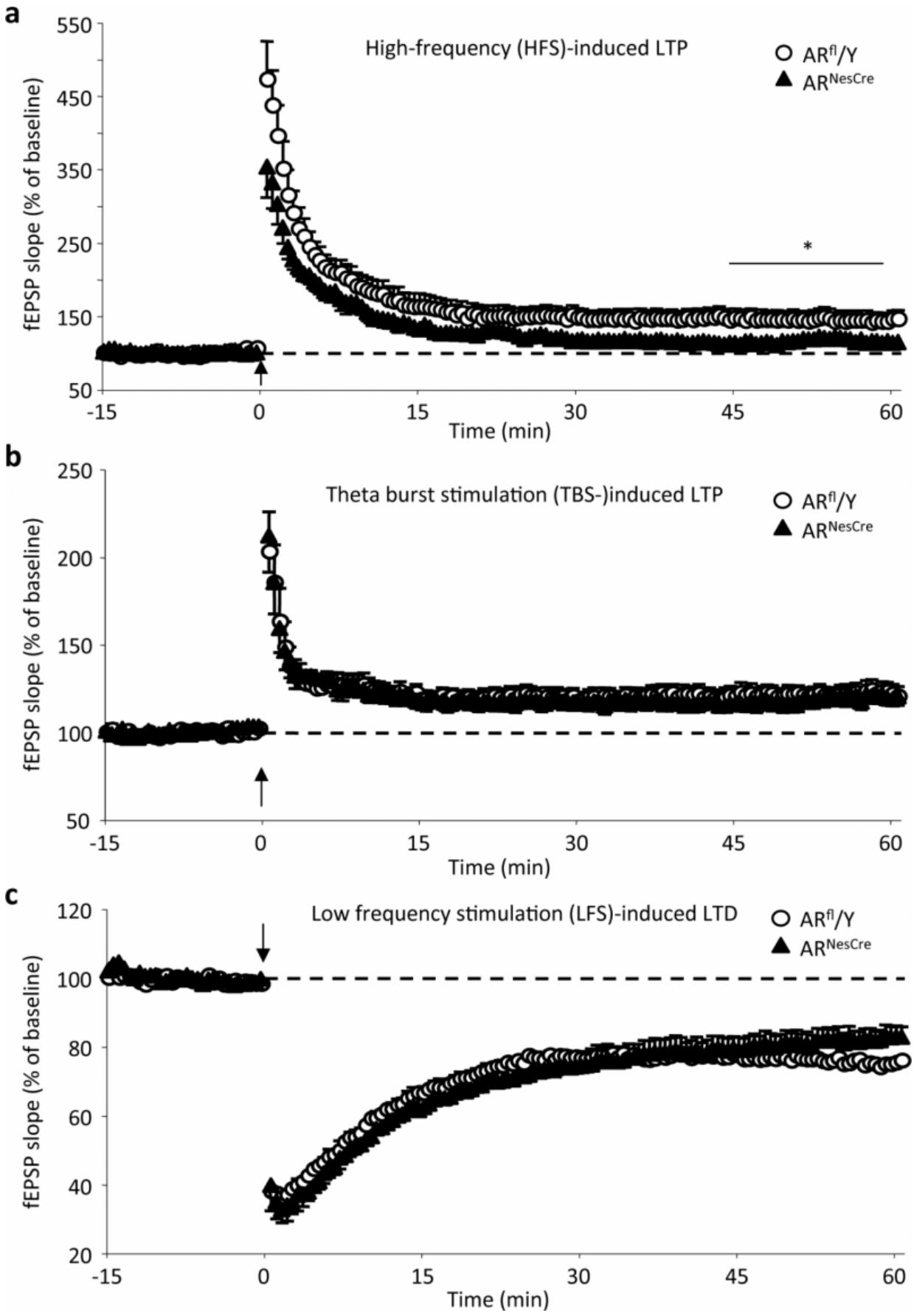
Testosterone beyond sex

February 23 2016, by Giuseppe Gangarossa


a
High-frequency (HFS)-induced LTP
AR^fl/Y
AR^NesCre
fEPSP slope (% of baseline)
Time (min)
*
b
Theta burst stimulation (TBS-)induced LTP
AR^fl/Y
AR^NesCre
fEPSP slope (% of baseline)
Time (min)
c
Low frequency stimulation (LFS)-induced LTD
AR^fl/Y
AR^NesCre
fEPSP slope (% of baseline)
Time (min)

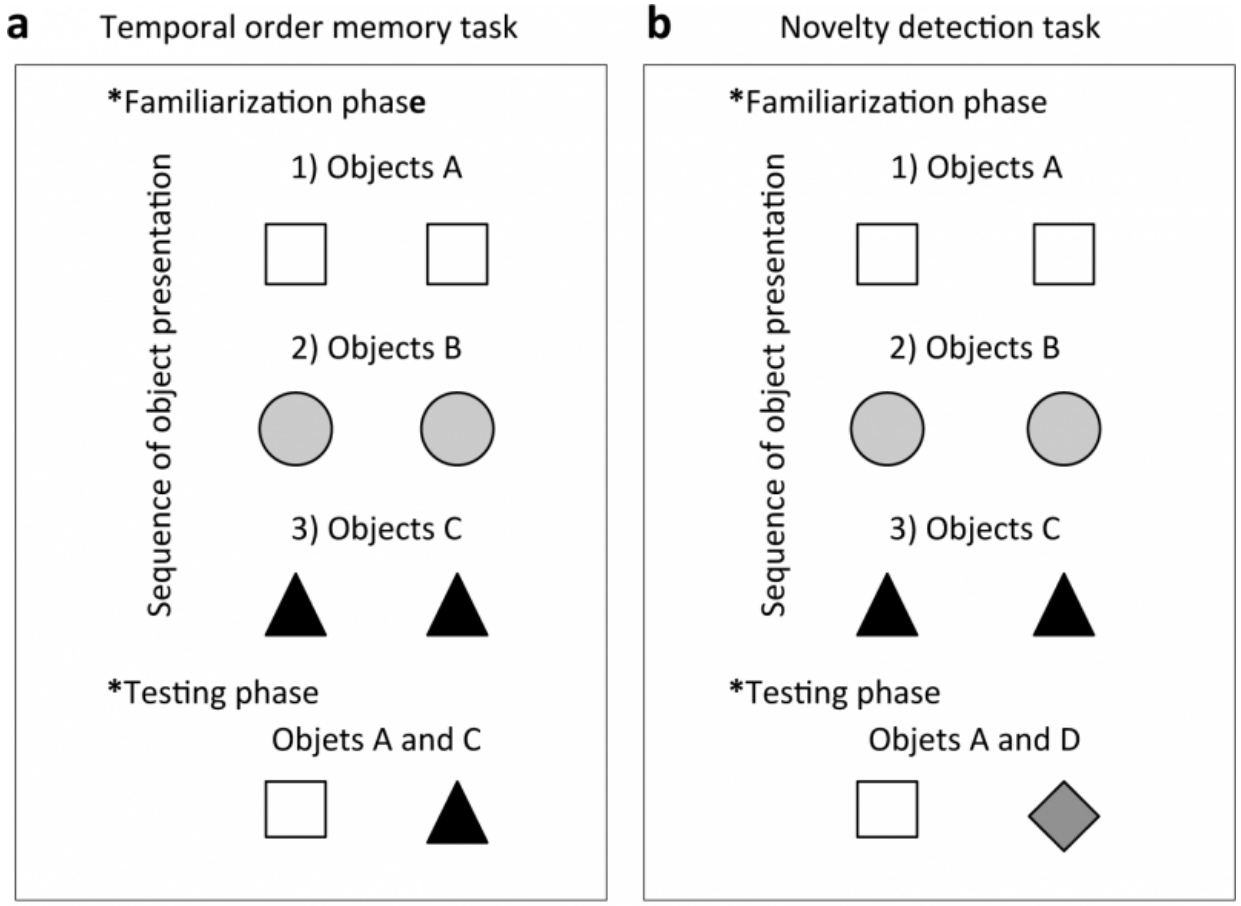
Genetic absence of AR alters long-term potentiation (LTP) in the hippocampus.

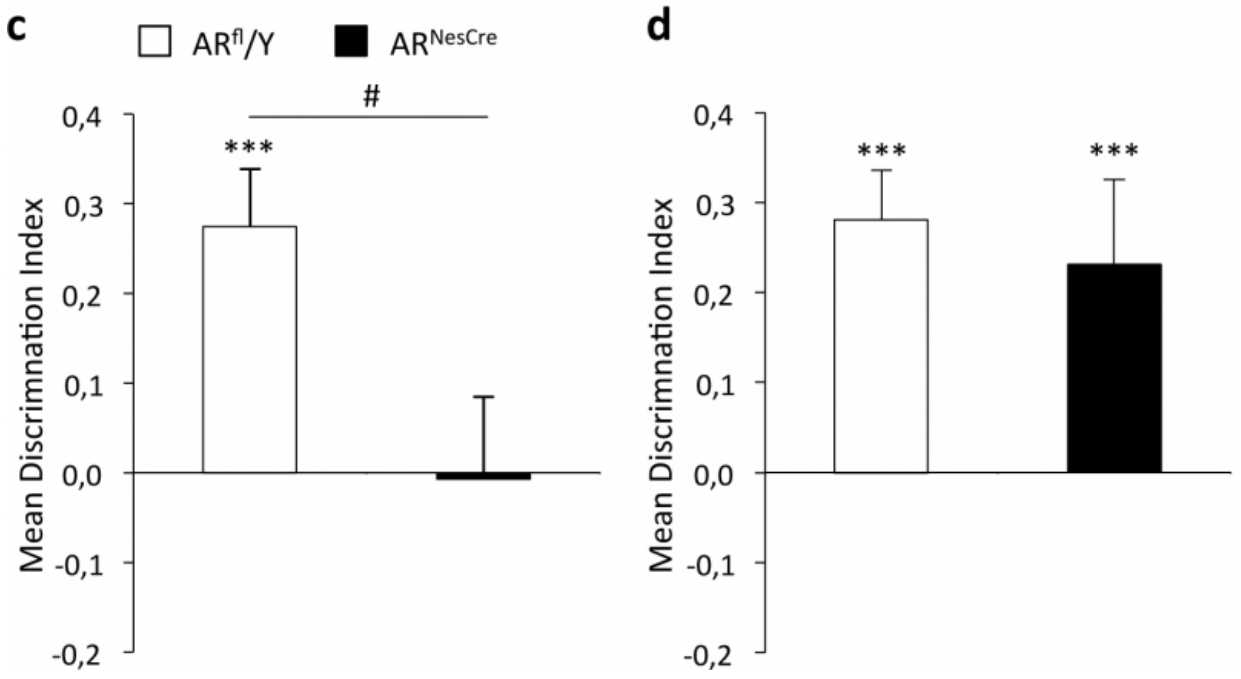
When we think about sex hormones, notably estrogens and androgens, we usually associate them with sex, gender and body development. Like all hormones, they are chemical messengers, substances produced in one part of the body that go on to tell other parts what to do. However, we often have the tendency to forget the enormous impact that these steroid hormones have on brain functions. From animal studies, it has become clear that during early development, exposure of the brain to testosterone and estradiol, hormones present in both males and females, leads to irreversible changes in the nervous system (McCarthy et al., 2012). A growing and very appealing body of science suggests that sex hormones play a neuromodulatory role in cognitive brain function (Janowsky, 2006). Moreover, testosterone dysfunctions (hypogonadism, chemical castration, etc.) have shown to be associated with memory defects. However, in spite of these advances, it still remains an enigma how sex hormones affect the brain.

In an interesting paper published in *PLOS ONE*, Picot and colleagues tried to fill in one piece of the puzzle. They investigated the neurobiological effects of cerebral androgen receptor (AR) ablation on hippocampal plasticity and cognitive performance in male rodents (Picot et al., 2016). Although several reports have already highlighted a link between sex hormones and cognitive function (Galea et al., 2008; Janowsky, 2006), much more needs to be done to fully elucidate the "non-sexual" functions of androgens.

Androgen receptors, testosterone and brain function

In the central nervous system, testosterone binds to AR that is localized in the cell cytoplasm. Upon binding and receptor activation, AR can translocate into the nucleus where it can act as a DNA-binding transcription factor, thus regulating gene transcription. When we look at the expression patterns of AR in the brain, we find that it highly localizes in the cerebral cortex and the hippocampus, which are regions associated with high cognitive functions such as memory, learning, motivation and attention.


a
Temporal order memory task
*Familiarization phase
Sequence of object presentation
1) Objects A
2) Objects B
3) Objects C
*Testing phase
Objets A and C
b
Novelty detection task
*Familiarization phase
Sequence of object presentation
1) Objects A
2) Objects B
3) Objects C
*Testing phase
Objets A and D


c
AR^fl/Y
AR^NesCre
#
***
Mean Discrimination Index
0,4
0,3
0,2
0,1
0,0
-0,1
-0,2
d
***
***
Mean Discrimination Index
0,4
0,3
0,2
0,1
0,0
-0,1
-0,2

Androgen receptor knock-out mice show impairments in a temporal order memory task (a, c) but normal novelty recognition (b, d).

Using a mouse line lacking AR expression specifically in the nervous system, the authors observed a net decline in the temporal processing of memory information. This type of memory represents the ability to remember the order in which objects or events have been experienced by a subject. Neural AR-deleted mice were unable to discriminate between two temporally distinct objects in a temporal classification task in which wild-type rodents were able to discriminate between visual objects that were presented in a specific temporal order (the first versus the most recent object seen). Temporal and recognition processing are two critical components of episodic memory. As such, in order to dissociate whether the observed deficit might be due to impairment in the former or the latter process, the authors performed a non-temporal processing task, the object recognition memory test, in which mice have to discriminate between a familiar and a non-familiar object. Interestingly, mutant mice were able to make the discrimination, which suggests that recognition processing is intact following AR genetic deletion. Altogether, this set of data indicates that androgens may impact processing of the temporal order of episodic memory, a function strongly impaired in Alzheimer's disease. However, "whether this deficit may be caused by a defective consolidation or by an impaired memory retrieval will need to be explored", says Dr. Sakina Mhaouty-Kodja, senior author of the study and team leader.

Androgen receptors and brain plasticity

The hippocampus is strongly implicated in the temporal processing of memory information. Given the behavioral results and the high level of AR expression in this memory-related structure, the authors decided to

investigate whether AR deletion was able to alter brain plasticity. Using electrophysiological techniques, Picot and colleagues found that the hippocampi of neural AR-ablated mice were less "plastic" as a significant reduction in the long-term potentiation (LTP) was detected. LTP is known to be the cellular and molecular substrate of learning and memory functions (Lynch, 2004). Although a direct link between behavior and LTP is somehow missing, it is tempting to imagine that cerebral AR may be critical for neuronal functioning. In fact, in agreement with the LTP experiments, the authors observed that AR-mutant mice showed reduced basal synaptic transmission, although no modification of the ionotropic glutamate receptors, AMPA and NMDA, was detected. "The loss or down-regulation of neural AR may then be detrimental to functions and behaviors implemented by specific brain regions", suggested the authors.

Future discoveries

This study represents an important step forward in the understanding of non-sexual functions of sex hormones. "It's very probable," Dr. Sakina Mhaouty-Kodja says, "that androgen hormones may play a key role also in the female brain and a current project in the lab is investigating this aspect." In fact, although with differences in the hormonal contents, both males and females express receptors for androgens (AR) and estrogens (ER), which suggests that our brain is indeed more complex than we thought. Many interesting questions arise from this and other studies. May we then talk about a sexual brain? Are male and female brains as extremely different as we believe, or on the contrary, surprisingly similar? This is an extremely exciting and expanding research field that will lead to important discoveries, which will change the way we understand the brain.

More information: McCarthy MM, Arnold AP, Ball GF, Blaustein JD, De Vries GJ(2012). Sex differences in the brain:

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Galea LAM, Uban KA, Epp JR, Brummelte S, Barha CK, Wilson WL, et al. (2008). Endocrine regulation of cognition and neuroplasticity: our pursuit to unveil the complex interaction between hormones, the brain, and behaviour. *Can J Exp Psychol Rev Can Psychol Expérimentale*. 62: 247–260

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