nociceptor selectivity and reduce unwanted side effects. ❐

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Competing interests

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SEX DIFFERENCES

Puberty reverses sex differences in learning

Adult male rodents have long been known to show stronger hippocampal long-term potentiation (LTP) and learning than females. Le et al. find that this sex difference is reversed in pre-pubescent animals, and identify a female-specific mechanism that increases LTP threshold and decreases spatial memory in females after puberty.

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Until recently, much of the research on the neurobiology of memory has focused on mechanisms of synaptic plasticity and memory in male animals, with the implicit assumption that because both sexes can learn — and learning is a fundamental and non-reproductive function — memory and its underlying mechanisms should be similar across sexes. That said, there are known sex differences in some — but not all — memory tasks, including differences in behavioral strategies[1] and the information acquired[2]. For example, in spatial tasks with multiple possible strategies for solving them, female animals and women are more likely to choose place or landmark cues, whereas males and men are biased toward spatial cues[3,4]. Indeed, across species, males typically show better memory than females in spatial tasks. These sex differences are not only quantitative; even in the absence of apparent behavioral differences, adult males and females engage divergent mechanisms for LTP and memory formation[5].

It is commonly assumed that sex differences in mechanisms of plasticity are driven by increased and fluctuating levels of estrogens and progestins after puberty, particularly in females. That is, in prepubescent animals, males and females should be similar. Nevertheless, sex differences in the brain are also driven by organizational effects of hormones[6] and by sex chromosomes[7] throughout development,

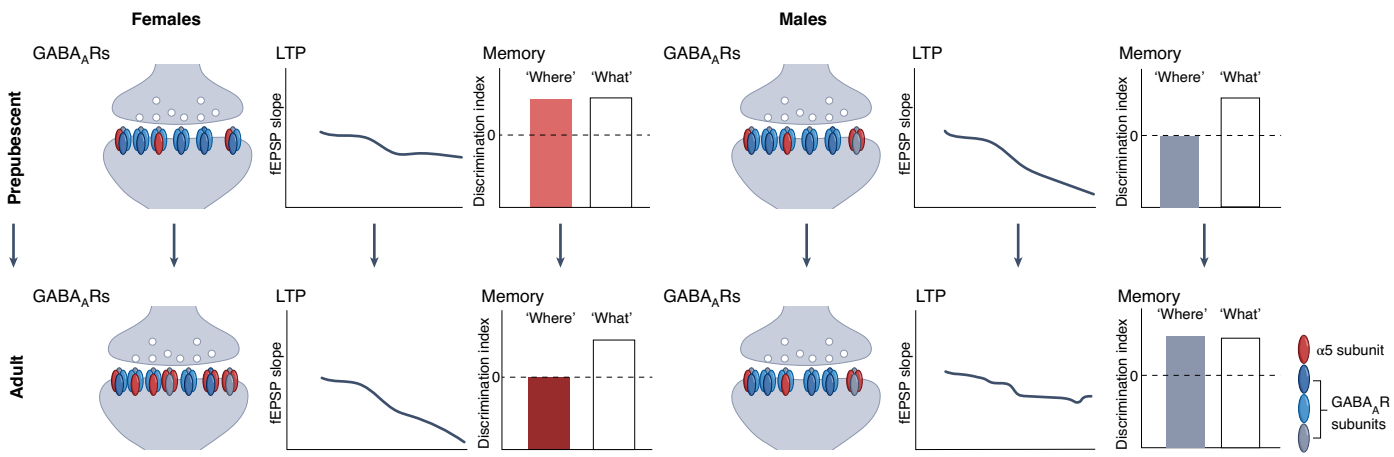

Fig. 1 | Schematic summary of the main results from Le et al. Differences in LTP and memory in female (left) and male (right) mice and rats before (top) and after (bottom) puberty[8]. fEPSP, field excitatory postsynaptic potential; GABA$_A$R, GABA$_A$ receptor.

which suggests that similarities before puberty cannot be assumed. As yet, the transition to adulthood has not been systematically examined for memory tasks in any sex, and there has been very little investigation of LTP in late-development female animals.

In this issue of *Nature Neuroscience*, Le and colleagues focus on the under-studied critical period of adolescence, and address the questions of when sex differences in LTP and memory emerge and what changes occur during this critical developmental period that cause these differences[8]. Contrary to expectations, they find that striking sex differences also exist before puberty, and that the direction of difference is reversed from adult animals. Young female mice and rats show lower LTP thresholds than males, with theta burst triplets inducing robust LTP in females but not in males. Similarly, in two spatial memory tasks, prepubescent females showed robust memory for both an object recognition task and a 'where' version of an episodic-like odor memory task, whereas males failed to learn these tasks (Fig. 1).

These differences in both LTP induction and memory performance were reversed after puberty — young adult females showed higher thresholds for LTP and required additional training to learn the spatial tasks, where young adult males showed decreased LTP thresholds and could effectively acquire spatial memory tasks. This was not a matter of adult females becoming unable to learn — in non-spatial memory tasks, females showed robust memory, suggesting that these sex differences are specific to hippocampus-dependent processes.

Le et al. also show that changes in hippocampal LTP and memory across puberty in females and males are driven by different underlying mechanisms. In females, the number of α5-$GABA_A$ receptor (α5-$GABA_A$R) subunits at inhibitory synapses in CA1 increases from pre- to post-puberty in females, corresponding to an increase in feed-forward inhibitory postsynaptic currents and a decrease in the NMDA receptor (NMDAR)-mediated component of LTP. Blocking α5-$GABA_A$R subunits using a negative allosteric modulator rescued the induction of LTP by theta burst stimulation in slice culture, and spatial memory ability in adult females, but had no effect in pre-pubescent females, which suggests that the increase in α5-$GABA_A$-containing GABA receptors at inputs from CA3 to CA1 mediate changes in LTP and memory across puberty in females.

By contrast, changes in α5-$GABA_A$Rs are not responsible for enhanced LTP and spatial memory after puberty in males. Inhibition of α5-$GABA_A$Rs had a similar enhancing effect in both pre- and post-pubescent males. These data are important for two reasons: first, they demonstrate a role for α5-$GABA_A$Rs in shunting NMDAR-mediated currents in both sexes; and second, they suggest a mechanism by which progesterone-related changes during puberty in females may contribute to changes in hippocampal GABA receptor subunit composition, and hence changes in LTP.

This paper also replicates a previously established sex difference in LTP — that in adult females, but not males, it requires α-type estrogen receptors (ERα) — and extends this finding to show that this sex difference does not arise during puberty. Rather, pre-pubescent females also require ERα for LTP. Whereas increases in α5-$GABA_A$ subunit-containing receptors enhance feedforward inhibition, the authors suggest that increases in ERα in the adult female hippocampus may, in part, compensate for this loss of the NMDAR-mediated component of LTP.

By highlighting the interaction between prepubertal sex differences, and the dramatically contrasting mechanisms and patterns of change after puberty in males and females, this work provides a framework for understanding both the emergence of a variety of sex-biased disorders after puberty and how prepubertal challenges (for example, stress in early life or adolescence or immune challenges) cause very different outcomes in adult males and females. For example, in rats, chronic stress during adolescence impairs hippocampus-dependent learning and synaptic plasticity in adult females but not males[9]; and maternal immune activation impairs cognitive function only in adult males[10]. It will be interesting to extend the findings described by Le et al. to examine how challenges in early life or peri-adolescence interact with sex-specific changes during late development to result in differential risks for dysregulation of synaptic plasticity and memory disorders (for example, Alzheimer's disease[11] or post-traumatic stress disorder[12]) in men and women throughout adulthood.

After decades of male-only research, this paper refreshingly addresses a female-specific mechanism of memory and synaptic plasticity function, and opens many additional questions on the role of circulating hormones in triggering or maintaining sex differences both before and after puberty. In addition, it should prompt investigation of whether puberty is a unique critical period for these changes, or whether other hormonal changes across the lifespan, including pregnancy, estropause or menopause, or exposure to hormonal contraceptives also cause temporary or persistent changes in hippocampal function.

From a more ethological perspective, perhaps we should also ask how this reversal of sex differences in synaptic plasticity at puberty interacts with other sex differences, including increases in anxiety and risk of depression, that emerge at this age. And perhaps this work will allow us to reframe the question: with the change in synaptic mechanisms, and the loss of rapid spatial memory formation, what do females gain? ❐

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Competing interests

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