is, de facto, a cell adaptive mechanism which restores neurophysiological homeostasis and allows calcium-dependent presynaptic and postsynaptic signaling to operate normally (Chakroborty et al. 2012). Specifically, electrophysiological recordings carried out in young 3xTg-AD hippocampal slices detected an increased activity of the ryanodine receptor (RyR) which augments RyR-evoked calcium release and rectifies defective synaptic transmission by compensating for the intrinsic predisposition of hippocampal synapses toward long-term depression. Further investigations (Chakroborty et al. 2015) identified nitric oxide (NO) as the effector of this compensatory synaptic modulation since blockade of NO synthesis prevented up-regulation of RyR, decreased RyR-evoked calcium release, and increased hippocampal synaptic depression. Of note, the beneficial effect of NO-induced calcium release is likely to be temporary as it could be mitigated by the dual role of NO in neuroprotection and neurodegeneration. Evidence that inducible nitric oxide synthase (NOS) from activated glia synthesizes NO, mobilizes calcium from the endoplasmic reticulum, and promotes vesicular glutamate release from astroglial cells which then leads to neuronal cell death (Yuste et al. 2015) indicates that the NO-mediated compensatory effect could become deleterious with disease progression.

### Conclusions

#### Cognitive activity discloses morphological and functional alterations in hippocampal circuits which are intact at rest

Data from mice with distinct hAPP mutations converge in showing that cognitive activity disrupts hippocampal circuits which are unaltered in resting conditions, and that other circuits instantly compensate to preserve, at least temporarily, cognitive functions. Compensatory mechanisms include overactivation of fragile canonical regions (overwiring of CA1 neurons in APP23 mice) or overactivation of regions unaffected by A $\beta$  load (overwiring of BLA neurons in Tg2576 mice) which both are reminiscent of neural compensation phenomena identified with fMRI methods in early AD patients (Stern 2012). Whether this phenomenon exclusively regards episodic memory remains, however, to be demonstrated.

## Is cognitive activity deleterious in AD?

The report that CFC encoding produces an immediate rise of A $\beta$  oligomers in the hippocampus of AD mice which selectively damages hippocampal synapses (Pignataro et al. 2019) suggests that cognitive activity can be deleterious in AD. These findings are globally in contrast with the beneficial effects of enriched environmental (EE) stimulation found in a variety of AD mouse models (Maesako et al. 2012; Verret et al. 2013; Rodríguez et al. 2015), and more specifically with two studies carried out in young 3xTg-AD mice which show that water maze training improves subsequent CFC acquisition, enhances hippocampal synaptic plasticity, and ameliorates tau and amyloid pathologies (Billings et al. 2007; Jiang et al. 2015). In these studies, however, hippocampal A $\beta$  release was not measured immediately after water maze training, making it possible that the transient rise observed in mice upon their exposure CFC was not detected. Assuming that this rise actually occurred, a possibility exists that the intense motor activity displayed by mice during water maze training acts as an enrichment-like neuroprotective factor of hippocampal synapses. Supporting this view, the presence of cognitive symptoms in APP23 mice examined at the preplaque stage appears to depend on unsuccessful EE-induced neuronal compensation (Pfeffer et al. 2018). Of note, discrepant results regarding the beneficial effect of cognitive stimulation have also been reported in AD patients. For example, in contrast with the demonstration that an active lifestyle protects aged patients from dementia (Verghese et al. 2003; Andel et al. 2006), AD patients facing an intense intellectual demand show a rise in A $\beta$  load which accelerates AD progression (Buckner et al. 2005). Overall, these findings suggest that diffuse motor/sensorial/social stimulation that does not dramatically solicit neural networks involved in highest cognitive functions can be beneficial for cognition while intensive solicitation of those networks can be deleterious.

## Can neural compensation phenomena help to design novel therapeutic strategies?

The advantage of detecting neural abnormalities in individuals with intact cognition is that the challenge is no longer to restore, but to preserve intellectual abilities. A compensatory neural circuit is by definition less fragile than a canonical circuit. Thus, uncovering how and where in the brain synapses and circuits reorganize does not uniquely allow to anticipate AD diagnosis but paves the way to novel rehabilitative strategies aimed at prolonging the molecular integrity of compensatory circuits, or featuring tasks to activate regions less prone to degenerate. Like for canonical mechanisms (Hijazi et al. 2020), it is apparent that the limits of compensatory mechanisms are reached when excitatory/inhibitory (E/I) activity is strongly unbalanced in the neural circuits of reserve (Barrett et al. 2016), suggesting that rectifying the E/I ratio in these circuits could significantly extend neural compensation phenomena.

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