Active and passive MDMA ("ecstasy") intake induces differential transcriptional changes in the mouse brain

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Introduction

3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") is a popular drug among adolescents and young adults.

The repeated administration of MDMA in humans produces long-term psychiatric disorders, including anxiety and mood alterations, as well as cognitive deficits, which may be associated with persistent neuroadaptations dependent on changes in gene expression. These neuroadaptations are modulated by additional factors, such as reward predictability, and motivational aspects that can only be assessed using active drug self-administration, and thus are different from those induced by the drug itself.

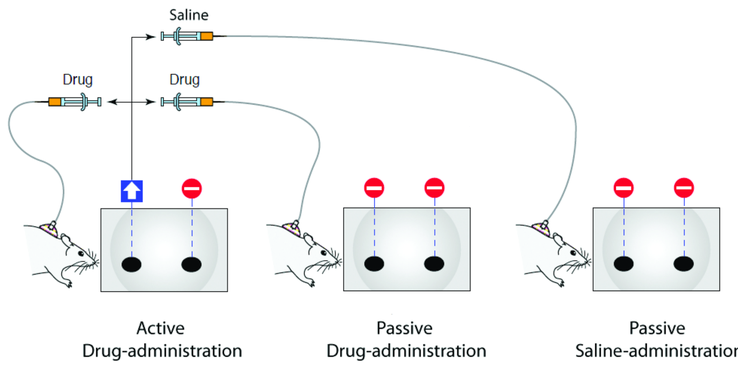
Aim

To dissociate, at a transcriptomic level in the mouse brain, the neuroadaptative changes involved in learning to self-administer MDMA from those produced by the direct effect of the drug. The only similar studies to date used passive MDMA administration.

Methods

Yoked-control operant paradigm: an animal that is self-administering the drug through **active** responding in an operant situation, causes another subject, a yoked animal, to receive the same dose of the drug or saline **passively**.

The Yoked Control-Operant Paradigm

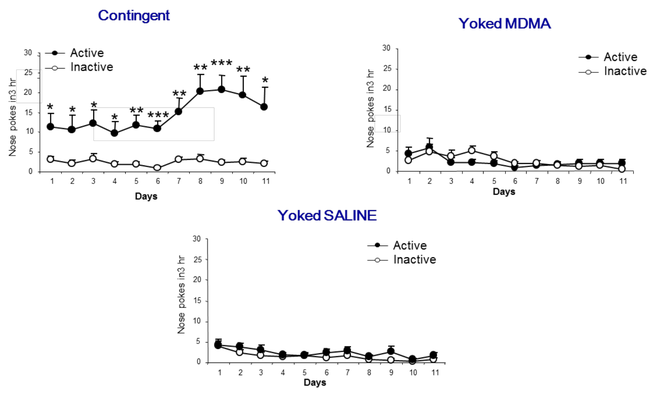


(Taken and modified from, Jacobs et al., 2003b).

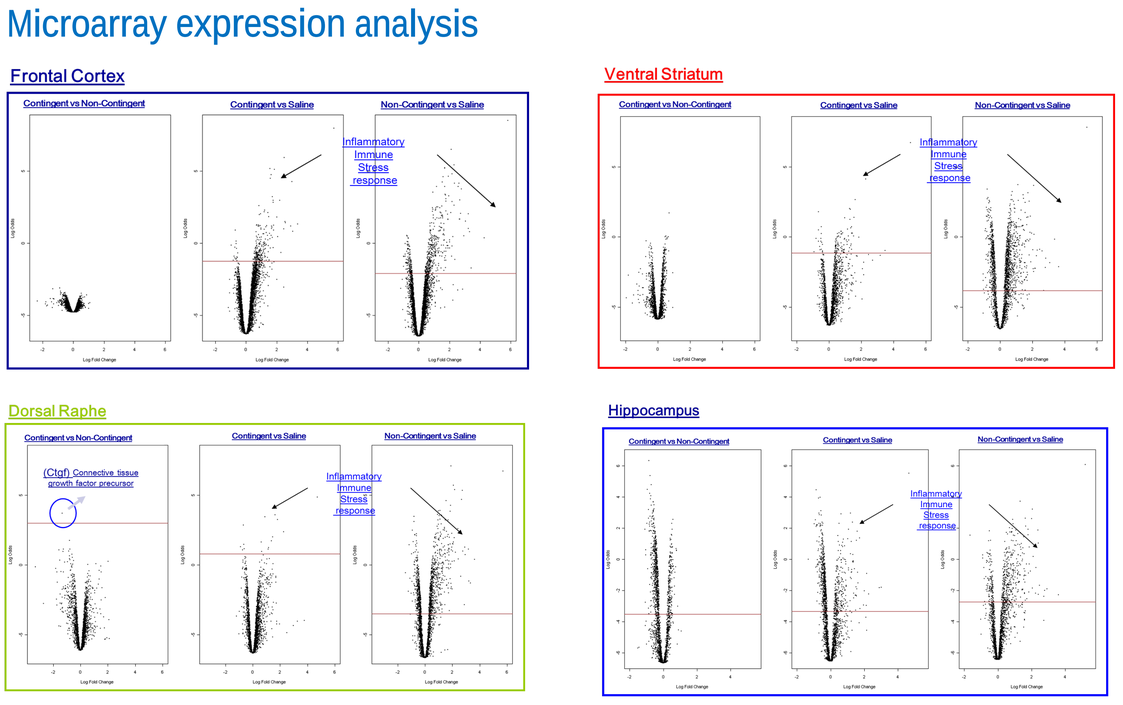
Followed by microarray expression analysis: transcriptomic profiles of the **ventral striatum**, **frontal cortex**, **dorsal raphe** and **hippocampus** were analyzed in 27 mice after 11 days of either **active** MDMA, **yoked** MDMA or **yoked saline** administration. The observed changes were validated by quantitative RT-PCR.

Results

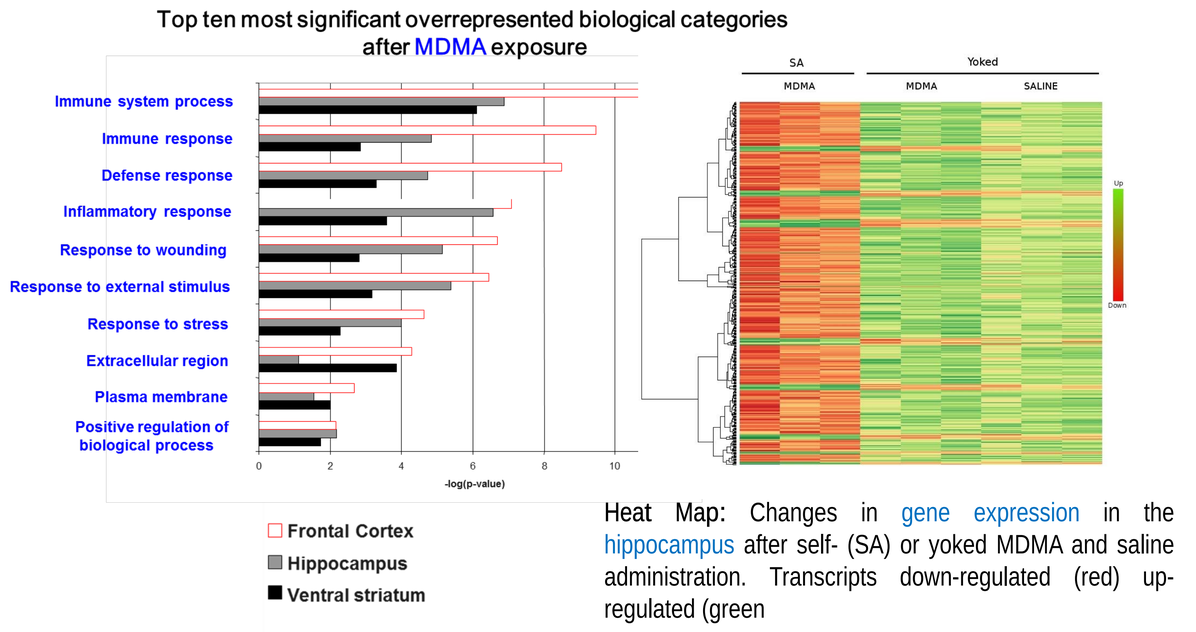
Active and Passive intravenous MDMA administration



Microarray expression analysis



Volcanoplots of the MDMA comparison showing the significance (logOdds) and the Log Fold Change. Significance threshold (FDR < 5%) is represented by a horizontal red line.



Heat Map: Changes in gene expression in the hippocampus after self- (SA) or yoked MDMA and saline administration. Transcripts down-regulated (red) up-regulated (green

qRT-PCR Validation

Contingent MDMA self-administration vs yoked MDMA: drug reinforced learning

Dorsal Raphe: Genes Selected for Validation

Symbol	Name	Validation
Camk2a	Calcium/calmodulin-dependent protein kinase II alpha	✓
Ddn	Dendrin	✓
Egr3	Early growth response 3	✓
Kalrn	Kalirin, Rho GEF kinase	✓

Genes involved in neuroplasticity and neuron remodelling indicate that the raphe nucleus may play an important role in active MDMA self-administration learning behaviour.

Active and passive MDMA administration vs saline: direct effect of the drug

Symbol	Name	Validation
Dorsal Raphe Nucleus		
Sgk1*	Serum/glucocorticoid regulated kinase 1	✓
Sgk3*	Serum/glucocorticoid regulated kinase 3	✗
Lcn2	Lipocalin 2	✓
Ventral Striatum		
Slc17a7*	solute carrier family 17 (sodium-dependent inorganic phosphate cotransporter)	✓ ✓
Lcn2	Lipocalin 2	
Frontal Cortex		
Lcn2	Lipocalin 2	✓
Ctla2a	Cytotoxic T lymphocyte-associated protein 2 alpha	✓
Gbp2	Guanylate binding protein 2	✓
Igtp	Interferon gamma Induced GTPase	✓
Iigp1	Interferon inducible GTPase 1	✓
Iigp2	Interferon inducible GTPase 2	✓
Tgtp	T-cell specific GTPase	✓
Hippocampus		
Lcn2	Lipocalin 2	✓
Ctla2a	Cytotoxic T lymphocyte-associated protein 2 alpha	✓
Gbp2	Guanylate binding protein 2	✓
Igtp	Interferon gamma Induced GTPase	✓
Iigp1	Interferon inducible GTPase 1	✓
Iigp2	Interferon inducible GTPase 2	✗
Tgtp	T-cell specific GTPase	✓

* Genes with function related to memory and plasticity

Discussion/Conclusions

Active and passive MDMA administration induces a different gene expression profile in brain areas involved in the reward circuit.

MDMA exposure induces a strong direct effect on the expression of genes related to immune, inflammatory and response to stress functions, which underpin the potential neurotoxic effects of this drug.

Active, but not passive, MDMA administration produces changes in the expression of genes related to learning and memory processes in the hippocampus and dorsal raphe nucleus. While changes in the hippocampus were subtle, we identified specific gene expression changes in the dorsal raphe nucleus, an area recently shown to be involved in reward related learning [1].

References

Nakamura K., et al, 2008. J Neurosci, 28(20):5331–5343

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None of the authors reported conflicts of interest.